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REVIEW

The Influence of Melatonin on Brain Tumors: A Comprehensive Review

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SUMMARY

Primary brain tumors are a heterogeneous group of neoplasms, originating from glial and other cell types in the central nervous system (CNS). Despite advancements in technology and medicine, the prognosis for malignant brain tumors remains poor. This situation requires novel therapeutic approaches. Melatonin, a hormone produced by the pineal gland, regulates sleep and circadian rhythms. It also possesses various biological functions, such as antioxidant properties, immune modulation, and tumor suppression. This review analyzes existing research on the effects of melatonin on brain tumors, focusing on its therapeutic potential and mechanisms of action, and highlights melatonin's promise as a complementary therapy against adult and pediatric high-grade gliomas.

Keywords: Brain tumors; high-grade gliomas; melatonin; therapeutic potential.

INTRODUCTION

Primary brain tumors are a heterogeneous group of neoplasms, originating from glial and other cell types in the central nervous system (CNS).[1] The treatment of brain tumors is complex and varies according to the tumor type, size, location, and overall health of the patient. Standard treatments include surgery, radiation therapy, and chemotherapy or immunotherapy. Despite advances in treatment options, the prognosis of primary high-grade brain tumors remains poor, with high morbidity and mortality rates, emphasizing the need for novel therapeutic approaches.[2]

Melatonin is a hormone produced by the pineal gland primarily during the dark phase of the light/dark cycle. It not only regulates sleep and circadian rhythms but also possesses various biological functions, which include antioxidant activities, immune response modulation, and influence in tumor growth and suppression.[3] Because of its oncostatic properties, melatonin has garnered attention in the context of cancer, and it has been extensively studied in various types of cancers, including breast, colorectal, and lung cancers.[4–6] Multiple studies have demonstrated that its mechanisms of action in cancer therapy involve modulating cell cycle regulation, inducing apoptosis, and inhibiting angiogenesis.[7]

One primary way melatonin exerts its antioxidant properties is through its ability to directly scavenge free radicals, such as hydroxyl and peroxyl radicals, thereby preventing oxidative damage to cells and tissues.[8] Additionally, melatonin has been shown to upregulate the activity of antioxidant enzymes, including superoxide dismutase, catalase, and glutathione peroxidase, which play crucial roles in neutralizing reactive oxygen species and maintaining cellular homeostasis.[9] This dual action makes melatonin an effective protector against oxidative stress, which

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is implicated in the pathogenesis and progression of several types of brain tumors.

Furthermore, melatonin has been found to enhance the expression and activity of various antioxidant defense systems, such as the nuclear factor erythroid 2-related factor 2 (Nrf2) pathway, which regulates the transcription of genes encoding antioxidant proteins. Through these mechanisms, melatonin effectively mitigates oxidative stress and promotes cellular resilience against oxidative injury.[10] Importantly, the ability of melatonin to exert its antioxidant effects is not limited to a specific cellular compartment or tissue, as it readily crosses cell membranes and accumulates in mitochondria, where it can directly scavenge reactive oxygen species and modulate mitochondrial function.[11]

The regulation of circadian rhythms by melatonin is a complex and fascinating area of study in the field of chronobiology. Circadian rhythms are the natural, internal processes that regulate the sleep-wake cycle and many other physiological and behavioral functions in living organisms. These rhythms are roughly 24 hours long and are influenced by environmental cues such as light and temperature. Melatonin plays a crucial role in the regulation of these rhythms by acting on the suprachiasmatic nucleus (SCN) of the hypothalamus, which is the central circadian clock in humans.[12] This regulation affects not only the sleep-wake cycle but also various biological functions that are relevant to tumorigenesis, including cell proliferation, DNA repair, and metabolism.

This review aims to collate and analyze existing research on the effects of melatonin on primary brain tumors, with a focus on elucidating its therapeutic potential and mechanisms of action. Given the challenges in treating primary brain tumors and the emerging role of melatonin in oncology, it is crucial to explore how this naturally occurring compound may contribute to more effective brain tumor therapies. This exploration could lead to new insights into combinatory treatment regimens and improve outcomes in patients with gliomas.

