Kragujevac J. Sci. 46 (2024) 000-036. UDC 591.481:159.963.23:577.17
Online First doi: 10.5937/KgJSci2400004S *Review*

MELATONIN AND ITS PHYSIOLOGICAL AND THERAPEUTIC EFFECTS: A REVIEW

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(Received March 14, 2024; Accepted May 20, 2024)

ABSTRACT. Melatonin, an evolutionarily old molecule, is found in many living organisms. This neurohormone is known to control many physiological processes, including circadian rhythm, mood, and behavior. Melatonin was discovered to be a direct free radical scavenger. By activating its receptors, it stimulates a wide range of signaling pathways. It has been proven that melatonin exerts neuroprotective and antidepressant-like effects. Also, many researchers have found that melatonin plays an important role in various cardiovascular diseases. In the near future, melatonin will be a promising agent to control the fate of mesenchymal stem cells by regulating the generation of reactive oxygen species and the release of immune factors in regenerative medicine. Collectively, the studies link melatonin to a variety of outcomes and have a strong regulatory impact on numerous physiological processes in the body.

Keywords: melatonin, circadian rhythm, depression, neurodegenerative diseases, cardiovascular system.

INTRODUCTION

Melatonin is a ubiquitous molecule, an indoleamine, produced endogenously by animals and plants. Since melatonin was found in the phototrophic bacterium *Lingulodinium polyedrum*, a dinoflagellate, the extensive search for this molecule has shown positive results in almost all taxa investigated thus far (POEGGELER *et al*., 1991). Melatonin is present in several evolutionary groupings that include Alphaproteobacteria, Cyanobacteria, Dinoflagellata, Euglenoidea, Rhodophyta, Phaeophyta, and Viridiplantae (HARDELAND *et al*., 2007; TAN *et al*., 2012). The fact that melatonin is widely distributed in primitive bacteria

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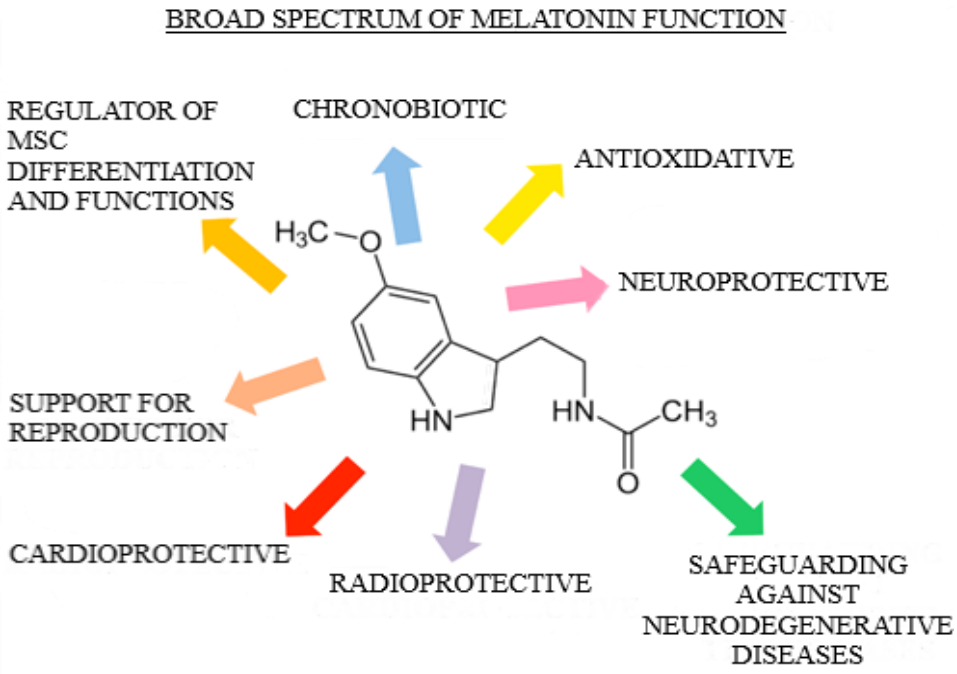
indicates that the molecule has a long history and has persisted throughout the evolution of living things (PSHENICHNYUK *et al*., 2017). Melatonin has developed through endosymbiosis in bacteria. It was previously believed that melatonin plays a role in metabolism, photosynthesis, and the detoxification of free radicals (MANCHESTER *et al*., 2015; TAN *et al*., 2015). But as evolution progressed, melatonin changed and became pleiotropic (Scheme 1), demonstrating a major role in regulating biological cycles, lowering inflammatory states, and fending off oxidative stress (TAN *et al*., 2010; TAMTAJI *et al*., 2019). Fungi have also been found to contain melatonin (MUSZYŃSKA and SUŁKOWSKA-ZIAJA, 2012).

Its functions include being an endocrine marker for photoperiodicity and darkness, indicating the time of day (clock function), and the season ("calendar" function). Humans ingest melatonin from the diet or produce it in different regions of the body (the pineal gland, brain, retina, cochlea, gut, lens, skin, thymus, spleen, and many others) (MAHMOOD, 2019). Melatonin (molecular weight 232.3 g/mol) is also present in almost all body fluids (cerebrospinal fluids, saliva, urine, feces, semen, and breast milk) (TAN *et al*., 2018). The pineal complex, which includes the pineal organ and a second component known as the parapineal organ, is photoreceptive, produces melatonin, and frequently has a circadian pacemaker that controls physiology and behavior in birds, reptiles, amphibians, and fish (FOSTER, 2021). In the pineal gland, humans produce melatonin from the amino acid tryptophan. Although the pineal gland is considered the main site of melatonin synthesis, humans produce 400 times more melatonin in the gut (CHEN *et al*., 2011). The level of melatonin increase from birth and reach a peak at puberty, then start to decline with aging, which will be described in detail later. In the modern world, there are several causes of disturbances in melatonin synthesis, such as jet lag, shift work, and the use of artificial light at night (from cell phones, computers, fluorescent, and LED lights).

The chemical structure of melatonin in plants and animals is very similar to that found in humans (SALEHI *et al*., 2019). Plants can synthesize tryptophan, and that could be the reason why plants have a higher amount of melatonin. The concentration of melatonin is higher in the reproductive organs of plants, such as seeds (SALEHI *et al*., 2019). The environment in which the plants are grown is also linked to the melatonin content of plant foods. This includes the temperature, exposure to the sun, or treatment with pesticides (WANG *et al*., 2016).



Scheme 1: Diagrammatic presentation of broad spectrum of melatonin functions.

REGULATION OF MELATONIN SECRETION

Suprachiasmatic nuclei (SCN) generate a 24-hour rhythmic oscillation. SCN allows mammals including humans to adjust their physiology according to the time of the day or year because it provides circadian information to all cells in the body (LEVI and SCHIMBLER, 2007). The SCN is also called the "master pacemaker" because it contains 20,000 neurons and is located in the anterior hypothalamus immediately above the optic chiasm (SILVER and RAINBOW, 2016). Neurons in SCN receive electrical signals from the retinas via the retinohypothalamic tract (HANNIBAL, 2006). In the retina, a third photoreceptor called intrinsically photosensitive retinal ganglion cells (ipRGCs) has been identified (PAUL *et al*., 2009). The ipRGCs perceive light. The axons of the ipRGCs project via the RHT to the SCN through a complex multisynaptic pathway. Only 1–2% of all ipRGCs are capable of responding to light because of the presence of melanopsin. This photopigment responds to wavelengths in the range of 460–480 nm (blue light) (LUCAS *et al*., 2014). The neural projections from the SCN to the paraventricular nuclei (PVN) of the anterior hypothalamus are very important because of the photic information being transferred to the pineal gland and determining melatonin synthesis. Once synthesized, melatonin is quickly released from pinealocytes into the cerebrospinal fluid and blood, raising the melatonin concentration. It is also very important to know that exposure to light at night severely suppresses melatonin synthesis. Aralkylamine N-acetyltransferase (AANAT) is the rate-limiting enzyme in melatonin biosynthesis. AANAT is also called “Timezyme”.

