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Melatonin: The Multifaceted Hormone

Beyzanur ŞİMŞEK[1], Esra AYDEMİR[1], Bülent KAYA[1*]

[1] Department of Biology, Faculty of Science, Akdeniz University, Antalya TR-07058, Turkey
Beyzanur ŞİMŞEK ORCID No: 0000-0003-3086-6836
Esra AYDEMİR ORCID No: 0000-0002-5206-7333
Bülent KAYA ORCID No : 0000-0002-0491-9781

**Corresponding author: bkaya@akdeniz.edu.tr*

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Abstract: Melatonin is a hormone secreted by the pineal gland and its main biological function is to regulate the circadian rhythm. Melatonin synthesis varies according to light and dark conditions. While melatonin production is suppressed in the light environment, melatonin production increases in the dark environment. Melatonin acts through different mechanisms. One of these mechanisms is receptor-dependent signal transduction mechanism. Two types of receptors have been identified as melatonin receptor, melatonin receptor 1 and melatonin receptor 2. Through these mechanisms of action, in addition to circadian rhythm regulation, melatonin has various physiological and pathophysiological roles, including sleep cycle regulation, antioxidant and anti-inflammatory effects, immune system modulation, effects on cancer, cardiovascular system, central nervous system and neurodegenerative diseases. In this review, it is aimed to examine the roles of melatonin in physiological and pathophysiological processes.

Melatonin: Çok Yönlü Bir Hormon

Anahtar Kelimeler
Kanser, Sirkadiyen ritim, Hormon, Melatonin,

Öz: Melatonin, epifiz bezi tarafından salgılanan bir hormondur ve temel biyolojik işlevi sirkadiyen ritmi düzenlemektir. Melatonin sentezi, aydınlık ve karanlık ortam koşullarına göre değişmektedir. Aydınlık ortamda, melatonin üretimi baskılanırken, karanlık ortamda melatonin üretimi artmaktadır. Melatonin farklı mekanizmalar aracılığıyla etki göstermektedir. Bu mekanizmalardan biri reseptöre bağımlı sinyal iletim mekanizmasıdır. Melatonin reseptörü olarak melatonin reseptörü 1 ve melatonin reseptörü 2 olmak üzere iki tip reseptör tanımlanmıştır. Bu etki mekanizmaları aracılığıyla sirkadiyen ritim düzenlenmesinin yanı sıra uyku döngüsünün düzenlenmesi, antioksidan ve anti-inflamatuar etkileri, immün sistem modülasyonu, kanser, kardiyovasküler sistem, santral sinir sistemi ve nörodejeneratif hastalıklar üzerine etkileri olmak üzere çeşitli fizyolojik ve patofizyolojik rolleri bulunmaktadır. Bu derlemede genel olarak melatoninin fizyolojik ve patofizyolojik süreçlerdeki rollerinin incelenmesi amaçlanmaktadır.

1. INTRODUCTION

Melatonin was first isolated from the bovine pineal gland by Aaron B. Lerner in 1958 [1]. The chemical structure of melatonin with the molecular formula $C_{13}H_{16}N_2O_2$ is shown in Figure 1. This indoleamine, also known as N-acetyl-5-methoxytryptamine, is primarily synthesised by the pineal gland in the human body, although other organs such as the bone marrow, retina, skin and gastrointestinal system also secrete melatonin. Notably, melatonin secreted by the pineal gland represents the most systemically significant source, while production by other structures is considered less impactful at the systemic level [3]. Melatonin is widely distributed in nature, and its mechanism representing one of the phylogenetically oldest biological signaling systems. This molecule has been found in all major taxa of organisms, including bacteria, unicellular eukaryotes and macroalgae. Additionally, it is found in various parts of plants such as roots, stems, flowers, and seeds and in both invertebrate and vertebrate species. This wide distribution suggests that melatonin has been conserved throughout evolution [4,5]. The synthesis and secretion of melatonin are regulated by light and darkness. While light suppresses melatonin production, darkness enhances it. Thus, melatonin is known as the 'hormone of darkness' [6]. Although important insights into the role of melatonin in human physiology and pathophysiology have been gained

