



REVIEW ON MELATONIN IS A NOVEL MOLECULE FOR MANAGEMENT OF VARIOUS DISORDERS

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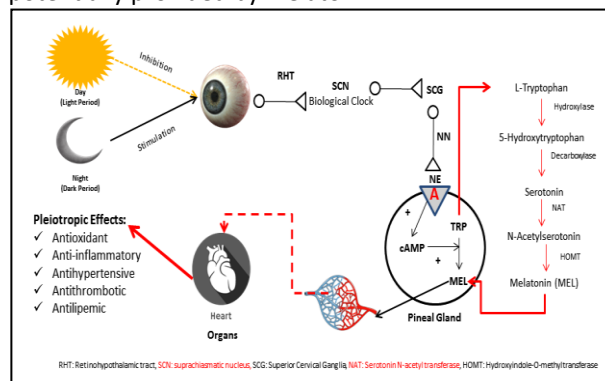
Melatonin is N-acetyl-5-methoxytryptamine and is an indoleamine. It is synthesized in the pineal gland by the conversion of tryptophan to serotonin, which is acetylated by N-acetyltransferase (NAT) to N-acetylserotonin. N-acetylserotonin is subsequently converted to melatonin by the enzyme hydroxyindole-O-methyltransferase. Melatonin receptors are G-protein coupled receptors and mainly classified into MT₁ (Mel1a) and MT₂ (Mel1b). Melatonin is an ubiquitous molecule, which has been found not only in the human pineal gland but also in vegetables and their fruits and seeds, medicinal herbs, and fermented products such as Piper nigrum, cherry, Kiwifruit, grapes, walnut, etc. In the present research we review the beneficial effect of Melatonin for management of various disorders on basis literature survey available on PubMed, science direct, magazine, e-journal, etc. From the review it conclude that the melatonin has been assessed as a treatment of ocular diseases, blood diseases, gastrointestinal tract diseases, cardiovascular diseases, diabetes, rheumatoid arthritis, fibromyalgia, chronic fatigue syndrome, infectious diseases, neurological diseases, sleep disturbances, aging and depression. Melatonin has been also used as a complementary treatment in anaesthesia, hemodialysis, in vitro fertilization and neonatal care. In the future, analogues of melatonin may be of value in treating various chronic disorders.

Keywords: Melatonin, N-acetylserotonin, Piper nigrum, Diabetes, Depression, Hemodialysis**Introduction**

Melatonin is N-acetyl-5-methoxytryptamine and is an indoleamine^{1, 2}. It is synthesized in the pineal gland by the conversion of tryptophan to serotonin, which is acetylated by N-acetyltransferase (NAT) to N-acetylserotonin. N-acetylserotonin is subsequently converted to melatonin by the enzyme hydroxyindole-O-methyltransferase. The pineal hormone production is dependent on the light-dark cycle because of circadian changes in the activity of NAT, the pineal rate limiting enzyme³ (Figure 01).

The melatonin effects are mediated by the specific high affinity receptors localized in plasma membranes and coupled to guanosine triphosphate-glutaryl transpeptidase-binding proteins⁴. Furthermore, investigations of the ovine pars tuberalis demonstrated that melatonin receptors couple both to pertussis-toxin-sensitive and cholera-toxin sensitive components, which are involved in the inhibition of cAMP, mediated by the melatonin receptors⁷. Recently, cloning of several G-protein-coupled melatonin receptors has revealed that three melatonin receptor subtypes exist^{8, 9, 10, 11}. It has also been demonstrated that melatonin effects are

mediated through specific nuclear receptors (orphan ROR-RZR receptors) and in some cases melatonin can act without receptors, too^{12, 13}. A significant factor of endogenous melatonin availability is the age. It has been reported that aging is associated with progressive reduction of circadian melatonin synthesis in pineal gland. Equally, the onset of many degenerative and proliferative diseases is associated with aging; what remains unclear is whether the increase of these diseases is related to reduce antioxidant protection potentially provided by melatonin¹⁴.

