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Melatonin in Cancer Research: Exploring Therapeutic Potential in Counteracting Cancer

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ABSTRACT

Melatonin, a hormone intricately linked to circadian rhythms, has garnered increasing attention for its potential therapeutic role in counteracting cancer. This review navigates the landscape of melatonin's influence in cancer research, emphasizing its promising capacity to counteract various facets of cancer development and progression. With widespread expression of melatonin receptors in diverse organs, its systemic impact underscores its potential as a cancer-modulating agent. The anticancer effects of melatonin have been extensively investigated, revealing its involvement in antiproliferative, antioxidative, and immunomodulatory mechanisms. Studies in cell lines and animal models have demonstrated its ability to impede cancer initiation, promotion, and progression. Clinical trials exploring melatonin's synergy with conventional therapies, including chemoradiotherapy, provide encouraging evidence of its therapeutic efficacy in counteracting cancer. Despite these promising aspects, challenges persist in translating melatonin's potential into clinical applications. Issues such as optimal dosage, administration methods, and standardization of melatonin measurements need meticulous consideration. Overcoming these challenges is essential to harness the full therapeutic potential of melatonin in cancer counteraction. This review advocates for further exploration into novel drug formulations to enhance melatonin bioavailability, establishment of standardized measurement criteria, and comprehensive clinical studies to delineate optimal dosages and long-term safety. Understanding the molecular intricacies of melatonin's counteracting effects on cancer will not only enrich our comprehension of its therapeutic potential but also pave the way for its strategic integration into cancer treatment paradigms. We hope that this assessment will motivate us to create standardized methods for researching and utilizing melatonin in the treatment of cancer.

Keywords: Cancer, Melatonin, Treatment, anticancer, combination therapy

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INTRODUCTION

Cancer, a complex and heterogeneous group of diseases, remains a global health challenge, accounting for approximately 10 million deaths per year (1). The pursuit of effective therapeutic strategies has led researchers to explore unconventional avenues, and among these, melatonin has emerged as a compelling candidate. Melatonin, traditionally recognized for its role in circadian rhythm regulation, has garnered increasing attention for its potential impact on cancer treatment (2).

The intricate interplay between melatonin and cancer spans various facets of tumorigenesis, progression, and response to treatment (3, 4, 5, 6). Beyond its chronobiological functions, melatonin exhibits diverse physiological roles, including antioxidant, anti-inflammatory, and immunomodulatory effects. As researchers delve into the molecular intricacies of cancer, the multifunctional nature of melatonin has sparked interest in harnessing its therapeutic potential (7).

MLT is not considered a hormone in the traditional sense; instead, it functions as a cell protector due to its absence of synthesis in a single organ and its lack of effects on a specific target organ. It has been acknowledged that MLT is a molecule exhibiting paracrine, autocrine, and antioxidant effects, displaying a range of receptor-dependent and receptor-independent actions (8, 9). These actions contribute to overall homeostatic functions and diverse effects relevant to cell protection and survival (10). Additionally, MLT is recognized for its robust antioxidant, immunomodulating, antiproliferative, oncostatic, and endocrine-modulating properties (11, 12). The oncostatic and tumor-inhibitory effects of MLT have become an increasingly fascinating area of exploration in various experimental models and clinical scenarios.

In this review, we navigate through the evolving landscape of melatonin in cancer treatment, emphasizing its diverse mechanisms of action and the growing body of evidence supporting its efficacy. From influencing key signaling pathways to modulating the tumor microenvironment, melatonin holds promise as an adjunctive therapy with conventional cancer treatments. As we explore the current state of knowledge, it becomes evident that melatonin's impact extends beyond its direct effects on cancer cells. Its ability to counteract chemotherapy-induced toxicity, enhance the efficacy of standard treatments, and improve overall patient well-being underscores the translational potential of melatonin in the oncological setting.