All organisms synthesize melatonin, which has autocrine and paracrine effects. As mentioned above there are several tissues and organs that produce melatonin, like the retina, gastrointestinal tract, bone marrow, lymphocytes, and skin (SLOMINSKI *et al*., 2008). All these tissues affect the homeostasis of the organism in different ways. The retina in the brain is the only place in which light and dark phase melatonin is secreted through paracrine pathways, and it plays an important role in the regulation of the sleep cycle. Moreover, it has also been shown that the abundance of melatonin receptors in the retina changes during the dark phase compared to the light phase, which therefore indicates a functional role for melatonin in the regulation of the sleep cycle. The bone marrow is also one of the tissues that produces melatonin locally, and it has been shown that it exerts a potent anti-inflammatory effect.

The superior cervical ganglion (SCG), from which sympathetic postsynaptic fibers reach the pineal gland and release norepinephrine only during the dark phase of the night, is responsible for timing the enzymatic conversion of tryptophan to melatonin. The PVN, which communicates with the higher thoracic segments of the intermediolateral spinal column, is where this information is sent (COLWELL *et al*., 2015). The enzyme machinery responsible for the biosynthesis of melatonin in pinealocytes was for the first time identified by Axlerod (AXELROD, 1974). Tryptophan is changed to 5-hydroxytryptophan by the enzyme tryptophan hydroxylase. The 5-hydroxytryptophan is converted to serotonin. Serotonin is acetylated to N-acetylserotonin by AANAT, and N-acetylserotonin is then transformed to melatonin by the enzyme acetylserotonin O-methyltransferase. Norepinephrine increases the activity of β_1 and α_1 adrenergic receptors, which in turn increases cAMP and protein kinase A (PKA) activity. This, among other mechanisms, causes the activation of melatonin synthesis by increasing cAMP response element binding protein (CREB) phosphorylation and AANAT activity (GANGULY *et al*., 2005). As a result of the β_1/AR/cAMP/PKA pathway being activated at night, there is a noticeable nocturnal rise in AANAT activity, which leads to a significant conversion of serotonin into N-acetylserotonin and then melatonin. Melatonin is converted to N^1-acetyl-N^2-formyl-5-methoxykynuramine in the CNS. N^1-acetyl-N^2-formyl-5-methoxykynuramine is then deformylated to N^1-acetyl-5-methoxykynuramine (HARDELAND, 2017).

In humans, melatonin begins to secrete shortly after sunset, reaches peak in the middle of the night (between two and four in the morning), and then progressively decline in the second half of the night (TORDJMAN *et al*., 2017). 80% of the hormone's synthesis occurrs at

night. Serum melatonin concentrations range between 80 and 120 pg/ml at night and 0–20 pg/ml during the day (KARASEK and WINCZYK, 2006). The half-life of melatonin in the blood is ~40 minutes. Recent research indicates that the melatonin rhythm is established at about 3 months of age (JOSEPH *et al*., 2014). Children at the age of 3 show a stabilization of the sleep-wake rhythm, which is consistent with a regular melatonin secretion rhythm (TORDJMAN *et al*., 2017). The highest nocturnal concentration peaks occur between the ages of 4 and 7 (KARASEK and WINCZYK, 2006), and then gradually drop. Pineal melatonin production drops to 60% of young adult levels beyond age 40. Importantly, females always produce more pineal melatonin than males (CAIN *et al*., 2010).

MELATONIN'S RECEPTORS

Melatonin receptors control glucose homeostasis, immunological responses, seasonal reproduction, circadian rhythms, sleep, and retinal physiology (DUBOCOVICH *et al*., 2010; JOCKERS *et al*., 2016). Two G protein-coupled receptors, MT1 and MT2, are found in all mammals, having 70% similarity inside the transmembrane regions and 55% homology across all amino acids (DUBOCOVICH and MARKOWSKA, 2005). The MT1 and MT2 receptors were cloned nearly 20 years ago from melanophores in frog skin (EBISAWA *et al*., 1994). MT2 receptors show 60% homology with MT1 receptors (KARASEK and WINCZYK, 2006). A third receptor subtype, MT3, has been identified as the enzyme quinone reductase 2, and it is involved in the protection against oxidative stress (BOUTIN, 2016). Finally, melatonin binds nuclear retinoid orphan receptors (ROR) or retinoid Z receptors (RZR). The suprachiasmatic nucleus (SCN), the anterior pituitary (pars tuberalis), and the retina have the highest density of melatonin receptors. In almost all mammals MT1 is predominant in the SCN with the exceptions of mink and sheep. Human MT1 is a 350 amino acid protein, and human MT2 is a 362 amino acid protein. They have predicted molecular masses of 39,374 Da and 40,188 Da, respectively, and were discovered in various CNS regions, such as the hypothalamus, thalamus, temporal, parietal, and frontal cortex, the hippocampus, the preoptic area, the basal ganglia, the retina, and the cerebellum (JOCKERS *et al*., 2016). The MT1 and MT2 melatonin receptors are also found in peripheral organs like adipose tissue, kidney, pancreatic islets, parotid glands, adrenal glands, liver, bone, skin, the reproductive tract, immune cells, and the cardiovascular system, among others (SLOMINSKI *et al*., 2012). MT1 has been shown to produce inhibitory responses to the cAMP signal transduction cascade, leading to a decrease in PKA activity and a decrease in CREB phosphorylation (DUBOCOVICH *et al*., 2010). In addition to the cAMP-dependent cascade, MT1 can be linked to a PLC-dependent signaling cascade (NIKOLAEV, *et al*, 2021). MT1 can bind to Ca^{2+}-activated K^+ channels (BK_{Ca}) (ZHAO *et al*., 2017). The action via the Gi protein is mediated by a decrease in cyclic adenosine monophosphate, which is followed by a reduction in protein kinase activity, and by the Gq protein, which is followed by the activation of phospholipase and protein kinase C. It's possible that variations in the pharmacological and signaling characteristics of MT1 and MT2 are crucial factors that regulate the effects of melatonin on particular physiological processes.
A new study by FANG *et al*. (2020) offers proof for the first time that the vitamin D receptor can function as a brand-new nuclear receptor that binds melatonin.

MELATONIN'S CATABOLISM

Melatonin is metabolized by liver cytochromes CYP1A2, CYP1A1, CYP1B1, and CYP2C19 (MA *et al*., 2005). Although they are mostly found in the liver, they are also found in other tissues. The resulting 6-hydroxymelatonin will often be conjugated to sulfuric acid after hydroxylation; however, a minor quantity may also be conjugated to glucuronic acid

before excretion (TORDJMAN *et al*., 2017). Drugs that affect these enzymes also affect the metabolism of melatonin. Anti-depressant medications like fluvoxamine inhibit CYP1A2 and disrupt the degradation of melatonin (PAPAGIANNIDOU *et al*., 2014). Because it is not deposited and has a short half-life, the concentration measured in serum or plasma accurately reflects the synthesis of melatonin in the pineal gland (CLAUSTRAT *et al*., 2005). The mitochondrial metabolism of melatonin is well-known. Cytochrome C in the mitochondria converts melatonin to N^1-acetyl-N^2-formyl-5-methoxykynuramine (AFMK). Other enzymes for melatonin metabolism are iron-containing hemoproteins, like cytochrome c. This group of enzymes are cytochrome P450 (CP450), horseradish peroxidase (HRP), indoleamine 2,3-dioxygenase (IDO), eosinophil peroxidase (EPO), and myeloperoxidase (MPO). Melatonin is converted to AFMK by all of these enzymes (TAN *et al*., 2007). In the brain, melatonin is metabolized by IDO (HARDELAND *et al*., 2009). Melatonin metabolism is primarily controlled by MPO and EPO at the site of inflammation. Plants do contain HRP, which may take part in melatonin metabolism. Melatonin metabolism in humans, plants, and animals is very complex, and very little is known about its metabolism in microorganisms. This field is very challenging for researchers.