MELATONIN

Biological and Chemical Composition

Melatonin is primarily synthesized in the pineal gland, a small endocrine gland located in the brain midline. The synthesis and regulation of melatonin production is a complex process that involves several key steps and is regulated by the circadian rhythm, which is influenced by external cues, such as light and darkness, and internal regulators, such as the hormone cortisol, which is produced by the adrenal glands in response to stress. Therefore, in dark environments, the suprachiasmatic nucleus in the brain, which receives input from the eyes regarding light levels, stimulates the pineal gland to produce and release melatonin into the bloodstream.[13] In addition, cortisol levels typically decrease in the evening, allowing melatonin production to increase.

The synthesis of melatonin, also known as N-acetyl-5-methoxytryptamine, begins with the amino acid tryptophan (Fig. 1). Through a series of enzymatic reactions, tryptophan is converted into serotonin, which is then further metabolized into melatonin, primarily in the pineal gland. It is structurally characterized by a substituted aromatic indole ring and an amine group. Melatonin is unique in its structure, containing a flexible N-acetyl side chain attached to the indole ring, which allows for various functionalities and interactions within the body. Due to its lipophilic nature, melatonin can easily pass through cell membranes and the blood-brain barrier, enabling it to exert its effects on the CNS.

Melatonin affects the brain and other tissues mainly through its receptors, MT1 and MT2, which belong to the G protein-coupled receptor (GPCR) family.[14] These receptors are key players in translating melatonin's signaling in various physiological and pathological processes, including tumorigenesis.

Oncostatic Mechanisms

As we delve into the intricate mechanisms through which melatonin inhibits tumor growth (oncostasis), it becomes evident that this hormone holds great potential for therapeutic applications in cancer management and prevention, and understanding those mechanisms is crucial for harnessing the full potential of this hormone in combating cancer and promoting overall health.[15,16]

Research has revealed several mechanisms through which melatonin exerts its influence on cancer. These diverse actions underline the significance of melatonin in maintaining oncostasis and protecting against carcinogenesis.[17,18] The elucidation of these mechanisms sheds light on the diverse pathways through which melatonin exerts its oncostatic effects, offering valuable insights for the development of novel interventions in cancer therapy.