in recent years, many of the functions and effects of this hormone are still not fully understood. Melatonin is recognised not only as a hormone but also as a cellular protector. It has demonstrated significant effects on biological processes such as oxidative stress, immune modulation, sleep, and circadian rhythm regulation. Moreover, melatonin plays a critical role in the treatment of various conditions, including depression, insomnia, epilepsy, Alzheimer's disease, diabetes, obesity, alopecia, migraine, cancer, immune disorders, and cardiovascular diseases (Figure 3) [3,6]. In this review, the physiological and pathophysiological roles of melatonin are explored.

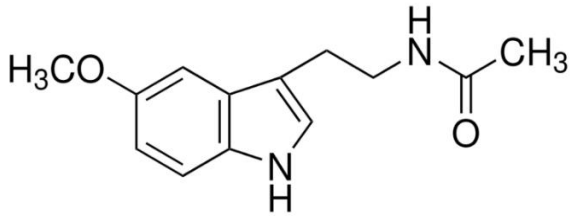

Figure 1. Chemical Structure Of Melatonin (N-acetyl-5-methoxytryptamine) [2]

2. MELATONIN METABOLISM

2.1. Biosynthesis

Melatonin biosynthesis in humans begins with tryptophan, an essential amino acid that serves as a precursor in this process. Tryptophan is absorbed from the plasma by the pineal gland and subsequently hydroxylated by the enzyme tryptophan hydroxylase within the pinealocytes. This reaction produces the first intermediate metabolite, 5-hydroxytryptophan, which then undergoes decarboxylation by the enzyme decarboxylase to form 5-hydroxytryptamine, commonly known as serotonin. Serotonin is acetylated by the enzyme NAT (N-acetyl transferase) and converted to N-acetylserotonin. Finally, acetylserotonin O-methyltransferase (ASMT), also known as hydroxy-indole O-methyltransferase (HIOMT), converts N-acetylserotonin to melatonin (Figure 2) [7,8].

Melatonin synthesis is a complex process regulated by light and dark cycles, and serum concentrations vary according to these cycles. This production in the pineal gland aligns with the 24-hour light/dark rhythm governed by the suprachiasmatic nucleus (SCN), where synthesis and release are elevated at night while inhibited by light during the day. Neural impulses to the pinealocytes via postganglionic sympathetic neurons play a critical role in regulating the melatonin rhythm.During the night, increased electrical activity in the SCN triggers melatonin production. The pineal gland functions as a neuroendocrine transformer, converting these electrical signals into hormonal secretions that elevate melatonin levels during darkness [9]. The enzyme N-acetyltransferase (NAT), a key regulator of melatonin synthesis, exhibits low activity during daylight hours but increases significantly in the dark, underscoring the dependency of this process on the light-dark cycle.At night, norepinephrine binds to α and β adrenergic receptors and causes an increase in intracellular calcium (Ca^{2+}). This increase potentiates the activation of enzymes such as protein kinase C (PKC) and calcium-calmodulin kinase (CaM kinase), which in turn increases cAMP levels and the phosphorylation of rate-limiting enzymes (AANAT and ASMT) in melatonin synthesis [10].

In summary, melatonin synthesis begins with the hydroxylation and decarboxylation of serotonin, a process regulated by cAMP-dependent transcription factors and photoperiodic conditions. Light inhibits melatonin synthesis by transmitting signals from the retina to the SCN and other structures in the hypothalamus. In darkness, norepinephrine released from postganglionic sympathetic fibres binds to β1 receptors and releases serotonin and NAT into the cell. This biochemical signalling cascade accelerates melatonin production and ensures its regular synthesis and release in accordance with the day-night rhythm [10,11].