MELATONIN IS A CHRONOBIOTIC SUBSTANCE

Melatonin is a natural model of "chronobiotics," drugs that synchronize or increase amplitude in circadian rhythms (CARDINALI *et al*., 2008). The crucial function of melatonin as a chronobiotic is defined by the light-dark fluctuation of melatonin production (ARENDT and SKENE, 2005). Melatonin is a hormone of darkness, which is crucial information for the neuroendocrine system (PANDI-PERULAM *et al*., 2008). Melatonin functions as an endogenous synchronizer to stabilize bodily cycles; it is a substance that modifies the biological clock's rhythms (PFEFFER *et al*., 2018). LIM *et al*. (2022) and FATEMEH *et al*. (2021) have confirmed the beneficial effects of exogenous melatonin on sleep onset latency and sleep quality in randomized controlled trials. Earlier, numerous studies have established that taking melatonin affects cortisol levels, sleep patterns, core body temperature, and biological cycles (ARENDT and SKENE, 2005). Melatonin's influence on phase-shifting is dependent on when it is administered. Phase-advanced circadian rhythms are those that occur when melatonin is given in the evening and first half of the night, while phase-delayed rhythms occur when melatonin is administered during the second half of the night or in the early morning. The dose of melatonin has a big impact on these outcomes (LEWY *et al*., 2006). It may play a role in synchronizing the biological clock in the fetus because melatonin crosses the placenta (CLAUSTRAT *et al*., 2005). In conditions like jet lag, circadian rhythmicity is adjusted using melatonin, which is one of the most potent synchronizers of human circadian rhythms (ARENDT and SKENE, 2005). Melatonin also has a significant synchronizing influence on seasonal rhythms, which are critical for the ability of the organism to adjust to changing environmental conditions throughout the year. Melatonin's effects on synchronizing seasonal rhythms are mediated by acting on the pituitary pars tuberalis, the hypothalamus, specifically designated glial cells known as tanycytes, and finally the distal hypophysis. Melatonin can therefore regulate growth, immunological response, energy metabolism, thermogenesis, reproduction, and body weight (PARENDT and MIDDLETON, 2018).

ANTIOXIDATIVE PROPERTIES OF MELATONIN

In the literature, melatonin is frequently described as an antioxidant (REITER *et al*., 2016; GALANO *et al*., 2018). Melatonin completes its antioxidative activity through a wide range of activities such as direct scavenging of reactive oxygen (ROS) and reactive nitrogen

(RNS) species; enhancing the rate of other antioxidative enzymes (GOMEZ *et al*., 2005); defense against oxidative damage (FISCHER *et al*., 2013); beneficial interactions with other antioxidants; lowering electron leakage to prevent the excessive synthesis of free radicals by enhancing the mitochondrial respiratory chain (WANG *et al*., 2012b). It is very important to know that melatonin's concentration is closely correlated with its ability to scavenge free radicals and reduce oxidative stress. The structure of melatonin has an indole ring rich in electrons. This ring functions as an electron donor and neutralizes free radicals, protecting proteins, DNA, and lipids from oxidative damage (MARTINEZ *et al*., 2005). Melatonin and its metabolites seem to have complementary roles in a various processes. Melatonin has been suggested as a workable preventative measure in the treatment of COVID-19, even though it does not directly kill viruses (SIMKO and REITER, 2020). Melatonin in the mitochondria boosts the respiratory chain's stability, lowers the production of superoxide anion, and neutralizes the negative effects of free radicals (REITER *et al*., 2016). Molecules in the inner mitochondrial membrane are shielded from ROS toxicity by melatonin (REITER *et al*., 2022). Overall, melatonin decreases radical production and enhances complex I and IV activity in the mitochondria, preserving the proton potential and promoting mitochondrial respiration and ATP synthesis. Studies addressing the antioxidant effects of melatonin are summarized in Table 1.

Table 1. Antioxidant effects of melatonin.

Authors	Antioxidative properties of melatonin
LEON *et al*., 2006	Suppress the activities of xanthine oxidase (XO), myeloperoxidase (MPO), and nitric oxide synthase (NOS).
FERRY e*t al*., 2005	Binds and inactivates iron, inhibiting the Fenton reaction and stopping reactive oxygen species (ROS) overproduction.
HARDELAND, 2019	Promote the production and activity of antioxidant enzymes such as superoxide dismutase (SOD), glutathione peroxidase, and catalase, helping in the body's detoxification.
WINIARSKA *et al*., 2006	Administration of melatonin in rabbits leads to increased activity of glutathione reductase and glutathione peroxidase, altering both glutathione (GSH) content and the GSH/GSSG ratio (the ratio of reduced GSH to oxidized GSH) under diabetic conditions.
TUTUNCULER *et al*., 2005	Melatonin crosses from the maternal to the fetal circulation, and pretreatment of mothers with melatonin boosts catalase activity in hypoxic rat brain tissue.
TANIGUTI *et al*., 2018	Melatonin treatment inhibits lipid peroxidation and reduces glutathione levels resulting from the administration of lipopolysaccharide from *Escherichia coli* in the hippocampus of male and female adult Swiss albino mice.
REITER *et al*., 2009	Melatonin, both *in vitro* and *in vivo*, significantly decreases lipid peroxidation by neutralizing the initiating agents, -OH and the peroxynitrite anion.

MELATONIN AND CENTRAL NERVOUS SYSTEM (CNS)

Melatonin is one of the neuroprotective medications that have been well investigated in clinical trials. For the physiological action of melatonin, the brain is a preferred target. Melatonin is directly released into the cerebrospinal fluid (CSF). The third ventricle has the highest melatonin concentration, where the pineal gland appears to release it directly.

Melatonin has quick access to neurons and glia due to its presence in the CSF. Importantly, several neurologic conditions, such as major depressive disorder and attention deficit and hyperactivity disorder, as well as neurodegenerative diseases like Parkinson's disease, Huntington's disease, and Alzheimer's disease, exhibit a marked decrease in pineal melatonin production. This supports the prevailing opinion that melatonin should be used as a therapeutic adjuvant in these conditions. Melatonin has a long history of being associated with the control of synaptic plasticity and neurotransmission because its receptors are widely distributed in several CNS structures, including neurons and glial cells (PANDI-PERUMAL *et al*., 2008). Neuroprotection is one of melatonin's most significant effects on the CNS. Melatonin is a strong, naturally occurring direct free radical scavenger and broad-spectrum antioxidant. Even at low doses, melatonin and its metabolites (N^1-acetyl-N^2-formyl-5-methoxykynuramine and N^1-acetyl-5-methoxykynuramine) are quite effective at preventing oxidative damage to the brain (TAN *et al*., 2007). Another way that melatonin affects the brain is through its anti-inflammatory actions (ESPOSITO and CUZZOCREA, 2010). Agomelatine, a melatonin agonist, is clinically effective in treating depression when both melatonin receptors are stimulated. The neuroprotective, hypnotic, and anxiolytic effects of melatonin are aided by its activation of the MT2 receptor (DE BERARDIS *et al*., 2015). Melatonin can activate survival pathways, which help treat several neurodegenerative disorders. Additionally, melatonin could restore damaged mitochondrial functions through its antiapoptotic mechanisms and delay the apoptotic death of neurons (JOSHI *et al*., 2015). It is thought that melatonin's effects on the JNK and PI3-K/Akt survival pathways are responsible for its neuroprotective properties (KOH, 2008). Through promoting cellular survival, proliferation, and neuronal development, melatonin also protects neural stem cells (NSCs) (YU *et al*., 2017). Melatonin may protect NSCs against the negative effects of hypoxia, inflammation, and a large amount of glucocorticoids, according to research by YU *et al*. (2017). Melatonin seems to have a critical role in preserving the integrity of the CNS, avoiding neuronal damage, and stopping the progression of neurodegenerative diseases. The potential benefits of melatonin in preventing and treating neurological diseases highlight the need for further research to fully understand its efficacy and safety profile.

MELATONIN AND DEPRESSION

Depression is characterized by wide range of symptoms and it is very challenging for researchers to simulate depression in animal models. However, some symptoms of depression can be replicated and studied in animal models. Anhedonia, anxiety (a symptom that occurs frequently in depression—neuroendocrine disorders, particularly those affecting the HPA system), changes in behavior, eating disorders, and sleep disorders, i.e. disorders of circadian rhythms and changes in the neuroanatomy of the brain, are a few of these symptoms (DEUSSING, 2006; CRYAN and SLATTERY, 2007).

