

# Melatonin: A Powerful Integrative Adjunctive Agent for Oncology

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## Abstract

Melatonin is an established hormone supplement and has been well recognized for its effect on the circadian cycle to improve sleep, REM (rapid eye movement), and aiding in jetlag recovery. The utility of melatonin extends beyond sleep aid, however. This hormone also possesses less well-known antioxidant action and even robust anticancer activity. Melatonin may be a key supplement for addressing age-related neurologic decline while serving as a valuable adjunctive cancer treatment that reduces drug resistance in tumors and downregulates angiogenesis. In immunotherapy, melatonin activates Natural Killer (NK) cells nested within tumoral tissue and does not have the side effect profile of other immunoreactive agents used for chemotherapy. Since melatonin is found in high concentrations in the brain and other hormone-linked tissues, the relevance of melatonin is increased for the treatment of estrogen-linked cancers. The immunomodulatory effect of melatonin may also help with chronic inflammation seen in patients with autoimmune disorders. All of these effects together represent a unique and versatile therapeutic agent for integrative medicine. No other commercially available drug possesses all of these therapeutic mechanisms while having a very minimal side effect profile and being considered overall to be safe to use. Currently, melatonin is underutilized in medicine, especially in the field of integrative oncology and represents a crucial supportive adjuvant to improve the lives of patients.

## Keywords

Melatonin, Oncology, Immunotherapy, Chronic Inflammation, Autoimmune, Envita, Antioxidant, Anticancer, Antiangiogenesis, Telomerase, Metastasis, Anti-Proliferation, Pro-Apoptosis, Immune System Activation, Cancer Adjuvant, Chemotherapy Synergy

## 1. Introduction

Melatonin (N-acetyl-5-methoxytryptamine) is a hormone produced primarily by the pineal gland and also by nearly every tissue in the body. Originally, melatonin was believed to be produced exclusively in the pineal gland, but it has been determined that melatonin is also produced in the mitochondria and thus by almost every cell in the body [1] [2] [3]. Melatonin is mainly responsible for regulating the sleep-wake cycle in humans but has other utilities, as we will discuss in this report [4]. There is ten to fifteen times the amount of melatonin in the blood at night as during the day, and release from the pineal gland is strongly influenced by exposure to light sources such as the sun but also electronic devices [5]. Individuals commonly supplement orally with it for difficulty sleeping, especially from working nights or jet lag [6] [7] [8]. Melatonin has been observed to be effective at treating symptoms of non-depression-related insomnia resulting from shift work and jet lag but is not FDA approved for these uses [9]. Melatonin has been investigated for health benefits beyond use as a natural sleep aid (Figure 1).

There is good reason to believe that melatonin could be useful as more than a remedy for mild insomnia. Research *in-vivo* and *in-vitro* has shown multiple biological functions for this neurohormone including, but not limited to, assisting in the immune response, reducing oxidative stress, helping eye function, regulating many internal cellular processes, and even protecting cells from ionizing radiation [5] [10] [11]. To start with, the quantity of melatonin fluctuates in the human body throughout the day as part of the circadian rhythm. In addition to the pineal gland, melatonin is produced by several other organs inside the body, in particular, the stomach [12]. Production of melatonin is strongly influenced by light exposure and the circadian rhythm. Exposure to the blue end of the visible

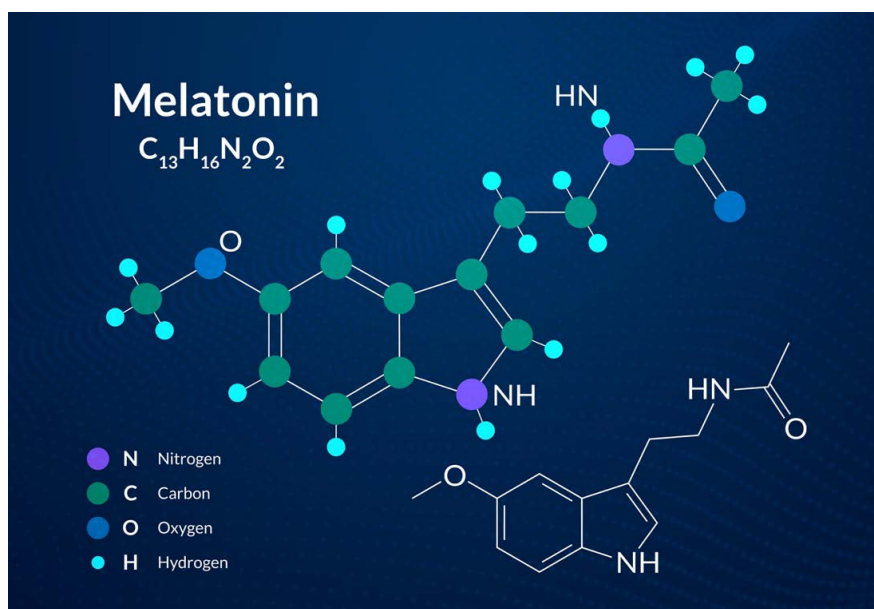


Figure 1. Melatonin molecular structure.

light spectrum has been shown to decrease melatonin drastically [13], but the absence of light does not by itself stimulate the production of this neurohormone; it only permits serum levels to rise [14]. Interestingly, melatonin levels also generally decrease with age, potentially explaining the marked reduction in sleep hours associated with old age [15].

