Role of Melatonin in the Pathophysiology of Cancer

Anurag Agrawal¹, Sandeep Darbari¹, Tuman P. Rai*¹, Giriraj T. Kulkarni²

1 School of Pharmacy, ITM University, Gwalior 474001 (India)
2 Amity Institute of Pharmacy, Amity University, Noida 201303 (India)

* For correspondence
Email: raituman1993@gmail.com

Key words
Melatonin, Cancer, Pathophysiology, DNA damage, Cytoprotective, Antioxidant

Abstract
Melatonin is considered to be a mysterious substance in human body which is secreted by pineal gland in night mainly and has a variety of physiological functions and plays significant role in the pathophysiology of many diseases. Apart from its own antioxidative effect melatonin also intensifies the activity of endogenous antioxidative enzymes, which collectively potentiate cytoprotective and free radical scavenging activities. Melatonin may play a protective role against oxidation disorders of cerebral nerve cells during nocturnal sleep as it easily crosses blood brain barrier Melatonin acts as a radical free scavenger and has indirect actions to detoxify carcinogens by activating the glutathione and antioxidative pathways, protecting the cells from DNA damage and also by repairing the DNA if certain damage has occurred. It is well documented that melatonin has cytoprotective and free radical scavenger activities therefore present review study is an attempt to link the mechanism of inhibition of initiation and progression of cancer by melatonin within human body.
INTRODUCTION
Melatonin is a hormone which is found in all the living creatures. Melatonin is also called as 5-methoxy-N-acetyltryptamine (Fig 1) and is mainly responsible for protecting the DNA due to its antioxidant property. Melatonin is produced primarily in the pineal gland, located in the brain. The production of melatonin is dependent on the day-night cycle and is produced primarily during the late night hours, i.e., between 2 and 3 AM. High-fat diets significantly decrease nocturnal melatonin production in the pineal gland (Fig 2). A group of cells called Suprachiasmatic nucleus present in the hypothalamus is primarily responsible for triggering the secretion of melatonin.\textsuperscript{1-4} Melatonin has a variety of physiological functions in the body such as regulation of sleep and cardiac rhythm. Disturbance of any of these leads to imbalance of melatonin in the body.\textsuperscript{5-7}

Cancer can be considered as a genetic disease triggered by certain environmental factors. In cancer, growth of tumours occurs; the tumours may be benign or malignant. The benign tumours are the non-invasive and the malignant tumours are considered to be the invasive.\textsuperscript{5} Free radical burden, and oxidative stress are reported to be involved in triggering different types of cancers, due to possible DNA damage by the free radicals.\textsuperscript{5} Melatonin has a defensive action against the cancer cells and stops them from proliferation. It has shown effectiveness against various types of cancers both \textit{in vivo} and \textit{in vitro}.\textsuperscript{5}

Melatonin is an important immune modulator and also a free radical scavenger, which greatly protects all the parts of the body, especially, brain cells against DNA damage.\textsuperscript{2} Since the melatonin secretion in the body reaches peak level during the late-night hours, the individuals working during those hours who get
exposed to light as well as sleep disturbances, will have impaired secretion of melatonin. Such individuals generally have an increased of developing different types of cancers.³

Melatonin mainly acts by the mechanism of autocrine and paracrine signalling, gradually affecting the functions of the lymphatic tissues, the gastrointestinal epithelium and the smooth muscles of the digestive system.⁴ In classical sense, melatonin is not regarded to be a hormone. But, it functions as a cell protector because its secretion is not bound upon a single organ or its effects on a specified target organ.⁷⁻⁸ Supplements of melatonin have been reported to help in the prevention of breast cancer, reduce the level of PSA in prostate cancer and provide a good therapeutic effect on brain and lung cancers. Solid tumours in cancer can also be treated by intake of melatonin which increases the effectiveness of interleukin-2, resulting in anti-tumor immune effect.⁹ Report on plasma melatonin levels on the subjects of various age groups reveal a decrease in melatonin production with growing age.¹⁰ Melatonin is metabolized in the liver by the microsomal enzymes and the high concentrations of melatonin can be found in the cerebro-spinal fluid and bile.¹¹

MELATONIN RECEPTORS
Melatonin easily crosses the blood brain barrier (BBB) and as the molecules are highly diffusible in nature, they can exert systemic effects like modulation of mitotic and cytoskeletal functions through the bond with calmodulin.⁷ Two specific receptors have been identified as MT1 and MT2. These receptors can be found all over the body including hemopoietic system containing lymphocytes, platelets, prostatic cells, renal tubules and cardiac miocytes.⁷ The MT1 and MT2 are G-Coupled and affect intracellular messengers such as cAMP, cGMP, and ca²⁺. A third binding site, as MT3 is characterized to be as enzyme quinine reductase².

Melatonin can also bind to the nuclear receptors such as the retinoid related orphan nuclear receptor (RZR/RORalfα), subtypes RZRz, RORz, RORz² and RZRz². Subtypes display tissue specificity but their functions are mostly unknown.¹² By binding with the nuclear receptors melatonin alters the transcription of several genes and inhibits several extra cell proliferation. MT1 and MT2 receptor interaction decreases the uptake of linoleic acid which results due to decrease in cAMP production by affecting a specific fatty acid transporter. Linoleic acid can be oxidized to 13-hydroxyoctadecadienoic acid by 15-lipoxygenase which supports tumor growth. Inhibition of lenoleic acid uptake can result into anti-tumor growth of the cancer cells.¹³

Melatonin has shown inhibitory activity against human breast cancer cells. It inhibits the mitotic cell division occurring during metaphase and also decrease the metastatic activity by changing the cell surface adhesion molecules and intercellular communication between the cells.