This review aims to synthesize existing literature, providing a comprehensive overview of the role of melatonin in cancer treatment. By examining the molecular underpinnings, experimental evidence, and clinical applications, we strive to contribute to the growing discourse on leveraging melatonin as a valuable tool in the oncologist's arsenal. In doing so, we envision advancing our understanding of melatonin's therapeutic landscape and fostering its integration into personalized cancer care.

BASIC BIOLOGY OF MELATONIN

Melatonin (N-acetyl-5-methoxy-tryptamine) is a hormone that plays a crucial role in regulating the sleep-wake cycle, also known as the circadian rhythm, in both humans and animals. It is produced primarily by the pineal gland, a small pea-sized gland located deep within the brain (13). The synthesis and release of melatonin (MLT) are influenced by the amount of light exposure an individual receives. The production of melatonin follows a natural circadian rhythm, with levels typically rising in the evening as it gets dark and peaking during the night. Light exposure, particularly to blue light, inhibits melatonin production, while darkness, or the absence of light, signals the pineal gland to release MLT into the bloodstream.

Melatonin production is intricately linked to the function of the suprachiasmatic nucleus (SCN) in the hypothalamus, often referred to as the body's "master clock" (14) . The SCN receives information about environmental light conditions through the eyes and signals the pineal gland to adjust melatonin production accordingly. This process helps synchronize the body's internal clock with the external day-night cycle. The melatonin concentration in both cerebrospinal fluid (CSF) and blood peaks between 2:00 a.m. and 4:00 a.m., gradually decreasing throughout the daytime. During the night, the serum melatonin level ranges from 80 to 120 pg/mL but significantly drops to 10–20 pg/mL during daylight hours (15). Numerous clinical trials have investigated exogenous melatonin for its potential in managing circadian and sleep disorders, and it is widely employed in clinical settings (16). Beyond its role in regulating sleep, MLT has been recognized for its antioxidant properties. It scavenges free radicals, unstable molecules that can damage cells and contribute to aging and various diseases. Additionally, melatonin has immunomodulatory effects, influencing the immune system's activity and response (2). Orally administered melatonin is susceptible to rapid degradation in the liver by cytochrome P450 enzymes, specifically CYP1A1 and 1A2 enzymes (17), leading to its limited and inconsistent bioavailability. To circumvent this initial metabolic process, alternative administration routes have been explored (18).

Comprehensive comprehension of melatonin's biosynthesis and secretion is crucial for its examination in living organisms and clinical implementation. Creating standardized schedules, doses, and administration methods has the potential to optimize the impact of externally administered melatonin in clinical settings. The considerable variability in concentration and unique solubility of this hormone poses a challenge in its application for cancer treatment.

MELATONIN MECHANISM OF ACTION

In short, it can be said; Melatonin (MLT) and its metabolites interact with proteins like calmodulin, nuclear-membrane receptors (RZR, ROR families) (19), and cell membrane receptors. High-affinity (MT1) and low-affinity melatonin receptors (MT2, MT3) have been identified. MT1 and MT2, part of the G-protein-coupled receptor (GPCR) group, inhibit adenyl cyclase and cyclic AMP (cAMP), reducing linoleic acid uptake, contributing to antiproliferative effects (20).

The X-linked orphan GPCR, GPR50, shares homology with MT1 and MT2 (21). Its role in hypothalamic functions is unclear, but it can heterodimerize with GPCRs, influencing their function. MT3 is quinone reductase 2 (QR2), a detoxifying enzyme (22, 23). Melatonin demonstrates oncostatic properties in various tumors, particularly hormone-dependent ones. Mechanisms include antioxidant effects, ERα regulation, cell cycle modulation, antiangiogenesis, immune system activation, and epigenetic factors (24, 25).

Melatonin's anticarcinogenic actions involve antioxidative and free radical-scavenging activity. Antiestrogenic effects result from ERα reduction and inhibition of E2-ER binding to DNA through specific MT1 receptors (25). Calmodulin inactivation by melatonin also interacts with the estrogen-signaling pathway. Melatonin's antiangiogenic effects involve VEGF inhibition and neutralizing tumor growth factors (26). Melatonin is synthesized by lymphoid organs, acting as an immunoenhancer by stimulating immune components. Its potential role in epigenetic modulation of gene transcription has been suggested.