Melatonin has been linked with potential oncostatic properties on tumors of different type and stage through epidemiological studies [16]. Also, experimental *in-vitro* and animal models have shown possible growth inhibition of some human tumor cells by melatonin [16]. Antioxidant activity, stimulation of apoptosis, regulation of pro-survival signaling and tumor metabolism, modulation of melatonin receptors MT1 and MT2, inhibition on angiogenesis, metastasis, and induction of epigenetic alteration have been considered as options for the underlying mechanisms of melatonin's anti-tumor activity. In addition to potential tumor growth inhibition, melatonin may also be beneficial as a cancer therapy adjunct by reducing the side effects and supporting the therapeutic effect of chemotherapy or radiation [16]. Melatonin has been correlated with the treatment of many types of cancer, such as lung cancer, prostate cancer, breast cancer, gastric cancer, and colorectal cancer [16]-[21].

Melatonin interacts with two primary receptors, MT1 and MT2 [22]. These receptors are associated with different stages of sleep. MT1 controls deep sleep and REM sleep, while MT2 controls the stage of sleep immediately preceding the dream cycle [22]. MT1/MT2 receptors are present in a variety of organs and immune cells inside the body, leading some researchers to speculate about the function of melatonin in controlling aspects of the host immune response and other functions throughout the body [23].

MT1 and MT2 are G protein-coupled receptors and are linked intrinsically to the endogenous oscillatory action of pineal melatonin, which occurs inside the suprachiasmatic nucleus (SCN) in response to daily light exposure. The light-dark cycle of each day, as well as seasonal changes, trains circadian oscillators inside the SCN, which contains a large number of MT1 and MT2 receptors and may serve as a feedback mechanism of the circadian rhythm [24]. MT1/MT2 receptors have many functions in the brain which are still being investigated. For example, MT1/MT2 can form heterodimers with serotonin receptor 5-HT<sub>2C</sub> [25]. This mechanism is of importance in understanding the antidepressant mechanism behind drugs like agomelatine, which is both a melatonin receptor agonist and a 5-HT<sub>2C</sub> receptor antagonist [25] [26]. A full understanding of the function of receptors like MT1/MT2, 5-HT<sub>2C</sub>, and others could unlock more therapeutic potential and lead to the development of new melatonin-like drugs.

The field of research into melatonin receptors is ongoing. For example, the X-ray free electron laser (XFEL) structures of MT1 and MT2 were just described in 2019 [27] [28]. Detailing the molecular structure of the receptors reveals interesting facts such as differences between MT1 and 5-HT receptors which have similar ligands and which both respond to agomelatine. The binding site of MT1

is very compact and is only accessible through a narrow channel allowing for only atypical ligand entry into MT1 [27]. MT2 function has been implicated in type 2 diabetes and other disorders such as mood disruptions and the development of cancer in addition to insomnia [28]. Studying the MT2 receptor's structure reveals the potential for an extra cellular ligand entry point in addition to the intramembrane entry point common to both melatonin receptors [28]. This is important for understanding the selectivity of the two receptors and potentially for designing better drugs in the future which impact melatonin receptors.

In the United States, major depressive disorder is the most prevalent mental disorder and is a significant cause of disability; it impacts approximately 100 million adults in the world [29]. Major depressive disorder is characterized by anxiety, neurochemical imbalances, disturbances in sleep pattern, circadian/seasonal rhythm entrainment, low vitamin D, lack of motivation/mood, and an increased rate of neuronal atrophy [29] [30]. Current treatment options include tricyclic antidepressants and selective serotonin reuptake inhibitors, but neither of these types of drugs treats sleep disturbances, and each can lead to undesirable side effects through long-term use [31] [32]. These side effects include sexual dysfunction, weight gain, and several other cognitive and motor manifestations which form the Serotonin Syndrome. MT1/MT2 are thus important targets for novel antidepressants.

There is some evidence to believe that melatonin or melatonin-like drugs which target melatonin receptors may be of use as a clinical antidepressant. The drug Luzindole blocks melatonin-mediated antidepressant effects in the forced swim test, suggesting that MT1/MT2 is involved in its function [33] [34]. Ongoing melatonin treatment has also been shown to positively affect neurogenesis in rats, a process believed to be essential for the effectiveness of antidepressants. Additionally, irregular melatonin levels correlate to the development of both cardiovascular disease and cancer [35]. These and other data that we will outline in the sections below imply a wide range of potential therapeutic benefits for melatonin, which would benefit from further published data and clinical trials.

## **2. Melatonin and Inflammation**

It was mentioned previously that a wide variety of cells contain melatonin receptors, and this includes several classes of immune cells [23]. Melatonin is an immunomodulatory hormone, which is to say that it reduces excessive immune activity in conditions of chronic inflammation and increases immune function in immune-suppressed individuals. For example, melatonin reduces the production of inflammatory cytokines (IL-6, IL-8, and TNF- $\alpha$ ) [36]. Melatonin also appears to reduce inflammation in the brain by reducing ROS/RNS in microglia, specialized immune cells specific to the central nervous system [37]. Melatonin is essential for maintaining a healthy immune response and has been observed to reverse immune suppression caused by factors including steroid and chemical exposure or old age [23].