Depressive mood may be an adaptation to stress and manifest in many behavioral phenomena, such as anhedonia, psychomotor disruption, loss of appetite, and sleepiness. These behavioral changes can cause a wide range of psychological symptoms, from a lack of energy and motivation to suicidal thoughts (BOIKO *et al*., 2022). In the plasma of depressive patients, melatonin levels are lowered. Studies on stress, anxiety, and/or depression have validated melatonin as an antidepressant and its neurogenic potential (KHOLGHI *et al*., 2022). The brain region most frequently linked to stress, depression, and antidepressant mechanisms is the hippocampus. The hippocampus is linked to memory and learning, so depression results in cognitive impairment. Prolonged stress causes atrophic alterations in the hippocampus, while depression causes a decrease in hippocampal volume (LEE *et al*., 2009; KIM *et al*., 2015).

Melatonin is produced when the pineal gland is stimulated through its sympathetic innervation pathway (LUMSDEN *et al*., 2020). In depressed individuals, melatonin secretion serves as a marker for norepinephrine activity. The pineal gland may be involved in the pathogenesis of mood disorders because clinical data suggests that antidepressants alter melatonin secretion in patients with major depressive disorder. Evaluating the effect of melatonin in patients with a depressive disorder is the subject of numerous research studies. Low melatonin levels have been described long ago as a 'feature indicator' for depression (BECK-FRIIS *et al*., 1985). As a result, melatonin deprivation is linked to a higher risk of developing depression and other related psychopathological and neurobiological disorders (including anhedonia, sleep disturbance, mood disorders, weight loss, increased monoamine oxidase activity, and elevated plasma cortisol levels). Melatonin in combination with the antidepressant buspirone leads to an improvement in the clinical outcomes of patients with depression (FAVA *et al*., 2012).

The effect of melatonin on the adrenal medulla (a key endocrine organ that regulates essential physiological processes) under chronic stress conditions was the subject of a very small number of studies. According to the research of STEFANOVIC *et al*. (2019), the adrenal medulla of stressed animals responds to melatonin administration in a way that improves catecholaminergic function by promoting catecholamine production, uptake, and their content in chromaffin cells.

The majority of depressed patients have trouble falling asleep, and sleep is usually followed by frequent nighttime awakenings. This leads to pronounced fatigue. Impaired cognition and concentration are also caused by this disruption (KAPLAN and HARVEY, 2009). These principles formed the basis for the chronobiological hypothesis of mood disorders (MALHI and KUIPER, 2013; ZAKI *et al*., 2018), which served as the starting point for research into the use of exogenous melatonin as a treatment for depression (ALSTON *et al*., 2019; BOYCE and HOPWOOD, 2013). Sedative drugs can help restore the circadian rhythm, but long-term use increases the risk of tolerance and addiction (TOUITOU and BOGDAN, 2007). In people with respiratory illnesses, metabolic abnormalities, and sleep disorders, melatonin improves the quality of their sleep (FATEMEH *et al*., 2021).

Melatonin and its analogs are increasingly intriguing as a potential new therapy for depression. Various studies have verified that melatonin has antidepressant effects (MADSEN *et al*., 2017). In preclinical investigations, melatonin has also been proven to protect against memory loss brought on by prolonged sleep deprivation stress (CARDINALI *et al*., 2012). A study by STEFANOVIC *et al*. (2018) examined how long-term melatonin treatment affected gene expression of α_1-, α_2-, β_1- and β_2-adrenoceptors in the hippocampus of rats under chronic unpredictable mild stress (CUMS). Results showed that melatonin treatment stopped the stress-related decline in the mRNA and protein levels of α_1- and β_2-adrenoceptors in chronically stressed rats. Melatonin may enhance neurotransmission as well as learning and memory by modulating these adrenoreceptors.

Moreover, using melatonin along with antidepressant therapy improves recovery in people (RAJARATNAM *et al*., 2009). Agomelatine, a melatonin analog, has demonstrated clinical antidepressant efficacy (GOODWIN *et al*., 2009), without the adverse effects that are typically associated with other antidepressants (eg, gastrointestinal changes, headaches, or weight gain) (LLORCA, 2010). After 6 weeks of treatment (at a dose of 25 mg daily) for patients with major depressive disorder, the effectiveness of agomelatine was also observed in the earlier study by OLIE and EMSLEY (2005). In another clinical study, agomelatine, at a dose of 25 mg per day, was found to be very good in treating not only depressive symptoms but also in treating anxiety (DEN BOER *et al*., 2006). Agomelatine has a special role that includes selective 5-HT2C receptor antagonists and melatonin receptor agonists (MT1/MT2) (PRINGLE *et al*., 2015). Agomelatine lacks activation of 5-HT2A. It seems that agomelatine is not associated with sexual dysfunction, which is very often a side effect of antidepressants. The side effect of antidepressants that is frequently related to sexual dysfunction does not appear

to be present with agomelatine. Agomelatine can increase neurogenesis and neuroplasticity in adult brain regions like the prefrontal cortex and hippocampus (POMPILI *et al*., 2013). Agomelatine may also be a useful and secure therapeutic option for treating depression, given encouraging findings on its efficacy and safety.

The influence of melatonin on the gene expression of VMAT2, MAO-A, and COMT in the hippocampus of chronic stress-induced depression rats was directly demonstrated for the first time in the study of STEFANOVIC *et al*. (2016). Authors showed that melatonin increases norepinephrine storage by influencing the vesicular transporter and enzyme degradation rather than de novo synthesis in the hippocampus of chronic stress-induced depression rats. This work is a restricted view of the full range of melatonin-induced effects, and more experiments are needed to identify the transcription factors that might control the expression of the target genes.

MELATONIN AND ANXIETY

The most prevalent mental illnesses are anxiety disorders. The pathophysiology of anxiety involves changes in the synthesis of free radicals, neuronal signaling pathways, and stress hormones. Anxiety and worry can be shown through symptoms such as restlessness, inadequate sleep, difficulties concentrating, irritability, tense muscles, disrupted sleep, palpitations, and perspiration. Anxiety can result in disordered behavior and irregular mood and sleep patterns, and it may also affect other systems, including the cardiovascular system (CVS). They may interfere with social and professional interactions as well as other aspects of functioning. Furthermore, it is widely acknowledged that anxiety and illnesses like cardiovascular disease have a bidirectional relationship that can either stimulate or potentiate one another. There is a persistent request for new methods of treating anxiety because pathological anxiety has a detrimental impact on a wide range of everyday human activities. Due to its favorable safety profile, melatonin is being suggested as an additional technique for treating this mental condition. The sympathetic nervous system (SNS) appears to play a substantial role in anxiety when it is active. PAINE *et al*. (2015) showed that increased sympathoadrenal activity was linked to anxiety, indicating a potential molecular mechanism by which anxiety could raise the risk of cardiovascular diseases. Anxiety levels are reduced by the SNS activity blockage. The etiology of neurodegenerative or neuropsychiatric diseases is influenced by altered neuronal function because reactive oxygen and nitrogen species and their byproducts damage the nucleic acids, proteins, and lipid membranes of neurons (KUMAR CHANANA, 2017). Notably, in the cerebellum, hippocampus, and neurons of the cerebral cortex, anxiety-like behavior in mice was connected to higher intracellular ROS levels (RAMMAL *et al*., 2008). Melatonin also slows down neurodegenerative processes and reduces anxiety and depression symptoms, which are both significant properties (REITER *et al*., 2010). In adults, melatonin seems to be a desirable alternative to benzodiazepines for lowering anxiety. Melatonin exhibits anxiolytic-like behavior that is mediated through MT1 and MT2 receptors, which have been implicated in anxiety-like reactions. These receptors have been found in the hippocampus and prefrontal cortex, two regions of the brain that process fear (HUANG *et al*., 2017). Melatonin reduced anxiety-like behavior and lowered serum corticosterone levels in rats subjected to chronic immobilization stress (GOMAA *et al*., 2017). According to a study by ZHANG *et al*. (2017), anxiety-like behavior due to sleep deprivation was abolished by melatonin. This effect may have been accomplished by melatonin's ability to lower oxidative stress and maintain the balance between GABAergic and glutamatergic transmission. It is also shown that the hippocampus dopamine content increased after rats received melatonin for 28 days due to enhanced TH protein levels (SPASOJEVIC *et al*., 2016). This lead to the conclusion that dopaminergic synthesis in the hippocampus may be stimulated by melatonin in order to inhibit stress-induced behavior. Since melatonin is freely

available, economically undemanding, and has no side effects, it may be considered an additional or alternative treatment for different conditions associated with anxiety.