ANTICANCER EFFECT OF MELATONIN

Melatonin, commonly known as the "sleep hormone," has garnered attention not only for its role in regulating circadian rhythms and sleep-wake cycles but also for its potential anticancer properties. Emerging research suggests that melatonin may exert protective effects against various types of cancer, making it a subject of interest in cancer prevention and treatment (27).

One of the key mechanisms through which melatonin demonstrates its anticancer effects is its ability to modulate the cell cycle (28). Melatonin has been shown to inhibit the proliferation of cancer cells by regulating the progression of the cell cycle, preventing abnormal cell growth and division. Additionally, melatonin may

induce apoptosis, a programmed cell death, in cancer cells, thereby eliminating damaged or abnormal cells. Moreover, melatonin possesses antioxidant properties, helping to neutralize harmful free radicals that can contribute to the initiation and progression of cancer. Free radicals can damage DNA and other cellular components, leading to mutations that may promote the development of cancer (29). By scavenging free radicals, melatonin may help protect cells from oxidative stress and reduce the risk of cancer development. Melatonin's influence on the immune system is another aspect contributing to its potential anticancer effects. It has been found to enhance the activity of immune cells, such as natural killer cells and macrophages, which play a crucial role in identifying and eliminating cancer cells. By bolstering the immune response, melatonin may contribute to the body's ability to defend against cancer (30).

Research studies have explored the impact of melatonin on various types of cancer, including breast, prostate, colorectal, and ovarian cancers, among others. While the results are promising, it's important to note that melatonin is not a standalone cure for cancer, and its potential role in cancer prevention and treatment should be considered as part of a comprehensive approach. Despite the promising findings, further research is needed to fully understand the specific mechanisms and optimal dosages of melatonin for anticancer effects. Additionally, individual responses to melatonin may vary, and its use in cancer care should be approached in consultation with healthcare professionals.

In conclusion, melatonin exhibits potential anticancer effects through its influence on cell cycle regulation, apoptosis induction, antioxidant activity, and immune system modulation. While research in this area is ongoing, the current evidence suggests that melatonin may play a valuable role in supporting cancer prevention and treatment strategies.

In a clinical investigation employing a randomized, double-blind design, melatonin was administered concomitantly to individuals diagnosed with head and neck cancer. The findings revealed that melatonin not only restrained the antioxidant capacity of the patients but also mitigated mucositis and alleviated pain (31, 32). Furthermore, when melatonin was combined with a standard cisplatin-based treatment, it led to a reduction in anemia, a prevalent side effect associated with cisplatin use (33). Exploring its impact on the adverse effects of chemotherapy, a study involving patients with gastrointestinal cancer demonstrated that while melatonin could maintain body weight, it did not effectively alleviate cachexia (34).

In the realm of metastatic colorectal cancer, a clinical study unveiled that individual who received low-dose, subcutaneous IL-2 in conjunction with melatonin following a first-line therapy of 5-FU exhibited a higher one-year survival rate compared to those subjected to 5-FU treatment alone. This suggests the potential use of low-dose, subcutaneous IL-2 and melatonin as a second-line therapy for colon cancer (35).

A randomized clinical trial focusing on metastatic breast cancer patients demonstrated that those undergoing treatment with both tamoxifen and melatonin exhibited a higher relative response in comparison to those solely receiving tamoxifen (36). However, contradictory results emerged in some clinical trials. Postmenopausal breast cancer patients in stages 0–III, who had completed anticancer treatment and received an oral melatonin supplement (3 mg/day for 4 months), did not show significant improvements in serum biomarkers (estradiol, IGF1, IGFBP-3) linked to breast cancer (37).

