Review

J. Biol. Regul. Homeost. Agents. 2024; 38(5): 3657–3671
https://doi.org/10.23812/j.biol.regul.homeost.agents.20243805.289

Physiological Benefits of Phytomelatonin and the Prospects for it as a Nutraceutical: A Comprehensive Review

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Published: 1 May 2024

Melatonin is a tryptophan-derived hormone recognized for its diverse physiological benefits such as circadian rhythm regulation and sleep modulation. Its antioxidant properties have implications for cancer prevention, immune enhancement, neuroprotection, and cardiovascular health. In contrast, phytomelatonin, a plant-derived counterpart discovered in 1995, shares similar antioxidant capabilities but follows distinct synthesis pathways. Phytomelatonin shows promise in managing sleep disorders and reducing oxidative stress, aligning with the growing interest in plant-based solutions. This review highlights melatonin's physiological roles and explores the potential of phytomelatonin as a nutraceutical for preventive and therapeutic interventions. Moreover, this review identifies research gaps to direct future investigations and refine the understanding of melatonin and phytomelatonin. Phytomelatonin, as a safer alternative to synthetic melatonin, holds therapeutic promise and warrants further research to elucidate its efficacy, bioavailability, and optimal usage. This review underscores the nuanced interplay between melatonin and phytomelatonin, offering insights into natural supplementation and therapeutics aligned with evolving preferences for effective healthcare practices.

Keywords: melatonin; phytomelatonin; antioxidant properties; circadian rhythms; bioavailability

Introduction

Melatonin, an indole amine hormone synthesized from the aromatic amino acid tryptophan, is often recognized for its pivotal role in regulating sleep and circadian rhythms [1]. Recent research has uncovered numerous physiological benefits associated with melatonin, positioning it as a versatile hormone with potential therapeutic implications. For example, studies have identified melatonin as an outstanding antioxidant, demonstrating its ability to counteract oxidative stress at physiological concentrations [2,3]. This property is of particular interest due to its relevance in combating various health issues linked to oxidative damage. Moreover, melatonin shows promise in cancer prevention, further emphasizing its importance in maintaining overall health. [4–7]. This review comprehensively explores melatonin's multifaceted advantages, including antioxidant properties, immune function enhancement, oncostatic potential, neuroprotection, and cardiovascular health.

The discovery of melatonin in various plant species introduces a new dimension to our understanding of this hormone. While phytomelatonin shares structural similarities with endogenous melatonin in humans, their synthesis pathways differ. Phytomelatonin not only mirrors the antioxidant and radical scavenging properties of melatonin but also interacts with the immune system of mammals [8]. Exploring phytomelatonin's therapeutic potential, especially in managing sleep disorders and mitigating oxidative stress, highlights its significance in human health. This emerging field provides insights into the interconnectedness of botanical compounds and human physiology, offering opportunities for advancements in natural supplementation and health interventions.

This review aims to summarize the inherent physiological roles of melatonin while bringing attention to the emerging field of phytomelatonin, contributing to the ongoing discourse on the therapeutic potential of plant-derived melatonin compounds. Additionally, we will delve into the promising prospects of phytomelatonin as a nutraceutical, highlighting its potential role in preventive and therapeutic interventions. The timeliness of this review aligns with the global shift towards embracing plant-based solutions and the increasing prevalence of lifestyle diseases.

As we navigate the current scientific landscape, it is crucial to acknowledge existing gaps in research and knowledge. Identifying these gaps will pave the way for future investigations, improving our comprehension of melatonin and phytomelatonin, and guiding potential therapeutic applications in human health. This review aims to consolidate existing knowledge and stimulate future research endeavors.

Discovery of Phytomelatonin

The significance of phytomelatonin emerged upon discovery in 1995, with concentrations surpassing levels observed in animals [9,10]. Plant synthesis of serotonin and melatonin, originating from tryptophan, parallels the process in animals, [11,12], albeit with distinctive characteristics [13]. However, the synthesis of phytomelatonin diverged from endogenous melatonin in humans due to inherent differences in enzymatic pathways. Animals, including humans, exhibit a limited ability to synthesize tryptophan, primarily due to their lack of key enzymes present in plants [14]. This enzymatic distinction fundamentally impacts the availability of tryptophan, thereby influencing the levels of melatonin production in both animals and plants. These distinctions contribute to the distinctive roles of phytomelatonin in the plant kingdom. The varying levels of phytomelatonin across different plant types highlight this molecule's complexity [8]. Cellular organelles, particularly mitochondria and chloroplasts, play a pivotal role in this biosynthetic process [12,15,16]. A comprehensive understanding of these pathways is crucial for exploring the potential benefits of phytomelatonin in both plant physiology and its implications for human health.

Recognized as a master regulator in oxidative stress management, phytomelatonin is critical in diverse plant processes [15,17]. These include flowering, seed germination, root elongation, senescence, the control of circadian rhythms, the maturation of fruits, and metabolite balance [13,18]. The diverse functions attributed to phytomelatonin underscore its versatility as a key player in orchestrating plant development and facilitating adaptation to environmental changes [19,20]. The intricate interactions between melatonin and other phytohormones, such as auxins, cytokinins, and abscisic acid, add complexity to its regulatory functions, particularly in stress response mechanisms [21,22]. Melatonin's influence extends to the modulation of root and shoot organogenesis by regulating auxin signaling [23,24]. The application of exogenous melatonin has been shown to notably alleviate hypoxia-induced inhibition of rice root growth, demonstrating its positive regulation of root growth and development under stress conditions by enhancing the antioxidant system and activating the auxin signaling pathway, either directly or indirectly [24].

Beyond growth and development, melatonin served as a pivotal regulator of redox processes in plants [25], functioning as an antioxidant molecule by scavenging reactive oxygen species (ROS) and modulating stress-related genes. This antioxidant capacity enables melatonin to efficiently neutralize ROS, thereby shielding plants from oxidative stress induced by various environmental factors. Additionally, melatonin enhances the activity of redox enzymes, such as superoxide dismutase (SOD), catalase (CAT), peroxidase (POX), and ascorbate peroxidase (APX), thereby regulating ROS and reactive nitrogen species (RNS) levels and maintaining redox homeostasis in crop plants [26].

