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Melatonin in Cancer Management: Progress and Promise

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Review

Melatonin in Cancer Management: Progress and Promise

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Abstract

Physiologic and pharmacologic concentrations of the pineal hormone melatonin have shown chemopreventive, oncostatic, and tumor inhibitory effects in a variety of *in vitro* and *in vivo* experimental models of neoplasia. Multiple mechanisms have been suggested for the biological effects of melatonin. Not only does melatonin seem to control development alone but also has the potential to increase the efficacy and decrease the side effects of chemotherapy when used in adjuvant settings. This review critically evaluates progress in the ability of melatonin to prevent or reverse cancer development and progression. We also discuss future prospects of the possible development of melatonin as a chemopreventive agent. (Cancer Res 2006; 66(20): 9789-93)

Introduction

Melatonin, *N*-acetyl-5-methoxytryptamine, is a small lipophile molecule that is essentially secreted by the pineal gland and its synthesis shows a circadian pattern. Many melatonin receptors are found in the body, which explains its multiple functions in biological rhythms resynchronization, sleep induction, vasoregulation, and even immunomodulation (1). It is synthesized from tryptophan under the control of the enzymes trypotphan hydroxylase, arylalkylamine *N*-acetyltransferase (AA-NAT), and hydroxyindole-*O*-methyltransferase (HIOMT; ref. 1). In addition to the pineal gland, melatonin is also synthesized in the retina, bone marrow, gastrointestinal tract, and bile (2). After synthesis, melatonin is released quickly into the bloodstream and then into the cerebral spinal fluid, saliva, and bile (2). Melatonin synthesis displays a circadian rhythm that is generated by a circadian clock located in the suprachiasmatic nucleus (SCN) of the hypothalamus region of the brain. The SCN clock is set to a 24-hour day by the natural light-dark cycle. Light signals through a direct retinal pathway to the SCN, which then sends circadian signals over a neural pathway to the pineal gland, thereby driving rhythmic melatonin synthesis. Specifically, the rhythm of the enzyme AA-NAT is under SCN control, with the resulting melatonin rhythm characterized by high levels at night. Thus, the synthesis and release of melatonin are stimulated by darkness and inhibited by light.

Peak levels of melatonin in blood vary between individuals and depend on age. High and young secretors have plasma levels of melatonin ranging from 54 to 75 pg/mL, whereas low and elderly secretors range from 18 to 40 pg/mL (2).

Studies have reported oral, i.v., intranasal, transdermal, and oral transmucosal administration to increase melatonin levels (3). Although all of these administration means have proven to be beneficial, the method that best suits the situation would probably depend on a host of other factors affecting bioavailability of melatonin. The endogenous half-life of melatonin in the serum is 30 to 60 minutes and exogenous melatonin has an even shorter half-life of 12 to 48 minutes, as it is not stored to any extent (2, 3). Melatonin has a high lipid/water solubility (octanol/water coefficient = 13) facilitating passage across cell membranes (4). In the blood, 50% to 75% of melatonin is bound reversibly to albumin and glycoproteins (2). First-pass metabolism in the liver (cytochrome *P*450 enzyme CYP1A2) results in a 90% clearance rate with small quantities excreted in the urine unmetabolized (2). The pharmacokinetic properties of melatonin make it a versatile indolamine compound.

Mechanism of Action of Melatonin

As shown in Fig. 1, studies have suggested several mechanisms for the known effects of melatonin.

Some of the biological effects of melatonin are shown to be signaled through a family of guanadine triphosphate–binding proteins or G protein–coupled receptors. Two forms of high-affinity melatonin receptors and two forms of low-affinity receptors have been identified. The high-affinity ML1 receptors are designated Mel1a and Mel1b. The low-affinity receptors are designated ML2 and ML3. The Mel1a receptor is expressed in the SCN and in the hypophyseal pars tuberalis. The SCN is the putative site of circadian action of melatonin, and the hypophyseal pars tuberalis is the putative site of its reproductive effects. The Mel1b receptor is expressed mainly in the retina. The distribution of the ML2 receptors has not yet been determined. These receptors are coupled to the stimulation of phosphoinositide hydrolysis. The ML3 melatonin receptor was identified with lower melatonin affinity, very rapid ligand association/dissociation kinetics, and an original pharmacologic profile in various tissue types in the body (5). Mass spectrometry and enzymatic data later confirmed that ML3 was the quinone reductase 2 (QR2), a known detoxifying enzyme (5). The induction of this enzyme is associated with a decreased susceptibility to cancer initiation and progression (6).