**Figure 1:** Synthesis of Melatonin in Pineal Gland^{4, 5}

Melatonin influences circadian and seasonal behavior and physiology^{15, 16, 17}. The nocturnal release of melatonin alters the timing of mammalian circadian rhythms and regulates reproductive changes in response to deviations in day length in seasonally breeding mammals¹⁸. The efficacy of melatonin has been assessed as a treatment of ocular diseases, blood diseases, gastrointestinal tract diseases, cardiovascular diseases, diabetes, rheumatoid arthritis, fibromyalgia, chronic fatigue syndrome, infectious diseases, neurological diseases, sleep disturbances, aging and depression. Melatonin has been also used as a complementary treatment in anaesthesia, hemodialysis, in vitro fertilization and neonatal care^{19,20}.

Biosynthesis of melatonin:

There are four enzymes involved in melatonin synthesis from its amino acid precursor, tryptophan: tryptophan hydroxylase, dopa-decarboxylase, arylalkylamine-N-acetyltransferase, and hydroxyindole-O-methyltransferase. Tryptophan (Trp), taken up from the bloodstream, is the synthetic precursor of all the pineal 5-methoxyindoles. Trp is metabolized into 5-hydroxy-Trp (5-HTP) in the pineal mitochondria by Trp-hydroxylase²¹. The reaction, which occurs in the presence of molecular oxygen, requires (6R)-tetrahydrobiopterin as a cofactor²². Tryptophan hydroxylase (TPH) initiates the melatonin biosynthetic pathway, and it is regarded as the rate-limiting enzyme in serotonin (5-HT) synthesis²³. The second enzyme in the melatonin biosynthetic pathway, dopa decarboxylase, or aromatic L-amino acid decarboxylate (AADC), it is present in large quantities in the cytosolic fraction of the pinealocytes. It is not a limiting factor for decarboxylates the product of TPH (5-hydroxytryptophan) to synthesize 5-hydroxytryptamine (5-HT), serotonin²⁴.

Arylalkylamine-N-acetyltransferase (AANAT) or 5-HT-N-acetyltransferase is highly localized in the pineal gland and converts serotonin into N-acetylserotonin (NAS), the rate-limiting step in melatonin synthesis. It is this enzyme which controls the circadian rhythm of melatonin production by the pineal gland²².

In all vertebrates, enzyme activity is highest at night time and activity decreases very rapidly upon exposure to light. Rhythms in the mammalian pineal gland are set by afferent information derived from the endogenous clock in the hypothalamic suprachiasmatic nucleus (SCN)²⁵. Acetylserotonin O-methyltransferase is the last enzyme of the melatonin biosynthesis pathway, catalyzing the transfer of a methyl group from S-adenosyl-L-methionine onto N-acetyl-serotonin, to produce melatonin from N-acetylserotonin (NAS)^{21, 22, 26}.

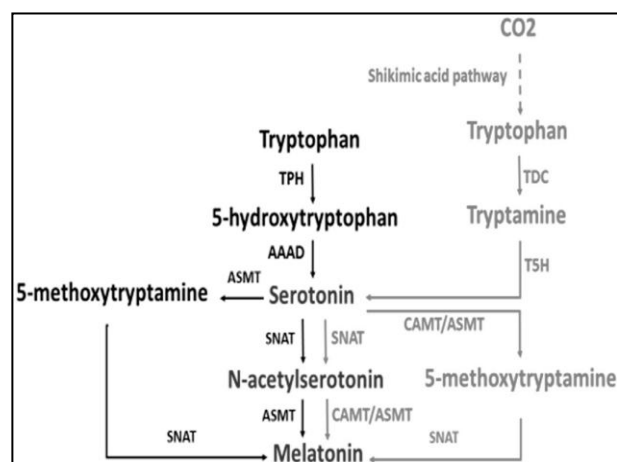


Figure 2: A comparison of the biosynthetic pathways of melatonin in animals and in plants. TPH: tryptophan hydroxylase; AAAD: aromatic amino acid decarboxylase; SNAT: serotonin N-acetyltransferase; ASMT: N-acetylserotonin O-methyltransferase, TDC: tryptophan decarboxylase; T5H: tryptamine 5-hydroxylase, CAMT: caffeic acid O-methyltransferase. Black occurs only in animals; green occurs only in plants; and red occurs in both animals and plants²⁷.

Melatonin receptors:

Melatonin receptors are G-protein coupled receptors and mainly classified into MT₁ (Mel_{1a}) and MT₂ (Mel_{1b}). Both melatonin receptors have a general structural motif consisting of seven transmembrane (TM)-spanning α -helical segments connected by alternating intracellular and extracellular loops, with the amino terminus located on the extracellular side and the carboxyl terminus on the intracellular side. These seven α -helical segments contain stretches of 20 to 25 predominantly hydrophobic residues that span the cell membrane²⁸.