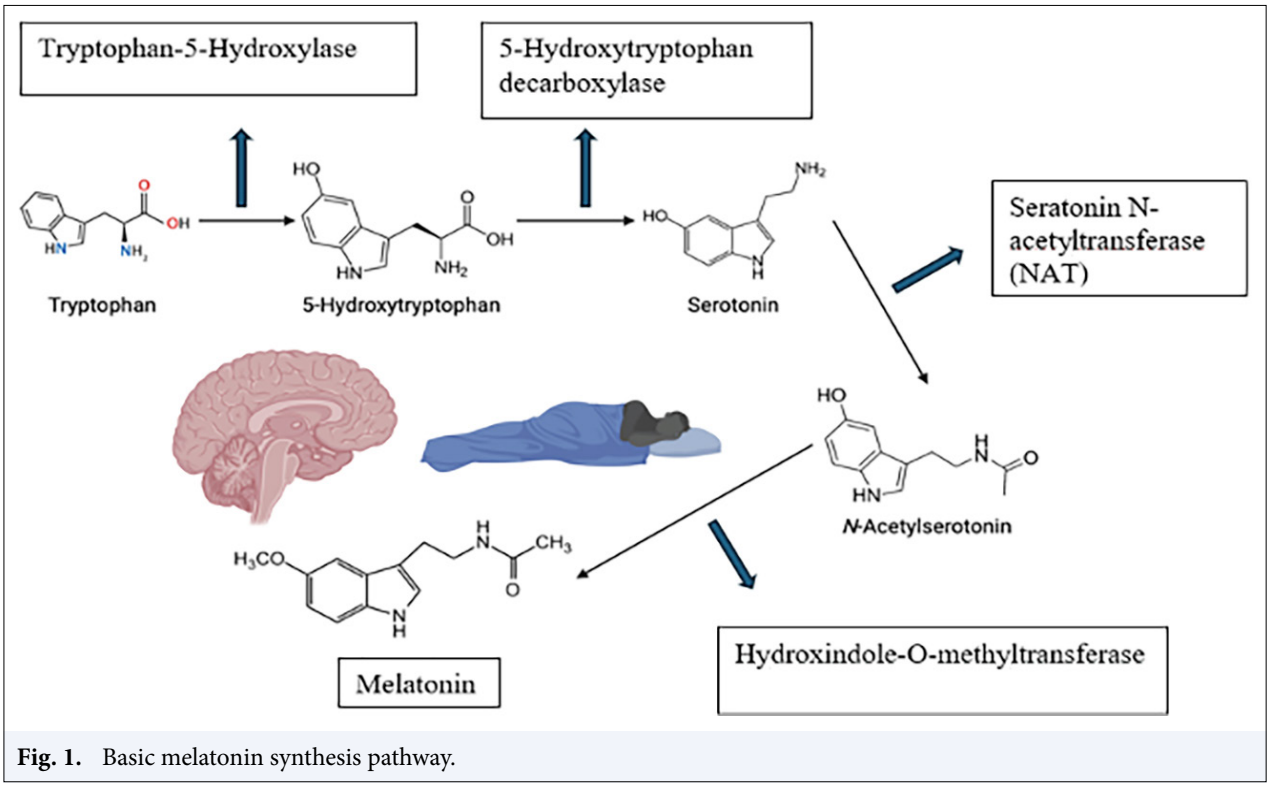

Fig. 1. Basic melatonin synthesis pathway.

Regulation of the Cell Cycle

Melatonin has been shown to modulate the expression of key proteins involved in the cell cycle, such as cyclins and cyclin-dependent kinases, leading to the suppression of tumor growth, via activation of MT1 and MT2.[19] Interestingly, melatonin-induced cell cycle arrest occurs in various phases, depending on the cancer type. For example, in the G1 phase in breast cancer cells and in the G0/G1 phase in prostate cancer cells.[20,21] Another study demonstrated that melatonin pretreatment in breast cancer cells before radiation exposure decreased the proportion of cells in the G2-M phase, suggesting that melatonin also affects the transition between the G2 and M phases.[22]

Regulation of Apoptosis, Angiogenesis, and Metastasis

In CNS cells, melatonin alters the expression of cell cycle proteins and regulates apoptosis through the intrinsic (mitochondrial) pathway, which is characterized by the release of cytochrome c and the activation of caspases. Therefore, melatonin may be involved in the pathogenesis of both neoplastic and non-neoplastic diseases, such as Parkinson's and Alzheimer's diseases.[23–25]

Additionally, melatonin affects angiogenesis and metastasis, which are crucial processes for tumor growth and progression, by inhibiting vascular endothelial growth factor (VEGF) and matrix metalloproteinases (MMPs).[26] Additionally, melatonin has been shown to inhibit angiogenesis, the process by which new blood vessels are formed, which is essential for tumor growth and metastasis.[27,28] Importantly, those actions help to eliminate cancer cells without affecting neighboring healthy cells, which is beneficial for reducing side effects in clinical settings.[24] Therefore, melatonin enhances the efficacy of chemotherapy and reduces its toxicity by acting as an adjuvant in cancer treatment protocols.[29]

Interaction with the Endocrine System

In addition to its direct actions on cells, melatonin also interacts with the endocrine system, modulating the secretion of estrogen and insulin, which play crucial roles in cancer development and progression.

Estrogen is a key hormone in the development and progression of hormone-dependent cancers, particularly breast cancer. Melatonin exerts antiestrogenic effects by reducing the expression of estrogen receptor alpha (ERα) and inhibiting the binding of the estradiol (E2-ER) complex to the estrogen response element (ERE) on DNA. This interaction is mediated through melatonin's binding to its MT1 receptor, which ultimately suppresses ERα mRNA expression and ERα transcriptional activity.[21,30] By disrupt-

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ing estrogen signaling, melatonin inhibits the proliferative and invasive potential of estrogen-responsive cancer cells, contributing to its oncostatic effects.

Insulin is another hormone implicated in cancer development. It plays a role in cell proliferation and survival by activating the insulin-like growth factor (IGF) signaling pathway, which can lead to increased tumor growth and progression. Melatonin modulates insulin secretion and insulin receptor signaling, which can reduce the proliferative signals in cancer cells. This modulation helps in lowering the risk of cancer development and progression associated with hyperinsulinemia and insulin resistance.[25,30]

In summary, melatonin's interaction with the endocrine system, particularly its modulation of estrogen and insulin, is a crucial mechanism in its ability to inhibit cancer development and progression. These interactions highlight melatonin's potential as a complementary therapeutic agent in hormone-dependent cancers.