Both ML1 and ML2 are coupled to adenylyl cyclase and cyclic AMP (cAMP) inhibition (4). The decrease in cAMP production decreases the uptake of linoelic acid, an essential and major fatty acid, by specific fatty acid transporters (7). Linoelic acid can be oxidized to 13-hydroxyoctadecadienoic acid (13-HODE) by 15-lipoxygenase (15-LOX-1) serving as an energy source for tumor growth and tumor growth signaling molecules (7). Inhibition of linoelic acid uptake by melatonin is regarded as a mechanism of its antiproliferative effects. Some studies have also suggested modulations in the expression and function of nuclear receptors, RZR/RORα and RZRβ, for which melatonin serves as a natural ligand, as the mechanism of biological effects of this hormone (1). On binding with nuclear receptors, melatonin alters the transcription of several genes that play a role in cellular proliferation [e.g., 5-lipoxygenase (*5-LOX*), *p21*, and bone sialoprotein (*BSP*); ref. 1].

A third mechanism of the biological effects of melatonin may be its ability to modulate calcium and calmodulin activity.

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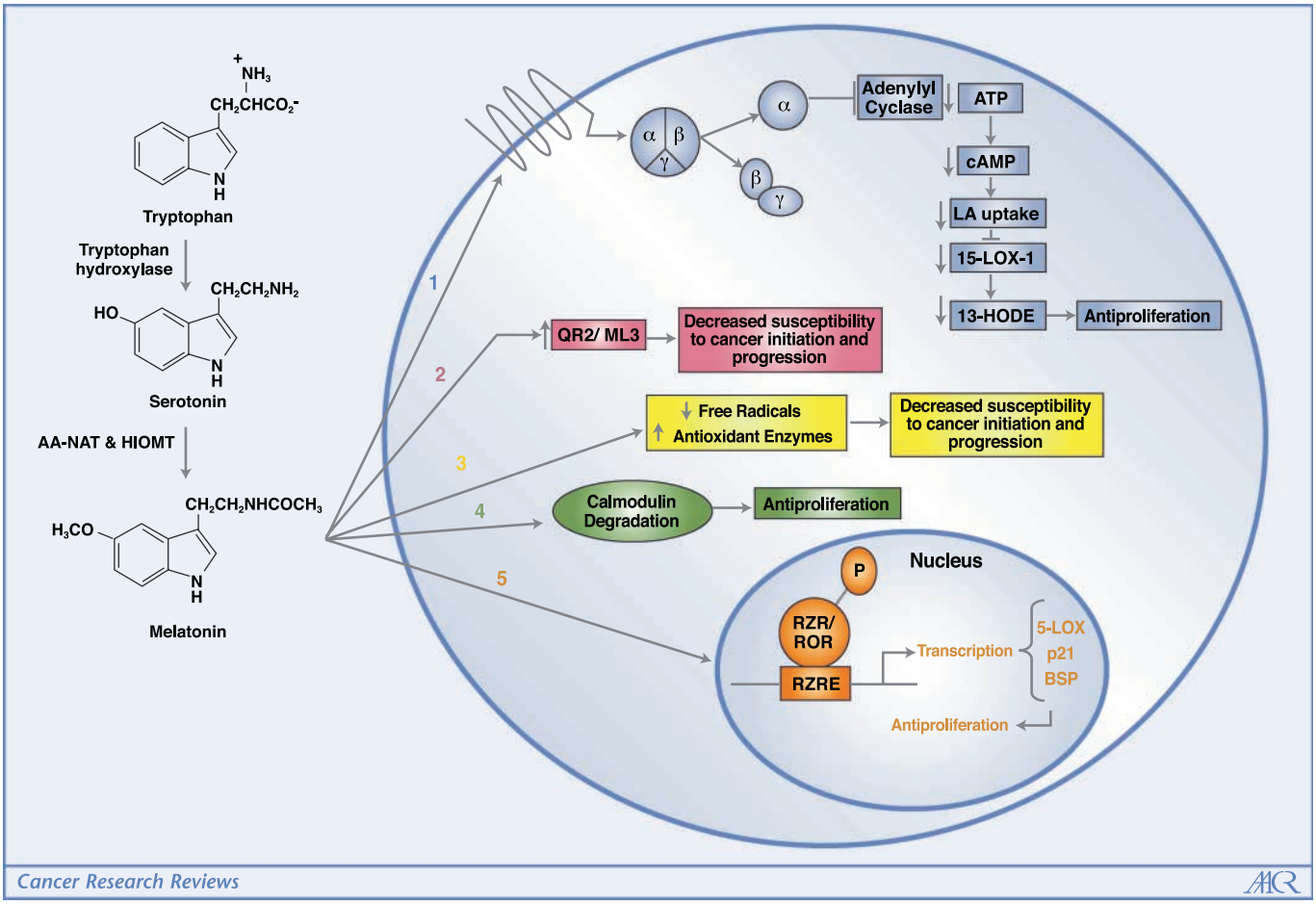