Melatonin stimulates both the innate and adaptive immune responses, according to multiple studies [23] [38] [39]. Melatonin may also contribute to an enhanced T-cell mediated immune response. This effect is produced by thymosin- $\alpha$ , thymulin, and other thymus-derived peptides, which melatonin enhances [40]. CD4<sup>+</sup> T-lymphocytes and monocytes may benefit from melatonin as well as a protective effect [41] [42]. A consensus drawn from several studies demonstrates that melatonin administration can be beneficial for patients with infectious diseases with melatonin-administered patients having shortened disease duration and improved clinical outcomes [23] [43].

### 3. Evidence for Anticancer Properties of Melatonin

Perhaps the most important use for melatonin supplementation is as an adjuvant for cancer treatment. There is much evidence that melatonin helps enhance the therapeutic effects of chemotherapy/radiation while reducing its side effects, as we will outline in this section. Researchers consider melatonin to be an excellent candidate for study and consider it to have the potential for the prevention and treatment of multiple kinds of cancer, including breast, prostate, gastric, and colorectal [16].

Various types of cancer are responsive to melatonin treatment in-vitro and in-vivo at daily doses of 10 - 50 mg. Among these include breast cancer [44] [45], metastatic renal carcinoma [46], non-small-cell lung cancer [47], hepatocellular carcinoma [48], and brain metastases [49]. As an example, a study of fourteen patients with tamoxifen-resistant, metastatic breast cancer demonstrated that 20 mg of melatonin could have a positive effect. In 28 percent of those patients, a partial response was seen where the disease was expected to progress rapidly, and in those who responded significantly lower serum levels of tumor growth factor IGF-1 were recorded ( $p < 0.001$ ). The tumor factor response was independent of estrogen-receptor status [45].

Of particular interest is the response to non-small-cell lung cancer (NSC), which is a type of cancer known for being unresponsive to conventional therapy. A randomized trial with 63 NSC patients, all in Stage 4, had patients who had already failed initial treatment with cisplatin placed on either melatonin or supportive care alone. Mean survival time was significantly greater in the melatonin group at 7.9 months compared to 4.1 months ( $p < 0.05$ ) [47].

For patients whose cancer spreads to the brain, there are often few treatment options available, and survival time is frequently less than six months. A different randomized study included fifty cancer patients with recorded brain metastases and who had all already received initial therapy. They were separated into two groups for either supportive care alone or supportive care with melatonin. The observed metrics (1-year survival, mean survival time, and time free from brain tumor progression) were all significantly higher in the melatonin group than the control group [49].

Much of the anticancer impact from melatonin appears to stem from its anti-

angiogenic property; antiangiogenic drugs are sometimes administered alongside chemotherapy to enhance the effect of the treatment. González *et al.* studied the impact of melatonin when used alongside chemotherapy drugs, docetaxel, and vinorelbine. They found that the drugs' inhibition of the processes involved in angiogenesis (cell proliferation, migratory capacity, and vessel formation) were all intensified by melatonin [50]. Specific to estrogen biosynthesis, melatonin also reduced the negative impact of vinorelbine by inhibiting the expression and activity of aromatase and sulfatase [50]. This indicates that estrogens are crucial in the tumorigenesis and progression process for at least some forms of cancer. For this review, we will refer primarily to estrogen receptor alpha, which is overexpressed in these types of cancers. After over 100 years of research into the area of breast cancer, there is considerable evidence pointing towards estrogens as a principle mammary carcinogen [51].

Cohen *et al.* proposed in 1978 that diminished pineal gland function (the gland which produces melatonin) may lead to an increased incidence of breast cancer through the mechanism of sustained quantities of elevated estrogens. The hypothesis was based on several observations [52]:

- 1) The incidence of breast cancer is low in areas where pineal gland calcification is also low.
- 2) Patients who take chlorpromazine (a sedative which increases melatonin) have lower rates of breast cancer.
- 3) In vitro research demonstrated a direct effect of melatonin against breast cancer cells.
- 4) Melatonin receptors are present in high quantities on human ovarian cells, suggesting that melatonin might have a direct impact on estrogen production in the ovaries.

Cohen *et al.* made these propositions over 40 years ago as of the time of this writing, and evidence has only increased for the relevance of melatonin in modern cancer treatment. For example, in animal studies, enhanced pineal gland function or exogenous melatonin supplementation (500 mg/day two weeks before challenge by DMBA) decreased the number of tumors and tumor size in the rodents [53]. The same study also showed higher tumor regression in the induced tumors in the animals which received melatonin.

The potential anticancer mechanism of melatonin has been given a great deal of scrutiny by investigators, especially in hormone-dependent cancers. Breast cancer is often hormone-dependent and is one of the most common cancers among women. According to the American Cancer Society, over 70% of initial-stage breast cancer cases are hormone-dependent [54]. The chemo-sensitization effect of melatonin is also of interest. Pariente *et al.* described melatonin enhancing the effect of 5-fluorouacil in patients with colorectal adenocarcinoma [55].

