International Journal of Basic & Clinical Pharmacology
Munirajureddy SK et al. Int J Basic Clin Pharmacol. 2026 Sep;15(5):1077-1088
https://www.ijbcp.com
pISSN 2319-2003 | eISSN 2279-0780

DOI: https://dx.doi.org/10.18203/2319-2003.ijbcp20262884

Review Article

Therapeutic benefits of melatonin beyond sleep regulation: a comprehensive review

Santosh Krishnappa Munirajureddy[1], Usha Humbi[2], Akash Nalajala[3]*, Bhavishya Nerella[3], Vishnu Arumainathan[4]

[1]Department of Internal Medicine, Narayana Hrudayalaya, Bengaluru, Karnataka, India
[2]Department of Neurology, Narayana Hrudayalaya, Bengaluru, Karnataka, India
[3]Shri Vishnu college of pharmacy, Bhimavaram, Andhra Pradesh, India
[4]Kleitmen sleep solutions Pvt Ltd, Hosur, Tamil Nadu, India

Received: 01 June 2026
Revised: 11 July 2026
Accepted: 14 July 2026

***Correspondence:**
Dr. Akash Nalajala,
Email: akashchowdary989@gmail.com

ABSTRACT

Melatonin is an endogenous indoleamine primarily synthesized by the pineal gland and is best known for its role in regulating the sleep–wake cycle and circadian rhythm. However, accumulating evidence suggests that melatonin exerts a wide range of biological actions beyond sleep regulation. It displays antioxidant, anti-inflammatory, and immunomodulatory properties, and has been investigated for potential benefits in neurological, cardiovascular, metabolic, respiratory, gastrointestinal, hepatic, renal, reproductive, oncological, and aging-related disorders. In addition, melatonin may influence gene regulation, mitochondrial function, appetite control, energy homeostasis, and thermoregulation, highlighting its pleiotropic therapeutic profile. Preclinical and clinical studies have also explored novel formulations, including sustained-release systems and nanotechnology-based delivery approaches, to improve its bioavailability and therapeutic utility. Although melatonin is generally considered safe and well tolerated, clinical evidence remains heterogeneous, and variations in dose, formulation, and treatment duration continue to limit standardization. Therefore, larger randomized controlled trials are needed to clarify its efficacy, optimize dosing strategies, and define its long-term safety across different disease settings. Overall, melatonin represents a promising multifaceted therapeutic agent with expanding clinical relevance beyond its traditional use in sleep medicine.

Keywords: Melatonin, Circadian rhythm, Antioxidant, Immunomodulation, Neuroprotection, Anti-inflammatory, Therapeutic applications, Pharmacology

INTRODUCTION

Melatonin (N-acetyl-5-methoxytryptamine), first isolated from the pineal gland in 1958, has long been recognized as the principal hormonal signal of darkness and a key regulator of circadian rhythms and the sleep–wake cycle. Its clinical use has therefore traditionally focused on the management of insomnia, circadian rhythm sleep–wake disorders, jet lag, and shift-work disorder.[1,2] However, over the past two decades, advances in molecular biology, chronobiology, and mitochondrial medicine have transformed our understanding of melatonin from a simple chronobiotic hormone into a pleiotropic biological regulator with extensive therapeutic potential extending far beyond sleep regulation.

Melatonin is synthesized not only in the pineal gland but also in numerous extra-pineal tissues including the gastrointestinal tract, retina, bone marrow, skin, immune cells, reproductive organs, and mitochondria. Unlike pineal melatonin, which is secreted rhythmically under the control of the suprachiasmatic nucleus to synchronize circadian rhythms, extra-pineal melatonin acts predominantly in an autocrine and paracrine manner, exerting local cytoprotective effects. This paradigm has fundamentally altered the concept of melatonin physiology by suggesting that, its primary evolutionary function may be cellular protection rather than just sleep regulation alone.[1,6]

The remarkable diversity of melatonin's biological actions stems from both receptor-mediated and receptor-independent mechanisms. Through activation of MT1 and MT2 receptors, melatonin influences circadian synchronization, neuroendocrine function, autonomic regulation, immune responses, and metabolic homeostasis. Equally important are its receptor-independent properties, including direct scavenging of reactive oxygen and nitrogen species, enhancement of endogenous antioxidant enzyme activity, preservation of mitochondrial function, stabilization of mitochondrial membranes, modulation of apoptosis, regulation of autophagy, and epigenetic influences on cellular signaling pathways.[14]

Accumulating experimental and clinical evidence now supports the therapeutic role of melatonin across a broad spectrum of disorders. Beyond improving sleep quality, melatonin demonstrates promising neuroprotective, cardioprotective, metabolic, immunomodulatory, hepatoprotective, nephroprotective, musculoskeletal, reproductive, oncostatic benefits and reduction in cancer treatment related toxicity. Although the strength of evidence varies among disease states, mechanistic findings consistently highlight melatonin as a unique molecule capable of simultaneously targeting multiple pathogenic pathways.[14]

An emerging concept is that melatonin should perhaps be regarded less as a conventional hypnotic agent and more as a homeostatic molecule. Instead of directly inducing sleep like sedatives and hypnotics, melatonin restores physiological homeostasis by synchronizing biological clocks, reducing oxidative injury, dampening chronic inflammation, improving mitochondrial bioenergetics, and enhancing cellular resilience.[14]

Despite an expanding body of literature, important challenges remain regarding optimal dosage, formulation, timing, treatment duration, and the translation of promising preclinical findings into robust clinical evidence. Although melatonin is generally regarded as safe and well tolerated, stronger evidence from large, well-designed randomized clinical trials is required to establish standardized therapeutic protocols and long-term safety across different disease conditions.[40,43]

This comprehensive review synthesizes current evidence regarding the therapeutic benefits of melatonin beyond sleep regulation, discusses its molecular mechanisms and clinical applications across multiple specialties, and highlights current limitations and future directions for translational research and precision medicine.

CHEMISTRY AND PHARMACOLOGY OF MELATONIN

Melatonin is a hormone that occurs naturally and is chemically called N-acetyl-5-methoxytryptamine. It comes mainly from the amino acid tryptophan and it fits in the indoleamine class of compounds. Melatonin is relatively small in molecular terms, and is soluble in both water and lipids, so that it can move through biological membranes, including the blood-brain barrier, without much trouble. Its molecular formula is $C_{13}H_{16}N_2O_2$, with a molecular weight of around 232.28 g/mol. Because of its amphiphilic nature, melatonin readily distributes across tissues and intracellular compartments.