Figure 1. Synthesis and mechanism of action of melatonin. The hormone melatonin is synthesized from tryptophan under the control of the enzymes tryptophan hydroxylase, AA-NAT, and HIOMT. Five potential mechanisms are proposed for the antiproliferative effects effects of melatonin. These mechanisms (*1-5*) are shown with different color schemes. *1,* (blue), melatonin binds to its receptor(s), ML1 and ML2, the α-subunit dissociates, inhibiting adenylyl cyclase followed by inhibition of ATP and cAMP that leads to a decrease in linoelic acid (*LA*) uptake followed by decreases in its metabolism to 13-HODE by 15-LOX-1; *2,* (red), melatonin can also bind its ML3 receptor, recently reported to be QR2. QR2 is a detoxifying enzyme, which, on induction, decreases the susceptibility to cancer initiation and progression; *3,* (yellow), melatonin has been reported to be a powerful scavenger of ROS as well as an inducer of many antioxidant enzymes. Both of these functions lead to a decrease in the susceptibility to cancer initiation and progression; *4,* (green), melatonin has been shown to increase calmodulin degradation to result in antiproliferative effects; *5,* (gold), melatonin also has been reported to bind to its nuclear receptors, RZR/RORα and RZRβ, altering the transcription of several genes that play a role in cellular proliferation, such as 5-LOX, p21, and BSP, all leading toward antiproliferation. The proposed mechanisms are based on the available literature and are not complete. Further studies are needed to unravel the detailed mechanism of action of melatonin.

Calcium-activated calmodulin is involved in the initiation of the S and M phases of the cell cycle, cell cycle–related gene expression, and the reentry of quiescent cells from G_0 back into the cell cycle (7). Melatonin has been shown to increase calmodulin degradation due to direct binding as well as causing redistribution of calmodulin, thereby inhibiting cell cycle progression (7).

A final well-documented function of melatonin is its antioxidant properties. It is a powerful scavenger of reactive oxygen species (ROS), such as hydroxyl, peroxyl radicals, singlet oxygen, and nitric oxide as well as a stimulator of the antioxidant enzymes: superoxide dismutase, glutathione peroxidase, and catalases, all leading to a decrease in DNA damage (2, 7). However, the antioxidant effects of melatonin have been shown to occur at much higher pharmaceutical concentrations.

Cancer and Melatonin

Although early studies on the possible correlation and effects of melatonin and cancer can be traced back to the 1960s, this area of research received attention when Cohen et al. (8) in 1978 put forth the theory of the possible role of the pineal gland on the etiology of breast cancer. These authors suggested that a decrease in pineal function (i.e., reduction in melatonin secretion) could induce a state of relative hyperestrogenism, and the early and prolonged exposure of the breast tissue to the estrogens could be involved in the etiology of breast carcinogenesis (8). Since then, numerous studies have suggested an association between melatonin levels and cancer progression (2, 9–11). Several studies have shown reduced levels of melatonin in patients with certain types of cancers, compared with normal, healthy people of the same age (2, 9–11). Many cancer types [breast, non–small cell lung, metastatic renal cell carcinoma (RCC), hepatocellular carcinoma, and brain metastases from solid tumors] have shown to be responsive to melatonin in different settings, and several others (ovarian carcinoma, human neuroblastoma, pituitary tumors, larynx carcinoma, oral carcinoma cells, bladder carcinoma, and erythroleukemia) are under investigation (2, 3).