Modulation of Immune Response

Melatonin modulates the immune response by enhancing the activity of immune cells and promoting anti-tumor immunity. It interacts with various immune cells and cytokines, exerting immunomodulatory effects that contribute to suppressing cancer progression. Specifically, melatonin enhances the function of natural killer (NK) cells, cytotoxic T lymphocytes (CTLs), and macrophages, which play crucial roles in identifying and destroying cancer cells.[31]

Melatonin enhances the function of various immune cells, including natural killer (NK) cells, cytotoxic T lymphocytes (CTLs), and macrophages. These cells play crucial roles in recognizing and destroying cancer cells. For instance, melatonin has been shown to stimulate the activity of NK cells, which are essential in the body's first line of defense against tumors. It also boosts the production of interleukin-2 (IL-2), a cytokine critical for the proliferation and activation of T cells.[32,33]

Melatonin influences the production of several cytokines that are pivotal in immune responses. It promotes the secretion of pro-inflammatory cytokines such as IL-2, IL-6, and tumor necrosis factor-alpha (TNF-α), which enhance the immune system's ability to target and kill cancer cells. Conversely, melatonin can also exhibit anti-inflammatory properties, reducing the levels of cytokines that may promote tumor growth and metastasis under certain conditions.[32,33]

Melatonin modulates the function of T cells, including T-helper (Th) cells and regulatory T (Treg) cells. It has been found to inhibit the differentiation of Th17 cells, which produce the pro-inflammatory cytokine IL-17 involved in autoimmune and inflammatory diseases. By regulating T cell responses, melatonin helps maintain a balance in the immune system, supporting anti-tumor immunity while preventing excessive inflammation.[32,34]

Through its actions on immune cells and cytokines, melatonin enhances immune surveillance, the process by which the immune system monitors and eliminates cancer cells. This effect is crucial in preventing tumor development and progression, as a robust immune surveillance system can detect and destroy emerging cancer cells before they establish a foothold.[33]

In summary, melatonin's ability to modulate the immune response, enhance the activity of immune cells, and regulate cytokine production makes it a valuable agent in cancer therapy. Its immunomodulatory effects contribute to the suppression of cancer progression and support its role as a complementary therapy in oncology.

Modulation of Oxidative Stress and DNA Damage

The potent antioxidant properties of melatonin play a crucial role in mitigating oxidative stress and DNA damage, both of which are implicated in the development and progression of cancer. By scavenging free radicals and enhancing the activity of antioxidant enzymes, melatonin helps protect cells from oxidative injury and maintains genomic stability.

One primary way melatonin exerts its antioxidant properties is through its ability to directly scavenge free radicals, such as hydroxyl and peroxyl radicals, thereby preventing oxidative damage to cells and tissues.[8] Additionally, melatonin has been shown to upregulate the activity of antioxidant enzymes, including superoxide dismutase, catalase, and glutathione peroxidase, which play crucial roles in neutralizing reactive oxygen species and maintaining cellular homeostasis. This dual action makes melatonin an effective protector against oxidative stress, which is implicated in the pathogenesis and progression of several types of brain tumors.[8,9]

Furthermore, melatonin has been found to enhance the expression and activity of various antioxidant defense systems, such as the nuclear factor erythroid 2-related factor 2 (Nrf2) pathway, which regulates the transcription of genes encoding antioxi-

dant proteins. Through these mechanisms, melatonin effectively mitigates oxidative stress and promotes cellular resilience against oxidative injury.[35] Importantly, the ability of melatonin to exert its antioxidant effects is not limited to a specific cellular compartment or tissue, as it readily crosses cell membranes and accumulates in mitochondria, where it can directly scavenge reactive oxygen species and modulate mitochondrial function.[11]