Zinc-dependent matrix metalloproteinases (MMP's) are a group of enzymes associated with remodeling of the extracellular matrix and are essential for many normal and disease states inside the body; these processes range from embryonic

development and bone remodeling to cancer, arthritis, and neurological disease [56]. Adenocarcinoma is one of these diseases reliant on MMP (or matrixin) function due to its dysfunctional extracellular matrix (ECM) turnover [57]. MMP-9 is an important matrixin which is often released by inflammatory cells such as neutrophils, monocytes, macrophages, and mast cells [58] [59]. It is required for bone regrowth [60], angiogenic revascularization of oxygen-starved tissues [61], and remyelination [62], but has also appeared in many pathological processes. MMP-9 is involved with inflammation, infection, progressive neurological disease, cardiovascular disease, and several autoimmune disorders [63] [64] [65] [66] [67]. Specifically, concerning cancer, MMP-9 may serve a function in the processes of cancer cell invasion, metastasis, and tumor progression [68] [69]. Specifically, concerning cancer, MMP-9 may serve a function in the processes of cancer cell invasion, metastasis, and tumor progression [68] [69]. MMP-9 facilitates the release of vascular epidermal growth factor, which activates the angiogenic switch [70]. In different forms of neoplasms, such as colon and breast tumors, internal measurements of MMP-9 have been found to be elevated compared to normal values [71] [72]. Due to these observations, inhibition of MMP-9 activity has since become a target for therapeutic research. Unfortunately, the development of broad-spectrum MMP inhibitors has so far produced disappointing results, among the chief problems being lack of specificity and toxic side effects to host physiological systems. While some progress has been made with phosphinic acid and carboxylate inhibitors [73], for this review, we wish to concentrate our attention on melatonin as an MMP inhibitor.

Melatonin downregulates MMP-9 when used to prevent induced gastric ulcers and alcohol-related liver injury in rodents [74] [75]. An antitumoral action for melatonin has also been described concerning suppressing the emergence of colon cancer in cases of chronic Irritable Bowel Disease (IBD) [76]. The antioxidant action of melatonin, as previously discussed, may also contribute to its protective effects [33] [77] [78] [79]. Rudra *et al.* describe how melatonin inhibits MMP-9 activity in a dose-dependent manner [80]. In describing the thermodynamics of the interaction between melatonin and MMP-9, Rudra, *et al.* claimed that the melatonin binding site on MMP-9 is highly favorable [80]. The conclusions that these researchers were able to draw was that melatonin had a direct suppressive effect on MMP-9 in-vitro and that melatonin also suppressed MMP-9 in gastric adenocarcinoma cells taken from humans [80]. Melatonin binds to the catalytic domain of MMP-9, thus inhibiting its function. Because MMP-9 is implicated in both inflammatory disease and disease processes of cancer, such as tissue invasion and angiogenesis, it may be a therapeutic target for several kinds of cancer. As an MMP-9 inhibitor, melatonin is a natural compound with a high amount of potential as a therapeutic agent to slow or reverse the impact of certain kinds of cancer relying on MMP-9 function.

The regulatory nature of melatonin and its connection to the body's biological clock, research has concentrated on melatonin for its relation to aging and

age-related disease, including the gradual decline of immune function and the development of neoplastic diseases. For many different kinds of tumors, melatonin has been observed to inhibit growth both *in-vitro* and *in-vivo* [81]. Extrapolating from this research, physicians are interested in the use of melatonin as a potential adjunctive agent for chemotherapy/radiotherapy either by itself or alongside interleukin-2. For patients with advanced solid tumors, administration of melatonin in this manner has been associated with improved outcomes and survival [81]. Just as importantly, the administration of melatonin has also been shown to assist patients with tolerating chemotherapy and reducing its potentially devastating side effects [81].

In addition to observing the effect of melatonin on matrix metalloproteases, there is also considerable evidence that melatonin is an immune modulator. There is a measurable increase in the number of circulating hemopoietic stem cells, progenitor cells, and mature leukocytes at night, the time of day when melatonin is naturally higher [82]. During the day, typically levels of cortisol, adrenaline, noradrenaline, TNF- $\alpha$ , and interleukin-1- $\beta$  are elevated compared to nighttime levels [82]. This circadian rhythm is fundamental in humans, and regular disruption in the sleep/wake cycle has been associated with an increased risk for cardiovascular disease and the development of neoplasms [83] [84]. Blask *et al.* studied women who worked night shifts and are thus exposed to light at night and found that this group had a significantly higher risk of developing breast cancer [85].

There is more than epidemiological evidence suggesting that melatonin is important for the prevention of cancer. When melatonin was administered to patients for 7 - 14 days, an increase in natural killer (NK) cells and monocytes was observed in the bone marrow as well as increased hemopoiesis [23] [38]. These monocytes are also known to contain melatonin receptors both on their outer membranes and within the nucleus [38]. In these immune cells (monocytes and macrophages), melatonin appears to stimulate the production of inflammatory cytokines (IL-1, IL-6, IL-12, and TNF- $\alpha$ ) while reducing IL-10. Melatonin stimulates ROS production within macrophages, an action which potentiates their phagocytic ability [38] [86]. This effect on NK-cells is critical because NK-cells play a significant role in the body's immune surveillance against early cancer formation and viral infections [87]. Even short-term supplementation of melatonin has been seen to increase interferon- $\gamma$  production from NK-cells, and long-term supplementation of melatonin increased the quantity and activity of NK-cells in serum [38].