The cumulative body of knowledge in this field not only contributes to our understanding of plant physiology but also hints at potential applications in broader contexts, including human health.

Physiological Functions of Melatonin in Animals

Beyond its circadian regulation, melatonin exhibits a spectrum of bioactivities, including antioxidant, immunemodulatory, oncostatic properties, cardioprotective effects, neuroprotective effects, and sleep regulation (Fig. 1).

Antioxidant Properties of Melatonin

Melatonin's antioxidative capabilities, rooted in its evolutionary role as a free radical scavenger, transcend animal boundaries to influence crucial processes within the plant kingdom [27,28]. Originating from bacteria like α-proteobacteria and photosynthetic cyanobacteria, melatonin's ancient lineage suggests its pivotal role in oxidative stress reduction throughout millennia [29,30]. Moreover, the proposed endosymbiotic theory suggests melatonin's enduring presence in the evolution of mitochondria and chloroplasts, highlighting its retained production in these organelles across species [12]. As a powerful scavenger of free radicals, melatonin not only eliminates excess radicals but also intricately modulates the cellular antioxidant system (Fig. 2, Ref. [29]) [31].

The complexity of melatonin's antioxidative capacity is further enriched by its cascade effect involving metabolites, such as 3-hydroxymelatonin and N1-Acetyl-5-Methoxykynuramine (AMK). These metabolites exhibit exceptional potency in reducing oxidative stress and hold promise for diverse therapeutic applications [32]. AMK specifically emerges as a potent inhibitor of neuronal nitric oxide synthase (nNOS) activity, surpassing its precursor, melatonin, in both *in vitro* and *in vivo* assessments. Its non-competitive behavior and higher antagonist efficacy against nNOS demonstrate its potential neuroprotective effects against NO-dependent excitotoxicity [33]. Sim-

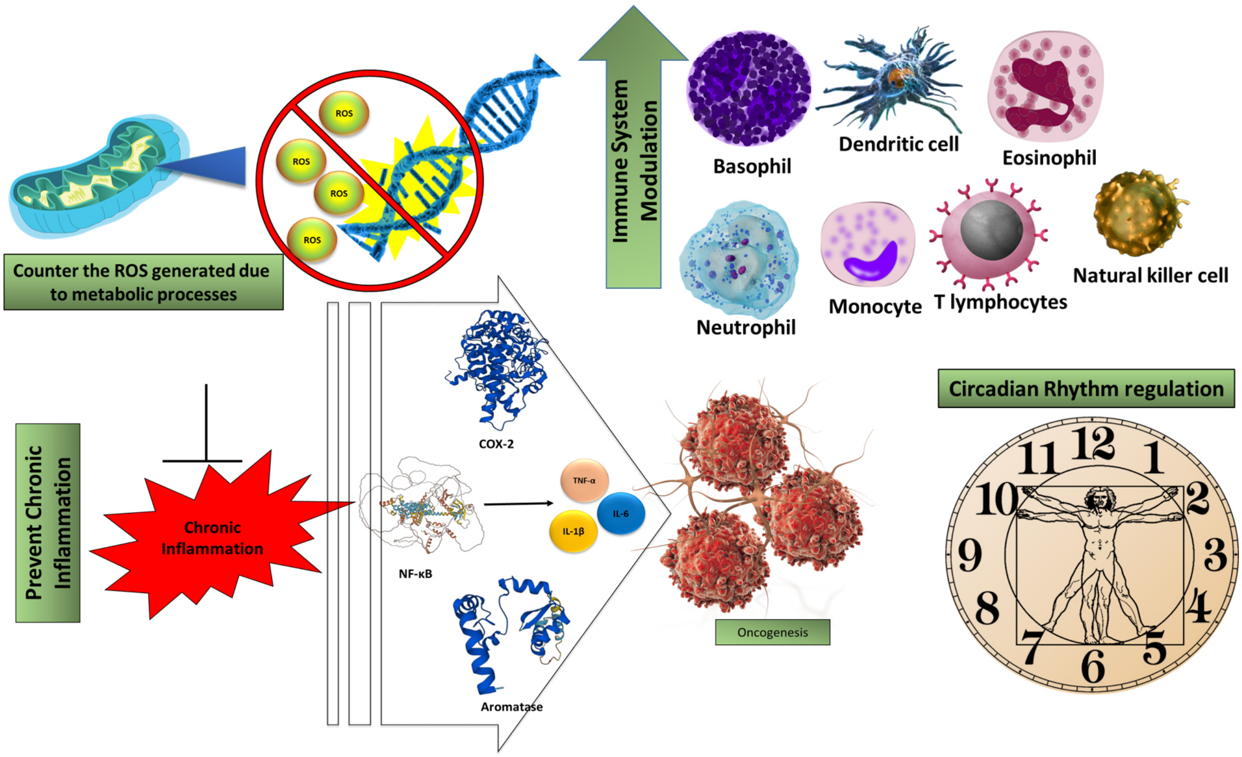

Fig. 1. The figure illustrates key physiological properties of melatonin. Melatonin serves as a potent neutralizer of reactive oxygen species (ROS) generated during metabolic processes, highlighting its significant role in cellular antioxidant defense mechanisms. Additionally, melatonin demonstrates its capacity to modulate the immune system, influencing various immune parameters and contributing to immune resilience. The figure further depicts melatonin's preventive effects on oncogenesis, showcasing its oncostatic properties in impeding cancer cell growth and proliferation. Finally, the regulatory role of melatonin in circadian rhythm is highlighted, emphasizing its orchestration of biological processes in alignment with the day-night cycle. This comprehensive representation underscores the diverse nature of melatonin's physiological effects. COX-2, cyclooxygenase-2; TNF-α, tumour necrosis factor alpha; IL-1β, interleukin-1beta; NF-κB, nuclear factor kappa B. This figure is copyright free and edited through Microsoft Power Point (MS office 2016, Redmond, WA, USA).