MELATONIN AND ALZHEIMER'S DISEASE (AD)

A neurological illness known as Alzheimer's disease is an age-related disease. The biggest risk factor is age, which typically affects people over 65 (SCHELTENS *et al*., 2016). Alzheimer's disease accounts for approximately 80% of instances of dementia worldwide, and it is one of the biggest health problems of the twenty-first century. It is distinguished by extracellular β-amyloid (Aβ) in the arterial walls of the blood vessels in the brain (ITTNER and GOTZ, 2011). The accumulation of these aberrant proteins in brain regions responsible for memory, including the hippocampus, is known to cause an impairment in cognitive performance (HE *et al*., 2010). NOBILI *et al*. (2017) discovered early morphological alterations in the dopaminergic neuron-rich ventral tegmental region (VTA) in a mouse model of the disease. Additionally, there is a decline in memory function and a reduction in dopaminergic innervation to the hippocampal regions. Although the exact cause of the disease is still unknown, it is known that several factors, including genetics, sex, lipid metabolism, and aging, contribute to the disease.

By maintaining the integrity and permeability of the blood-brain barrier through a variety of processes, melatonin may function as a protective molecule against neurodegenerative illnesses brought on by aging. Melatonin is a strong antioxidant in AD (SHUKLA *et al*., 2017). Melatonin levels in saliva at night were lower in AD patients as compared to age-matched controls (WEISSOVÁ *et al*., 2016). Decreased concentrations of melatonin in the blood and cerebrospinal fluid were found in these patients (NOUS *et al*., 2021). Because of the many neuroprotective effects of melatonin and because its levels decrease with age, this indoleamine is used as a therapy to possibly slow the progression of AD (GALANO *et al*., 2013). The first study to suggest that melatonin might be helpful in the treatment of AD (BRUSCO *et al*., 1998) was performed in 79-year-old male twins. They had been diagnosed AD for eight years. The twin who received melatonin showed a significant improvement in sleep quality and a slowing of the progression of cognitive impairment.

The γ-aminobutyric acid (GABA)-ergic system may play a role in melatonin-mediated neuroprotection. Melatonin exerts anti-excitatory and sedative effects (CAUMO *et al*., 2009) and maybe could protect neurons from the deleterious effects of the Aβ peptide by activating GABAergic receptors. Melatonin may modulate $GABA_A$ receptors. The proof is that the up-regulation of GABA activity by melatonin couldn't be stopped by the melatonin receptor antagonist luzindole, but it could be stopped by the benzodiazepine antagonist flumazenil (CHENG *et al*., 2012). The studies reviewed on melatonin in AD in this paper are outlined in Table 2.

Table 2. Melatonin and Alzheimer's disease (AD).

Authors	Melatonin actions in AD
VERMA *et al*., 2021	Melatonin's positive benefits included antioxidant, anti-inflammatory, and mitochondrial protective properties, which stopped neural degeneration.
OLCESE *et al*., 2009	In a transgenic rat model of Alzheimer's, long-term melatonin administration was found to reduce β-amyloid (Aβ) accumulation in the cortex and hippocampus.
SHUKLA *et al*., 2017	Melatonin decreases Aβ-mediated oxidative stress and lipid peroxidase.

Table 2. continued

OLCESE *et al*., 2009	Melatonin regulates the level of mRNA for the antioxidant enzymes superoxide dismutase (SOD-1), glutathione peroxidase, and catalase in the brains of transgenic AD mice.
WADE *et al*., 2014	They confirmed an improvement in sleep quality in AD patients who received melatonin compared to those who received a placebo. This study also showed a positive effect of melatonin on cognitive functions and behavior in AD patients after 4 weeks of melatonin administration.
COMAI and GOBBI, 2014	Melatonin is linked to memory and regulates memory development by affecting hippocampus neurons.
WADE *et al*., 2007	Documented better performance in neuropsychological tests and depressive symptoms as well as sleep quality in 61 individuals with mild cognitive impairment treated for up to 15-60 months with 3–24 mg/day of melatonin.

MELATONIN IN PARKINSON'S DISEASE (PD)

Parkinson's disease (PD), the second most common neurological condition, affects 1-4% of individuals over 60 years of age (TYSNES and STORSTEIN, 2017). Age is the biggest risk factor for the beginning and development of PD, just like it is for AD (HINDLE, 2010). Loss of dopamine in the substantia nigra, which results in striatal dopamine depletion, is a hallmark of Parkinson's disease (PD). This neuronal loss disrupts coordinated motor movements, giving the impression of rigidity, tremor, bradykinesia, and postural instability (MAGUIRE-ZEISS and FEDEROFF, 2010). In the substantia nigra of PD patients, high levels of lipid peroxidation and increased monoamine oxidase activity, along with decreased glutathione levels, were observed. Patients with PD also experience sensory and sleep problems. The correlation between oxidative stress and age-related PD is becoming more and more clear. In the substantia nigra of PD animal models, melatonin therapy increases in catalase and superoxide dismutase levels (SARAVANAN *et al*., 2007).

Melatonin, a powerful antioxidant, can improve the prognosis of Parkinson's disease by controlling oxidative stress. In addition, the earlier study discovered a connection between the motor symptoms of PD and the amount of melatonin in the CSF (LESTON *et al*., 2009). In the substantia nigra of patients with PD, MT1 and MT2 receptor expression was diminished (ADI *et al*., 2010), and this decrease is associated with sleep disturbances. There are few clinical studies on the use of melatonin for the treatment of PD symptoms, and most of them have focused on its use in the treatment of sleep disorders.

The pilot study with melatonin (DOWLING *et al*., 2003) included eight PD patients who showed insignificant improvement in sleep quality after receiving 5 mg of melatonin for 1 week. Following this study, two more trials were conducted to test whether longer treatment or a higher dose of melatonin had a stronger effect on sleep disturbances in PD patients. In the first study, the effects of daily treatment with 5 or 50 mg of melatonin for two weeks were investigated in 40 patients with PD who had sleep disturbances (DOWLING *et al*., 2005). This study confirmed an improvement in sleep quality in PD patients receiving 50 mg of melatonin compared to those receiving 5 mg. In another study, the effect of melatonin administered for 24 days at a dose of 3 mg was investigated in 18 patients with PD (MEDEIROS *et al*., 2007). The results showed a significant improvement in sleep quality. A recent study (DATIEVA *et al*., 2013) confirmed that the administration of 3 mg of melatonin for 6 weeks improves the quality of sleep in patients with PD. These findings are significant because they indicate the role of the melatoninergic system in the pathophysiology of Parkinson's disease in people.

MELATONIN AND CARDIOVASCULAR SYSTEM

The pathogenesis of cardiovascular disorders such as myocardial infarction, cardiac hypertrophy, cardiac arrhythmias, atherosclerosis, ischemia/reperfusion injury, stroke, and other age-related pathologies have also been linked to a lack of endogenous melatonin (MOCAYAR MARÓN *et al*., 2020; OZKALAYCI *et al*., 2021). Melatonin receptors were found in vascular tissue by VISWANATHAN *et al*. (1990). Melatonin has well-known effects on the cardiovascular system (CVS). Many studies have focused on how melatonin affects cardiac muscle in the context of a variety of disorders, including sepsis, muscular dystrophy, and even heart transplantation; in all of these situations, melatonin administration had beneficial effects. Numerous studies have demonstrated the circadian fluctuation of catecholamine levels and blood pressure (BP). Patients with hypertension were found to have decreased serum melatonin levels (ZEMAN *et al*., 2005). Pinealectomized rats lacking circulating melatonin develop hypertension, but melatonin supplementation either reverses or eliminates this effect. Some studies addressing melatonin action in the cardiovascular system are listed in Table 3.
Melatonin has two main mechanisms of action: it acts centrally in the hypothalamic paraventricular nucleus, likely decreasing the outputs of the sympathetic and hypothalamic-pituitary-adrenal axis, and it acts peripherally on the heart, kidney, and directly on blood vessels to mediate vasoconstriction and vasodilation (SIMKO *et al*., 2016). The vasoregulatory action of melatonin is complicated since it has both a vasodilatory and a vasoconstrictive effect via the MT2 and MT1 receptors. Vasoconstriction is accomplished by inhibiting cAMP-mediated phosphorylation of calcium-activating potassium channels (BK_{Ca}), which is carried out by Gi/Go protein-coupled MT1 melatonin receptors found in smooth muscles (DUBOCOVICH and MARKOWSKA, 2005).