Melatonin receptor type 1a (MT₁) receptors:

It is encoded in human chromosome #4 and consists of 351 amino acids. MT₁ receptor constitutes adenylate cyclase inhibition by binding to various G-proteins. MT₁ receptors are commonly found in human skin. During aging process and Alzheimer's disease, the expression of MT₁ receptor in suprachiasmatic nucleus (SCN) and cortex decreases. MT₁ receptors reduce the neuronal discharge rate in SCN and suppress prolactin secretion²⁹. MT₁ melatonin receptors modulate neuronal firing, arterial vasoconstriction, cell proliferation in cancer cells, and reproductive and metabolic functions³⁰. By using recombinant melatonin receptors it has been shown that the MT₁ melatonin receptor is coupled to different G proteins that mediate adenylyl cyclase inhibition and phospholipase C β activation^{31, 32}. MT₁ melatonin receptor has the following functions

- a) Inhibition neuronal firing (suprachiasmatic nucleus)
- b) Phase shift of onset of circadian rhythm of running wheel activity.
- c) Regulation of photoperiodic information.

Endogenous agonists: Melatonin

Agonist: Ramelteon, Agomelatine

Antagonist: Luzindole, PDOT, S29434

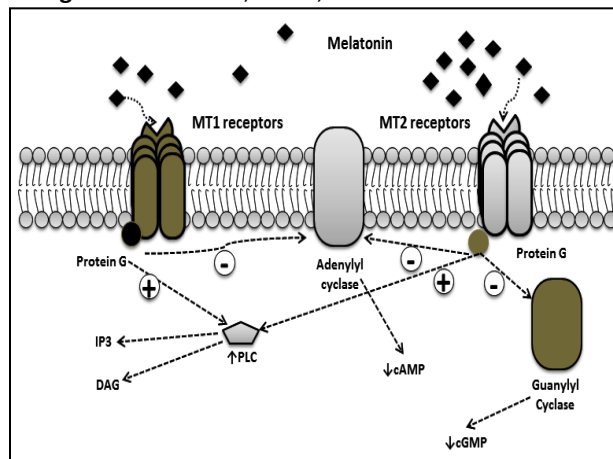


Figure 3: Mechanism of Melatonin on Melatonin receptors³³

Melatonin receptor type 1b (MT₂) receptor:

It is encoded in human chromosome #11 and consists of 363 amino acids. MT₂ receptor creates adenylate cyclase inhibition by binding to various G-proteins. Additionally, it inhibits the soluble guanylyl cyclase pathway. Through melatonin receptor activation, adenylate cyclase inhibition occurs and the production of cyclic AMP (cAMP) is reduced. In the skin, MT₂ receptors are located within normal and malign melanocytes and eccrine sweat glands. MT₂ receptors inhibit GABA-A receptor-related functions in the hippocampus in rats²⁹. Activation of MT₂ melatonin receptors phase shift circadian rhythms of neuronal firing in the suprachiasmatic nucleus, inhibit dopamine release in retina, induce vasodilation and inhibition of leukocyte rolling in arterial beds, and enhance immune responses³⁰. The MT₂ receptor is also coupled to inhibition of adenylate cyclase and additionally it inhibits the soluble guanylyl cyclase pathway³¹. MT₂ melatonin receptor has the following functions

- a) Phase shift of the peak of the circadian rhythm of neuronal firing (suprachiasmatic nucleus)
- b) Inhibition dopamine release (rabbit retina)
- c) Inhibition: insuline relase (pancreatic islets) and others.

Endogenous agonists: Melatonin

Agonists: Agomelatine, Ramelteon

Antagonist: Luzindole (Selective), PDOT, S29434

Nutritional source of melatonin:

Melatonin is an ubiquitous molecule, which has been found not only in the human pineal gland but also in vegetables and their fruits and seeds, medicinal herbs, and fermented products such as Grape berries (skin), Spanish wines, Italian wines, Extra virgin olive oil (D. O.), nuts, tomatoes, beetroots, cucumber, banana, strawberry, cherry, apple, Malus, Kiwifruit, Pineapple, Ananas, orange, grapes, walnut, pistachio, bread, cocoa powder, green coffee, mustard seeds, feverfew, St John's Wort, Piper nigrum (Family Piperaceae), B. ramiflora (Family Euphorbiaceae), S. glandiflora (Family Fabaceae), M. charantia (Family Cucurbitaceae), S. tora (Family Fabaceae), S. sesban (Family Fabaceae) beer, etc., at concentrations varying between 5 pg/g or mL to 230 µg/g or mL^{34, 35, 36, 37}.