ilarly, melatonin outperforms vitamin E in hepatoprotective studies, demonstrating superior efficacy in reducing bilirubin levels and mitigating free radical damage under acute biliary duct ligation in rats [34]. Additionally, melatonin's antioxidative prowess in preventing dopamine oxidation showcases its significance in neuroprotective mechanisms [35]. Melatonin's ability to enhance the cellular antioxidant defense system is evident through the induction of gamma-glutamylcysteine synthetase (γ-GCS) expression and the regulation of antioxidant enzyme activities such as catalase (CAT), superoxide dismutase (SOD), glutathione reductase (GSH-Rd), and glucose-6-phosphate dehydrogenase (G6PD) [36–39].

When combined with other antioxidants, melatonin exhibits synergistic effects against lipid peroxidation, showcasing its versatility and potent antioxidative capabilities, even at low concentrations [40]. Notably, its nuanced interactions within complex antioxidant systems, especially with vitamin C, highlight melatonin's multifaceted role in cellular redox balance.

Immune System Modulation

Melatonin, a crucial immune regulator, intricately manages the interactions between environmental stimuli and the body's defense mechanisms [41]. Its essential role in immune resilience is evident in the correlation between melatonin peaks and progenitor cell proliferation, emphasizing its significance in photoperiodic immune control [42]. Studies on seasonal animals highlight melatonin's substantial impact on immune organ weight, revealing its potential immune modulatory effects [43–45]. Pinealectomized squirrels with disturbed melatonin synthesis exhibited increased levels upon exogenous melatonin administration, demonstrating its critical role in immune homeostasis [44]. Additionally, melatonin demonstrated the ability to regenerate the thymus and restore immunological function in elderly mice, indicating its broader role in responding to environmental stress [43].

Melatonin exhibits a multifaceted impact by influencing both the innate and adaptive immune systems. Specifically, melatonin enhances the cellularity of macrophages

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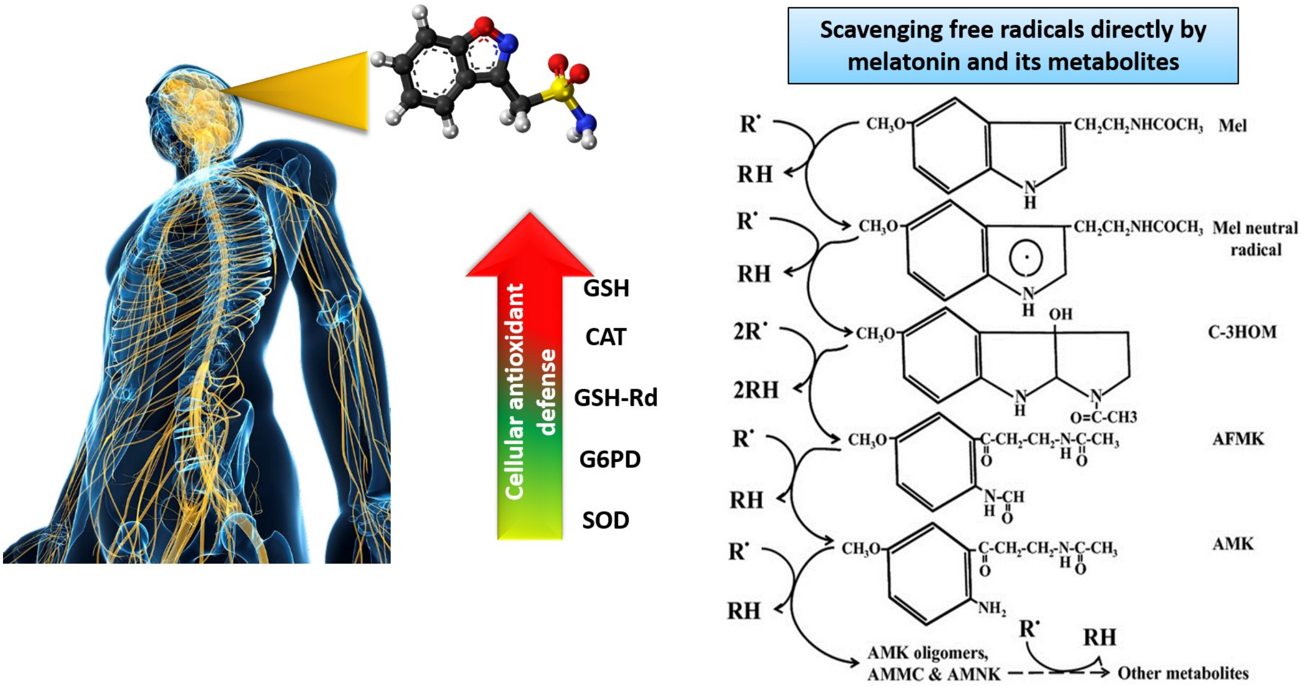

Fig. 2. This figure provides a detailed depiction of melatonin's antioxidant activity. The illustration highlights melatonin's modulation of crucial components within the cellular antioxidant system, including glutathione (GSH), catalase (CAT), glutathione reductase (GSH-Rd), glucose-6-phosphate dehydrogenase (G6PD), and superoxide dismutase (SOD). Furthermore, the figure elucidates the direct scavenging action of free radicals by melatonin itself, and its metabolites. This comprehensive representation illustrates the intricate mechanisms through which melatonin actively participates in cellular antioxidant defense, showcasing its multifaceted role in maintaining redox homeostasis. Reproduced with permission from Tan *et al.* [29], Mitochondria and chloroplasts as the original sites of melatonin synthesis: a hypothesis related to melatonin's primary function and evolution in eukaryotes; published by Journal of Pineal Research, 2013.

and microglia, the first-line defenders against pathogens, while also elevating levels of natural killer (NK) cells and monocytes crucial in innate immunity [46–50]. Despite hindering lymphocyte proliferation, melatonin's intricate influence on gene expression and cytotoxic effects underscores its nuanced impact on immune modulation [51].