2.2. Secretion

The amphiphilic structure and small molecular size of melatonin enable it to easily permeate cell membranes, allowing it to reach various biological fluids and tissues, including saliva, urine, cerebrospinal fluid (CSF), preovulatory follicles, sperm, amniotic fluid, and milk. These characteristics imply that melatonin is not stored in pinealocytes but is instead released immediately upon synthesis. The dense vascular network of the pineal gland and its dorsal and posterior attachment to the wall of the third ventricle allow melatonin to be released into the central nervous system, particularly the CSF and bloodstream, during the night [3,8]. The half-life of melatonin in the body ranges between 20 and 40 minutes, and after secretion, it rapidly disperses into the blood and CSF. Approximately 60-70% of melatonin in the bloodstream is bound to albumin. However, the distribution of melatonin in the body is not homogenous; the concentration of melatonin in the CSF is higher than in the blood. Blood melatonin levels typically range from a few pg/mL during the day to 50-100 pg/mL during the night, reflecting overall systemic concentrations. Age significantly influences melatonin levels. In the first three months of life, these levels are relatively low but begin to rise between three and six months, leading to the development of a day-night rhythm. Nocturnal melatonin concentrations are approximately 250 pg/mL in children aged 1-5 years, decrease to 65 pg/mL between 5-15 years, and further decline to 20 pg/mL in individuals aged 50-70 years. In adults, average plasma melatonin levels range between 50-70 pg/mL during the night [12,13].

2.3. Catabolism

The liver is the primary organ responsible for clearing more than 90% of circulating melatonin and is the central site of melatonin metabolism [14]. Melatonin is primarily metabolised to 6-hydroxymelatonin in the liver by cytochrome P450 isoforms, particularly CYP1A2, CYP1A1 and CYP1B1 enzymes. Subsequently, this metabolite undergoes conjugation and is excreted in urine as the major metabolite, 6-sulfatoxymelatonin (aMT6S).

Urinary aMT6S levels closely reflect plasma melatonin concentrations. Melatonin in the CSF is metabolised by neurons and glial cells via cleavage of the pyrrole ring, resulting in the formation of N-acetyl-N-formyl-5-methoxyquinuramine (AFMK). AFMK is the primary metabolite formed through oxidation of melatonin, which is subsequently converted to N-acetyl-5-methoxyquinuramine (AMK). Both AFMK and AMK exhibit potent free radical scavenging properties. Notably, AMK interacts with reactive oxygen and nitrogen species, generating a range of metabolites [15,16].

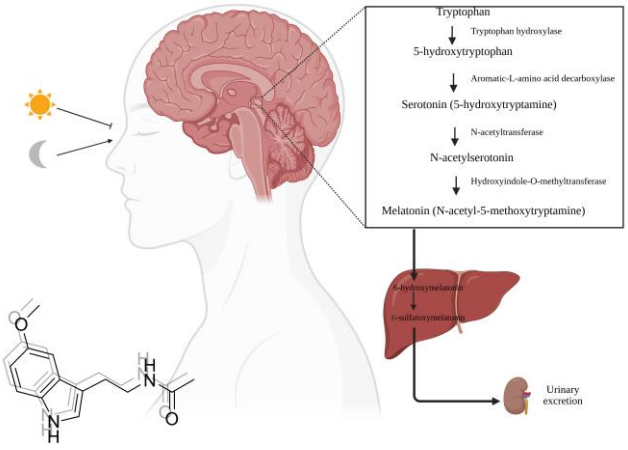

Figure 2. Synthesis of Melatonin (Created in BioRender license: https://BioRender.com/gde2tmi)