Medicinal approaches for melatonin:

Melatonin is a hormone secreted from the pineal gland at night. Its peak levels in the dark are associated with age as well as various illnesses. Melatonin plays roles in regulating sleep-wake cycle (**figure 01**), pubertal development and seasonal adaptation, memory, control of body posture and balance. Melatonin has antinociceptive, antidepressant, anxiolytic, antineophobic (being afraid of new things) and locomotor activity-regulating effects. There are neuroprotective, anti-inflammatory, pain-modulating, blood pressure-reducing, retinal, vascular, seasonal reproductive, ovarian physiology, osteoblast differentiation, anti-tumor and antioxidant effects of melatonin²⁹. The goal of present is to review the importance of melatonin in management of various disorders.

1. Melatonin and Blood Sugar Level:

Diabetes is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. The chronic hyperglycemia of diabetes is associated with long-term damage, dysfunction, and failure of different organs, especially the eyes, kidneys, nerves, heart, and blood vessels³⁸. The current classifications for diabetes mellitus type 1–4 are described and the main features of type 1 and type 2 diabetes are compared to allow for better discrimination between these diabetes by correct biochemical diagnosis during fasting and oral glucose tolerance tests as well as the use of hemoglobin A_{1c} (HbA_{1c})³⁹. Melatonin decreases as well the levels of cholesterol, triglyceride, low density lipoprotein, sialic acid, glucose, GSH and might regulate the activities of antioxidant enzymes in diabetic disease.

Melatonin influences insulin secretion both in vivo and in vitro through the MT₁-and MT₂-receptor-mediated activity. Melatonin through the IP₃ pathway is mediated by Gq-proteins, phospholipase C and IP₃, which mobilize

Ca²⁺ from intracellular stores, with a resultant increase in insulin. Insulin secretion *in vivo*, as well as from isolated islets, exhibits a circadian rhythm. This rhythm, which is apparently generated within the islets, is influenced by melatonin, which induces a phase shift in insulin secretion. The observation of the circadian expression of clock genes in the pancreas could possibly be an indication of the generation of circadian rhythms in the pancreatic islets themselves. Melatonin influences diabetes and associated metabolic disturbances. The diabetogens, alloxan and streptozotocin, lead to selective destruction of β -cells through their accumulation in these cells, where they induce the generation of ROS. β -cells are very susceptible to oxidative stress because they possess only low antioxidative capacity. Certain results suggest that melatonin in pharmacological doses provides protection against ROS. Finally, melatonin levels in plasma, as well as the arylalkylamine-N-acetyltransferase (AANAT) activity, are lower in diabetic than in non-diabetic rats and humans. In contrast, in the pineal gland, the AANAT mRNA is increased and the insulin receptor mRNA is decreased, which indicates a close interrelationship between insulin and melatonin^{40, 41, 42, 43}.

2. Melatonin and Plasma Cholesterol:

Some studies have suggested an action of pineal gland on lipid metabolism and, administration of pineal extracts has been shown to lower the serum, hepatic, adrenal and testicular cholesterol levels. In rabbits, pineal extracts could decrease cholesterolemia, biliary cholesterol and serum phospholipids⁴⁴. Cholesterol lowering effect of melatonin has been considered a potent effect as long term melatonin administration could significantly decrease the plasma cholesterol level and prevent fatty liver in genetic hypercholesterolemic rats⁴⁵. Melatonin suspension (10 mg/kg), were administered orally to the rats fed HCD for 30 days. Melatonin significantly reduced cholesterol absorption in rats fed on HCD and caused significant decreases in total cholesterol, TG, VLDL- and LDL-cholesterol in the plasma and contents of cholesterol and TG in the liver. The level of HDL cholesterol was significantly increased after melatonin. These results suggested that inhibition of cholesterol absorption caused by melatonin could be a mechanism contributing to the positive changes in plasma cholesterol, lipoprotein profile and the lipid contents in the liver⁴⁹.