Melatonin can directly induce apoptosis in the cancer cells leading to death of cells, which stops cell proliferation.¹⁴ Melatonin receptors have been reported to be highly useful in the treatment of hepatocellular carcinoma, in which, the cell line HepG2 determines the influence of melatonin on cell proliferation and signal transduction.¹⁵

Estrogens produced in the females are involved in many of the malignant processes; thus, reduction of estrogens by melatonin produces an oncostatic effect, especially, in breast cancer. Melatonin also affects the hypothalamic-pituitary-ovarian axis by lowering circulating levels of estrogens and progesterone.¹⁶ The oncogenic potential of the growth hormone (GH), with prolactin-insulin-like growth factor-1 (IGF-1), and of GH dependent growth factors, such as epidermal growth factors (EGF), vascular endothelial growth factors (VEGF), fibroblast growth factors (FGF), platelet derived growth factor (PDGF), transforming growth factor (TGF) or hepatocyte growth factor are the areas where melatonin plays an anticancer relevance.⁷

CHRONOBIOLOGIC IMPLICATIONS OF MELATONIN IN PATHOPHYSIOLOGY OF CANCER
Melatonin regulates circadian rhythms, reproductive systems and mammary gland functions. The secretion of melatonin takes place in the pineal gland and its production is dependent on the biological clock which
is present in all the living beings. Circadian rhythms are controlled by this biological clock. Exposure to light can suppress the melatonin secretion. After the production of melatonin in the body, it gradually gets transported all over the tissues and organs and helps in the prevention of cancer through its various anti-cancer mechanisms. Melatonin is also regarded as an endocrine regulator as it affects the synthesis and functions of estrogens, progesterone along with prolactin.

Melatonin is synthesized from the amino acid tryptophan and again is converted into serotonin. Acetylation of the serotonin takes place to form N-acetylserotonin by the enzyme arylalkylamine N-acetyltransferase (AANAT). N-acetylserotonin is converted into melatonin by the enzyme hydroxyindole-O-methyltransferase (HIOMT). Melatonin acts as a radical free scavenger and has indirect actions to detoxify carcinogens by activating the glutathione and antioxidative pathways, protecting the cells from DNA damage and also by repairing the DNA if certain damage has occurred. The main mechanism of melatonin is to inhibit the proliferation of the tumor cells and also inhibiting the healthy cells to convert into tumor cells. Apoptosis is the major mechanism by which melatonin replace the tumor cells into healthy cells. Melatonin if given with retinioic acid on MCF-7 hormone dependent breast cancer cells reduces tumor cell growth y the mechanism of apoptosis. Lower level of melatonin in the human body can result into increase chances of cancer cells, and higher levels of melatonin play a major role in prevention of cancer.

Higher levels of melatonin suppresses the tumor promoting gene TP53, inhibits the uptake of leniloic acid, which is responsible for fatty acid growth and promotes the tumor cells. An angiogenic factor which promotes the growth of tumors in the blood vessels is endothelin-1, the synthesis of which is inhibited by melatonin, thus, blocking the proliferation of the cancer cells. Higher levels of melatonin induces apoptosis in the cancer cells. Melatonin also stops the proliferation of cancer cells by reducing the telomere length and inhibiting the telomerase activity, which is mainly responsible for the growth of unhealthy cells. Pharmacological concentrations of melatonin play a very important regulatory role in both the physiological and pathological process in the humans and animals. Specific plasma membrane associated melatonin receptors control many of the melatonin action at the cellular level. Melatonin induces phase shift in the firing of neurons comprising the SCN and this action lies in the heart of the melatonin’s chronobiologic actions. This action is mainly responsible for the production and secretion of melatonin and is also related with the biological clock present in the humans. The host defence system present in the human body is mainly protected by melatonin and inhibits cancer cell growth by activating the cytokine system and by stimulating the cytotoxic activity. Melatonin stimulates many cells and genes in order to inhibit the cancer cell growth such as natural killer cells, monocytes, leukocytes, interleukins, interferon-gamma and activates its receptors to bind in a specific membrane. Melatonin, as a immunomodulator, helps the natural killer cells to maintain the immunity against cancer cells. The immune regulation of the body by melatonin can be both stimulating and inhibitory. In the gastro-intestinal tract, melatonin affects the secretion of insulin and glucagon by MT1 and MT2 receptors. It is also seen that as the rate of secretion of melatonin in the GIT decreases, the chances of tumor and type 2 Diabetes increases. Melatonin also inhibits the over production of estradiol as estradiol induces attack of MCF-7 cells and causes the mitogenic effects on breast cells. Thus melatonin blocks the mitogenic effect of estradiol and prevents breast cancer. One of the most important functions of melatonin is that it protects the bone marrow and the lymphoid tissues against the toxic effects of chemotherapy and regulates the body with its essential proper composition.

**CONCLUSION**

There are clear evidences that melatonin inhibits oxidation processes and also induces other antioxidant mechanisms. It is generally accepted that breast and endometrial carcinomas occur less frequently in blind individuals than in non-handicapped ones. Therefore, it is required that more experimental studies should be carried out to clarify the effect of melatonin on the pathophysiology of cancer. Conclusively, the secretion and regulation of melatonin in the body might have significant impact on cancer pathophysiology.
DECLARATION OF INTEREST

It is hereby declared that this paper does not have any conflict of interest.

REFERENCES