Investigations into the application of melatonin in non-small cell lung cancer (NSCLC) patients indicated that while melatonin enhanced quality of life, it did not demonstrate protective effects against chemotherapy-related side effects (38). Additionally, adjuvant melatonin administration following resection of NSCLC improved the 2-year disease-free survival (DFS) in late-stage patients but did not exhibit discernible benefits in terms of quality of life, symptoms, or immune function (39). Further studies are imperative to explore the potential benefits of melatonin on this global leading cause of cancer-related deaths.

Despite a substantial body of clinical evidence supporting melatonin's anticancer effects, conflicting results persist. More in vivo studies and clinical trials are warranted to ascertain its precise clinical application in cancer treatment.

EFFECT OF MELATONIN IN COMBINATION WITH OTHER THERAPY IN CANCER

In the realm of cancer treatment, chemotherapy, despite significant progress, remains a prevalent approach, encountering challenges such as widespread organ and systemic side effects along with the emergence of drug resistance. Melatonin has emerged as a promising adjuvant to chemotherapy, exhibiting various benefits such as heightened drug efficacy and mitigation of side effects. As you can see in Chart 1. studies have indicated that melatonin can sensitize cancer cells to chemotherapy, fostering apoptosis and autophagy (26, 40, 41, 42, 43, 44, 45, 46). Notably, one study highlighted an intriguing interplay where melatonin and doxorubicin enhanced apoptosis in human breast cancer cells through autophagy-dependent reduction in AMPKα1 transcription (40).

The combination of melatonin with radiotherapy also shows potential for synergistic antitumoral effects and overcoming drug resistance. For instance, melatonin counteracted the inhibitory effects of radiation on pre-adipocyte differentiation, exhibiting a potential role in stimulating specific gene expressions (47). While in vitro studies have demonstrated melatonin's ability to enhance radiotherapy effects, clinical investigations in humans are limited. A study involving glioblastoma patients reported increased 1-year survival rates and improved life quality with the combination of melatonin and 60 Gy of radiation (48). However, no clinical benefit was observed in patients with cerebral metastases receiving 30 Gy of radiotherapy and 20 mg of melatonin (49).

Immunotherapy, an approach focused on boosting the immune system's activity, has become a forefront in cancer treatment. Melatonin's immunomodulatory effects position it as a potential adjunct to immunotherapy. Studies have explored its synergistic effects with immunotherapy drugs, enhancing the effectiveness of IL-2 (50) and improving outcomes in combination with anti-PD-1