Melatonin Receptors in Brain Tumors

The relationship between melatonin receptors and brain tumors has gained significant attention in recent years. Studies have shown that melatonin and its receptors may exert anti-tumor effects by inhibiting tumor cell growth, inducing apoptosis, and regulating angiogenesis. Dysregulation of melatonin receptor expression has been observed in certain brain tumors, including gliomas and medulloblastomas, indicating potential implications for targeted therapeutic interventions.[19] The MT1 receptor is widely distributed in the CNS, with high expression levels in the hippocampus, cerebellum, and cortex. In contrast, the MT2 receptor is predominantly found in the retina and brain, including the thalamus and hippocampus. These receptors are also present in brain tumor cell lines and appear to inversely correlate with tumor aggressiveness. Activation of these receptors can inhibit tumor cell proliferation and induce apoptosis, with higher expression of MT1 and MT2 receptors generally associated with better outcomes.[19,36] However, MT1 and MT2 have opposite effects on oncogenesis. According to Kinker et al.,[19] gliomas have decreased mRNA expression of MT1 (also known as MTNR1A) and increased mRNA expression of MT2 (also known as MTNR1B) compared to the normal brain cortex. The MT1/MT2 expression ratio negatively correlates with the expression of cell cycle-related genes and is a positive prognostic factor in gliomas. Specifically, MT1 impairs while MT2 promotes the proliferation of glioma and medulloblastoma cell lines. Therefore, gliomas exhibit decreased expression of MT1 and increased expression of MT2 compared to normal brain cortex.

Upon binding of melatonin to its receptors, a cascade of intracellular signaling events is initiated, leading to the modulation of gene expression, protein synthesis, and cellular functions. These signaling pathways involve the activation of various protein kinases, including protein kinase A (PKA), protein kinase C (PKC), and mitogen-activated protein kinases (MAPKs). Additionally, melatonin receptors can also modulate the activity of transcription factors such as NF-κB and CREB, further influencing gene expression and cellular responses.[37] Through these pathways, melatonin and its receptors can exert significant neuroprotective and oncostatic effects in brain tumors.[7]

In addition to their direct effects on tumor cells, targeting melatonin receptors may also enhance the efficacy of existing treatments such as chemotherapy and radiation therapy. Studies have suggested that melatonin receptor modulation may sensitize tumor cells to these treatments, making them more effective in inhibiting tumor growth.[38] Furthermore, the use of melatonin receptor-targeted therapies may also help mitigate some of the side effects associated with conventional treatments, improving the overall quality of life for brain tumor patients.[37,39] Understanding the role of melatonin receptors in brain tumors is paramount in elucidating the underlying mechanisms of tumor development and identifying novel therapeutic strategies.

MELATONIN EFFECTS IN BRAIN TUMORS

The background and rationale for the preclinical and clinical studies of melatonin in brain tumors are rooted in the need to explore alternative treatments for this complex and devastating condition. Brain tumors present a unique set of challenges due to their location, heterogeneity, and resistance to conventional therapies. This has prompted the search for novel treatment approaches that can target tumor cells while minimizing harm to healthy brain tissue. As mentioned in previous sections, melatonin protects neural cells from oxidative stress and apoptosis, which are significant concerns in brain pathologies, including brain tumors, and is crucial not only for inhibiting tumor growth but also for preserving the surrounding healthy brain tissue during aggressive cancer treatments.[39] Another important mechanism is melatonin's ability to regulate immune responses. It enhances immune surveillance against tumor cells, which is often compromised in brain tumors owing to the immunosuppressive microenvironment commonly associated with these tumors.[40] Melatonin has shown promise in various preclinical studies for its anti-tumor properties. Its ability to regulate various cellular processes, such as proliferation, apoptosis, and angiogenesis, makes it a compelling candidate for further investigation in the context of brain tumors.[39,41]

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Table 1 Recent preclinical tumor cell line studies of melatonin in brain tumors

Study	Cancer type	Cell line	Dosage	Treatment duration	Outcome
Stanford,[42]	Glioblastoma	T98G	2 mM	24 hours	Reduced migration and invasion, induced apoptosis
Cardinali,[43]	Neuroblastoma	SH-SY5Y	1 mM	72 hours	Increased sensitivity to chemotherapy, reduced cell proliferation
Moretti et al.,[41]	Glioblastoma	U87	1 mM	72 hours	Enhanced radiosensitivity, reduced proliferation
Gurunathan et al.,[44]	Glioma	U251	0.5 mM	48 hours	Induced apoptosis, decreased cell viability
Talib et al.,[15]	Medulloblastoma	DAOY	1.5 mM	48 hours	Decreased angiogenic factors, inhibited growth