Furthermore, a melatonin agonist and antagonist stimulate or lower seasonal obesity in the garden dormouse. The role of melatonin on lipid metabolism is also suggested by the observation of delayed post prandial clearance of triacylglycerol indicating possible lipid intolerance in human subjects under simulated nine hour phase-shifts^{50, 51}. Melatonin could also prevent

hyperlipidemia caused by glucocorticoid administration in rats or by cholesterol rich feed^{45, 50}. Melatonin itself has been shown to inhibit LDL receptor activity and cholesterol synthesis in human mononuclear leucocytes indicated that melatonin also influences lipoprotein lipase activity, a key regulatory enzyme in circulating triacylglycerol in adipose tissue^{50, 51}.

3. Melatonin and antioxidant activity:

Neurodegeneration is frequently associated with damage by free radicals. However, increases in reactive oxygen and nitrogen species, which may ultimately lead to neuronal cell death, do not necessarily reflect its primary cause, but can be a consequence of otherwise induced cellular dysfunction. However, a rise in radical formation should not only be seen as a cause of further damage, but also as a possible consequence of an otherwise initiated malfunction, e.g., by neuronal or cardiac over excitation, calcium overload, ER stress, protein misfolding or reduced expression of relevant proteins which may end up in enhanced mitochondrial electron leakage. The role of mitochondria should not be misinterpreted in terms of earlier concepts, in which the generation of free radicals was directly related to damage of mitochondrial DNA (mtDNA).

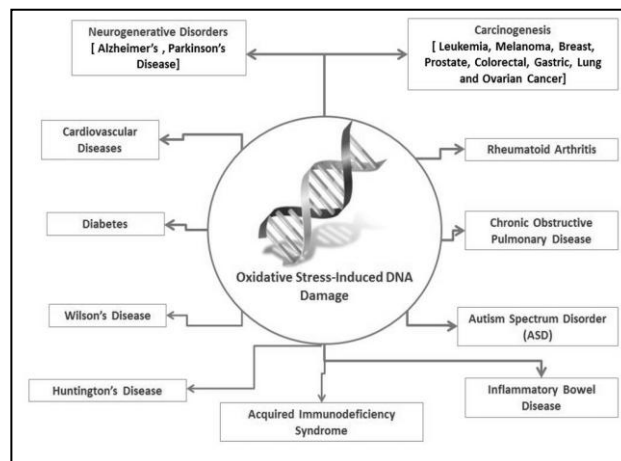


Figure 4: Disorder related to Oxidative Damage to DNA

The enhanced radical generation is that of neuronal over excitation, especially in connection with calcium overload. Glutamate toxicity can be largely explained on this basis, including the secondary rise in the formation of nitric oxide (NO). The vulnerability to calcium imbalance and excitotoxic insults via NMDA receptor activation can be greatly enhanced in a neurodegenerative disorder like Huntington's disease. Insufficiencies in cell respiration, as observed during aging, may also result from a decline in mitochondrial biogenesis⁵².

Melatonin is highly effective in reducing oxidative Damage by enzymatic dismutation of O₂, in mitochondria, it involves the stimulation of SIRT₃ by

melatonin; this leads to the deacetylation and activation of SOD. The varieties of melatonin analogues, like cyclic 3-hydroxymelatonin, N1-acetyl-N2-formyl-5-methoxykynuramine (AFMK), N1-acetyl-5-methoxykynuramine (AMK) and others, which are produced *in vivo*, also function as antioxidants. The Melatonin also protects mitochondria from elevated mitochondrial Ca^{2+} stress^{53, 54, 55}. The Melatonin have direct antioxidative protection free radical scavenging activity, and also indirect ways by inhibition of metal-induced DNA damage; protection against non-radical triggers of oxidative DNA damage, continuous protection after being metabolized, activation of antioxidative enzymes, inhibition of pro-oxidative enzymes, and boosting of the DNA repair machinery. The melatonin to exhibit multiple neutralizing actions against diverse threatening factors, together with its low toxicity and its ability to cross biological barriers, are all significant to its efficiency for preventing oxidative damage to DNA⁵⁶. Melatonin also stimulates antioxidative enzymes like superoxide dismutases (SOD), both MnSOD and CuZnSOD, catalase (CAT), glutathione peroxidase (GPx), glutathione reductase (GRd) and glucose-6-phosphate dehydrogenase (G6PD)⁵⁷. Melatonin has powerful antioxidant, anti-inflammatory and immune properties. These properties function as brain, heart, neurological, cognitive and cancer protection through the reduction of trauma from brain injury; preventing heart muscle damage; neuroprotection; increasing cognitive functioning; and offering cancer support and reducing the toxic effects of chemotherapy⁵⁸.