Melatonin affects key cytokines involved in immune responses [52–55]. For example, melatonin inhibits tumour necrosis factor alpha (TNF-α) and interleukin-1beta (IL-1β) through signaling pathways like PI3K/Akt and nuclear factor kappa B (NF-κB), suggesting potential in mitigating inflammatory conditions [53,54]. Its anti-inflammatory mechanism, identified through NF-κB inhibition, highlights its significant role in regulating genes responsible for both innate and adaptive immune responses [56].

Melatonin also exerts its effects on T cells by modulating the equilibrium between Th1 and Th2 responses, demonstrating its comprehensive influence on immune regulation [57–59]. Its antioxidant properties contribute to anti-inflammatory effects by regulating the ROS/TXNIP/Hypoxia-Inducible Factor 1α (HIF-1α) pathway, positioning melatonin as a promising avenue for therapeutic exploration in conditions marked by immune dysregulation and excessive inflammation [60].

Oncostatic Property of Melatonin

Melatonin's oncostatic properties offer a multifaceted approach against cancer cell growth and proliferation. Recent research on human ovarian and gastric cancer cell lines revealed melatonin's ability to enhance apoptosis, inhibit proliferation, and mitigate metastasis—a pivotal stage in tumorigenesis [4,6].

Melatonin's antioxidant properties vastly contribute to its oncostatic capabilities by countering oxidative stress and preventing DNA damage, key drivers of cancer initiation. By neutralizing reactive oxygen species (ROS), melatonin optimizes mitochondrial oxidative phosphorylation and regulates antioxidant gene expression, positioning itself as a guardian of cellular redox equilibrium with therapeutic potential in cancer prevention and treatment [61–65].

Beyond its antioxidant role, melatonin acts as a regulator of inflammatory pathways, exemplified by its inhibition of cyclooxygenase-2 (COX-2), a crucial enzyme in the inflammatory cascade [66–68]. This anti-inflammatory prowess broadens melatonin's oncostatic effects and extends its therapeutic potential to inflammatory illnesses. In breast cancer, melatonin's effects occur through interactions with estrogen signaling pathways, inhibiting aromatase and sulfatase expression and activity, positioning it as a promising tumor suppressor, especially in hormone-dependent mammary tumors [69–71].

Melatonin's oncostatic repertoire extends further to its interaction with Hypoxia-Inducible Factor 1α (HIF-1α). Melatonin destabilizes HIF-1α by hindering nuclear translocation, enhancing von Hippel-Lindau protein (VHL) ligase-mediated degradation, and influencing the SUMO-specific pathway linked to HIF-1α [72–74]. Its antioxidant capabilities play a pivotal role in reducing mitochondrial hypoxia-induced ROS production, positioning melatonin as a promising oncostatic agent by disrupting metabolic adaptations, inhibiting angiogenesis, and impeding tumor cell survival [75,76].

Cardiovascular Diseases

Melatonin's cardioprotective effect has garnered considerable attention in numerous studies [77–79]. Oxidative stress is implicated in various diseases, including heart disease, highlighting the value of potent antioxidants like melatonin in maintaining redox balance [80].

Melatonin promotes cardiovascular health by preventing atherosclerosis, myocardial ischemia-reperfusion injury, and hypertension [81]. Its inhibitory effects on mitophagy and NLRP3 inflammasome activation within atherosclerotic plaque areas, coupled with its positive impact on plasma cholesterol levels, showcase melatonin's multifaceted protective effects. Melatonin's role in facilitating mitochondrial homeostasis via mitophagy solidifies its potential as a therapeutic candidate for atherosclerosis. Similarly, melatonin plays a pivotal role in blood pressure regulation and overall cardiovascular well-being, demonstrated in both rodent and human models [82–84]. In rodent models, melatonin administration reverses pinealectomy-induced hypertension and modulates hypertension-related factors in spontaneously hypertensive rats (SHR). In healthy individuals, low-dose melatonin administration significantly reduces blood pressure, lowers norepinephrine levels, and improves heart rate variability. The regulation of melatonin 2 receptor (MT2) receptors on endothelial cells emerges as a central factor in blood pressure dynamics, involving intricate signaling pathways contributing to vasodilation and overall cardiovascular health.

Melatonin's preventive influence extends to cardiac pathology, safeguarding cardiac muscle against ischemia-reperfusion-induced damage [85,86]. These cardioprotective properties occur as a result of decreased oxidative damage triggered by ischemia/reperfusion, leading to a marked decrease in infarct size and cardiac arrhythmias. These findings highlight melatonin's potential therapeutic role in protecting the heart from ischemia-reperfusion-induced damage, offering broader applications for cardiovascular health.

Neurodegenerative Diseases

Melatonin emerges as a pivotal player in neuroprotection, characterized by its robust antioxidative properties [87–89]. Its efficacy in neutralizing neuronal free radicals associated with cellular damage serves as a key factor in the development and progression of neurodegenerative diseases. Moreover, melatonin plays a crucial role in mitochondrial protection, countering the observed mitochondrial dysfunction common in neurodegenerative conditions [89–91].

The neuroprotective effects of melatonin extend to its role as a cytoprotective molecule, effectively reversing low-grade inflammatory damage and counteracting chronic inflammation seen in neurodegeneration. In Alzheimer's disease (AD), where inflammation is a significant risk factor, melatonin intervenes in crucial pathways, specifically targeting NF-κB activation and downstream cytokine induction [92]. Melatonin's ability to regulate Aβ-induced cytokine upregulation and protect against pyroptosis through N-terminal gasdermin D (N-GSDMD) underscores its potential as a versatile neuroprotective agent against inflammatory damage in neurodegenerative diseases. Melatonin administration shows promise in reversing AD-induced abnormalities in acetylcholine (ACh) neurotransmission and enhancing acetylcholine levels [88,93]. Additionally, melatonin's impact on GABAergic neurotransmission and its potential to mitigate glutamatergic system abnormalities position it as a candidate for addressing neurotransmission abnormalities associated with neurodegenerative diseases.