3. PHYSIOLOGICAL AND PATHOPHYSIOLOGICAL ROLES OF MELATONIN

3.1. Antioxidant and Anti-inflammatory Actions

Oxidative stress is defined as the disruption of cellular homeostasis as a result of the increase in reactive oxygen species (ROS) generated during cellular metabolism and the inadequacy of antioxidant defence mechanisms. This condition arises due to an excessive accumulation of free radicals and a deficiency of both enzymatic and non-enzymatic antioxidants. As a consequence, oxidative stress exerts harmful effects on key biomolecules, including lipids, proteins, and DNA. Reactive oxygen species (ROS) and reactive nitrogen species (RNS) accumulate in cells as a result of exposure to various stressors such as inflammation, infection, ultraviolet (UV) and ionising radiation. While low levels of ROS play a crucial role in physiological processes such as cell proliferation, apoptosis, and immune response, excessive ROS production induces significant cellular damage, leading to DNA mutations and severe pathological conditions, including cancer [3,17]. Moreover, the disruption of metal homeostasis contributes to DNA damage, lipid peroxidation, and protein modification. Research has reported that metals such as iron, copper, chromium, and cobalt contribute to free radical formation. Among these, cobalt is a potent inducer of oxidative stress, primarily through the generation of free radicals. Studies have shown that metals cause oxidative damage and melatonin has been shown to reduce this damage [18,19]. The body tries to prevent the effects of oxidative stress through the action of endogenous and exogenous antioxidants. Oxidative stress has been implicated in numerous chronic diseases, including cardiovascular disease, diabetes, rheumatoid arthritis, cancer, and neurodegenerative disorders. This condition highlight the significance of maintaining a balance between oxidants and antioxidants in the prevention and treatment of such diseases. To sustain this balance, antioxidant-rich diets, dietary supplements, and phytotherapeutic approaches have been highlighted as essential strategies [20].

Melatonin is a widely distributed compound in nature that plays a crucial role in various biological processes. While its fundamental physiological function is hormonal properties, one of its most notable properties is its potent antioxidant activity. The antioxidant property of melatonin is based on the pyrrole ring in its structure. Moreover, due to its solubility in both aqueous and lipid phases, melatonin effectively protects cellular components, including the cell membrane, organelles, and nucleus, from oxidative damage [3,21]. Melatonin neutralises free radicals by providing electrons directly to oxidant substances and also shows an indirect effect by activating endogenous antioxidant systems. The ability to neutralise harmful reactive oxygen species, such as superoxide, hydroxyl radical, hydrogen peroxide and peroxynitrite is shown as an example of the direct effect of melatonin. In addition, melatonin mitigates oxidative stress indirectly by upregulating the expression of antioxidant enzymes, including superoxide dismutase, catalase, glutathione peroxidase, and glutathione reductase. In conditions of high oxidative stress, melatonin produces antioxidant metabolites, such as 6-hydroxymelatonin, 2-hydroxymelatonin, 4-hydroxymelatonin, N-acetyl-N-formyl-5-methoxykynuramine (AFMK), N-acetyl-5-methoxykynuramine (AMK), and cyclic 3-hydroxymelatonin, which are reported to exert a protective role against free radicals [3,22]. One of the distinctive properties of melatonin is that it does not convert into prooxidant compounds after exerting its effects, and its intermediates also exhibit antioxidant activity. Due to this characteristic, melatonin is regarded as a ‘terminal antioxidant,’ in contrast to other antioxidants [22].

3.2. Effects on Sleep and Regulation of Circadian Rhythm

Circadian rhythms are approximately 24-hour cycles that regulate various biological processes, including sleep-wake cycles, hormone secretion, cognitive function, and emotional states. These biological rhythms can range from short-term cycles to long-term cycles lasting years. Circadian rhythms play a crucial role in regulating physiological processes such as body temperature, hormone secretion and sleep patterns. Disruptions of these rhythms can lead to varying degrees of health problems. Moreover, external factors such as light exposure, physical activity, dietary habits, and pharmacological interventions can either enhance or disrupt circadian rhythm function [23,24]. The suprachiasmatic nucleus (SCN), located in the hypothalamus, is the central pacemaker that regulates these rhythms. In mammals, the SCN regulates optimal physiological and behavioural

rhythms by synchronising internal biological clocks with external environmental signals, particularly cycles of light and darkness. Through its connections with other hypothalamic nuclei, the SCN ensures that endogenous biological processes are aligned with environmental changes. This synchronisation is crucial for survival of organisms and the maintenance of healthy daily activities [23,25].