Table 2. Recent preclinical animal studies of melatonin in brain tumor

Study	Cancer type	Animal model	Dosage	Treatment duration	Outcome
Moretti et al.,[41]	Neuroblastoma	Mice	10 mg/kg IP	30 days	Reduced tumor volume, decreased metastasis
Talib et al.,[15] proliferation	Glioma	Mice	15 mg/kg IP	30 days	Enhanced sensitivity to chemotherapy, reduced cell
González et al.,[18]	Medulloblastoma	Mice	20 mg/kg SC	45 days	Decreased angiogenesis, improved survival rates
Roy et al.,[45]	Glioblastoma	Rats	10 mg/kg PO	60 days	Inhibition of tumor progression, increased apoptosis

IP: Intraperitoneal; SC: Subcutaneous; PO: Oral

Preclinical Studies

Preclinical studies involving experiments on cell lines, tissues, and animal models have provided valuable insights into the potential therapeutic effects, safety, and efficacy of melatonin in brain tumors, by describing the pharmacokinetics and pharmacodynamics of melatonin, informing the optimal dosing regimens for clinical trials (Table 1, 2).[15]

Table 1 summarizes recent preclinical studies investigating the effects of melatonin on various brain tumor cell lines. Key findings include reduced migration and invasion, increased sensitivity to chemotherapy, enhanced radiosensitivity and induction of apoptosis.

Table 2 summarizes recent preclinical animal studies investigating the effects of melatonin on brain tumors. Key findings include reduced tumor volume, decreased metastasis, enhanced sensitivity to chemotherapy.

Researchers have explored the effects of melatonin on the growth and proliferation of brain tumor cells, as well as its ability to induce apoptosis in these malignant cells. Preclinical studies have also investigated the mechanisms by which melatonin exerts its anticancer effects, shedding light on its interactions with different signaling pathways and molecular targets within the tumor microenvironment. These studies have shown that melatonin can inhibit proliferation and induce apoptosis in glioma cells, one of the most common types of malignant brain tumors.[46] For instance, a study demonstrated that melatonin effectively reduced the viability of glioblastoma cells by modulating the PI3K/AKT pathway, an important signaling pathway involved in the regulation of cell cycle and apoptosis.[47] Moreover, melatonin has been found to increase the sensitivity of brain tumor cells to conventional treatments. In a notable study, melatonin was combined with temozolomide, the standard chemotherapeutic agent for glioblastoma, showing a synergistic effect that significantly enhanced cytotoxicity against cancer cells compared to the drug alone.[48]

In vivo studies have also demonstrated promising results in preclinical settings. In these studies, researchers have utilized animal models to investigate the efficacy of melatonin in suppressing the growth and progression of brain tumors. The pioneering study by Maestroni et al.[49] revealed that melatonin could inhibit the growth of various tumors, including brain tumors in mice, by modulating the immune system and boosting the body's natural cancer-fighting mechanisms. This research laid the foundation for subsequent investigations into melatonin's anti-cancer properties. More studies have expanded on these initial findings, consistently demonstrating that melatonin can reduce the proliferation and induce apoptosis in glioma cells. Moretti

et al.[41] showed that melatonin significantly decreased the viability of glioblastoma cells by influencing the PI3K/AKT pathway, which is vital for cell cycle regulation and apoptosis. Additionally, Talib et al.[15] found that combining melatonin with temozolomide, a standard chemotherapeutic for glioblastoma, created a synergistic effect, greatly increasing the cytotoxicity against cancer cells compared to temozolomide alone. González et al.[18] demonstrated that melatonin treatment in mice with induced glioblastomas resulted in significant tumor regression and improved survival rates.

Overall, preclinical research highlights melatonin's multifaceted role in combating brain tumors. It provides a strong foundation for further clinical trials, aiming to translate these promising preclinical findings into effective treatment strategies for patients with brain tumors.