In Parkinson's disease (PD), melatonin also contributes to neuroprotection, mitigating neurotoxicity induced by the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) in PD animal models [94]. Its efficacy in restoring abnormal autophagic activity, preserving neuromorphological changes, and protecting dopaminergic neurons underscores its potential as a valuable therapeutic intervention in preventing neurodegenerative conditions in PD. Huntington's disease (HD), which is characterized by neural oxidative stress and mitochondrial dysfunction, is also positively benefited by melatonin's protective effects. In an HD rat model induced by 3-nitropropionic acid, melatonin reversed neural oxidative stress and mitochondrial injury caused by the neurotoxin [95–98]. Melatonin's ability to prevent oxidative damage to cell membranes, organelles, and nuclear mitochondrial DNA underscores its potential as a neuroprotective agent in mitigating the effects of neurodegenerative conditions, including those associated with HD.

Sleep Regulation

As it relates to its pivotal role in circadian rhythm regulation, melatonin has emerged as a potent intervention for sleep disorders and jet lag, functioning both as a dietary supplement and therapeutic drug [99–101]. The circadian sys-

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tem, overseen by the suprachiasmatic nucleus (SCN), plays a pivotal role in governing physiological processes and behaviors [102].

The well-established effectiveness of melatonin in improving sleep parameters occurs through its chronobiotic role in adjusting and maintaining regular circadian rhythmicity [103–105]. Studies indicate that melatonin and its derivatives expedite sleep initiation and modulate sleep architecture, with research on melatonin-proficient and melatonin-deficient mice highlighting its modulatory effects on clock gene expression, particularly in the retina, where it coordinates circadian rhythms in neuronal remodelling [106,107]. Referred to as the 'hormone of darkness,' melatonin regulates sleep by activating MT1 and MT2 receptors [108].

In humans, melatonin promotes sleep and lowers body temperature at night, aligning with the nocturnal sleep cycle [101,109]. Particularly relevant in industrialized countries, melatonin supplementation is sought to improve sleep, reducing symptoms of "jet lag". The European Food Safety Authority recognizes melatonin's role in reducing sleep onset latency and recommends a daily dose of 1 mg close to bedtime for the general population [110]. Moreover, melatonin's status as a dietary supplement has been acknowledged via the creation of consumption guidelines by regulatory bodies such as European Food Safety Authority and Food Standards Australia New Zealand [111]. Given that approximately one-third of the general population suffers from sleep disorders, sleep-promoting interventions like melatonin are crucial.

Leveraging melatonin's capacity to regulate sleep quality, exogenous melatonin can be integrated as a dietary supplement to address sleep-related disorders. Ongoing research solidifies melatonin's position as a versatile and promising tool in sleep medicine and circadian rhythm regulation. As a pivotal regulator of immune functions, melatonin influences immune circadian organization, immune organ weight, innate immune system components, and cytokine modulation, showing potential for the treatment of conditions characterized by immune dysregulation and inflammation.

Exogenous Melatonin as Dietary Supplements

Exogenous melatonin is readily available as a dietary supplement and continues to exhibit diverse health benefits. Melatonin originates from the pineal gland and is used to regulate the sleep-wake cycle. Its exogenous supplementation has emerged as a versatile tool in various clinical applications. Beyond its application to sleep disorders and jet lag, melatonin regulates various physiological aspects, including but not limited to inflammation, hypertension, oxidative stress, and metabolic syndrome [112–116].

Aside from sleep-related issues, melatonin could potentially improve numerous health conditions including diabetes, neurodegenerative diseases, heart diseases, and cancers. The meta-analysis study hinted at melatonin's potential as a viable alternative treatment for irritable bowel syndrome (IBS) [117]. Nevertheless, additional research is needed to validate this area. Furthermore, melatonin supplements have shown promise in reducing weight gain and have found integration into the management of various medical and surgical conditions [118,119]. The core of melatonin's effectiveness in treating insomnia lies its ability to mimic the natural endogenous melatonin, binding to the same receptors and activating similar pathways [120].

Administered orally, melatonin was characterized by efficient absorption, widespread distribution, and complete metabolism, allowing it to traverse the blood-brain barrier and exert its effects on the central nervous system [121,122].

Melatonin has been generally considered safe with no reported toxicity, even in extreme doses. Mild adverse effects such as dizziness, headache, nausea, and sleepiness have been reported [123]. Despite this safety profile, caution was advised, and the intake of exogenous melatonin during pregnancy and breastfeeding was not recommended due to a lack of comprehensive studies. Melatonin was approved by the U.S. Dietary Supplement Health and Education Act of 1994, officially recognizing melatonin as a dietary supplement [10]. This acknowledgment has led to standardized recommendations, with authoritative bodies like the National Sleep Foundation suggesting a dosage ranging between 0.2 to 5mg for adults, to be taken approximately 60 minutes before bedtime [107]. This regulatory support established a foundation for the widespread acceptance and use of melatonin supplements, particularly in contexts where sleep-related issues or circadian rhythm disturbances were prevalent.

While the attributes of melatonin hold promise across various applications, it is crucial to approach supplementation with caution. Despite its potential, the evidence supporting its efficacy was not uniform across all applications [117]. As with any dietary supplement, individuals considering melatonin supplementation should consult healthcare professionals to ensure safe and appropriate usage, considering individual health conditions and potential interactions with medications. Additionally, ongoing research is vital to further elucidate the full range of melatonin's health benefits and optimize its application in various clinical settings, providing a solid foundation for evidence-based recommendations and expanding our understanding of this multifaceted hormone's potential contributions to health and well-being.