The timing of melatonin administration seems to be an important factor in its chemopreventative properties, with the most

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effective protocol being a diurnal cycle similar to the physiologic rhythm of melatonin secretion (2). Studies have suggested that melatonin given to tumor-bearing animals in the late afternoon are more effective in suppressing tumorigenesis than morning melatonin administration, suggesting that tumors exhibit their own circadian rhythm of sensitivity (7). Thus, it seems that nighttime administration of melatonin may be more beneficial than administration during the day time.

Among cancer patients, melatonin is often used as an alternative or complimentary approach because it is believed to be safe as no adverse side effects have been observed after oral administration of recommended doses (2). The most likely side effect is the tendency to produce sedation or sleepiness, which is not considered an adverse effect by the users (9). Further, because melatonin is a naturally occurring physiologic agent, it is also perceived to be a chemical produced by the body, thus, eliminating the fear of foreignness to the living system.

Preclinical Studies on Melatonin and Cancer

The effects of melatonin, using a wide range of physiologic to high pharmacologic doses, have been evaluated in many *in vitro* studies (3). The oncostatic and/or cytotoxic effects of melatonin against a variety of cancer cells have been investigated in cell culture models (3). The data suggest that melatonin possesses antiproliferative effects against a variety of cancer cells (3). However, a marked variability has been observed among the findings of these investigations, possibly due to the differences in the study parameters such as plating densities, culture conditions, and melatonin concentrations (3).

The antiproliferative effects of melatonin have also been examined in a variety of animal models at a wide range of doses corresponding to physiologic and pharmacologic relevance (3). *In vivo* studies have been conducted to determine the effectiveness of melatonin against many cancers, including mammary carcinomas, prostate carcinomas, pituitary tumors, melanomas, Lewis lung carcinomas, colon cancer, uterine tumors, and malignant gliomas (3, 12). These studies show varying results ranging from the oncostatic effects of melatonin to no effect at all, albeit under different experimental conditions, such as doses, time of dosage, and length of treatment (3). A common finding of most of these *in vivo* studies was that melatonin does not have any unfavorable side effects (3).

The preclinical studies with melatonin and cancer have suggested a variety of potential mechanisms that may be responsible for the observed biological effects of melatonin. Figure 1 shows a schematic representation of these mechanisms. It is important to mention here that the available literature reports inconsistent data on the effects and mechanisms of melatonin. Therefore, further detailed and well-planned studies are needed to determine the cause and effect mechanisms of action of melatonin at a wide range of physiologic and pharmacologic concentrations.

Clinical Studies on Melatonin and Cancer

Several clinical studies have been conducted to investigate the effects of melatonin against certain cancer types, including cancers of the breast, non–small lung, skin, kidney, and solid tumors with brain metastases.

Many studies on the antiproliferative effects of melatonin have focused on breast cancer, possibly because melatonin has been shown to modulate the activity of several aspects of endocrine physiology (3). Studies have shown that patients with breast cancer have a decrease in circulating melatonin blood level. From this, the "melatonin hypothesis" was derived where the decrease in melatonin is believed to lead to an increase in estrogen levels and an increase in the turnover of breast epithelial stem cells ultimately increasing the risk for malignant transformation (13). There has been extensive work done on melatonin and breast cancer models and several potential mechanisms have been suggested. These include but may not be limited to the following: (*a*) melatonin may down-regulate hormones of the neuroendocrine reproductive axis, leading to a decrease in circulating gonadal steroids; (*b*) it may act as an antiestrogen by countering the effects of estrogens at their targets; and (*c*) melatonin may down regulate the expression of estrogen receptor (ER) α receptors, thus inhibiting the binding of the estradiol-ER complex to the estrogen response element (14). These actions might be the cause of the negative proliferative response of melatonin toward breast cancer cells (14). Several clinical trials have suggested the potential of melatonin in the management of breast cancer. In one study, 14 metastatic breast cancer patients who were unresponsive to tamoxifen alone were given 20 mg melatonin daily in the evening along with tamoxifen (15). A response was achieved in 28% of these patients (15). It has also been shown that melatonin increases the cytostatic antiestrogen sensitivity of tamoxifen via an unknown mechanism (3, 16). Studies have also found a correlation between a decrease in nocturnal melatonin and an increase in tumor size in individuals with primary breast cancer (3).