In normal physiological settings it's quite stable, however if it's under excessive light or heat, it undergoes degradation. Also, the special chemical arrangement of melatonin seems to support its strong antioxidant role and its ability to scavenge free radicals.[6]

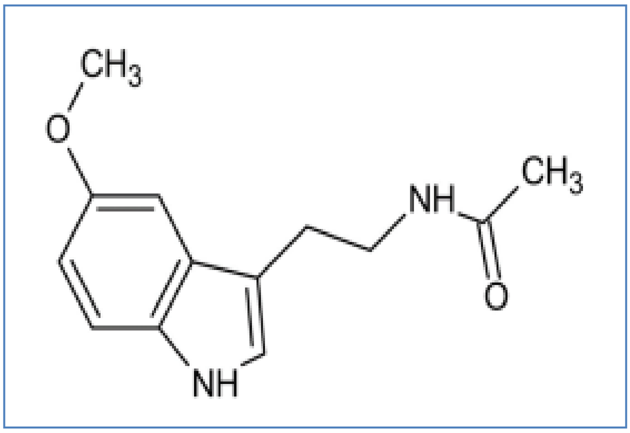

Figure 1: Structure of melatonin.

Table 1: Pharmacokinetics.

Pharmacokinetic parameters	Melatonin pharmacokinetic value
Absorption	Rapidly absorbed after oral administration
Bioavailability	Approximately 10-56%
Tmax (Peak plasma time)	20-60 minutes
Protein Binding	Approximately 60-70%
Half-life (T½)	Approximately 30-50 minutes
Metabolism	Primarily hepatic via CYP1A2 enzyme
Major metabolite	6-hydroxymelatonin sulfate
Excretion	Mainly excreted in urine (~80-90% as metabolites)[7]

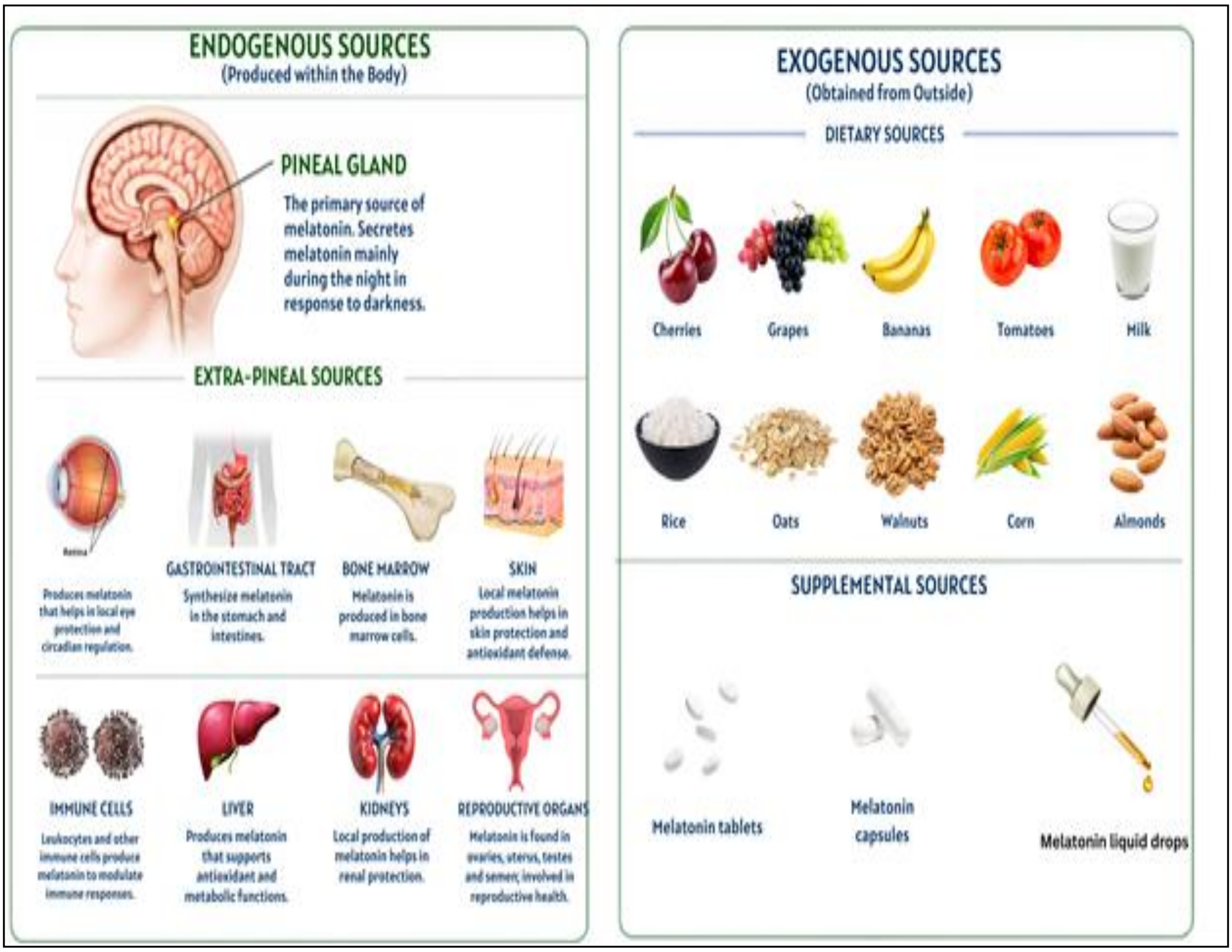

Figure 2: Sources of melatonin.

MELATONIN RECEPTORS

Melatonin's physiological effects are mostly carried out by particular G-protein coupled receptors, MT1 and MT2. There's also another attachment spot, called MT3, which has been linked with enzymatic activity rather than the usual signaling pathway. These receptor types are broadly present across the brain and peripheral tissues; hence melatonin can steer multiple biological processes such as sleep, circadian rhythms, immune responses, and antioxidant activity.

MT1 receptors

MT1 receptors are mostly tied to nudging sleep along and managing circadian timing. They're found mostly in the suprachiasmatic nucleus within the hypothalamus. When MT1 is activated, neuronal firing gets reduced, and sleep onset becomes more likely.

Beyond that, MT1 also connects to reproductive hormone regulation, retinal performance, and cardiovascular physiology, though in a more indirect way.[8]

MT2 receptors

MT2 receptors are mainly connected with aligning circadian rhythms and adjusting the biological clock, especially phase shifting. They help manage sleep timing and also seasonal rhythms, plus they influence retinal signaling. MT2 receptor activation is also thought to support neuroprotection, bring about anti-inflammatory benefits, and aid vascular regulation. Because of that, MT2 is often treated as a key therapeutic target for sleep disorders and circadian disturbances.