Recent Interest in Phytomelatonin for Human Health

The intricate interactions between phytomelatonin and endogenous melatonin in humans include similar biochemical origins and shared functionalities as signaling molecules. The identical structures of phytomelatonin and endogenous melatonin establish their conserved roles in cellular communication and regulation [8,124]. Understanding these shared functions informs the evolutionary significance and potential therapeutic applications of melatonin-related mechanisms.

In the context of human health, the exploration of phytomelatonin as a natural, plant-based supplement has garnered considerable attention. The multifaceted role of melatonin in regulating crucial physiological activities, including mood, sleep, body temperature, locomotor activity, food intake patterns, circadian rhythms, and immunological processes, demonstrates its significance in human health [125]. Despite their distinct synthesis pathways, the nuanced interactions between phytomelatonin and endogenous melatonin suggest functional convergence, implying that both compounds may contribute to similar physiological outcomes in humans.

Furthermore, phytomelatonin's antioxidant properties [25,26] contribute to its allure in the realm of human health. Antioxidants play a pivotal role in mitigating oxidative stress, a factor implicated in various human diseases. The potential benefits of phytomelatonin open avenues for novel approaches in managing oxidative stress-related conditions, given its antioxidant properties. For example, phytomelatonin exhibited remarkable potential in treating respiratory infections such as Coronavirus disease-2019 (COVID-19) [126], and in preventing liver diseases [127]. These outcomes position phytomelatonin as a potential therapeutic agent and simultaneously highlight the broader implications of understanding the interplay between botanical compounds and human health.

Positive correlations between melatonin-rich foods and clinical-metabolic indicators have been identified, highlighting the potential impact of dietary melatonin on overall well-being [128]. Given the age-associated decrease in endogenous melatonin and its correlation with a higher incidence of sleep disorders, the investigation of phytomelatonin becomes increasingly relevant [129].

A pivotal aspect of phytomelatonin's influence on circadian rhythms lies in its interaction with light-dark cycles [126]. Melatonin has demonstrated a unique capacity to respond to environmental light cues, contributing to the entrainment of circadian rhythms [130,131]. Similarly, phytomelatonin emerged as a contributor to the regulation of the body's internal clock, aligning biological processes with the natural day-night cycle. This potential renders phytomelatonin a key player in maintaining the balance of physiological processes and promoting overall well-being by influencing circadian rhythms.

Upon ingestion, phytomelatonin was absorbed through the gastrointestinal tract, modulating blood melatonin levels. The relatively short half-life of melatonin (20 to 40 minutes) was attributed to its metabolism and elimination in urine [132,133]. As exploration into the properties of phytomelatonin progressed, it emerged as a potentially influential nutraceutical capable of affecting various aspects of human physiology.

Moreover, the exploration of phytomelatonin as a potential nutraceutical gained significance considering its perceived advantages over synthetic melatonin prevalent in the market. The notion of reducing the intake of by-product compounds resulting from the chemical synthesis of melatonin was stressed by the chemical compounds associated with synthetic melatonin, including tryptophan derivatives such as 1,2,3,4-tetrahydro-β-carboline-3-carboxylic acid, 3-(phenylamino)-alanine, 1,1′-ethylidenebis-(tryptophan), 2-(3-indolylmethyl)-tryptophan, formaldehyde-melatonin, formaldehyde-melatonin condensation products, hydroxymelatonin isomers, 5-hydroxy-tryptamine derivatives, 5-methoxy-tryptamine derivatives, and N-acetyl- and diacetyl-indole derivatives [134,135]. These by-products have the potential to induce eosinophilia-myalgia syndrome [136–138]. The potential risks associated with these compounds prompt a shift towards phytomelatonin, which appears poised to mitigate such risks. In fact, phytomelatonin has demonstrated increased absorption efficiency and superior antioxidant and anti-inflammatory properties [139].

Phytomelatonin has emerged as a key player in promoting improved sleep quality and duration. Consuming foods containing melatonin has been shown to promote a positive impact on sleep quality. Additionally, there was an observed elevation in plasma melatonin levels, accompanied by improvements in various sleep quality parameters [140–142]. For example, tart cherries are rich in phytomelatonin and have been reported to have a positive effect on insomnia and sleep quality [143–146]. This overall involvement suggests phytomelatonin's potential to improve sleep patterns.

Moreover, research highlighted the versatility of phytomelatonin and its potential as a valuable component in the development of immunotherapeutic strategies. The immune modulatory effects of phytomelatonin have also been investigated in nocturnal male rodent, golden hamsters, using melatonin-rich foods, such as cabbage (*Brassica oleracea*) and carrots (*Daucus carota*) [147]. Remarkably, supplementation with these phytomelatonin-rich foods resulted in a significant increase in spleen weight, aligning with other findings associated with exogenous melatonin treatment and resultantly indicating a potential role for phytomelatonin in influencing immune function. Additionally, an animal study showcased an enhancement in reproductive health following consumption of a phytomelatonin-rich diet, suggesting a novel avenue for phytomelatonin in reproductive physiology [148]. While the exploration of phytomelatonin as a supplement holds promise, its efficacy and practical applications warrant careful evaluation. While melatonin-rich foods are recognized as potential nutraceuticals, concerns have been raised regarding the true potential of these foods and the efficacy of their respective dietary supplements. Critics highlight the lack of a clear quantitative correlation between the intake of phytomelatonin-rich foods or supplements and plasma melatonin levels of melatonin, casting doubt about the reliability of achieving therapeutic effects solely through dietary means. This observation emphasizes the need for a more nuanced understanding of the relationship between phytomelatonin intake and physiological outcomes.

As the landscape of supplementation evolves towards natural alternatives, the exploration of phytomelatonin establishes potential avenues for novel and potentially groundbreaking approaches to health and well-being. Nevertheless, a judicious and evidence-based approach is essential to navigate the complexities surrounding phytomelatonin supplementation to provide clarity on its true potential, ensuring its integration into mainstream health practices.