In both humans and animals, melatonin has the power to regulate the heart rate variability that is regulated by the sympathetic nervous system. Melatonin may protect against cardiovascular diseases as well as mood disorders associated with overexpression of sympaticus, such as anxiety, because it lowers heart rate variability, suggesting the sympatholytic character of this hormone. According to collected experimental and clinical evidence, melatonin is important in human cardiovascular deseases such as ischemia/reperfusion injury, hypertension, and vascular disorders (SUN *et al*., 2016). Not only the heart but also the liver (KANG and LEE, 2012) and kidney (CETIN *et al*., 2014) are profoundly protected against ischemia-reperfusion injury by melatonin.

Discoveries by HAN *et al*. (2019) include that both MT1 and MT2 subtypes were found in the myocardium, although MT2 is upregulated in response to myocardial ischemia/reperfusion injury (MI/R), and melatonin reduced the size of infarcts after MI/R by blocking the pathways that lead to oxidative and nitrative stress and mitochondrial apoptosis.
Aging is a risk factor for the development of cardiac arrhythmias, and because melatonin is a potential anti-aging drug, this indoleamine can also be regarded as an antiarrhythmic molecule (SEGOVIA-ROLDAN *et al*., 2021). Treatment with melatonin in aged mice not only maintained their normal cardiomyocyte function and increased their number but also lowered levels of β-myosin heavy chain expression (a sign of cardiac hypertrophy). Additionally, melatonin promotes the renewal of mitochondrial function, reduces apoptosis, and suppresses proinflammatory cytokines, including IL-1 and IL-6 (SAYED *et al*., 2021). Activation of NADPH oxidase by angiotensin II causes DNA damage and accelerates aging and age-related diseases, in particular cardiovascular illnesses. Through the activation of the mitochondrial calcium uptake 1 pathway, which prevents mitochondrial calcium overload that may lead to enhanced formation of damaging ROS, melatonin may facilitate oxidative stress caused by angiotensin II (SEHIRLI *et al*., 2021).

Table 3. Melatonin and cardiovascular system.

Authors	Melatonin actions in cardiovascular system
TENGATTINI *et al*., 2008	Melatonin regulates blood pressure (BP), helping it drop during the night, and has an antifibrotic impact on the left ventricle.
BORGHI and CICERO, 2017	Exogenous melatonin treatment lowers BP in patients with hypertension as well as those with normotension. In this meta-analysis, melatonin supplementation was found to lower both nocturnal systolic and diastolic BP.
REXHAJ *et al*., 2015	Researchers believe that melatonin can stop the methylation of endothelial nitric oxide synthase and cause vasodilatation.
GUBIN *et al*., 2016	Administration of 1.5 mg of melatonin before bedtime for two weeks resulted in a decrease in systolic and diastolic blood pressure as well as a reduction in heart rate between three and eight in the morning, which is when cardiovascular risk is at its maximum.
GREEN *et al*., 2014	Two hours after melatonin administration, the standing heart rate was considerably lower in the 78 individuals with postural tachycardia syndrome who participated in this study.
YEUNG *et al*., 2015	Melatonin treatment for four weeks modifies calcium homeostasis and alleviates the levels of oxidative stress and the expression of inflammatory mediators in rats with chronic heart failure caused by hypoxia.
SIMKO *et al*., 2014	Results in this study showed that melatonin partially prevented the beta-tubulin change in the left ventricle and reduced the levels of oxidative stress, total collagen, and insoluble collagen. Most notably, melatonin increased the average survival time.
STEFANOVIC *et al*., 2021	This study showed that melatonin treatment has advantages such as enhanced uptake and decreased degradation of catecholamines in an animal model of depression. These results were likely a compensation mechanism that shields cardiomyocytes from the harmful effects of noradrenaline overstimulation.
YANG *et al*., 2013 AN *et al*., 2016	The stimulation of the Janus kinase 2/signal transducers and activators of transcription 3 (JAK2/STAT3) signaling and the phosphatidylinositol 3-kinase (PI3K)/serine-threonine kinase (Akt) signaling by melatonin treatment significantly reduces apoptosis and the infarct size in cardiac ischemia-reperfusion injury.
VAZAN and RAVINGEROVA, 2015	This article examines melatonin's protective properties against epinephrine-induced myocardial injury. Findings indicated proof that melatonin directly protects the ability of the myocardium to contract and relax, exerting anti-adrenergic effects in the heart.

RADIOPROTECTION BY MELATONIN

Among the many substances that have passed preclinical testing as radioprotectors, melatonin is particularly effective because it diminishes the effects of ionizing radiation (IR) both *in vitro* and *in vivo* (ZETNER *et al*., 2016). It has been reported in multiple studies that melatonin lessens the effects of IR on the liver (EL-MISSIRY *et al*., 2007) spleen (SHARMA *et al*., 2010), and lens (KARSLIOĞLU *et al*., 2005) among other organs. Melatonin may be a useful drug to lessen the damage caused by IR because of its capacity to enter the nucleus, accumulate there, and scavenge hydroxyl radicals. The characteristics of studies dealing with the role of melatonin in radioprotection are described in Table 4.

Table 4. Radioprotection by melatonin.

Authors	Melatonin in radioprotection
ESMAELY *et al*., 2020	The article demonstrated that ingestion of melatonin 1 or 2 hours before ionizing radiation (IR) is useful for radioprotecting human cells (lymphocytes) against IR-induced DNA damage. These findings imply that patients should take 100 mg of melatonin before being exposed to IR in radiography.
ABDULLAEV *et al*., 2021	This study has proven that melatonin activates the expression of genes encoding DNA repair enzymes and antioxidant enzymes but suppresses the activity of pro-oxidant enzymes in the spleen and cerebral cortex of irradiated mice.
LIU *et al*., 2012	In the mouse brain, the neuroprotective mechanism of melatonin against carbon ion-induced cell apoptosis was assessed by the authors. The outcomes showed that melatonin significantly reduces the oxidation of proteins and lipids brought on by carbon ion radiation. Also, melatonin blocks the mitochondrial apoptotic signaling cascade, which has positive neuroprotective effects against carbon ion-induced brain injury in mice.
MANDA *et al*., 2008	Those authors investigated the protective effects of melatonin pretreatment against high-energy ^{56}Fe-induced oxidative modification of biomolecules as well as histological alterations in the cerebellum. They also concluded that melatonin protects against oxidative damage caused by radiation by significantly decreasing the number of necrotic Purkinje cells and apoptotic granule cells.

Another important consideration for space missions beyond Earth's orbit is the effect of cosmic radiation on astronauts (CHANCELLOR *et al*., 2014). The analysis of data from numerous studies has been supported by the fact that melatonin could be used to protect astronauts from intense cosmic radiation (LIU and REITER, 2019). Cosmological irradiation may have a variety of negative effects, including a reduction in the immune system (LAIAKIS *et al*., 2021), degenerative effects, and even neurological issues. Melatonin appears to have a bright future as a neuroprotective drug against space radiation. Melatonin protects the nuclear genome in a variety of ways (GALANO *et al*., 2018). Mitochondrial dysfunction is the cause of elevated oxidative stress in the cells of irradiated mammals (YOSHIDA *et al*., 2012). In addition, there is a marked decline in antioxidant activity in the blood and tissues of the irradiated rodents (SUN *et al*., 2021). Because mitochondria use oxygen to produce energy, the brain has many of them (FEDERICO *et al*., 2012). Mitochondria are one of the main producers of ROS. Furthermore, when melatonin is given, mitochondria actively produce and absorb it, according to the newest research (HUO *et al*., 2017; ACUÑA-CASTROVIEJO *et al*., 2018). An antioxidant such as melatonin that targets mitochondria can control mitophagy and

mitochondrial dynamics to preserve mitochondrial homeostasis in mice exposed to carbon ion radiation (REITER *et al*., 2017). Melatonin is frequently used as an adjuvant for radiotherapy and radiomitigative effects (MOLOUDIZARGARI *et al*., 2021).