4. Melatonin and Cancer:

Melatonin modulates cancer initiation and progression. The processes by which melatonin may protect against cancer risk, because of its radical scavenging actions and prevents damage to nuclear DNA that results when it encounters reactive oxygen or nitrogen species. It also restrains cancer promotion by limiting the cellular uptake of a growth-promoting fatty acid, i.e., linoleic acid (LA). After its entrance into the cell, LA is converted to 13-hydroxyoctadecadienoic acid (13-HODE) which causes a series of intracellular events that culminate in cancer cell proliferation. Some of these events involve epithelial growth factor (EGF), the phosphorylation and stimulation of downstream signaling molecules, and the mitogen-activated kinases, mitogen-activated protein kinase (MEK) and Extracellular signal-regulated kinase (ERK) 1 and 2⁵⁹.

Melatonin exhibits cytotoxic activity in cancer cells. In some cancer cells melatonin lowers their invasive and metastatic status through alterations in adhesion molecules and maintenance of gap junctional intercellular communication. Biochemical and molecular

mechanisms of melatonin's oncostatic action may include regulation of estrogen receptor expression and transactivation, calcium/calmodulin activity, protein kinase C activity, cytoskeletal architecture and function, intracellular redox status, melatonin receptor-mediated signal transduction cascades, and fatty acid transport and metabolism. A major mechanism mediating melatonin's circadian stage-dependent tumor growth inhibitory action is the suppression of epidermal growth factor receptor (EGFR) / mitogen-activated protein kinase (MAPK) activity. This occurs via melatonin receptor-mediated blockade of tumor linoleic acid uptake and its conversion to 13-hydroxyoctadecadienoic acid (13-HODE) which normally activates EGFR / MAPK mitogenic signaling^{60, 61, 62, 63}.

Melatonin induces programmed cell death in a wide range of different tumors (breast, gastro-intestinal, hematological, prostate, osteosarcoma, melanoma, kidney, etc...). Melatonin in the nanomolar range activates the intrinsic and/or the extrinsic apoptotic pathway in cancer cells, namely through an increase in the p53/MDM2p ratio and down regulation of Sirt1⁶⁴. Melatonin's blockade of BMAL1 expression is associated with the decreased expression of SIRT1, a member of the Silencing Information Regulator family and a histone and protein deacetylase that inhibits the expression of DNA repair enzymes (p53, BRCA1 & 2, and Ku70) and the expression of apoptosis-associated genes. In addition to suppressing tumor initiation, melatonin can block or suppress the promotional and progressional phases of cancer development by inhibiting the uptake of linoleic acid and its conversion to 13-HODE, decreasing the mitogenic MAPK/ERK signaling pathway, suppressing/blocking the mitogenic estrogen signaling pathway, repressing ERa expression and transcriptional activity; and potentiating the transcriptional activity of the RARa, RXRa, and VDR to stimulate their growth suppressive and even apoptotic-activating mechanisms⁶⁵.