MT3 receptors

MT3 receptors are, in comparison, less well defined than MT1 or MT2. They are thought to resemble quinone reductase 2, which is an enzyme that carries out specific biochemical reactions. Because of this, MT3 may contribute to antioxidant defense in a more "enzymatic" manner. MT3 is involved in detoxification processes and also helps guard cells against oxidative stress related injury; so, the overall picture is protective rather than purely signaling.[9]

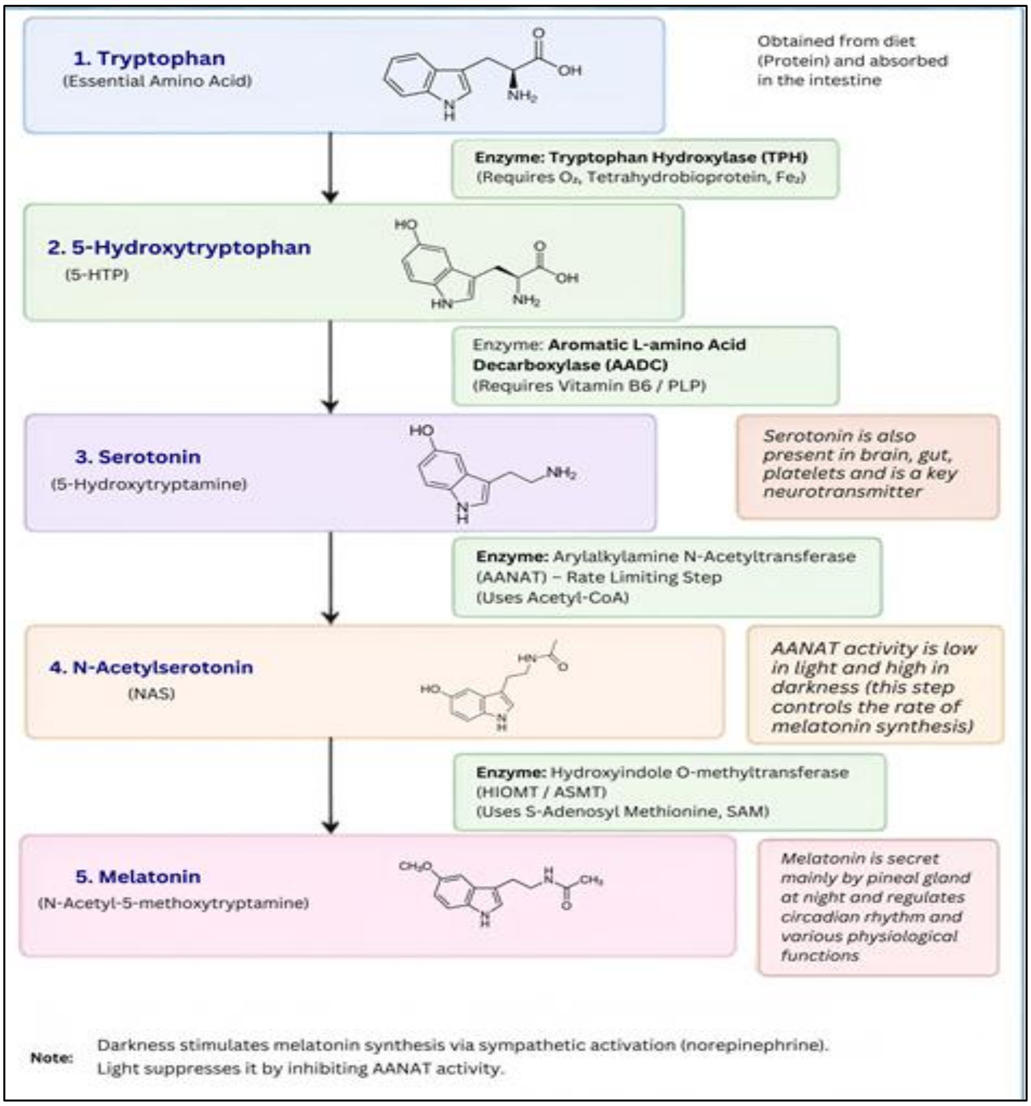

Figure 3: Biosynthesis pathway of melatonin.

PHYSIOLOGY OF SLEEP

Sleep is an essential physiological process, needed for physical and mental well-being, memory, immunity, and whole-body functioning, in a decent way. It is active biological state where the body goes through restoration, repairs tissue, saves energy, and also handles hormonal regulation. Sleep is controlled by complex interactions between the central nervous system, neurotransmitters, hormones, and the circadian rhythm mechanisms. Getting enough sleep matters for cognitive performance, emotional stability, learning, and metabolic balance. If sleep gets disturbed, it can negatively impact everyday activities and raise the chances of chronic conditions like hypertension, diabetes, obesity, cardiovascular disorders, and even mental health problems.

NREM sleep consists of three stages. Stage N1 represents light sleep and serves as the transition between wakefulness and sleep. Stage N2 is characterized by reduced heart rate, decreased body temperature, and slowing of brain activity. Stage N3, also called deep sleep or slow-wave sleep, is the most restorative stage and is important for tissue repair, energy restoration, immune strengthening, and growth hormone secretion. REM sleep usually occurs after NREM sleep and is associated with rapid eye movements, vivid dreaming, increased brain activity, emotional processing, and memory consolidation. Proper balance between NREM and REM sleep is necessary for cognitive performance, emotional stability, and overall health.[10]

Sleep regulation mainly depends on two mechanisms, the homeostatic sleep drive, and the circadian rhythm system. The homeostatic mechanism tends to build up sleep pressure when we stay awake for too long whereas the circadian rhythm system handles when sleep and wake should happen based on the light–dark cycle. The suprachiasmatic nucleus (SCN) located in the hypothalamus, works like the body's biological clock and it coordinates the whole circadian rhythm. A bunch of neurotransmitters and hormones also take part, including gamma-aminobutyric acid (GABA), serotonin, dopamine, acetylcholine, cortisol and melatonin. Melatonin, which is released by the pineal gland during the dark, facilitates sleep initiation and it also supports aligning the sleep-wake schedule. When we're actually asleep, several physiological parameters like heart rate, blood pressure, respiratory rate, and body temperature go down, so the body including the brain can recover and maintain its normal physiological function.[11]