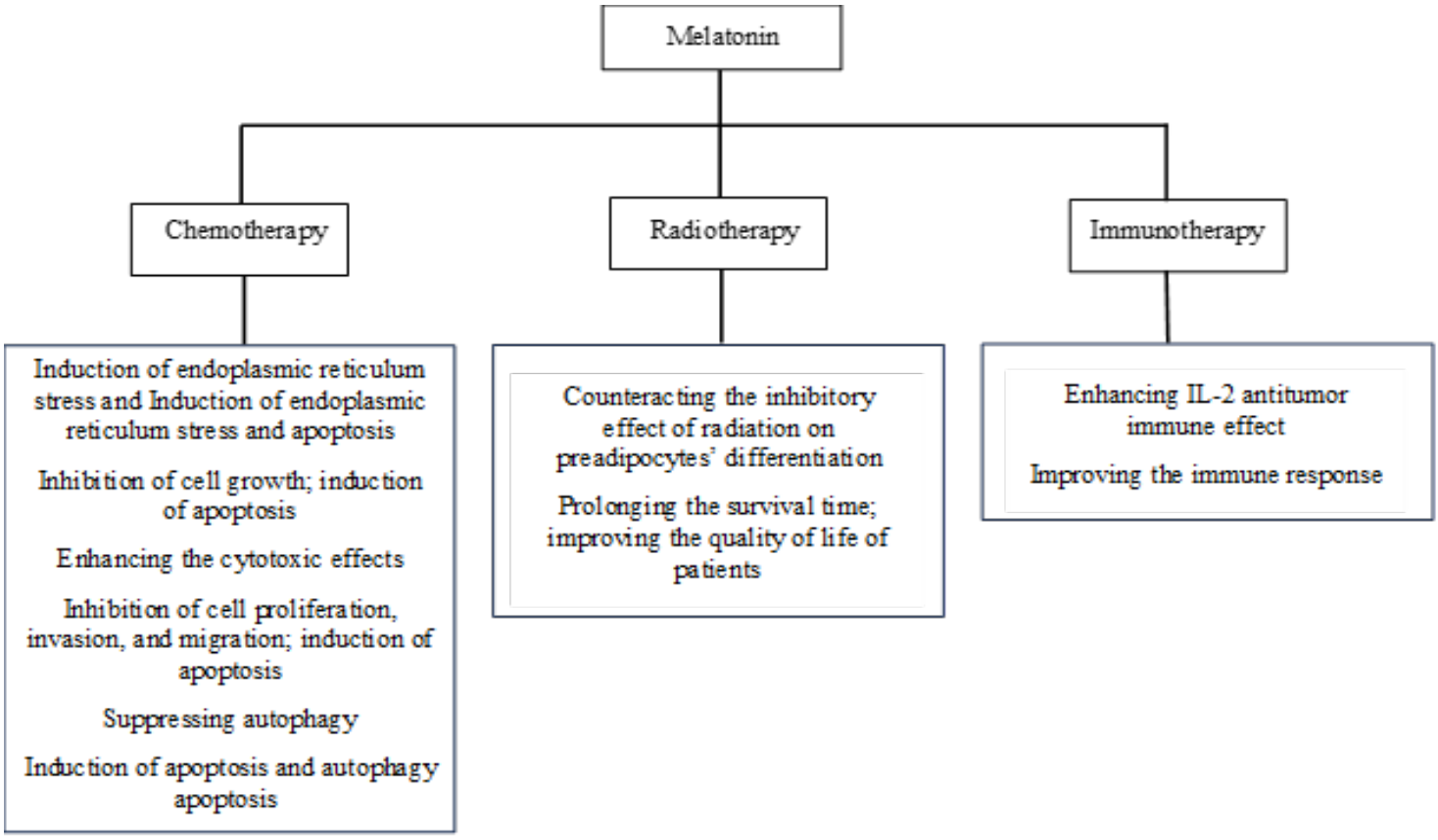

Chart 1. The result of combining melatonin with other cancer treatments

treatment (2). Melatonin's ability to stimulate lymphocyte proliferation, suppress the YAP/PD-L1 axis, and augment antitumor immunity further supports its potential as an immunotherapy adjunct (51, 52). Regarding its immunopotentiating effects, MLT enhances immunosurveillance by promoting the activity of lymphocytes, monocytes/macrophages, and natural killer cells. Human lymphoid cells themselves produce MLT, regulating the immune system in both a paracrine and autocrine manner. MLT has been demonstrated to elevate the production of various cytokines, including IL-1, IL-2, IL-6, IL-12, IFN-γ, and TNF-α (11). Except for free-radical scavenging, these activities are believed to be receptor-mediated, specifically through receptors MLT1 and MLT2 (11). Nuclear binding sites for MLT have been identified in most tissue types, suggesting that MLT may influence genomic activity at these sites, which include receptors belonging to the retinoic acid receptor family (11, 12). In the landscape of cancer treatment, melatonin's multifaceted contributions make it a promising candidate for combination therapies, offering potential avenues for enhanced therapeutic outcomes.

COMBINATION OF MELATONIN WITH OTHER ANTICANCER DRUGS

The use of melatonin as a potential anticancer drug has been a subject of research interest, but there are several challenges and limitations associated with its application. While preclinical studies and some early-phase clinical trials have suggested potential anticancer effects of melatonin, there is a lack of large-scale, well-designed clinical trials providing robust evidence of its efficacy in cancer treatment. but determining the optimal dose and timing of melatonin administration for anticancer effects poses a challenge. The effective dose may vary among individuals, and the timing of administration, considering circadian rhythms, is crucial for maximizing its benefits.