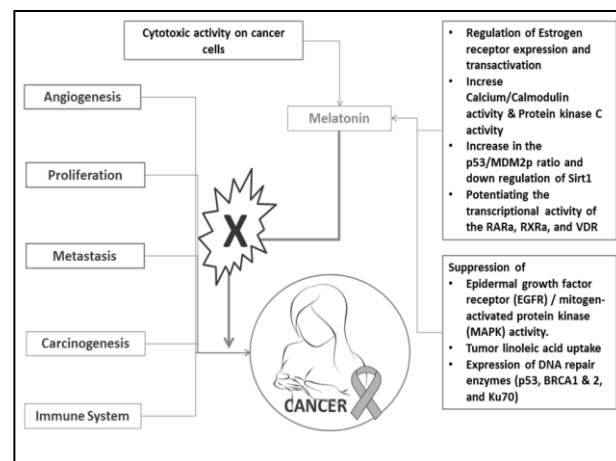


Figure 5: Role of Melatonin in cancer⁶⁶

5. Melatonin and cardiovascular disease:

Nitric oxide (NO) provides cardiovascular protection by reducing blood pressure and via its antiproliferative and antifibrotic actions. Chronic L-NAME ((NLG)-nitro-L-arginine methyl ester) administration causes hypertension and target organ damage via the inhibition of NO synthase activity reducing NO production. Moreover, L-NAME-induced deterioration of the vasodilatory function of the renal artery may trigger renin release and renin-angiotensin-aldosterone system (RAAS) activation. Melatonin in the dose of 10mg/kg bw can reverse the L-Name induced hypertension by controlling Renin release by a number of neurohumoral stimuli including sympathetic nervous system or oxidative load, both being suppressed⁶⁷. Melatonin confers profound protective effects against ischemia-reperfusion injury in various organs, including the heart, liver, and kidney through significantly reduced the level of creatine kinase-MB, by activating silent information regulator 1 (SIRT1) signaling in a receptor-dependent manner, increased expression of Cu/Zn superoxide dismutase (SOD-1) and other antioxidant enzymes, basic fibroblast growth factor, insulin-like growth factor 1, epidermal growth factor, and hepatocyte growth factor, inhibits myocardial apoptosis during myocardial ischemia-reperfusion in rats. It was shown that patients treated with melatonin (2–5 mg/day for 7–90 days) had a decrease in nocturnal SBP as well as DBP. Melatonin reduced the number and area of atheromatous plaques in a rabbit model of atherosclerosis by modulating mitogen-activated protein kinase (MAPK) pathway signal transduction. Melatonin also decreased upstream expression of extracellular signal-related kinase (ERK) and p38. Melatonin has significant effects on ischemia-reperfusion injury, myocardial CIH injury, pulmonary hypertension, hypertension, vascular diseases, valvular heart diseases, and lipid metabolism. As an inexpensive and well tolerated drug, melatonin may be a new therapeutic option for cardiovascular disease^{68, 69,70}.

In arteriosclerotic patients, the bad cholesterol which blocks arteries is oxidized to produce a more harmful product. Since melatonin is a lipid-loving molecule it can enter the bad cholesterol particles, and stop breakdown of fat molecules to prevent arteries from clogging. A recent study in living organisms showed that melatonin neutralizes free radicals, which are molecule willing to steal electrons from other molecules and cause damage to cells. This reduces the oxidative stress on cells of the heart. Melatonin increased intracellular cGMP level, PKG α expression, p-VASP/VASP ratio and further modulated myocardial Nrf-2-HO-1 and MAPK signaling. However, these effects were blunted by KT5823 (a selective inhibitor of PKG) or PKG α siRNA except that intracellular cGMP level did not changed significantly. Melatonin ameliorated diabetic MI/R injury by

modulating Nrf-2-HO-1 and MAPK signaling, thus reducing myocardial apoptosis and oxidative stress and preserving cardiac function. Importantly, melatonin membrane receptors (especially MT₂ receptor)-dependent cGMP-PKG α signaling played a critical role in this process⁷¹. Melatonin protected against CIH-induced myocardial inflammation, fibrosis, and ischemia reperfusion injury by significantly reduced the expression of inflammatory cytokines tumor necrosis factor- α (TNF- α) and IL-6, IL-12, interferon γ and markers of fibrosis [PC1 and transforming growth factor β (TGF β)]. Melatonin also increases anti-inflammatory IL-10⁷².

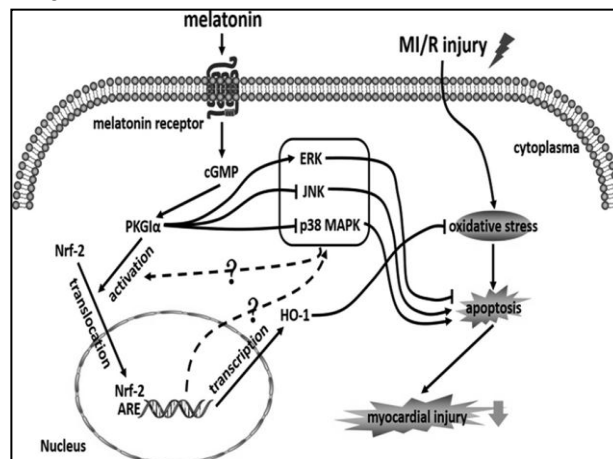


Figure 6: Mechanism of Melatonin in management of Myocardial Injury

6. Melatonin and Neuropathy Pain:

The taxane induced neuropathy is thought to be due to aggregation of intracellular microtubules in neuronal cells. It is also thought that taxanes cause intrinsic toxicity and injury to cells. Types of neuropathy caused by taxanes include peripheral neuropathy, motor weakness, myalgias, and arthralgias. About 60%–90% of patients receiving taxanes develop mild-moderate neuropathy and as many as 30% of treated patients will develop a disabling sensory neuropathy.