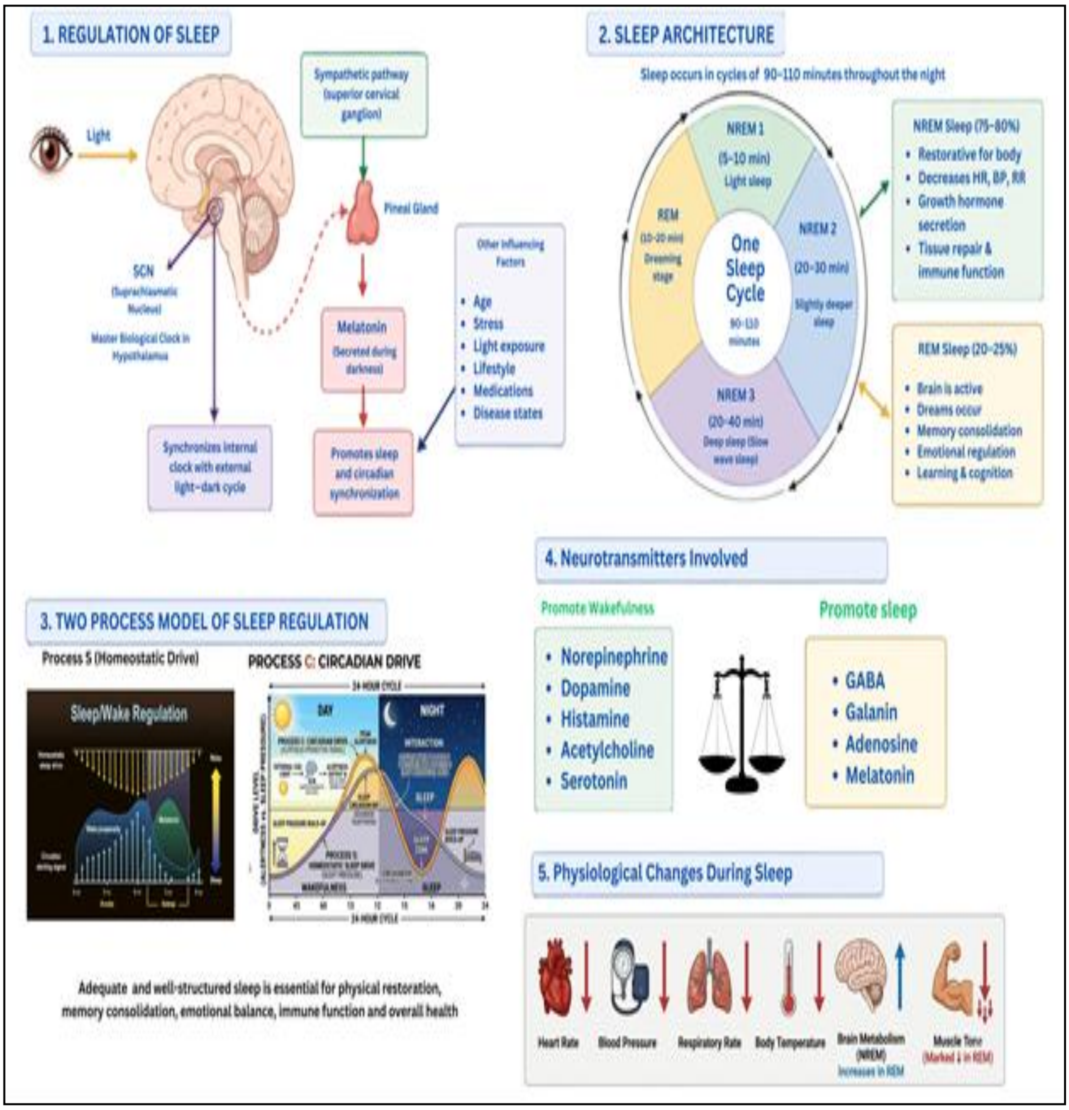

Figure 4: Mechanisms of sleep.

CIRCADIAN RHYTHM

Circadian rhythm is like the body's own internal biological clock, which regulates different physiological, behavioral and metabolic activities across a 24 hour cycle. The word "circadian" comes from the Latin word, "circa" meaning "about" and "diem" meaning "day". So, it's really just about the days length. This rhythm keeps things in order, and helps line up major body functions like the sleep-wake cycle, hormone secretion, body temperature, blood pressure, cognitive performance and overall metabolism including digestion, depending on the light and dark pattern in the environment.

The circadian rhythm is mainly regulated by the Suprachiasmatic Nucleus, which is composed of clusters of cells in the brain's hypothalamus region. The SCN uses light signals received through the eyes and the retina to regulate body functions in coordination with the environment. The SCN receives light related information from the retina, and then it synchronizes the internal bodily processes with what's happening outside in the environment. Light is the primary factor influencing circadian rhythm regulation. During daylight hours, being exposed to sunlight suppresses melatonin release and builds alertness, wakefulness and physical activity. At night, darkness pushes the pineal gland to release melatonin, which tells the body to prepare for sleep. That rhythmic melatonin secretion, helps keep sleep timing on track and keeps circadian synchronization in order. Other biological processes also move in circadian patterns, such as cortisol secretion, body temperature swings, cardiovascular activity and digestive function.

Circadian rhythm may be disrupted due to causes such as night shifts, jet lag, inconsistent sleeping hours, prolonged time spent in front of screens, stress, aging, and exposure to artificial light during nighttime. Circadian rhythm misalignment may cause various health problems, including insomnia, fatigue, difficulties concentrating, depression, poor immune system functioning, metabolic problems like obesity, type 2 diabetes, heart disease, and other issues. Chronic disturbance of circadian rhythm has been linked with an elevated risk of neurodegenerative conditions and some types of cancer as well. Proper regulation of melatonin and adherence to consistent sleeping habits are crucial to ensure correct circadian functioning.

ROLE OF MELATONIN IN SLEEP REGULATION

Melatonin is a sleep-inducing hormone which helps to ease the transition into sleep by increasing feelings of drowsiness and decreasing alertness. Most of the brain's MT1 and MT2 melatonin receptors, through which melatonin works, are located in the brain and in particular, in the suprachiasmatic nucleus (SCN). The activation of the MT1 receptor slows down the activity of certain neurons in the brain and produces relaxation. The activation of the MT2 receptor on the other hand assists with regulating the timing or synchronization of our circadian rhythms or "body clocks". Melatonin will also help to lower the core temperature of the body slightly, which creates an optimal sleeping environment. Unlike sedatives that produce sleep by working on the central nervous system, melatonin encourages natural sleep by supporting our biological timing system. People who have low levels of melatonin in their own body will typically experience difficulty falling asleep or experience a delay or disruption in their sleep.[13]

In addition to sleep initiation, melatonin also helps maintain sleep continuity and improve overall sleep quality. Sustained nighttime melatonin secretion supports stable sleep architecture and reduces nighttime awakenings. Melatonin influences both non-rapid eye movement (NREM) and rapid eye movement (REM) sleep, hence contributing to restorative sleep, memory consolidation, emotional regulation, and cognitive functioning. It is widely used in the management of sleep disorders such as insomnia, jet lag, delayed sleep phase syndrome, and shift work sleep disorder. Melatonin supplementation is particularly beneficial in elderly individuals, where natural melatonin production declines with age. Due to its favorable safety profile, low risk of dependence, and ability to restore circadian rhythm synchronization, melatonin has become an important therapeutic agent in sleep medicine and circadian rhythm management.

THERAPEUTIC BENEFITS OF MELATONIN BEYOND SLEEP REGULATION

Antioxidant properties of melatonin

Melatonin is widely recognized for its antioxidant activity. It can directly neutralize reactive oxygen and nitrogen species and also stimulate endogenous antioxidant defenses, including superoxide dismutase, glutathione peroxidase, and catalase. In addition, melatonin may help preserve mitochondrial function and reduce lipid peroxidation, protein oxidation, and DNA damage. Because oxidative stress contributes to aging and many chronic diseases, these antioxidant actions are considered central to the therapeutic potential of melatonin across multiple organ systems.[14]

Neuroprotective effects

Melatonin has attracted considerable attention for its potential neuroprotective effects. The brain is especially vulnerable to oxidative stress and inflammation because of its high oxygen demand and lipid-rich structure. Melatonin may counter these processes by scavenging free radicals, enhancing antioxidant defenses, and stabilizing mitochondrial function. Experimental studies suggest that it may help reduce neuronal injury in conditions such as Alzheimer’s disease, Parkinson’s disease, stroke, epilepsy, and traumatic brain injury. These findings support melatonin as promising adjunct in neurological disorders, although stronger clinical evidence is still needed.[15]