Melatonin has a short half-life and may exhibit poor bioavailability, which can impact its effectiveness as a therapeutic agent. Improving its pharmacokinetic profile is a consideration for enhancing its anticancer potential. melatonin's standard oral dose ranges from 3 mg to 10 mg daily (53). and higher doses of melatonin are required in cancer, which may lead to increased risks and severity of side effects. Therefore, exploring alternative administration routes to enhance bioavailability and determine optimal cancer treatment dosages is imperative (54).

melatonin is known for its antioxidant properties, at higher doses or under certain conditions, it may exhibit pro-oxidant effects. This dual nature of melatonin's actions requires careful consideration in therapeutic applications (55). The exact mechanisms through which melatonin may exert anticancer effects are not fully understood. Better understanding of its molecular targets and pathways is essential for targeted and effective cancer therapy. Melatonin is generally considered safe, but determining the optimal dosage for cancer therapy remains a challenge. on the other; Melatonin's interactions with other cancer treatments, such as chemotherapy and

radiation therapy, are complex and not fully understood. Co-administration may lead to unpredictable outcomes and potential complications.

Responses to melatonin can vary widely among individuals Tailoring melatonin-based therapies to individual patients adds another layer of complexity. In conclusion, while melatonin shows promise as an anticancer agent, addressing the above challenges is crucial for its successful integration into cancer treatment strategies. Further research, especially large-scale clinical trials, is needed to establish its efficacy, optimal usage, and safety profile in diverse cancer contexts.

CONCLUSION

MLT stands out as a remarkably widespread and functionally diverse molecule, with its membrane receptors dispersed across various organs and cell types. Recognized both as a chronobiotic and a chronobiological regulator, MLT has increasingly drawn attention in aging and age-related disease processes, particularly involving the pineal gland. Nuclear receptors of the ROR family and other binding sites suggest potential systemic actions that remain incompletely understood.

The safety profile of MLT appears to be notably high, as indicated by human trials and reported usage. On the contrary, MLT demonstrated a reduction in some of the side effects resulting from chemotherapy and radiation therapy. Extensive research has delved into MLT's anticancer effects, examining cell lines across different cancer types and animal models. Evidence from studies on MLT's antiproliferative, antioxidative, and immunostimulatory mechanisms, coupled with clinical trials incorporating MLT in chemoradiotherapy and supportive care, hints at its role as a physiological anticancer substance.

Further exploration of MLT as an adjunctive treatment for cancer is warranted, especially considering the increasing observational evidence suggesting that dysregulated MLT rhythms may elevate cancer risk. Investigating the chemo preventive potential of exogenous MLT in a clinical setting is crucial. Studies indicate that MLT might safely enhance 1-year survival rates and response rates when incorporated into various standard cancer care approaches. It may also mitigate chemotherapy-related toxicity and improve cancer-related symptoms. Nevertheless, well-controlled trials with larger cohorts and extended follow-up periods are imperative to establish the link between observed effects, underlying mechanisms, and the significance of MLT as a therapeutic oncostatic agent.

Addressing challenges in melatonin's application, such as low biocompatibility, non-uniform melatonin level measurement, uncertainty in dosing regimens and side effects, and an unclear administration approach, is crucial for its clinical use. The development of new drug forms or carriers to enhance bioavailability, clarifying sample collection criteria, understanding optimal dosage and long-term safety, and delving into molecular mechanisms through clinical studies are essential steps. This review aims to shed light on melatonin's potential in anticancer therapy, offering varied perspectives to enrich our understanding and potentially paving the way for its development as a standalone or combination therapy in cancer treatment.

CONFLICT OF INTERESTS

The authors declare no conflict of interest.

ABBREVATIONS

MLT; Melatonin, SCN; Suprachiasmatic nucleus, CSF; Cerebrospinal fluid, GPCR; G-protein-coupled receptor, QR2; Quinone reductase, NSCLC; Non-small cell lung cancer, DFS; Disease-free survival.

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