In Z. Nahleh et al 2010, study the Melatonin decreases peripheral nerve injury and motoneuron loss on melatonin-treated axotomized rats. Clinical studies have evaluated the role of melatonin for counteracting chemotherapy-toxicity, particularly myelosuppression and immunosuppression. Melatonin has been found to inhibit the production of free radicals, which play a part in mediating the toxicity of chemotherapy⁷³.

In a pilot study conducted by Lissoni and colleagues, 80 patients with a variety of metastatic solid tumors received chemotherapy with or without melatonin 20 mg daily. Thrombocytopenia, malaise, asthenia, stomatitis, and neuropathy were less frequent in patients treated with melatonin. The effectiveness of

chemotherapy was not altered by the addition of melatonin. In another study, 70 patients with non-small cell lung cancer using cisplatin (20 mg/m²/day intravenously for 3 days) and etoposide 100 mg/m²/day for 3 days received melatonin 20 mg daily or chemotherapy alone⁷⁴.

7. Melatonin and autism spectrum disorder (ASD):

ASD refers to a diverse range of neurodevelopmental disorders characterized by social deficits, impaired communication, and stereotyped or repetitive behaviors. Melatonin also plays a crucial role in fetal development. Melatonin can cross physiological barriers, including the blood-placenta barrier, without denaturation, and subsequently influences placental function. During pregnancy, melatonin crosses the placenta and enters the fetal circulation, conveying photoperiodic information to the fetus. Normal melatonin concentrations during pregnancy aid in neuroprotection and normal neurodevelopment of the fetus through the inhibition of excessive oxidative stress in the vulnerable central nervous system. Additionally, as the normal sleep pattern and circadian rhythm are maintained by sufficient melatonin levels, normal melatonin secretion may also influence neurodevelopment. Eventually, the well-known functions of melatonin in neuroprotection and circadian entraining may reduce the risk of ASD⁷⁵.

8. Melatonin and Convulsion:

Melatonin, at 40 and 80 mg/kg, and Agmatine, at 10 and 20 mg/kg, exerted anticonvulsant effects. The anticonvulsant effect of Melatonin (40 and 80 mg/kg) was prevented by luzindole (2.5 mg/kg) ($P < 0.001$) but not prazosin (0.5 mg/kg), indicating the possible involvement of ML1/2 receptors in the anticonvulsant effect of melatonin. In conclusion, melatonin and Agmatine exhibit an additive effect in decreasing pentylentetrazole-induced seizure threshold in mice, probably through ML1/2 receptors⁷⁶.

9. Melatonin and Cryptorchidism

Cryptorchidism, a congenital abnormality found in 2%–5% of newborn males, is defined as failure of descent of one (unilateral) or both (bilateral) testes into the scrotum, leaving it in the intra-abdominal position (2%), external ring (9%), ectopic (11%) and commonly the inguinal canal (63%)⁷⁷. It can be congenital or acquired, and can be caused by environmental and genetic factors⁷⁸.

Cryptorchidism has been associated with spermatotoxicity and oxidative stress while melatonin is a well-known anti-oxidant. This study investigated the possible ameliorative effect of melatonin on cryptorchidism-induced spermatotoxicity and oxidative

stress. Cryptorchidism reduced sperm parameters oestradiol, luteinising hormone, follicle stimulating hormone and glutathione peroxidase activity, but increased testosterone and lactate dehydrogenase activity. The cryptorchidism-induced spermatotoxicity and oxidative stress were ameliorated by low dose of melatonin but exacerbated by its high dose⁷⁹.

Conclusion:

From this review it is concluded that melatonin is potent antioxidant; it may helpful for management of various disorders. The further study is required for molecular mechanism of melatonin involved in the treatment of diabetes, cancer, cardiovascular disorders and autism spectrum disorder and also need epigenetic studies.

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