Cardioprotective effects

Melatonin may contribute to cardiovascular health through its antioxidant, anti-inflammatory, and circadian regulatory actions. In cardiovascular disease, it has been studied for its ability to reduce oxidative injury, improve endothelial function, and protect tissues during ischemic stress. It may also help limit damage associated with hypertension, heart failure, and impaired vascular regulation. Since sleep and circadian disruption are linked to cardiovascular risk, melatonin may have both direct and indirect protective effects. These properties make it a potential adjunctive agent in cardiovascular disorders.[16]

Anticancer potential

Melatonin has been widely investigated for its potential anticancer effects. Preclinical and clinical studies suggest that it may inhibit tumour growth through antioxidant, anti-inflammatory, and pro-apoptotic mechanisms. It has also been reported to interfere with angiogenesis, cell proliferation, and metastatic signalling in several cancer types, including breast, prostate, colorectal, and liver cancers. In addition, melatonin may reduce treatment-related toxicity and improve tolerance when used as an adjunct to chemotherapy or radiotherapy. Although these findings are encouraging, larger and better-designed clinical trials are required before melatonin can be considered a standard anticancer intervention.[17]

Immunomodulatory effects

It exerts important immunomodulatory actions that may be relevant in both systemic and respiratory disorders. It has been shown to influence cytokine production, support immune balance, and reduce excessive inflammatory signalling. These effects may help limit tissue injury in conditions characterized by chronic inflammation/immune dysregulation. By supporting cellular defense mechanisms, melatonin may contribute to better host resilience during infection and inflammatory stress.[18]

Anti-inflammatory actions

Melatonin may also act as an anti-inflammatory agent by reducing the release of pro-inflammatory cytokines and mediators such as tumor necrosis factor-alpha, interleukins, and nitric oxide. Its anti-inflammatory effect is closely linked to its ability to reduce oxidative stress and protect tissues from inflammatory injury. This action has made melatonin of interest in chronic inflammatory disorders and autoimmune conditions.[19]

Role in metabolic disorders

Melatonin may contribute to metabolic health through its antioxidant, anti-inflammatory, and circadian-regulating actions. It has been associated with improved glucose homeostasis, enhanced insulin sensitivity, and regulation of lipid metabolism. Melatonin may also influence appetite, body weight, and energy balance through circadian and hormonal pathways. Since sleep and circadian disruption are closely linked with obesity, type 2 diabetes, and metabolic syndrome, melatonin may have both direct and indirect protective effects.[20]

Gastroprotective effects

Melatonin has shown protective effects in the gastrointestinal tract, largely because of its ability to limit oxidative stress and inflammation. It may support mucosal defense, reduce acid-related injury, and help protect against ulceration and inflammatory damage. Melatonin has been investigated as a supportive agent in gastritis, peptic ulcer disease, and intestinal injury.[21]

Hepatoprotective effects

In the liver, melatonin has been investigated for hepatoprotective effects in conditions such as fatty liver disease, fibrosis, hepatitis, and toxin-induced injury. It may help preserve mitochondrial function, reduce lipid peroxidation, and limit inflammatory damage to hepatic tissue. These findings suggest a possible role for melatonin in protecting the liver under oxidative stress.[22]

Renoprotective effects

Melatonin may attenuate oxidative and inflammatory injury in acute kidney injury, diabetic nephropathy, chronic kidney disease, and drug-induced nephrotoxicity. By supporting antioxidant defenses and reducing renal tissue injury, melatonin appears to act as a cytoprotective molecule in kidney disorders.[23]

Reproductive and fertility benefits

Melatonin appears to play a supportive role in reproductive health in both males and females. Its antioxidant properties may protect gametes and reproductive tissues from oxidative damage, while its influence on hormonal signaling and circadian timing may contribute to reproductive function. In males, melatonin has been associated with improved sperm quality and motility. In females, it has been investigated for its possible role in follicular development, oocyte quality, endometriosis, infertility, and polycystic ovary syndrome. Melatonin has also been studied in assisted reproductive techniques, where it may improve oocyte quality and treatment outcomes.[24]

Bone health and osteoprotection

Melatonin may support bone remodeling by promoting osteoblast activity and limiting osteoclast-mediated bone loss. By reducing oxidative and inflammatory injury, it may help preserve skeletal integrity and could have potential relevance in age-related bone loss and osteoporosis.[25]

Role in mental health disorders

Melatonin has been explored in mood and sleep-related disorders, where circadian stabilization may contribute to improved emotional regulation, reduced anxiety symptoms, and better sleep quality. Because sleep disturbance is common in depression, anxiety, bipolar disorder, and stress-related conditions, melatonin may have supportive value in these settings. Its neuroprotective and antioxidant effects may further contribute to its potential psychiatric benefits.[26]

Anti-aging and longevity effects

Melatonin has been studied for its possible anti-aging effects because of its antioxidant, anti-inflammatory, and mitochondrial protective actions. Declining melatonin levels with age may contribute to sleep disturbance, oxidative stress, and cellular dysfunction. By limiting oxidative damage and supporting mitochondrial activity, melatonin may help preserve tissue function during aging.[27]

Analgesic and pain-relieving effects

Melatonin has also been investigated for analgesic and antinociceptive effects. These may involve melatonin receptor pathways, GABAergic mechanisms, and modulation of inflammatory mediators involved in pain transmission. It has been studied in conditions such as fibromyalgia, migraine, neuropathic pain, rheumatoid arthritis, postoperative pain, and irritable bowel syndrome.[28]

Role of melatonin in respiratory disorders

Melatonin has been studied in asthma, chronic obstructive pulmonary disease, pulmonary fibrosis and viral infections including COVID-19.

Its antioxidant and anti-inflammatory actions may help reduce lung injury and inflammatory damage in respiratory disease. Although current evidence is largely adjunctive, melatonin remains of interest because of its broad biological activity and favorable safety profile.[29]

Melatonin in oral and dental health

Melatonin may help reduce oxidative stress, inflammation, and tissue damage in oral conditions such as periodontitis and mucosal injury. It has also been investigated for its possible role in supporting bone formation, tissue regeneration, and wound healing in the oral cavity.[30]

Role of melatonin in gene regulation and epigenetics

Melatonin has been linked to gene regulation and epigenetic modulation, including effects on DNA methylation, histone modification, and microRNA expression. These actions may influence pathways involved in circadian regulation, inflammation, aging, and disease progression. This area remains under active investigation and may expand the therapeutic relevance of melatonin in future research.[31]

Role of melatonin in appetite and energy homeostasis

Melatonin may contribute to appetite control and energy homeostasis through its interactions with circadian and metabolic pathways.

It may influence leptin and ghrelin signaling, glucose metabolism, and lipid balance, thereby affecting body weight and metabolic regulation. Disruption of melatonin secretion due to sleep loss or night shift work may contribute to appetite dysregulation and metabolic imbalance.[32]

Melatonin in thermoregulation

Melatonin is involved in thermoregulation through its role in maintaining circadian temperature rhythms. Its nocturnal rise is associated with the gradual decline in core body temperature, which supports sleep onset. This thermoregulatory action is another example of melatonin's broader role in physiological homeostasis.[33]

Table 2: Clinical evidence and representative studies.