Melatonin serves as an endogenous synchroniser that balances and strengthens the bodily rhythms and is therefore called a 'chronobiotic', i.e. a molecule that regulates the timing of the biological clock. It is the primary marker that regulates the circadian rhythm by responding to light-dark cycles. Moreover, this hormone plays a crucial role in maintaining homeostatic balance through the epigenetic regulation of clock genes in cells. Additionally, melatonin contributes to the reduction of body temperature during the night, thereby facilitating the transition to sleep [4,9,25]. Melatonin production follows a distinct cycle as part of the circadian rhythm. Light exposure reaches the suprachiasmatic nucleus (SCN) through signals from the retina and inhibits melatonin synthesis in the pineal gland. Melatonin secretion peaks during the night, typically reaching its highest levels between 02:00 and 04:00. In summary, melatonin and the circadian rhythm contribute to the regulation of various physiological functions depending on the body's internal clock [24]. The sleep-wake cycle is one of the most prominent circadian rhythms and is tightly regulated by neurochemical processes. Sleep fulfils many critical functions of the brain, such as energy regeneration, switching off external stimuli and processing learning and memory. These processes are crucial for brain development as well as mental and physical health. Melatonin is a hormone long known for its role in regulating sleep, with its sleep-promoting effects typically associated with its secretion 1-2 hours before sleep time. The ability of melatonin to facilitate the transition to sleep and regulate the sleep cycle has led to its investigation in the treatment of insomnia and sleep disorders. Especially in individuals with chronic insomnia, other psychiatric disorders such as depression and anxiety are also common. This condition is more prevalent in older individuals due to the age-related decline in melatonin production. This decrease in melatonin levels is thought to be one of the main causes of insomnia. This hormone regulates the sleep cycle by working in harmony with circadian phase markers and synchronising with other biological functions, thus playing a crucial role in the treatment of sleep disorders [25,26].

3.3. The Role of Melatonin in Cancer

Cancer is the second leading cause of death globally, following cardiovascular disease [27]. It is a genetic disorder resulting from defects in cellular DNA, leading to the abnormal expression of genetic information. Cancer typically develops due to the activation of genes that regulate critical cellular functions such as growth, survival, and invasion/motility, alongside the repression of genes that limit these functions. However, these characteristics alone are insufficient for cancer formation. The hallmarks of cancer such as sustaining proliferative signaling, evading growth suppressors, ability to evade programmed cell death, enabling replicative immortality, inducing angiogenesis, activating invasion and metastasis, genome instability and mutation, tumor-promoting inflammation, reprogramming energy metabolism and evading immune destruction are also integral to this process. The fundamental mechanism underlying cancer is typically linked to the accumulation of mutations. However, epigenetic changes, particularly DNA methylation, are increasingly playing a central role in cancer development [28,29].

Studies conducted by Bergmann and Engel between 1935 and 1952 demonstrated that pineal gland extracts slowed growth in experimental animals, suggesting a potential inhibitory effect on cancer progression. Additionally, some epidemiological studies have reported an increased risk of breast cancer among occupational groups engaged in night shift work, particularly female healthcare professionals, pilots, and flight attendants. Experimental studies in mice have reported that circadian disruption promotes tumour growth [22,30]. Melatonin has been identified as an effective and safe agent against various types of cancer, with this indoleamine targeting multiple mediators that regulate cancer metabolism at both transcriptional and post-transcriptional levels. Epidemiological studies have demonstrated that melatonin exhibits significant oncostatic (tumour growth-inhibiting) effects across various types of cancer. Furthermore, both *in vitro* and *in vivo* experiments have indicated that melatonin can suppress tumour growth. Findings suggest that reduced melatonin levels may accelerate tumour progression, whereas lung and colorectal cancer patients receiving melatonin treatment demonstrate improved quality of life and higher remission rates [31,32].