In regard to the space radiation risks, those outcomes offer a promising perspective for the neuroprotective tactics of melatonin.

MELATONIN AND REPRODUCTION

A complex and bidirectional relationship exists between melatonin and sex steroids, particularly estrogen (CIPOLLA-NETO *et al*., 2022). In males, melatonin controls the release of testosterone and improves the reactivity of Sertoli cells to FSH during testicular development. MT1 and MT2 receptors are also present in the rat ovary. WANG *et al*. (2012a) clarify that melatonin may preserve follicular health by preventing granulosa cells from undergoing apoptosis, which is crucial for the ability of granulosa cells to interact with oocytes (UYAR *et al*., 2013).

Melatonin and its metabolites, which are potent antioxidants, may lead to enhanced fertilization through improved male and female fertility as well as improved sperm and oocyte quality (SOLEIMANI RAD *et al*., 2013; 2015; KRATZ *et al*., 2016; KRATZ and PIWOWAR, 2017). Aging is one of the main causes of declining fertility and oocyte quality in women, and melatonin may help with infertility in older adults and enhance the results of *in vitro* fertilization treatments (OLCESE, 2020). In addition, the clinical link between melatonin and sex steroid hormones is particularly significant when utilizing melatonin during the menopausal transition and beyond. Studies related to the effects of melatonin on reproduction are listed in Table 5.

Table 5. Melatonin and reproduction

Authors	Melatonin actions in reproduction
COS *et al*., 2008 GONZALEZ *et al*., 2008	It is suggested that melatonin can act as a selective regulator of the estrogen enzyme. Results in those studies indicate that women's reproductive hormones respond to external melatonin treatment.
CAIN *et al*., 2010	Although both sexes showed equal sleep time, in this study, women showed a considerably larger amplitude of melatonin synthesis when melatonin was measured in plasma from 28 women and men (10–30 years old).
FRUNGIERI *et al*., 2017	Melatonin plays a part in cellular growth, proliferation, and the secretory activity of testicular cells. Those authors also reported the expression of MT1 and MT2 receptors in rat and bovine Sertoli cells, which improves spermatogenesis efficiency and fertility.
CIPOLLA-NETO *et al*., 2022	Melatonin affects spermatogenesis and modulates the physiology of Sertoli cells through a variety of transduction pathways.
WANG *et al*., 2012a	Melatonin itself controls the expression of the MT1 and MT2 receptors in the granulosa cells of the bovine gonad.
ROMEU *et al*., 2011 MAGANHIN *et al*., 2013	Propose that melatonin contributes to the preservation of appropriate follicular morphology because of its essential role in ovulation.

Table 5. continued

XIAO *et al*., 2019	Melatonin and estrogens work together to support angiogenesis and follicular growth. This observation could clarify the reason behind the three-fold increase in melatonin concentration in follicles compared to circulation levels.
REITER *et al*.**,** 2014	This study investigated the clinical relevance of melatonin in ovarian and placental physiology, and results showed that ovarian follicular cells, placental cytotrophoblasts, and oocytes are the sites of melatonin synthesis. Increases in prenatal melatonin production may be linked to better outcomes in cases of intrauterine growth restriction, hypertension, preeclampsia, and eclampsia, conditions that lower maternal melatonin levels.
MOTTA-TEIXEIRA *et al*., 2018	Pregnancy-related low melatonin levels can have negative effects on the mother as well as the growth of the fetus, energy metabolism, cognition, and behavior later in life.
TAGLIAFERRI *et al*., 2018	In a study with 40 women of normal weight who have polycystic ovarian syndrome (PCOS), melatonin treatment for six months caused significant changes in sex hormones. Measures of insulin or glucose were unchanged, while androgens, testosterone, hydroxyprogesterone, anti-Mullerian hormone, and low-density lipoprotein all showed significant declines. Irregular menstruation decreased in 95 percent of the women. Melatonin directly affects the ovaries, which is the cause of this outcome.
ALIZADEH *et al*., 2021	Eighty-four PCOS individuals were given a placebo, melatonin, magnesium, or melatonin plus magnesium throughout an eight-week experiment. Melatonin produced notable improvements in sleep and serum cholesterol.
LI *et al*., 2022	For twelve weeks, fifty-eight women (aged 18 to 40) participated in a randomized, double-blind, placebo-controlled study in which they were given a placebo or 10 mg of melatonin an hour before bed. Results showed enhanced subjective sleep quality, decreased serum insulin, total cholesterol, and LDL-cholesterol, and increased quantitative insulin sensitivity.
BELLIPANNI *et al*., 2005	Melatonin treatment dramatically altered the levels of reproductive hormones (Follicle-stimulating hormone (FSH) and Luteinizing hormone (LH) in menopausal women and diminished climacteric symptoms.
CHOJNACKI *et al*., 2018	This study also confirmed that melatonin treatment reduced climacteric symptoms in postmenopausal women, such as sleep, mood, and vasomotor dysfunctions.

MELATONIN AND MESENCHYMAL STEM CELL DIFFERENTIATION

Stem cells have the property of unlimited proliferation. There are two types of stem cells: embryonic stem cells (ESC), which are found in embryonic organisms, and somatic stem cells (SSC), which are found in adults. Both cell types can differentiate into different specialized cells and may form tissues. Any type of adult cell can be produced by totipotent and pluripotent stem cells, but multipotent and oligopotent cells have limited potential for

differentiation. Totipotent stem cells (SC) are produced from the union of gametes and create embryonic cells, whereas pluripotent stem cells are embryonic cells obtained from the blastocyst or the inner cell mass of the embryo. Those cells create tissue from all three germ layers (endoderm, mesoderm, and ectoderm). Multipotent SC plays a significant role in regeneration processes as well as immunoregulatory and homeostatic systems. They are present in practically all tissues of an adult organism and originate from a single germ layer (KOLIOS and MOODLEY, 2013). Mesenchymal stem cells (MSC) belong to this cell type. They can differentiate into adipose tissue, bone, and cartilage. Oligopotent stem cells (SC) develop into the final, differentiated cells of a particular tissue. MSC were originally called colony-forming unit fibroblasts (CFU-Fs). Friedenstein and colleagues initially described them in the 1970s (FRIEDENSTEIN *et al*., 1970). These fibroblast-like cells, after ex vivo isolation, formed colonies in culture conditions and differentiated in vitro into various tissues like bone, cartilage, and adipose tissue. The simple taxonomy criterion for MSC is the tissue source. MSCs almost exist in all adult tissues. An excellent source of MSCs besides bone marrow is adipose tissue. It is less invasive to obtain MSCs from adipose tissue than to obtain them from bone marrow.

The International Society for Cellular Therapy defined some features that MSC needs to satisfy. Those criteria are: a) plastic adherence in typical culture conditions; b) expression of specific markers like CD105, CD90, and CD73 but also lack of expression for CD34, CD45, CD14, CD79a, and HLA-DR; and the most important is differentiation into adipocytes, chondrocytes, and osteocytes after in vitro stimulation. MSCs are fantastic scientific tools that are easily identified, cultivated, and controlled for differentiation and therapeutic applications. The primary regulator of MSC development into the osteogenic or chondrogenic lineage is Wnt/b-catenin signaling, which is characterized by relatively high or low Wnt activity, respectively (TAIPALEENMAKI *et al*., 2011). On the other hand, adipogenic differentiation is accelerated in the absence of Wnt signaling.