Bioavailability of Dietary Phytomelatonin

When administered externally, melatonin has demonstrated remarkable efficiency in oral absorption, widespread distribution, and thorough metabolism within the intricate landscape of the human body [149]. Whether introduced through beverages or encapsulated in galenic tablets, melatonin has exhibited prompt assimilation into the bloodstream [150,151]. However, despite advancements in understanding melatonin's pharmacokinetics, the oral bioavailability of melatonin from various sources, including dietary supplements, food items, and naturally occurring phytomelatonin, remains incompletely understood.

The substantial variations observed in melatonin-related absorption, metabolism, and elimination among individuals, underscore the pressing need for more exhaustive research to unravel the intricacies of melatonin's pharmacokinetic properties. This was particularly relevant as melatonin was found in a diverse array of foods, including nuts, fruits, seeds, cereals, oils, coffee, wine, and beer. Each food presented a unique matrix for melatonin bioavailability [111,152–154]. Phytomelatonin from plants modulates blood melatonin levels with a half-life of 20 to 40 minutes. However, it was crucial to acknowledge that the bioavailability of melatonin can vary due to several factors, including individual metabolism, diet composition, and the presence of other compounds that may interact with melatonin [111,155,156]. Species-specific differences in melatonin bioavailability, influenced by dosage, further contributed to the complexity of its pharmacokinetics.

Bioavailability on Animal Models

Assessments of the bioavailability of dietary melatonin have often been conducted using vertebrate models due to their physiological similarities with humans. For instance, a study performed on a rat model demonstrated that the consumption of germinated kidney beans altered melatonin and serotonin levels, resulting in increased excretion of 6-sulfatoxymelatonin in urine [142]. The comparison of melatonin bioavailability from kidney bean sprouts with synthetic melatonin showed a 16% increase in plasmatic melatonin and urine 6-sulfatoxymelatonin levels after 90 minutes, suggesting kidney bean sprouts as a potential dietary source of phytomelatonin. This finding is particularly significant as 6-sulfatoxymelatonin serves as the primary melatonin metabolite in urine, acting as a reliable surrogate biomarker mirroring melatonin concentration in the blood [157]. Another study using chicken feed with 24 different melatonin-rich plants also highlighted similar results [158]. These results indicated the effectiveness of melatonin in raising circulating melatonin levels, providing a scope for the development of phytomelatonin-based dietary supplements. These findings suggested the efficacy of plant-derived melatonin sources in elevating circulating melatonin levels, offering physiological benefits upon consumption, and presenting potential avenues for the development of dietary supplements utilizing phytomelatonin.

In a retrospective analysis across various studies utilizing diverse models such as rats, dogs, and monkeys by Yeleswaram *et al*. [159], species-specific and dose-dependent variations in melatonin bioavailability were observed. Notably, a 10 mg/kg oral dose in rats demonstrated a 53.5% bioavailability, while dogs and monkeys exhibited nearly 100%. Interestingly, a lower dose (1 mg/kg) resulted in a significant decrease in bioavailability to 16.9%, emphasizing the dosage-dependent nature of melatonin absorption across different species.

Bioavailability on Human

Two independent studies on humans, conducted following the consumption of melatonin-rich food, demonstrated the capability of dietary melatonin to reach circulatory levels and induce physiological benefits [141, 160]. For example, one study found that the ingestion of freeze-dried sweet cherries in powder form elevated 6-sulfatoxymelatonin, demonstrating a direct association with antioxidant capacity [141]. Comparable outcomes were observed in investigations involving plums and grape juice across various age cohorts. Additionally, research on 18 beer samples correlated melatonin concentration with alcohol content, with blood melatonin levels significantly rising post-ingestion, along with an increase in total antioxidant status [160].

The bioavailability of melatonin varies significantly depending on the source and administration route, whether oral or intravenous [149,156]. These variations include absorption, metabolism, and elimination, emphasizing the imperative for comprehensive studies to explore melatonin's pharmacokinetic properties further. In a crossover cohort study on melatonin pharmacokinetics, oral administration led to rapid absorption (Tmax at 41 minutes) but with considerable variation in maximal plasma concentrations (Cmax) and area under the curve (AUC) of plasma concentrations among volunteers [161]. Despite rapid absorption, oral melatonin bioavailability was only 3%, indicating significant variability among participants. Following oral intake, melatonin underwent extensive hepatic metabolism, known as the first-pass effect [32,161,162]. This process significantly reduced its bioavailability, explaining why only a small percentage of the consumed melatonin reached the bloodstream. However, it is imperative to acknowledge that supplementary factors, notably the plausible enzymatic breakdown facilitated by gastrointestinal cytochrome P450 1B1 [32,163], in conjunction with nonenzymatic mechanisms, also played contributory roles in this process. It was noteworthy that melatonin's bioavailability exhibited inter-individual disparities, with variations extending up to 37-fold [32]. This substantial heterogeneity was likely underpinned by the diverse expression patterns of cytochrome P450 subtypes within the human genome, thereby introducing a layer of complexity to the understanding of melatonin metabolism and its subsequent availability in different individuals.

While numerous studies highlighted the effective absorption and wide distribution of orally administered melatonin throughout the human body, the specific absorption dynamics of melatonin from herbal remedies or products, along with the oral bioavailability of phytomelatonin, require further investigation. As the scientific community continues to investigate the properties of phytomelatonin, there is a need for systematic studies that elucidate its absorption kinetics, bioavailability, and potential interactions with other compounds. The absorption of melatonin will likely occur regardless of consumption method, yet this process is not entirely understood. Such investigations will not only contribute to a more comprehensive understanding of phytomelatonin's efficacy but also guide its incorporation into dietary supplements and health interventions.