Clinical Studies

Although preclinical results have been promising, clinical trials are crucial to validate these findings in human subjects. Extensive clinical trials specifically focusing on melatonin and brain tumors are limited; however, the review of clinical trials evaluating the efficacy of melatonin in brain tumor patients provides valuable insights into the potential benefits of this hormone as an adjuvant treatment. Two significant studies have been conducted to assess the impact of melatonin, and have shown that melatonin could have a positive effect on the treatment of brain tumors, with potential benefits that include inhibiting tumor growth, enhancing the quality of life for patients, and possibly even improving survival rates.[50,51]

For instance, one study by Talib et al.[15] investigated the effect of melatonin on glioblastoma patients. The study administered 20 mg of melatonin daily for six months and reported reduced tumor progression and enhanced treatment efficacy. Another study by Wang et al.[16] evaluated the impact of melatonin on glioblastoma, with patients receiving 10 mg of melatonin twice daily for five months. This study found no significant improvement but noted that the treatment was well-tolerated.

Moreover, several case reports have highlighted the individual responses of patients with brain tumors to melatonin therapy.[52] These reports often discuss improved quality of life, reduction in symptom severity, and unexpected remission durations in some cases. Although anecdotal, these outcomes suggest potential areas for more rigorous clinical investigations and highlight the need for personalized treatment approaches that consider the role of melatonin.[50]

A notable randomized phase II trial[53] investigated the combination of melatonin with radiation therapy in patients with brain metastases from solid tumors. This study aimed to enhance the sensitivity of tumor cells to radiation while protecting normal cells, ultimately improving therapeutic outcomes and reducing adverse effects. However, high-dose melatonin did not show any beneficial effect in this group of patients.

Wang et al.[16] hypothesize that the findings indicate that melatonin may exhibit anti-tumor properties through its antioxidant and immunomodulatory effects. This hypothesis is indeed supported by the findings in the original reports. Specifically, the study demonstrates that melatonin's antioxidant capacity reduces oxidative stress in tumor cells, which is crucial for preventing cancer progression. Additionally, the immunomodulatory effects of melatonin were shown to enhance the immune response against tumor cells, thus contributing to its anti-tumor properties. Furthermore, melatonin has been shown to mitigate the side effects of conventional cancer therapies, such as chemotherapy and radiotherapy, thereby improving the overall well-being of brain tumor patients.[54] The results from these trials have provided valuable insights into the potential efficacy of melatonin in treating brain tumors. This has allowed for a deeper understanding of the potential pathways and targets for therapeutic intervention, paving the way for further research and the development of more targeted and effective treatment strategies. However, it is essential to note that the results of these trials are not definitive, and further research is warranted to establish the efficacy of melatonin as a therapeutic intervention for brain tumors.[15]

The optimal dosing schedules for melatonin in cancer treatment are not well established. The pharmacokinetics of melatonin, especially in the context of brain tumors, require a detailed study to understand its metabolism, absorption, and elimination, which are critical for maximizing its therapeutic effects and minimizing potential side effects.[16] Recent clinical studies of melatonin in brain tumors summarize the melatonin dosages used in various clinical settings to treat brain tumors. The typical dosage ranges from 3 to 20 mg per day, with adjustments based on patient age, tumor type, and concomitant treatments. These studies highlight the variability in melatonin admin-

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istration, reflecting its tailored use in oncological therapies, depending on individual patient needs and specific clinical outcomes.[15,16] The pharmacokinetics of melatonin suggest that it is rapidly absorbed and metabolized, with peak plasma concentrations occurring within 60 min of oral administration and a half-life ranging from 40 to 60 min. This rapid action necessitates careful timing of doses to coincide ideally with the body's natural melatonin cycle, typically administered at bedtime to mimic physiological secretion patterns.[55]

A notable randomized phase II trial (NCT00031967) investigated the combination of melatonin with radiation therapy in patients with brain metastases from solid tumors. This study aimed to enhance the sensitivity of tumor cells to radiation while protecting normal cells, ultimately improving therapeutic outcomes and reducing adverse effects. The inclusion criteria focused on patients with histologically confirmed brain metastases who were ineligible or unwilling to participate in alternative stereotactic radiosurgery studies. The findings suggested that melatonin might enhance the therapeutic effects of radiation and improve the quality of life for patients with brain metastases.[56]

Overall, the outcomes of the key clinical trials have laid a solid foundation for ongoing research and have sparked optimism within the scientific and medical communities regarding the potential of melatonin in the management of brain tumors. These results serve as a catalyst for future studies and hold promise for the advancement of treatment options for patients battling this challenging disease. While the clinical trials present promising evidence, they also highlight the need for continued investigation to determine the true potential of melatonin in the treatment of brain tumors.[57]