Processes such as tumour development, growth, invasion, and metastasis can be regulated by the actions of melatonin. Early studies have reported that melatonin reduces the likelihood of healthy cells undergoing malignant transformation by suppressing growth factors, including insulin-like growth factor-1 (IGF-1), epidermal growth factor receptor (EGFR), hepatocyte growth factor (HGF), transforming growth factor (TGF), and platelet-derived growth factor (PDGF). As the tumour progresses, the proliferative and invasion potential of cancer cells increases rapidly. During this process, melatonin not only inhibits cancer cell proliferation but also prevents invasion and metastasis by suppressing factors such as matrix metalloproteinase 9 (MMP-9) and fibroblast growth factor 19 (FGF19) [33,34,35]. Melatonin is known to have antiproliferative effects on many types of cancer through melatonin receptors (MT1 and MT2). These effects are mediated by different molecular mechanisms involving the activation of membrane-specific G protein-coupled receptors. The melatonin receptors are called MT1 and MT2, with MT1 exhibiting high affinity and MT2 low affinity. These receptors have different pharmacological properties and chromosomal arrangements and bind to α, β, and γ subunits of G proteins in intracellular signaling pathways. Stimulation

of MT1 receptors inhibits the adenylate cyclase pathway, whereas MT2 receptor activation induces phospho-inositides hydrolysis. MT1 receptors are widely distributed in the anterior pituitary, hypothalamus, and various brain regions, while MT2 receptors are primarily concentrated in the retina, hippocampus, and cerebellum. Additionally, melatonin receptors are also found in tissues, including the ovaries, blood vessels, immune cells, kidneys, and pancreas [32,35]. In addition to directly interacting with cancer cells via these receptors, melatonin regulates T helper cells by activating natural killer (NK) cells and stimulating the release of cytokines such as IL-2 and IFN-γ [35].

Epithelial-mesenchymal transition (EMT) is a process that plays a crucial role in the initiation of cancer metastasis. During this process, epithelial cells lose their polarity and intercellular adhesion properties, acquiring mesenchymal stem cell characteristics, which enhance their motility and invasiveness and enable their differentiation into various cell types. Research has demonstrated that melatonin suppresses the migration and invasion of prostate cancer cells by inhibiting EMT. Angiogenesis is a critical process in tumour growth and metastasis. Vascular endothelial growth factor (VEGF) is a potent pro-angiogenic factor that induces endothelial cell proliferation and increases vascular permeability. Several data suggest that anti-VEGF therapy inhibits tumour progression and extends progression-free survival in patients. Additionally, melatonin has been reported tohave an important regulatory effects on angiogenesis. Interestingly, melatonin may have different effects on neovascularisation depending on pathological and physiological conditions; while it supports angiogenesis in some physiological conditions, it may suppress this process in tumours and in hypoxic environments [33,36]. While melatonin functions as a potent apoptotic agent, particularly in cancer cells, it supports anti-apoptotic processes in normal cells. Melatonin can activate both intrinsic and extrinsic apoptotic pathways. Within the intrinsic pathway, it stimulates caspase-3, caspase-8, and caspase-9, increases cytochrome c levels in the cytosol, suppresses the anti-apoptotic Bcl-2 protein, and upregulates the pro-apoptotic Bid protein. In the extrinsic apoptotic pathway, melatonin accelerates cell death by enhancing Fas and Fas ligand (FasL) expression. These mechanisms demonstrate that melatonin effectively promotes programmed cell death in cancer cells. Furthermore, melatonin can induce genetic modifications through various mechanisms, including epigenetic alterations, oncogene suppression, and the regulation of long non-coding RNAs (LncRNAs) and microRNAs (miRNAs). These processes allow melatonin to inhibit cancer cell proliferation, migration, and invasion, while also enhancing the sensitivity of these cells to radiotherapy and chemotherapy. Additionally, several studies indicate that melatonin exhibits oncostatic properties against cancers in various tissues, including the breast, prostate, ovary, liver, kidney, lung, pancreas, colorectal, skin, and gastrointestinal tract [31,37,38].