In addition to NK-cells, melatonin also appears to impact regulatory T-cells. Regulatory T-cells have an inhibitory effect on anticancer immune activity, with some tumors recruiting regulatory T-cells to block the immune system. Melatonin inhibits the activity of regulatory T-cells [88]. Liu *et al.* showed that melatonin led to significant downregulation of regulatory T-cells present inside tumors along with Foxp3 gene expression, leading to an overall reduction in tumor size



[89]. While this was in an animal study, decreasing regulatory T-cells have also been demonstrated in cancer patients given melatonin [90].

Both of NK-cells and regulatory T-cells are related to inflammation in the tumor microenvironment. These and other immune cells, as well as activated fibroblasts, infiltrate the tumor and secrete a variety of complex signaling agents, including cytokines, chemokines, and growth factors. The tumor and the host immune system both react to these secreted signaling compounds [91]. Marotta *et al.* has shown that inflammation signaling through agents such as IL-6, JAK2, and Stat3 plays a critical role in the stem cell-like capabilities of breast cancer cells [92]. Tracking changes in cytokine levels in serum is already well established in clinical practice. For example, IL-6 is known to potentially stimulate cancer growth, contributing to tumor recurrence and metastasis in breast cancer patients [93].

Melatonin signaling appears to be prevalent in T-cells, which contain both membrane (MT1/MT2) binding sites and nuclear binding sites [94] [95] [96] [97]. Membrane receptors MT1 and MT2 have already been mentioned, and the nuclear receptors include orphan receptor retinoid Z (the first to be identified) and retinoic acid-related orphan receptor alpha [98] [99]. In 1995, human CD4<sup>+</sup> cells were confirmed to have high-affinity binding sites for melatonin, while rat thymus gland cells have been described to possess melatonin receptors, including CD4<sup>+</sup>, CD8<sup>+</sup>, CD4<sup>+</sup>CD8<sup>+</sup>, and CD4<sup>-</sup>CD8<sup>-</sup> [100] [101]. There are also receptor-independent interactions between melatonin and T-cells. Melatonin has been described to enhance T-cell survival through inhibition of calcineurin, which is a nuclear factor of activated T-cells [42]. It is through these T-cell mediated mechanisms that melatonin exerts beneficial effects on a variety of inflammatory conditions, including diabetes, multiple sclerosis, and systemic lupus erythematosus [102]. In the case of multiple sclerosis, T<sub>H</sub>17 helper T-cells may also be relevant. These cells are associated with disease flares in patients with multiple sclerosis, and melatonin has been shown to interfere with the polarization and effector functions of T<sub>H</sub>17 helper T-cells, lowering their population in serum [103]. In addition to multiple sclerosis, T<sub>H</sub>17 cells may be relevant for broader autoimmunity conditions and cancer [104]. T<sub>H</sub>17 is in several ways opposed to regulatory T-cells, which have functions related to self-tolerance and defense against autoimmune disorders, processes that are also relevant to intermediary and late stages of cancer [104]. Regulatory T-cells secrete inhibitory cytokines such as IL-10 and TGF- $\beta$  as part of their mechanism of action. They are also capable of engaging inhibitory checkpoint molecules TIGIT and CTLA. Like two ends of a scale, TH17 promotes autoimmunity, carcinogenesis, and antitumor immunity, while regulatory T-cells are required for self-tolerance and tend to dampen autoimmunity and antitumor immunity [104]. This is further supported by evidence from Kawaguchi *et al.* which describe the connection between inflammatory cytokines like IL-10 and TGF- $\beta$  and the progression of tumors as observed in breast cancer patients [91].

In mice that have undergone pinealectomy, the expressions of T<sub>H</sub>1, T<sub>H</sub>2, and T<sub>H</sub>17-related cytokines are all reduced [23]. As mentioned previously, the pineal gland is the principal source of melatonin in the body. In the pinealectomized mice, melatonin supplementation rapidly increased cytokine levels, leading to a gradual recovery of normal cytokine expression levels [104]. Following the procedure, activation of T and B-cells fell significantly with a reduction in the population of both types of cells, and downstream factors of these cells (TLR3, P38, JNK, and NFκ-B) were down-regulated by melatonin supplementation even compared to levels seen in the control group. These results led Luo *et al.* to conclude that melatonin is actively involved in immune regulation in mice and other vertebrates [105].