Authors	Year	Titles	Conclusion
Reiter et al	2014	Melatonin as an antioxidant: under promises but over delivers	Melatonin showed potent antioxidant effects protecting cellular structures from oxidative stress and inflammatory tissue damage in multiple diseases.[34]
Rondanelli et al	2013	Update on the role of melatonin in cancer treatment and prevention	Melatonin demonstrated anticancer properties by reducing tumor growth, oxidative stress, and chemotherapy-associated toxicity in cancer patients effectively.[35]
Hardeland	2018	Melatonin and inflammation-story of a double-edged blade	Melatonin reduced inflammatory cytokines and oxidative injury, showing therapeutic potential in inflammatory and immune-mediated diseases significantly.[36]
Zheng et al	2025	Melatonin: a potential nighttime guardian against Alzheimer's disease	Melatonin showed neuroprotective effects through mitochondrial stabilization, circadian regulation, and reduction of neurodegenerative pathological processes effectively.[37]
Tan et al	2020	Melatonin as a potential adjuvant treatment for COVID-19	Melatonin exhibited immunomodulatory, antioxidant, and anti-inflammatory actions that may reduce severe respiratory complications during viral infections.[38]

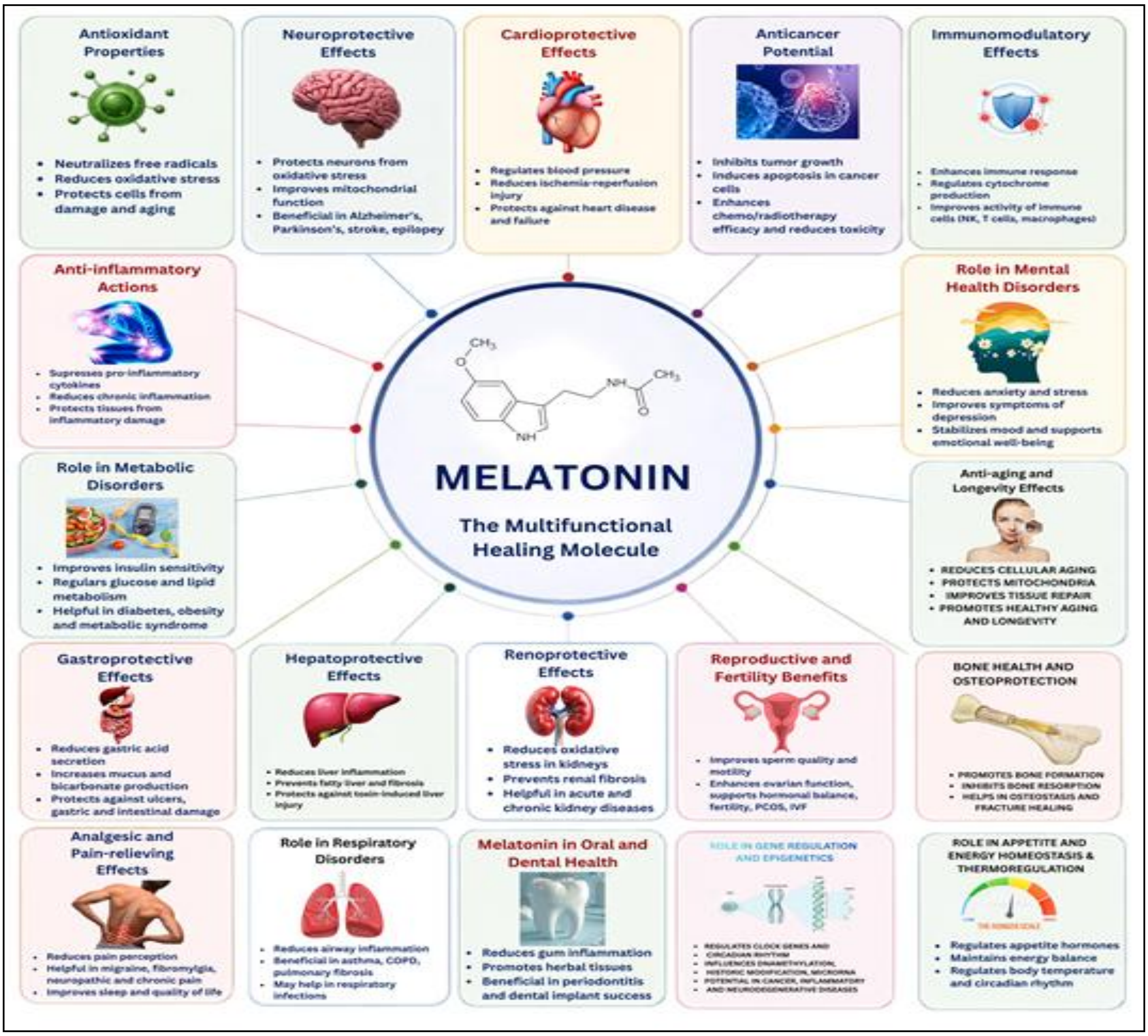

Figure 5: Therapeutic effects of melatonin.

SAFETY AND TOXICOLOGICAL PROFILE OF MELATONIN

Melatonin is regarded as generally safe when applied in recommended dosage. Because of its natural production in the body, melatonin has been associated with very few side effects in comparison to conventional sleeping pills. From scientific studies on the use of melatonin, it is known that it has an excellent safety record in adult, geriatric, and some chosen pediatric patients. The use of melatonin has been found to be effective in the treatment of sleep disorders and circadian rhythm disorders among others. Unlike most sedative agents, melatonin hardly leads to tolerance and addiction.[39]

The commonest side effects reported about melatonin are transient and mostly mild. They may include drowsiness during daytime, headaches, dizziness, nausea, fatigue, dry mouth, and mild gastrointestinal irritation. Mood changes and changes in sleeping habits may be experienced by few people, especially at higher dosage. Drowsiness and decreased alertness and concentration may occur with excessive daytime consumption of melatonin. Melatonin can have drug interactions with various drugs because of its pharmacologic activity and metabolic effects on these drugs. When taken with anticoagulants like warfarin, melatonin can cause excessive bleeding because of changes in platelets and coagulation processes. Taking melatonin with antihypertensive drugs can result in low blood pressure due to reduced heart rate and cardiac output. The effects of melatonin on glucose homeostasis and insulin action can affect blood sugar regulation when melatonin is taken with anti-diabetic medications. Melatonin's ability to modulate immune response can also interfere with the efficacy of immunosuppressants used for transplant or autoimmune disorders. Melatonin can also increase sedation when combined with CNS depressants.