Recent Advancements in the Utilization of Phytomelatonin Beyond Plant Systems

The recent upsurge in phytomelatonin research, especially beyond plant systems, has yielded valuable insights into its diverse applications and potential advantages. For example, a recent review highlighted melatonin's role in regulating physiological processes and investigated the distinctions in biosynthetic pathways between animal and plant cells, extending the pharmacological benefits of exogenous melatonin on animals via dietary supplements [8].

Despite recent advancements in synthesizing melatonin chemically, concerns persist regarding the generation of unwanted by-products as contaminants during chemical reactions. In response, Pérez-Llamas *et al*. [164] proposed using raw plant material to obtain dietary supplements rich in phytomelatonin instead of synthetic melatonin, along with its associated chemical by-products. They presented a phytomelatonin-rich extract procedure from a herbal mix composed of various plants as an alternative to synthetic melatonin, suitable for cost-effective industrial-scale production. Additionally, another study highlighted the superior antioxidant and anti-inflammatory properties of the natural phytomelatonin-rich extract compared to synthetic melatonin when administered exogenously to animal models [139]. This research emphasized the potency of phytomelatonin due to the richer chemical profile of natural sources, leading to enhanced intestinal absorption of melatonin.

Another review article explored the potential phytotherapeutic intervention for individuals exposed to COVID-19, establishing phytomelatonin as a compelling consideration as a natural adjuvant [126]. In a recent review article by Arnao *et al*. [135], they provided a comprehensive overview of phytomelatonin from plants, algae, and genetically modified microorganisms as alternatives to synthetic melatonin. They meticulously analyzed the pros and cons of obtaining melatonin from different sources, delving into the economic and quality aspects of these products, some of which are already on the market.

As awareness of the potential physiological benefits of melatonin grows, there is a heightened interest in consuming melatonin-rich plant sources. Based on this concept, Kennaway's [165] review scrutinized the effects of consuming melatonin-rich foods on plasma or saliva melatonin and its urinary metabolite across multiple studies. The author highlighted methodological flaws and result assessment issues in these studies, leading to the conclusion that expecting melatonin-rich foods to influence sleep or have physiological effects may be overly optimistic. In contrast, other researchers continue to advocate for the benefits of such consumption. For instance, a recent study demonstrated that phytomelatonin-rich diets significantly improved sperm quality and seminal plasma composition in rams [148]. However, the ongoing discourse surrounding the efficacy of melatonin-rich foods persists, leaving both consumers and researchers striving for conclusive insights.

Conclusion

The physiological benefits of melatonin are extensive and multifaceted, positioning it as a promising avenue for therapeutic exploration across various health conditions. As a key regulator of immune functions, melatonin demonstrates remarkable adaptability and resilience by synchronizing immune responses with internal rhythms, influencing immune organ weight, enhancing immune responses, and modulating cytokines. In cancer, cardiovascular health, and neuroprotection, melatonin exhibits oncostatic, antioxidant, anti-inflammatory, and regulatory properties, showcasing its versatility in addressing diverse physiological challenges.

Moreover, melatonin's role in regulating circadian rhythms and treating insomnia further solidifies its clinical potential, extending to conditions such as inflammatory bowel disease and obesity-related damage. Furthermore, exogenous melatonin supplementation may compensate for age-related declines in endogenous melatonin. The prospects for phytomelatonin as a nutraceutical present an intriguing avenue, with emerging research highlighting its potential health benefits. Positive correlations between melatonin-rich foods and clinical-metabolic indicators, coupled with its influence on circadian rhythms, underscore phytomelatonin's role in promoting overall wellbeing.

While exogenous melatonin supplements are readily available and have demonstrated diverse health benefits, phytomelatonin presents a natural alternative with the potential for added advantages. However, a judicious and evidence-based approach is imperative in navigating the complexities surrounding phytomelatonin supplementation. The lack of comprehensive knowledge on oral melatonin bioavailability in the human diet emphasizes the need for further clinical trials and systematic studies to elucidate absorption kinetics, bioavailability, and interactions, ensuring informed incorporation into health interventions and dietary supplements.

Recent research on phytomelatonin showcases its diverse applications and potential benefits extending beyond plant systems. These studies emphasize melatonin's crucial role in regulating physiological processes, propose sustainable methods for obtaining phytomelatonin-rich supplements, and highlight the superior properties of natural extracts over synthetic alternatives. Exploring the potential phytotherapeutic role of phytomelatonin in mitigating the impact of COVID-19, a comprehensive overview analyzes the economic and quality aspect of phytomelatonin products from various sources.

While caution is advised against overestimating the effects of melatonin-rich foods on sleep, evidence supports the positive impact of phytomelatonin-rich diets on animal health. Furthermore, the nuanced interplay between melatonin and phytomelatonin, rooted in their shared functionalities as signaling molecules, offers a foundation for scientific inquiry. Melatonin's diverse and distinct roles, coupled with the prospects for phytomelatonin, hold promise for advancing our understanding of natural supplements and therapeutics. As the scientific community continues to unfold these complexities, a balanced and evidence-based perspective will be crucial in guiding the integration of melatonin and phytomelatonin into healthcare practices, aligning with evolving preferences and expectations for natural and effective supplementation options.

Abbreviations

G6PD, glucose-6-phosphate dehydrogenase; AMK, N1-Acetyl-5-Methoxykynuramine; nNOS, neuronal nitric oxide synthase; VHL, von Hippel-Lindau protein.

Availability of Data and Materials

Not applicable.

Author Contributions

HSD and CR curated the data and provided supervision throughout the manuscript preparations. HSD, CR, MC, CS, CT, RAY, LSS, SRKS, MNS, KT, SSR conducted formal analysis and contributed to software development. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

The authors are grateful to Regional College, Lilong Chajing, for their invaluable physical and administrative support to Dr. Chongtham Rajiv. Additionally, we appreciate the support provided by the Central Agricultural University, Imphal to Dr. Haobijam Sanjita Devi. Both institutions have significantly contributed to the successful completion of this research.

Funding

This research received no external funding.

Conflict of Interest

The authors declare no conflict of interest.

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