Many in-vitro studies have reported an oncostatic effect for melatonin in multiple strains of cancer cells, including mammary-ovarian, prostate, melanoma, hepatocarcinoma, and colorectal cancer. The general conclusion from these experiments is that melatonin inhibits cell proliferation and induces apoptosis in most tumor cell lines [106]. Other studies suggest that melatonin may synergize well with newer cancer treatments that utilize checkpoint inhibitors [15] [106] [107]. The observed oncostatic effect is mediated through several different effects which are listed below:

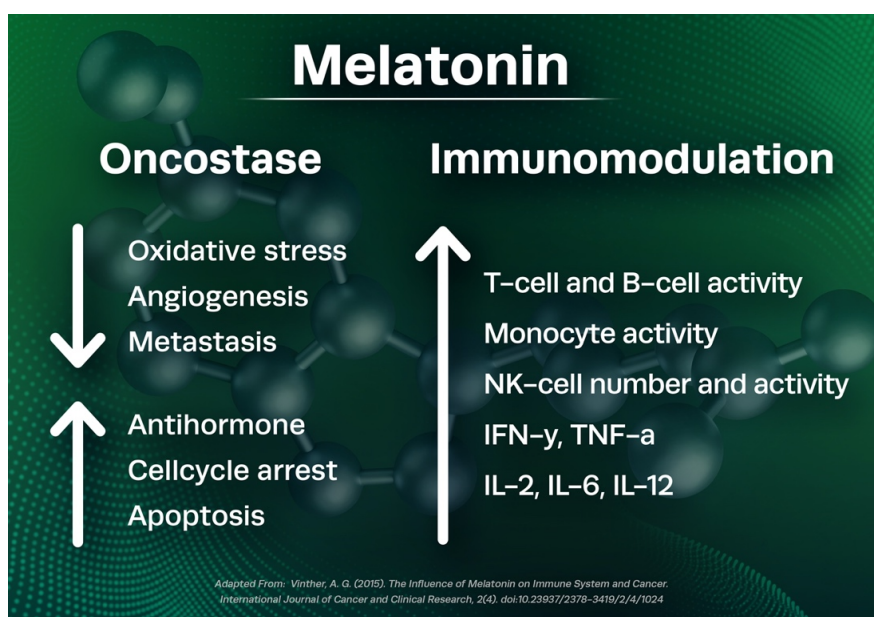
- Antioxidant
  - Melatonin detoxifies multiple free radicals, including the hydroxyl radical and reactive nitrogen species [108].
  - Melatonin recharges other antioxidant enzymes like glutathione and superoxide dismutase [106] [108].
  - Reducing ROS cell damage is relevant in all three steps of carcinogenesis (initiation, progression, and metastasis) [106] [108].
- Estrogen Receptor Expression
  - Melatonin decreases the expression of estrogen-receptor-α [106].
- Modulation of the Cell Cycle and Cell Differentiation
  - Melatonin increases the duration of the cell cycle in multiple cancer lines by expanding the G1 phase and delaying entrance into the S phase. This effect is mediated through the upregulation of tumor suppressor gene p53 and kinase inhibitor p21 [106].
- Telomerase and Metastasis inhibition
  - Melatonin decreases telomerase activity in most cancer cells. Lower invasiveness is also observed with an increase in microfilaments and adhesion plaques [109].
- Antiangiogenesis
  - Antiangiogenesis is observed with melatonin likely through an inhibitory action on tumor growth factors that stimulate angiogenesis (IGF, EGF, VEGF, and ET-1) [89].
- Immune System Activation
  - Melatonin stimulates the production of monocytes, NK-cells, and other

immune cells while downregulating regulatory T-cells [88].

- Synergy with Chemotherapy
  - Melatonin increases the sensitivity of cancer cells to certain chemotherapy agents [108]. There is also a synergistic effect with other antineoplastic drugs through the promotion of the apoptotic pathway [107].
- Anti-proliferation and Pro-apoptosis regulation
  - Melatonin has been observed to decrease cell proliferation while increasing apoptosis, including in apoptosis-resistant cell lines like hepatocarcinoma [110] (Figure 2).

#### 4. Importance of Melatonin in the Brain

As mentioned previously, melatonin possesses antioxidant activity, which is relevant to controlling inflammation both as an end to itself and as a means of controlling other conditions associated with chronic inflammation, including tumorigenesis [111] [112] [113]. Melatonin increases several antioxidant enzymes, including superoxide dismutase, glutathione peroxidase, and  $\gamma$ -glutamyl cysteine synthetase [11] [15] [114]. Each of these enzymes can increase or recharge other antioxidants like glutathione. It is essential to maintain healthy levels of these enzymes because they are vital to the optimal function of mitochondria, where a lot of reactive oxygen species (ROS) are created as a byproduct of aerobic respiration [115]. Failure to maintain adequate levels of antioxidants and their supporting enzymes results in oxidative stress, which can damage the cell and the body's tissues and both cause and accelerate a variety of chronic diseases and potentially accelerate the complications of aging itself. In addition to helping increase the levels of these enzymes, however, melatonin can also bind directly to ROS and Reactive Nitrogen Species (RNS), neutralizing the



**Figure 2.** Summary of melatonin anticancer properties.

oxidative threat [15]. This mechanism allows melatonin to both directly and indirectly protect tissues and organ systems from oxidative damage. The most important tissues that produce melatonin and rely on its protection from ROS/RNS (oxidative damage) include the gut, ovaries, testicles, bone marrow, eye lenses, and the brain [36]. Most of the metabolites of melatonin are also ROS/RNS scavengers as well, which means that melatonin provides significant oxidative protection even after the first stages of metabolism [15]. Just one molecule of melatonin can neutralize up to 10 ROS/RNS molecules based on the chemistry of the hormone and its resulting products [116]. Melatonin also blocks the activity of nitric oxide synthase, which is an enzyme that produces RNS and promotes inflammation [117].