While generally considered safe for consumption, melatonin should be used with care by pregnant women, nursing mothers, young children, and patients with severe medical conditions. Information regarding its safety over long periods of time under high dosages is not yet sufficient, and standardized dosing protocols for use of melatonin have not yet been set. According to animal and human toxicity studies, melatonin has extremely low toxicity levels, causing no major side effects or organ damage when taken in therapeutic dosages. In elderly patients, it may be effective since production of melatonin in such people decreases naturally with age. Melatonin thus still stands as a potentially safe drug with many applications in medicine.[40]

NOVEL DRUG DELIVERY SYSTEMS AND MELATONIN THERAPY

There are certain limitations of traditional forms of melatonin preparation in terms of poor bioavailability, rapid metabolism, and short action period. Upon oral administration, melatonin is subject to 1st-pass effect, during which melatonin metabolism results in decrease in amount of active substance delivered into systemic circulation. Due to short half-life of melatonin, some patients might not experience desired pharmacological effect for all night hours. Novel drug delivery technologies have been used to solve above mentioned problems by improving the stability, bioavailability, sustained-release characteristics and therapeutic potential of melatonin preparations.[41]

The sustained-release and controlled-release melatonin preparations are some of the most common new drug delivery systems. The preparation ensures gradual release of melatonin over an extended period, thereby maintaining stable levels in the blood at night. It is very effective in people suffering from sleep maintenance insomnia as well as the elderly whose bodies produce less natural melatonin. The other new methods of delivery are transdermal patch, intranasal spray, sublingual tablet, liposomes, and implants. Transdermal melatonin delivery provides continuous and controlled absorption of melatonin through the skin directly into systemic circulation, bypassing first-pass hepatic metabolism. This improves bioavailability and maintains stable plasma concentrations for prolonged therapeutic action. Sustained melatonin levels may promote longer sleep duration and better sleep maintenance. However, excessive absorption/ higher doses may sometimes cause prolonged drowsiness, sedation, daytime sleepiness, reduced alertness, and impaired concentration in sensitive individuals.

However, new developments in nanotechnology have widened the scope of treatment using melatonin drugs through use of nanoparticles, nano emulsion, polymer carriers and liposomes. The use of nanoparticles, for instance, helps in providing stability, targeted delivery, prolonged circulation time, and also helps in controlling the release of the drug. Nanotechnology also facilitates the passage of melatonin in body tissues such as brain and hence can be used to effectively treat disorders affecting these tissues. Melatonin combined with antioxidants; vitamins or any other form of therapeutic agent is another emerging method of treatment under study. Although these innovative methods appear promising, further research is required to prove their safety and effectiveness as compared to conventional treatments.[42]

FUTURE PERSPECTIVES

Melatonin research in the future is likely to go beyond the use of melatonin just for sleep regulation and sleep disorders, with the focus on more diverse treatments for disorders affecting neurological, cardiovascular, metabolic, inflammatory and cancer among others. Pharmacogenomics, together with advances in molecular biology, could help personalize melatonin treatment depending on circadian rhythm and other biological characteristics of each individual. Drug delivery techniques like nanoparticulate, transdermal delivery, prolonged release delivery, and liposome drug delivery may enhance melatonin availability and effectiveness. Furthermore, the development of melatonin agonists and combined drugs is already being considered.[43]

Melatonin's other possible functions are indicated by new scientific data pointing to its possible application in regenerative medicine, stem cell therapy, protection against mitochondria damage, and even epigenetics. Due to its remarkable antioxidant capacity and immunomodulating abilities, it can be considered as an alternative for treatment of age-related disorders, neurodegenerative disorders, and infections. It is critical to conduct large clinical randomized trials to determine proper dosages and protocols of melatonin's application in future.

CONCLUSION

Melatonin is a hormone with significant biological value, owing to the numerous functions it performs apart from regulation of sleep-wake cycle and maintenance of circadian rhythms. In recent years, melatonin has become popular due to its biological actions, which have made it highly useful therapeutically. Owing to its antioxidant, anti-inflammatory, immunomodulatory, neuroprotective and anti-apoptotic properties, melatonin has emerged as a great therapeutic tool in cases of neurological disorders, cardiovascular diseases, metabolic disorders, respiratory disorders, hepatic and renal disorders, reproductive disorders, and cancers. Melatonin also plays an important role in gene expression, mitochondrial protection, appetite regulation, thermoregulation, and aging. Besides the wide-ranging physiological properties, melatonin has also been reported to be effective in balancing the immune system, decreasing inflammation, improving mental functions and improving patient quality of life in different chronic conditions. The recent developments in sustained release drug delivery systems, melatonin receptor agonists and nanotechnology have broadened the applicability range of this compound. Melatonin has been regarded as a generally safe and well tolerated compound; however, there are limitations in dosage, administration methods and lack of sufficient clinical data for making a decision about the role of this substance. Thus, more randomized clinical trials need to be done to establish treatment protocols.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