3.4. Effects on Neurodegenerative Diseases

Neurodegeneration is associated with progressive central nervous system disorders, which are defined clinically, morphologically, and biochemically. The human brain, with its high levels of polyunsaturated fatty acids (PUFAs), increased oxygen demands, elevated ascorbate and iron accumulation in certain regions, and limited antioxidant defense capacity, is vulnerable to damage caused by reactive oxygen species (ROS). Excessive elevation of ROS levels leads to mitochondrial imbalance in brain cells during aging and neurodegenerative processes, resulting in the dysfunction of the electron transport chain [39]. These diseases cause a slowly progressive loss of neurons in the central or peripheral nervous system, leading to impairments in movement or cognitive function. They include Alzheimer's, Parkinson's, Huntington's disease, and amyotrophic lateral sclerosis (ALS), but may also be associated with neurodevelopmental disorders and psychiatric conditions such as schizophrenia. These diseases can lead to progressive loss of brain function, causing severe disability and death in older people. Moreover, neurodegenerative diseases share similar clinical features and molecular mechanisms, such as cognitive deficits, motor disorders, and sleep disturbances [40,41].

Circadian rhythm disturbances and alterations in sleep-wake cycles are frequently observed in neurodevelopmental disorders. This highlights the need to investigate melatonin metabolism in these conditions, given its crucial role in regulating circadian rhythms, synchronisation of sleep-wake cycles and supporting neural development. Melatonin production significantly decreases with age and in neurodegenerative diseases such as Alzheimer's and Parkinson's, suggesting that melatonin deficiency may contribute to the onset or progression of these diseases. In patients with Alzheimer's disease, low levels of melatonin have been detected in both blood and cerebrospinal fluid, even in the early stages of the disease [40,42,43]. The protective effects of melatonin on neurological diseases include mechanisms such as reducing oxidative stress, regulating inflammatory responses, preventing cellular apoptosis and supporting the neurogenesis process. Melatonin can positively affect the differentiation and migration processes of neural stem cells by promoting the survival, proliferation and maturation of neural stem cells without causing toxic side effects [44]. In addition, melatonin supplementation has been shown to be beneficial in improving cognitive and motor function in neurodegenerative diseases, as well as alleviating sleep disorders. The age-related decline in melatonin synthesis may contribute to the acceleration of neurodegenerative processes. Studies have reported that melatonin reduces the DNA damage response (DDR) in neuronal cells of humans, and female mice with accelerated aging. In conclusion, melatonin deficiency is a significant factor that contributes to increased oxidative damage and the development of age-related neurodegenerative diseases [39,40,45].

3.5. Effects on Cardiovascular System

Cardiovascular disease (CVD) is one of the leading causes of death worldwide, particularly affecting the elderly population. According to the World Health Organization (WHO), 17.9 million people died from CVDs in 2019. These diseases, which encompass conditions such as coronary heart disease, myocardial infarction, heart failure, cardiomyopathy, arrhythmias, congenital heart disease, peripheral vascular disease, and hypertensive heart disease, continue to represent a significant public health problem. Modifiable risk factors, including physical inactivity, obesity, smoking, and poor dietary habits, play a crucial role in the development of CVD [46,47].

Melatonin is recognized for its potential protective effects against cardiovascular disease. It exerts its protective actions through both receptor-mediated and receptor-independent mechanisms. Melatonin receptors are distributed across both central and peripheral tissues, and the distribution and types of these receptors determine the physiological effects of melatonin. The MT1 and MT2 receptors within the cardiovascular system underscore melatonin's cardioprotective properties. Activation of MT1 receptors induces a vasoconstrictive effect by regulating vascular tone, and provides protection against oxidative damage by increasing the production of antioxidant enzymes. This mechanism safeguards endothelial cells from damage caused by reactive oxygen species and helps prevent vascular disease. MT2 receptors, on the other hand, cause vasodilation by stimulating the production of nitric oxide. This property regulates blood flow and plays a key role in reducing blood pressure. Additionally, melatonin’s antioxidant properties support vascular health by preventing damage caused by oxidative stress. Melatonin significantly supports cardiovascular health through mechanisms such as vasodilation, antioxidant and anti-inflammatory effects, blood pressure regulation and modulation of lipid metabolism. These multifaceted effects position melatonin as a promising therapeutic agent for the treatment of cardiovascular disease [48,49,50].