When considering brain health and the importance of antioxidants, most ROS/RNS are generated in the cell. Mitochondria are the power stations of the cell where most of the energy needed for ATP production and survival is produced [118]. Inside the cell, the mitochondria and the nucleus are the areas that contain the most melatonin, [119] considering that mitochondria produce most of the ROS/RNS in the body. Even though the mitochondria are the source of ROS and RNS, the proteins and structures of mitochondria can be damaged by ROS/RNS, making oxidative control systems extremely important in managing this dangerous waste product of aerobic respiration. Damage from ROS/RNS can damage proteins and create holes in lipid membranes, and if mitochondria begin to leak from holes in their membranes, this can lead to cell death [15].

In examining the function of toxins, several that disrupt mitochondrial function also lead to symptoms of neurodegenerative disease. Laboratory animals that have been poisoned by these compounds are often used to study neurodegenerative diseases. A few of these compounds and their effects are outlined in the table below.

Brain tissue is very vulnerable to free radical damage owing to the large amount of oxygen consumption necessary to brain function (about 20% of total oxygen intake) as well as high concentrations of polyunsaturated fatty acids [126], and transition metals that can participate in the creation of hydroxyl radicals [127]. In the brain, the primary antioxidant is Glutathione (GSH), which is present in the millimolar range [128]. However, melatonin is ubiquitous in the brain tissue and is also an important free radical scavenger with indirect antioxidant activity [79] [129]. This is relevant to many neurodegenerative diseases because existing evidence points towards an accumulation of aberrant, misfolded proteins, protofibril formation, oxidative and nitrosative stress, ubiquitin proteasome dysfunction, mitochondrial injury, and failures in the axonal/dendritic transport systems as all being unifying factors in the origin and progression of these diseases [130]. These factors can lead to accelerated cognitive decline and contribute to complications in chronic diseases that impact the central nervous system. In **Table 1**, three compounds are listed which produce effects similar to neurological disease. In each case, melatonin had a therapeutic effect in reducing signs of neurological damage.

**Table 1.** Compounds and their effects.

Rotenone	Produces symptoms similar to Parkinson's disease in rats [120].
MPTP (1-methyl-4 phenyl-1,2,3,6-tetrahydropyridine)	Produces symptoms similar to Parkinson's disease [121]. In mice, an injection of melatonin prevents much of the damage to fats and DNA in several parts of the brain after MPTP poisoning [122]. This may be the result of reconfiguring proteins to their normal state after MPTP exposure
3-NPA (3-nitropropionic acid)	Derived from a fungus that infects sugarcane, there have been recorded incidents of children eating the fungal-contaminated sugarcane and afterward developing a condition similar to Huntington's disease [123]. In rats dosed with 3-NPA, melatonin was observed to prevent nerve cell loss, correct damaging behavior, prevent protein damage, and restore dopamine levels to their normal range [123].
Cyanide	Cyanide is a very lethal poison that causes mass-death of nerve cells and seizures, which can easily lead to death [124] [125]. It also damages mitochondria inside of nerve cells. In mice, a prior dose of melatonin reduced the severity of seizures caused by a cyanide injection [125]. As well, in-vivo and in-vitro tests showed that mitochondrial DNA damage from potassium cyanide was lessened by melatonin [124].

## 5. Safety Data and Side Effects

Melatonin is generally considered safe to use even by conventional institutions such as the Mayo Clinic and the National Center for Complementary and Integrative Health [131] [132]. This definition applies to small doses of melatonin usually taken for short-term relief from insomnia and other sleep disturbances. NIH still considers other uses of melatonin to be as yet unproven and to be utilized with caution and under the supervision of a healthcare professional until clinical drug trials are conducted.

NIH mentions the following risk factors when taking melatonin [131]:

- Interactions with medication
  - With all supplements, a healthcare provider should be consulted for possible interactions with other medications. In particular, patients with epilepsy or who are taking blood thinners should be under medical supervision while taking melatonin supplements.
- Possible allergic reactions
  - There is always a potential for an allergic reaction when taking any supplement.
- Safety for pregnant and breastfeeding women
  - There has not yet been sufficient research into the impact of melatonin on pregnant women or women who are breastfeeding.
- Concerns for the elderly
  - The 2015 guidelines released by the American Academy of Sleep Medicine recommended against the use of melatonin by people with dementia [131].
  - Melatonin may remain active in the bodies of older people for a longer time, resulting in daytime drowsiness.