Differentiation is a complex process during which, under the influence of various external stimuli, there is a temporally organized activation of specific transcription factors that regulate the expression of certain genes and thus define the phenotype of differentiated cells. Various harmful factors *in vitro* and *in vivo* often interfere with the differentiation process of MSCs.

During osteogenic differentiation, the transcription factor Runx2/Cbfa1 (runt-related transcription factor 2, i.e., core-binding factor subunit alpha 1) is activated, which is considered crucial for osteogenic differentiation because it activates osteo-specific genes: Osterix, collagen type I alpha 1 chain, and osteocalcin. Runx2/Cbfa1 is therefore considered an early marker of osteogenic differentiation (VATER *et al*., 2011). Among other early markers of osteogenic differentiation is the enzyme alkaline phosphatase (ALP). Osteocalcin and osteopontin are considered late markers of osteogenic differentiation, as well as accumulated calcium, which can be detected by various staining methods (alizarin red, von Kossa).

The main factors added to the medium for adipogenic differentiation of MSCs in vitro are dexamethasone, insulin, and 3-isobutyl-1-methylxanthine (IBMX). The transcription factor PPAR-γ2 (peroxisome proliferator-activated receptor-γ2) is one of the key factors in the activation of genes responsible for the induction and progression of adipogenesis and, together with lipoprotein lipase and collagen type VI alpha 2 chain, is used as an early marker of adipogenic differentiation. Leptin, FABP4 (fatty acid-binding protein 4), and adiponectin can be used as late markers of adipogenic differentiation. Chondrogenic differentiation is characterized by the expression of the transcription factor Sox-9 (SRY-related high-mobility group 9), which controls the expression of genes for collagen types II, IX, X, and XI, as well as aggrecan. Key factors for in vitro chondrogenic differentiation are dexamethasone, ascorbic acid, and transforming growth factor-β (TGF-β) (VATER *et al*., 2011). Chondrogenic

differentiation can also be demonstrated by staining cell or tissue preparations with dyes that bind to glycosaminoglycans, such as safranin and fast green.

Melatonin is a hormone that may regulate MSC differentiation and function. Melatonin suppresses PPAR-γ2 expression and increases Runx2, which promotes osteogenesis and inhibits adipogenesis (ZHANG *et al*., 2010). The role of melatonin in the control of adipogenesis may also have an important role in the pathophysiology of insulin resistance and type 2 diabetes. Zucker diabetic fatty rats are a model of obesity-related type 2 diabetes. In the study by JIMENEZ-ARANDA *et al*. (2013), it is described how melatonin reduces obesity. The findings of FARIA *et al*. (2013) demonstrate that MT1/MT2-dependent hypothalamic Akt activation initiates a brain-liver communication that is activated by melatonin, which in turn suppresses hepatic gluconeogenesis via peripheral muscarinic receptors. This is the proof that this neurohormone has control over adipocyte metabolism. The onset of obesity is associated with alterations in circadian systems and sleep, which are influenced by melatonin (LAPOSKY *et al*., 2008). The decreased concentration of melatonin at night increases the risk of obesity and diabetes (BARCLAY *et al*., 2012). In the study of TAN *et al*. (2011), it is demonstrated that the physiology of BAT is regulated by melatonin, which not only increases the recruitment of brown adipocytes but also elevates their metabolic activity in mammals.

The role of melatonin on MSC during osteogenic differentiation was described by RADIO *et al*., (2006), who showed that this indolamine, added to osteogenic medium, significantly increased ALP, a biomarker for osteoblast differentiation. According to the authors, it is most likely that melatonin accomplishes these effects through its MT2 receptors. LIU *et al*. (2012) reported a stimulative effect of melatonin on osteogenic differentiation of MSC. In this study, melatonin reduces the generation of reactive oxygen species (ROS) through improved expression of antioxidant enzymes (CuZnSOD and MnSOD) and decreased expression of Bax (LIU *et al*., 2013).

GO *et al*. (2008) investigated how melatonin influences the chondrogenic differentiation of MSCs. Cells during chondrogenic differentiation were induced via melatonin added to the chondrogenic medium. Examinations of glycosaminoglycan, collagen isotypes II and X, and genes involved in chondrogen differentiation such as aggrecan and Sox-9 were enhanced by melatonin treatment.

In conclusion, melatonin improves the cell survival of MSCs through its receptors expressed on their surface, suggesting that this neurohormone plays a protective role for MSCs. MSCs have invaluable therapeutic potential in experimental models of ventricular remodeling during myocardial infarction and experimental models of CNS injury, including traumatic brain injury (GNECCHI and MELO, 2009; ZHANG *et al*., 2013a).

According to numerous lines of research, melatonin may be very important in encouraging osteogenic differentiation in human bone cells, osteoblasts, and bone marrow stem cells (BMSCs) (ZHANG *et al*., 2013b). It has been shown that melatonin supplements improve bone mineral density (BMD) in postmenopausal women with osteopenia (KOTLARCZYK *et al*., 2012) and restore bone marker turnover equilibrium in perimenopausal women (AMSTRUP *et al*., 2015).

Melatonin has an osteoinductive effect by encouraging human adult mesenchymal stem cells to mature into osteogenic cells and articular chondrocytes to produce cartilage matrix (PEI *et al*., 2011). A study by YANG *et al*. (2017) examined melatonin's pharmacological effects to counteract the iron overload-induced dysfunction of BMSCs. According to the findings of this study, melatonin could reverse the senescence that an overload of iron causes in BMSCs by preventing ROS accumulation and activating p53/ERK/p38, as well as reverse the suppression of proliferation and osteogenic differentiation brought on by iron overload.

Human neural stem cell (NSC) transplantation has recently been suggested as a new treatment for neurodegenerative diseases (FORTIN *et al*., 2016). NSCs have the ability to

differentiate into oligodendrocytes, neurons, and astrocytes (JACKSON and ALVAREZ-BUYLLA, 2008). In the adult brain, NSCs are located in the subventricular zone (SVZ) and subgranular zone (SGZ) of the dentate gyrus of the hippocampus (QIN *et al*., 2015). Since NSCs in the SVZ are continuously participating in neurogenesis (LIM and ALVAREZ-BUYLLA, 2016), NSC-based therapy is thought to be a promising therapeutic strategy for preserving and regenerating injured neurons (MARTINO *et al*., 2011). Melatonin enhances SVZ-NSC neurogenesis by upregulating the expression of mature neuron markers such as TH and β-III-tubulin (SHARMA *et al*., 2008; KONG *et al*., 2008; SOTTHIBUNDHU *et al*., 2010). The experiments by MENDIVIL-PEREZ *et al*. (2017) investigate the effects of melatonin on the proliferation and differentiation of NSCs generated from the SVZ of adult mice and attempt to ascertain if these effects are dependent on mitochondrial activity. They also investigated how melatonin-treated NSCs affected tissue regeneration in PD and AD mouse models. They suggest that therapy with the transplant of NSCs pretreated with therapeutic doses of melatonin might, depending on the effect of mitochondria, successfully restore neuronal populations in patients with PD and AD.

CONCLUSION

The right comprehension of melatonin's physiological and clinical impacts is difficult since many factors need to be taken into account and properly perceived for its functional properties to be appropriately understood in any system or function under examination. It is important to remember that melatonin physiology is integrative per se and depends on the ontogenetic, daily, and seasonal history of its secretion profile, as well as on its broad range of actions and outcomes. Pineal melatonin is a hormone that works at practically all levels of the physiology of the organism because of its unique properties. Early in 2018, a review of the literature revealed that melatonin has been utilized in between 3000 and 4000 clinical research studies. The general opinion is that melatonin is a safe medicine for clinical therapies because it has no hazardous adverse effects. It is essential for the endocrine and neural sciences to define clinical syndromes involving changes in melatonin production, such as those previously described. The clinical usage of melatonin for therapeutic purposes must be discussed, and established guidelines must be developed. Undoubtedly, one of the objectives of this review was to strongly encourage greater research into the role of melatonin in the prevention and treatment of illnesses in both humans and animals.

Acknowledgments

This work was supported by the Ministry for Science and Technological Development of the Republic of Serbia (451-03-66/2024-03/200017).

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