4. LIMITATIONS AND FUTURE PERSPECTIVES

Melatonin, as a versatile hormone with minimal toxicity, can be effective in many physiological and pathophysiological processes. However, its application as an anticancer agent is constrained by several challenges, including low bioavailability, inconsistent measurement methods, and uncertain dosage regimens and routes of administration. The pharmacokinetics of exogenous melatonin are not fully understood; interindividual differences in absorption, metabolism, and elimination lead to high variability in bioavailability. Indeed, Fourtillan et al. reported bioavailability to be between 1% and 37% [51], while DeMuro et al. reported it to be 15% [52]. Although oral administration is the most common route, bioavailability is low and highly variable. In a systematic review, Zetner et al. evaluated the effects of various routes of administration, including intranasal, transdermal, oral transmucosal, and subcutaneous [53]. According to their findings, intranasal administration results in higher bioavailability than oral melatonin. Melatonin's low solubility, poor chemical stability, and short half-life exacerbate this problem. Therefore, developing biocompatible carrier systems that increase solubility and bioavailability is important. In particular, nanoparticle-based systems are attracting attention due to their potential to increase therapeutic efficacy, reduce side effects, and improve quality of life. For instance, delivering melatonin with doxorubicin (DOX) via magnetic Fe_3O_4 nanoparticles has increased apoptosis in osteosarcoma cells and demonstrated synergistic antitumor effects in nanoformulations [33,54]. Findings regarding melatonin levels in epidemiological studies are often inconsistent. This may be due to differences in sample types (e.g., urine, plasma, or serum), variable collection times, and diverse assessment methods. Circadian rhythm-dependent variation in melatonin levels also contributes to this situation. Therefore, future studies should standardize the sample type and collection time and adopt the most reliable assessment approach by comparing existing methods. These changes would reduce inconsistencies in the literature and yield more accurate results regarding the therapeutic level of melatonin [38,55]. Current findings indicate that melatonin can be used as both an adjuvant and a protective agent in cancer treatment. When used as an adjuvant, it can enhance the therapeutic effects of chemotherapy and radiotherapy while also mitigating the adverse side effects caused by these treatments. Furthermore, clinical studies have reported that melatonin improves the efficacy of anticancer drugs, enhances sleep patterns, and contributes to an improved quality of life. However, inconsistencies arising from different doses and application durations necessitate the development of a standard treatment protocol [3,38]. The safety profile of new treatments in oncology is of great importance. Melatonin has not exhibited significant toxicity, even at high doses, and has not been linked to serious adverse effects in clinical studies. In fact, it has been reported to reduce some adverse effects caused by radiotherapy and chemotherapy. Melatonin has also been found to be safe when taken in doses ranging from 10-50 mg per day, which is above the recommended dose of 0.5-5 mg per day [56]. Furthermore, it has been reported that melatonin may increase survival rates, accelerate response rates to antitumor treatments, and alleviate both treatment-related toxicities and malignancy-related symptoms [57]. To enhance melatonin's anticancer potential, it is suggested that more stable and effective analogues be developed through chemical modifications [58]. In particular, it is thought that derivatives exhibiting multi-target effects could provide potent antitumor results by simultaneously interfering with different pathways in tumors. However, for melatonin to be used as a clinical agent, a better understanding of its molecular mechanisms and comprehensive clinical studies are required. Current findings support the idea that melatonin, either alone or in combination with other anticancer agents, could be a promising therapeutic option.

Figure 3. Biological Effects of Melatonin

5. CONCLUSIONS

Melatonin is widely distributed in nature and is present in a diverse range of organisms, from unicellular organisms to humans. This molecule plays a critical role in fundamental physiological functions, including circadian rhythm regulation, sleep cycle management, and antioxidant and anti-inflammatory properties. Moreover, it exerts significant effects in pathological conditions such as neurodegenerative diseases, cancer, and cardiovascular diseases. Melatonin triggers receptor-dependent signal transduction mechanisms by binding to membrane receptors while also demonstrating receptor-independent effects. Due to these multifaceted mechanisms of action, melatonin is gaining attention as a potential agent both in maintaining physiological homeostasis and in the treatment of various diseases. Further research is needed to elucidate its therapeutic potential by providing a more in-depth understanding of its role in these diverse processes.

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