There are several side effects of melatonin use as noted by both NIH and the Mayo Clinic [131] [132] [133] [134]:

- Headache
- Dizziness
- Nausea
- Sleepiness
- Rebound insomnia
- Heart palpitations
- Abdominal pain
- Potential hepatotoxicity

Because of the slight hepatotoxicity, liver failure, renal failure, alcohol addiction, and high lipid levels should be considered as contraindications when prescribing melatonin [135]

Rarely reported side effects of melatonin include the following [134]:

- Nasopharyngitis
- Arthralgia
- Tachycardia
- Vomiting
- Nightmares
- Difficulty swallowing and breathing
- Hypnotic activity
- A feeling of heaviness in the head
- Heartburn
- Belching
- Swelling in the arms or legs
- Sweating
- Hot flashes
- Exanthema
- Sleep problems
- Depression
- Sleepwalking

Intravenous administration of melatonin has been described to increase peripheral blood circulation, leading to potentially undesirable side effects. These include vasoconstriction in cerebral arteries and a decrease in body temperature owing to increased blood flow to distal parts of the body [136]. The immune stimulatory effect of melatonin may also be undesired in patients with autoimmune disorders, and melatonin or melatonergic drugs may be contraindicated in these cases [137]. In some animal studies, melatonin has been described as carcinogenic in very high doses [133]. As with any agent, correct dosing is important (Table 2).

## 6. Conclusions

Melatonin was identified early on as a key component of the body's organic clock and circadian rhythm, but since then, it has become clear that this natural compound has other potential therapeutic uses as well. Melatonin is an indirect

**Table 2.** Melatonin dosage options.

<b>Melatonin Dosage for Cancer Care</b>				
Oral	Starting Dosage	20 mg daily	Max Dosage	100 mg daily (Toxic dosage has never been reached)
Intravenous	Starting Dosage	10 mg daily	Max Dosage	50 mg daily (titrate by 10 mg until max dose is reached)
Topical	Starting Dosage	X	Max Dosage	X
<b>Melatonin Dosage for Sleep Issues</b>				
Oral	Starting Dosage	1 mg daily	Max Dosage	5 mg daily for sleep
Intravenous-IV melatonin for sleep is only appropriate if unable to absorb or administer orally	Starting Dosage	10 mg daily	Max Dosage	10 mg daily.
Topical	Starting Dosage	2.5 mg daily	Max Dosage	5 mg daily
<b>Melatonin Dosage for Neurological Issues</b>				
Oral	Starting Dosage	10 mg daily	Max Dosage	80 mg daily
Intravenous	Starting Dosage	10 mg daily	Max Dosage	50 mg daily (titrate by 10 mg until max dose is reached)
Topical	Starting Dosage	X	Max Dosage	X

antioxidant and an efficient free radical scavenger, the combination of which makes melatonin very important for the body's ability to manage oxidative stress. As we discussed, managing oxidative stress is vital for the body's long-term health with high oxidative stress having a deleterious effect on the body, leading to cell death and conditions such as chronic inflammation, obesity, heart disease, and even neurological disease [138] [139] [140].

Perhaps, the most promising application of melatonin discussed in this report is as an anticancer agent. These anticancer properties have been widely studied in the literature; however, much remains to be discovered regarding the use of melatonin as a complementary anticancer agent. *In vitro* studies have yielded positive results, but clinical trials will be necessary to refine the use of melatonin for actual cancer patients. So far, researchers have been able to identify several relevant pathways for this anticancer effect. These mechanisms are related to antioxidant activity, modulation of MT1/MT2 receptors, apoptosis, pro-survival signaling, tumor metabolism, inhibition of angiogenesis, tissue invasion, and metastasis, and epigenetic alteration [16]. Overall, melatonin shows potential as an adjuvant for cancer therapy as it enhances the therapeutic effect of chemotherapy and radiation while mitigating some of the side effects [16]. Existing evidence from clinical use in humans is promising, showing that melatonin improves sleep and the quality of life in cancer patients [16]. With impressive efficacy from early trials and demonstrable safety in humans, melatonin seems to be

a promising candidate for the prevention and treatment of cancer among its other potential therapeutic uses.

After reviewing the existing literature, the reviewers of this report on melatonin feel that good avenues of future research utilizing melatonin include more extensive epidemiological studies in consideration of the fact that the ones which exist now have provided inconsistent results, so far [16]. The inconsistent results may be due to sample size and composition, as well as the assessment methods used during the study. Larger studies in the future may yield more consistent results that fall in line with the experimental and clinical evidence collected in other trials. The effects of the different collection methods, such as between urine, plasma, and serum, should be elucidated and defined with the same sort of sample collection methods compared against one another. Sample collection time is another crucial factor since levels of melatonin fluctuate drastically depending on the time of day and the patient's sleep cycle. Future studies should account for this fluctuation explicitly by collecting samples during the same period for each patient and also ensuring that they are as close to the same point in their circadian rhythm as possible. For instance, a night shift worker will have a different melatonin pattern than a day worker even if samples are collected at the same time of day.

With regard to experimental and benchtop studies, we suggest that the regulatory nature of melatonin and the heterogeneous nature of cancer be taken into account. For example, during our research, we were able to find very few articles mentioning the process of autophagy with melatonin, which is a prominent mechanism of apoptosis. There are other molecular mechanisms that are also worthy of further scientific scrutiny, considering melatonin's protective effect with mitochondria and prevention of mitochondrial dysfunction. Finally, in the area of clinical trials, we recommend that melatonin be evaluated as an adjuvant for more anticancer drugs in order to obtain a broader sense of its potential applicability. Using melatonin in future clinical trials should provide valuable data on accurate dosage and define the long-term safety of melatonin administration.

## Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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