Some studies investigated the effect of melatonin on non–small lung cancer (NSCLC), which often does not respond well to conventional therapy. In a clinical trial, 63 NSCLC patients with metastatic disease that did not respond to initial therapy with cisplatin were randomly placed on either 10 mg melatonin daily at 7 p.m. or supportive care alone (17). The data from this study showed that the mean survival time was significantly higher for patients treated with melatonin than those receiving supportive care alone (17). A second trial with 60 patients was carried out to evaluate the efficacy of immunotherapy with low-dose interleukin (IL)-2 plus melatonin versus chemotherapy in advanced NSCLC. This study included 60 patients with locally advanced or metastatic NSCLC who were randomized to receive immunotherapy (IL-2 and melatonin) or chemotherapy (cisplatin and etoposide). The data from this study showed that immunotherapy with low-dose IL-2 plus melatonin was better tolerated and more effective in terms of survival time than chemotherapy containing cisplatin in patients with NSCLC (2, 18).

Melatonin has been shown to play a critical role in a variety of normal skin functions, such as hair growth cycling, fur pigmentation, and melanoma control. Melatonin receptors are expressed in several skin cells, including normal and malignant keratinocytes, melanocytes, and fibroblasts (19). Melatonin has been shown to protect skin cells from UV radiation–mediated damage via its antioxidant property. It has been proposed that melatonin (synthesized locally or delivered topically) might counteract or buffer external (environmental) or internal stresses to preserve the biological integrity of the skin and to maintain its homeostasis (19). In one study conducted, four different doses (5-700 mg/m^2/d) of melatonin were applied topically as a monotherapy in 40 patients with metastatic malignant melanoma for 5 weeks (20). A partial response was achieved in six patients; the disease was stabilized in six more patients and an overall response rate of 30% was achieved (20). Based on the data, the authors suggested that further studies of melatonin for melanoma are warranted (20).

Bangha et al. (21) conducted a double-blind randomized study with 20 volunteers to test the efficacy of topically applied

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melatonin in the suppression of UV (0.099 J/cm^2)–induced erythema. The doses of melatonin (0.05%, 0.1%, and 0.5%) used were not found to have any adverse effects on healthy skin and a dose-dependent decrease in the redness of the skin and UV-induced erythema was observed (21).

Neri et al. (22) conducted a trial in 22 patients with documented progressing RCC. In this study, the authors assessed the effect of a long-term regimen (12 months) with human lymphoblastoid IFN and melatonin on RCC. There were a total of seven (33%) remissions: four complete (involving lung and soft tissue) and four partial, with a median duration of 16 months. Nine patients achieved stable disease, and five progressed (22). The response rate observed in this study definitely warrants additional trials to determine the usefulness of concomitant administration of melatonin in the clinical response to IFN in metastatic RCC (22).

Another cancer type for which the effect of melatonin has been investigated is advanced solid tumors with brain metastases. In a trial, 50 patients with brain metastases whose disease had progressed under initial therapy were randomized to receive supportive care alone or supportive care and melatonin (23). Nine of the 24 patients who received melatonin survived 1 year compared with 3 of 26 who did not receive melatonin (23). The mean survival time was 9.2 $\pm$ 0.9 versus 5.5 $\pm$ 0.7 months and the time free from brain progression was 5.9 $\pm$ 0.8 versus 2.7 $\pm$ 0.6 months in patients receiving melatonin (23). In another trial, 30 patients with untreatable metastatic solid tumors were treated daily with 20 mg oral melatonin in conjunction with low doses of the antitumor cytokines, IL-2 and IL-12 (24). The lymphocyte proliferation and anticancer immunity of cytokines were found to be significantly increased with melatonin treatment (24). Both of these studies show the potential of melatonin in the management of advanced solid tumors with brain metastases.