REFERENCES

1. Ahmad SB, Ali A, Bilal M, Rashid SM, Wani AB, Bhat RR, et al. Melatonin and Health: Insights of Melatonin Action, Biological Functions, and Associated Disorders. Cell Mol Neurobiol. 2023;43(6):2437-58.
2. Masters A, Pandi-Perumal SR, Seixas A, Girardin JL, McFarlane SI. Melatonin, the Hormone of Darkness: From Sleep Promotion to Ebola Treatment. Brain Disord Ther. 2014;4(1):1000151.
3. Galano A, Tan DX, Reiter RJ. Melatonin: A Versatile Protector against Oxidative DNA Damage. Molecules. 2018;23(3):530.
4. Repova K, Baka T, Krajcirovicova K, Stanko P, Aziriova S, Reiter RJ, Simko F. Melatonin as a Potential Approach to Anxiety Treatment. Int J Mol Sci. 2022;23(24):16187.
5. Tuft C, Matar E, Menczel Schrire Z, Grunstein RR, Yee BJ, Hoyos CM. Current Insights into the Risks of Using Melatonin as a Treatment for Sleep Disorders in Older Adults. Clin Interv Aging. 2023;18:49-59.
6. Mannino G, Pernici C, Serio G, Gentile C, Bertea CM. Melatonin and Phytomelatonin: Chemistry, Biosynthesis, Metabolism, Distribution and Bioactivity in Plants and Animals-An Overview. Int J Mol Sci. 2021;22(18):9996.
7. Harpsøe NG, Andersen LP, Gögenur I, Rosenberg J. Clinical pharmacokinetics of melatonin: a systematic review. Eur J Clin Pharmacol. 2015;71(8):901-9.
8. Liu J, Clough SJ, Hutchinson AJ, Adamah-Biassi EB, Popovska-Gorevski M, Dubocovich ML. MT1 and MT2 Melatonin Receptors: A Therapeutic Perspective. Annu Rev Pharmacol Toxicol. 2016;56:361-83.
9. Waly NE, Hallworth R. Circadian Pattern of Melatonin MT1 and MT2 Receptor Localization in the Rat Suprachiasmatic Nucleus. J Circadian Rhythms. 2015;13:1.
10. Xie X, Ding D, Bai D, Zhu Y, Sun W, Sun Y, et al. Melatonin biosynthesis pathways in nature and its production in engineered microorganisms. Synth Syst Biotechnol. 2022;7(1):544-53.
11. Carley DW, Farabi SS. Physiology of Sleep. Diabetes Spectr. 2016;29(1):5-9.
12. Steele TA, St Louis EK, Videnovic A, Auger RR. Circadian Rhythm Sleep-Wake Disorders: a Contemporary Review of Neurobiology, Treatment, and Dysregulation in Neurodegenerative Disease. Neurotherapeutics. 2021;18(1):53-74.
13. Zisapel N. New perspectives on the role of melatonin in human sleep, circadian rhythms and their regulation. Br J Pharmacol. 2018;175(16):3190-9.
14. Chitimus DM, Popescu MR, Voiculescu SE, Panaitescu AM, Pavel B, Zagrean L, Zagrean AM. Melatonin's Impact on Antioxidative and Anti-Inflammatory Reprogramming in Homeostasis and Disease. Biomolecules. 2020;10(9):1211.
15. Lee JG, Woo YS, Park SW, Seog DH, Seo MK, Bahk WM. The Neuroprotective Effects of Melatonin: Possible Role in the Pathophysiology of Neuropsychiatric Disease. Brain Sci. 2019;9(10):285.
16. Domínguez-Rodríguez A, Abreu-González P, Báez-Ferrer N, Reiter RJ, Avanzas P, Hernández-Vaquero D. Melatonin and Cardioprotection in Humans: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Front Cardiovasc Med. 2021;8:635083.
17. Talib WH, Alsayed AR, Abuawad A, Daoud S, Mahmod AI. Melatonin in Cancer Treatment: Current Knowledge and Future Opportunities. Molecules. 2021;26(9):2506.
18. Srinivasan V, Maestroni GJ, Cardinali DP, Esquifino AI, Perumal SR, Miller SC. Melatonin, immune function and aging. Immun Ageing. 2005;2:17.
19. Cho JH, Bhutani S, Kim CH, Irwin MR. Anti-inflammatory effects of melatonin: A systematic review and meta-analysis of clinical trials. Brain Behav Immun. 2021;93:245-53.
20. Wajid F, Poolacherla R, Mim FK, Bangash A, Rutkofsky IH. Therapeutic potential of melatonin as a chronobiotic and cytoprotective agent in diabetes mellitus. J Diabetes Metab Disord. 2020;19(2):1797-825.
21. Chen CQ, Fichna J, Bashashati M, Li YY, Storr M. Distribution, function and physiological role of melatonin in the lower gut. World J Gastroenterol. 2011;17(34):3888-98.
22. Mathes AM. Hepatoprotective actions of melatonin: possible mediation by melatonin receptors. World J Gastroenterol. 2010;16(48):6087-97.
23. Cheng MC, Wu TH, Huang LT, Tain YL. Renoprotective effects of melatonin in young spontaneously hypertensive rats with L-NAME. Pediatr Neonatol. 2014;55(3):189-95.
24. Reiter RJ, Rosales-Corral SA, Manchester LC, Tan DX. Peripheral reproductive organ health and melatonin: ready for prime time. Int J Mol Sci. 2013;14(4):7231-72.
25. Maria S, Samsonraj RM, Munmun F, Glas J, Silvestros M, Kotlarczyk MP, et al. Biological effects of melatonin on osteoblast/osteoclast cocultures, bone, and quality of life: Implications of a role for MT2 melatonin receptors, MEK1/2, and MEK5 in melatonin-mediated osteoblastogenesis. J Pineal Res. 2018;64(3):10.
26. Moon E, Kim K, Partonen T, Linnaranta O. Role of Melatonin in the Management of Sleep and Circadian

Disorders in the Context of Psychiatric Illness. Curr Psychiatry Rep. 2022;24(11):623-34.
27. Martín Giménez VM, de Las Heras N, Lahera V, Tresguerres JAF, Reiter RJ, Manucha W. Melatonin as an Anti-Aging Therapy for Age-Related Cardiovascular and Neurodegenerative Diseases. Front Aging Neurosci. 2022;14:888292.
28. Xie S, Fan W, He H, Huang F. Role of Melatonin in the Regulation of Pain. J Pain Res. 2020;13:331-43.
29. Li L, Gang X, Wang J, Gong X. Role of melatonin in respiratory diseases (Review). Exp Ther Med. 2022;23(4):271.
30. Wang C, Wang L, Wang X, Cao Z. Beneficial Effects of Melatonin on Periodontitis Management: Far More Than Oral Cavity. Int J Mol Sci. 2022;23(23):14541.
31. Monayo SM, Liu X. The Prospective Application of Melatonin in Treating Epigenetic Dysfunctional Diseases. Front Pharmacol. 2022;13:867500
32. Nogueira LFR, Marqueze EC. Effects of melatonin supplementation on eating habits and appetite-regulating hormones: a systematic review of randomized controlled clinical and preclinical trials. Chronobiol Int. 2021;38(8):1089-102.
33. Refinetti R. Circadian rhythmicity of body temperature and metabolism. Temperature (Austin). 2020;7(4):321-62.
34. Reiter RJ, Mayo JC, Tan DX, Sainz RM, Alatorre-Jimenez M, Qin L. Melatonin as an antioxidant: under promises but over delivers. J Pineal Res. 2016;61(3):253-78.
35. Rondanelli M, Faliva MA, Perna S, Antoniello N. Update on the role of melatonin in the prevention of cancer tumorigenesis and in the management of cancer correlates, such as sleep-wake and mood disturbances: review and remarks. Aging Clin Exp Res. 2013;25(5):499-510.
36. Hardeland R. Melatonin and inflammation-Story of a double-edged blade. J Pineal Res. 2018;65(4):e12525.
37. Zhang Z, Xue P, Bendlin BB, Zetterberg H, De Felice F, Tan X, Benedict C. Melatonin: A potential nighttime guardian against Alzheimer's. Mol Psychiatry. 2025;30(1):237-250.
38. Wichniak A, Kania A, Siemiński M, Cubała WJ. Melatonin as a Potential Adjuvant Treatment for COVID-19 beyond Sleep Disorders. Int J Mol Sci. 2021;22(16):8623.
39. Guardiola-Lemaître B. Toxicology of melatonin. J Biol Rhythms. 1997;12(6):697-706.
40. Tordjman S, Chokron S, Delorme R, Charrier A, Bellissant E, Jaafari N, Fougerou C. Melatonin: Pharmacology, Functions and Therapeutic Benefits. Curr Neuropharmacol. 2017;15(3):434-43.
41. Thanawala S, Abiraamasundari R, Shah R. Comparative Pharmacokinetics of Sustained-Release versus Immediate-Release Melatonin Capsules in Fasting Healthy Adults: A Randomized, Open-Label, Cross-Over Study. Pharmaceutics. 2024;16(10):1248.
42. Mirza-Aghazadeh-Attari M, Mihanfar A, Yousefi B, Majidinia M. Nanotechnology-based advances in the efficient delivery of melatonin. Cancer Cell Int. 2022;22(1):43
43. Stanford SC. Recent developments in research of melatonin and its potential therapeutic applications. Br J Pharmacol. 2018;175(16):3187-9.

Cite this article as: Munirajureddy SK, Humbi U, Nalajala A, Nerella B, Arumainathan V. Therapeutic benefits of melatonin beyond sleep regulation: a comprehensive review. Int J Basic Clin Pharmacol 2026;15:1077-88.