Melatonin and Epidemiologic Studies

Epidemiologic studies, although conflicting, have suggested a correlation between melatonin and cancer risk. Several studies have found an increase in breast cancer risk among subjects who frequently did not sleep during the period of the night when melatonin levels were typically at their highest, such as those women who worked the graveyard shift (25–27). A significant correlation has been found between melatonin plasma levels and the presence of endometrial cancer, suggesting that decreasing melatonin levels may be an indicator of endometrial cancer (28). Another epidemiologic study investigated women who worked 1 to 14 years on night shift or 15 or more years rotating compared with women who never worked night shift found that women working a rotating shift at least three nights monthly for 15 or more years may have an increased risk of colorectal cancer (29). However, some studies conducted have found no correlation between various cancer types and melatonin levels. These discrepancies may lie in the populations studied and/or other assorted variables.

Melatonin in Adjuvant Settings

As described above, several studies have suggested that combination therapies, such as melatonin and chemotherapeutic agents, may increase success by increasing efficacy and decreasing side effects. Thus, the chemotherapeutic agents induce DNA damage, whereas melatonin blocks specific pathways, such as the paradoxically activated mitogen-activated protein kinase pathway, increasing the lethality of chemotherapy treatments (7). Therefore, a combination could effectively lower the threshold for chemo-agents, protect normal tissues from being sensitized to the cytotoxicity of these therapies, and reduce side effects via its free radical scavenging/antioxidant properties (7). In most of the combination trials where melatonin was used in conjunction with therapeutic drugs, the presence of melatonin was found to prolong disease progression-free time and overall survival as well as improve patient suffering (3, 30). For example, in a noteworthy study, Lissoni et al. (31) evaluated the effects of concomitant melatonin administration on toxicity and efficacy of several chemotherapeutic combinations in advanced cancer patients with poor clinical status. The study included 250 metastatic solid tumor patients (lung cancer, 104; breast cancer, 77; gastrointestinal tract neoplasms, 42; head and neck cancers, 27), who were randomized to receive melatonin plus a wide regimen of chemotherapy (single agent or combination of agents) or chemotherapy alone (31). In this study, the 1-year survival rate and the objective tumor regression rate were significantly higher in patients concomitantly treated with melatonin than in those who received chemotherapy alone (31). Moreover, the concomitant administration of melatonin was found to significantly reduce the frequency of thrombocytopenia, neurotoxicity, cardiotoxicity, stomatitis, and asthenia (31). This study suggested that melatonin may enhance the efficacy of chemotherapy and reduce its toxicity, at least in advanced cancer patients of poor clinical status (31). As stated previously, the positive cancer prevention capabilities of melatonin are believed to be at their strongest when taken at night. Thus, it may be beneficial for chemotherapeutic drugs to be given at night along with melatonin, thereby maximizing the effect of both types of drugs.

Melatonin in Immunoenhancement

Recently, melatonin is being appreciated as a modulator of hemopoiesis and immune cell production and function (32). Physiologically, melatonin is associated with T-helper 1 (Th1) cytokines, and its administration favors Th1 priming (32). Studies have shown that melatonin administration to normal as well as leukemic mice results in quantitative and functional enhancement of natural killer (NK) cells, whose role is to mediate defenses against virus infections and cancer cells (32). Based on several studies, melatonin seems to regulate cell dynamics of virtually all hemopoietic and immune cell lineages, including NK cells, T and B lymphocytes, granulocytes, and monocytes in bone marrow as well as in tissues (32). In particular, melatonin has been shown to possess a strong antiapoptotic property, thereby promoting the survival of normal granulocytes and B lymphocytes (32). In mice bearing midstage leukemia, daily administration of melatonin has been shown to result in a survival index of 30% to 40% (32). Based on these properties, Miller et al. (32) have suggested that melatonin has a fundamental role as a system regulator in hemopoiesis and immunoenhancement, which is believed to be closely involved in several fundamental aspects of host defense and has the potential to be useful as an adjuvant tumor immunotherapeutic agent.

Conclusion

Melatonin has strong antioxidant properties (stronger than those of vitamin E) and anticancer and oncostatic action. Interestingly, recent epidemiologic studies have suggested that

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women who work exclusively at night for long periods have a significantly elevated relative risk of breast cancer. Several *in vitro, in vivo*, and clinical studies have indicated the beneficial effects of melatonin against a wide range of neoplasms. However, more mechanistic studies are required to confirm these results. More cancer types, different doses, administration timing, routes of administration, and combinations of melatonin with other anticancer agents administered at night should be investigated. The chemopreventive potential of melatonin needs to be explored in appropriate animal tumor models, which possess relevance to human disease.

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