Unique Considerations in Pediatric Settings

Pediatric gliomas are brain tumors that arise predominantly in glial cells and are among the most common solid tumors in children. They range from low-grade tumors, which are more localized and treatable, to high-grade tumors, such as glioblastoma multiforme, which are aggressive and often have poor prognoses.[58] The treatment of pediatric glioma usually involves a combination of surgery, chemotherapy, and radiation therapy; however, these treatments can lead to significant long-term side effects, given the vulnerability of the developing brain.[59]

However, the lack of data on the impact of melatonin on pediatric gliomas indicates a need for further research. This gap, coupled with the high prevalence of complementary and alternative medicine use among pediatric cancer patients, underscores the necessity for pre-clinical and clinical studies to explore the role of melatonin, particularly in combination with radiotherapy. Such research can pave the way for novel therapeutic strategies and improve the outcomes of pediatric gliomas. The use of melatonin in children requires careful consideration of dosing and timing to align with natural circadian rhythms and avoid disrupting developmental processes. Additionally, the long-term effects of melatonin supplementation in children are still under investigation, necessitating a cautious approach and thorough monitoring.

Preclinical studies on the impact of melatonin on pediatric glioma are relatively few but promising. Melatonin has been shown to exhibit oncostatic properties in various pediatric cancer cell lines, including neuroblastoma and medulloblastoma, suggesting similar potential in glioma cells. Despite these findings, specific studies involving melatonin and pediatric glioma cell lines are not well-documented in the available literature. The focus has predominantly been on adult glioma cell lines and other types of pediatric brain tumors. This indicates a gap in research that could be valuable for future studies. A notable study conducted on glioma cell lines demonstrated that melatonin enhances the efficacy of chemotherapeutic agents, reducing their required doses and potentially limiting their toxic side effects. This synergistic effect is crucial for pediatric populations, as reducing treatment toxicity is a significant goal in pediatric oncology.[60]

Clinical research on the role of melatonin in the treatment of pediatric glioma is in its early stages. However, case studies and small-scale clinical trials have explored its potential benefits. One pediatric study reported improved outcomes in children with high-grade gliomas when melatonin was used as adjuvant therapy along with traditional treatments, and highlighted not only a reduction in tumor progression but also an improvement in the quality of life and a reduction of treatment-related side effects.[61] DIPG and other pediatric brain tumors have poor prognoses with limited effective treatment options. Surveys show a high prevalence of complementary and alternative medicine use among pediatric oncology patients, including melatonin; however, specific research on its therapeutic impact is lacking.[62]

Given these preliminary positive findings, more robust clinical trials are needed to establish standardized protocols for melatonin use in pediatric glioma treatment. Research should focus on optimizing dosing schedules, long-term safety evaluations, and potential interactions with standard therapies to fully understand and leverage melatonin's therapeutic potential in pediatric settings.

DISCUSSION

The findings from various studies suggest that melatonin holds significant promise as a complementary therapy for brain tumors. Its low toxicity profile and multifaceted biological activities make it a compelling candidate for integration into existing cancer treatment protocols. Melatonin's antioxidant properties help mitigate oxidative stress, a key factor in tumor progression, while its ability to modulate immune responses enhances the body's natural defense mechanisms against cancer cells.[63,64] Clinical studies, though limited, indicate that melatonin can improve survival rates, reduce side effects, and enhance the quality of life for brain tumor patients.[65] These findings suggest that melatonin could enhance the efficacy of traditional treatments and reduce their associated toxicities.

To solidify the role of melatonin in cancer therapy, especially for brain tumors, larger and more rigorous clinical trials are necessary. These studies should aim to establish optimal dosing regimens, clarify their therapeutic potential, and define their role in combination therapies. Additional studies should aim to elucidate the specific molecular mechanisms by which melatonin influences cancer cell biology and the tumor microenvironment. Such insights could lead to targeted therapies that exploit these pathways. Investigating the genetic and molecular predictors of response to melatonin could enable more personalized therapeutic strategies, maximize efficacy, and minimize unnecessary exposure to potential side effects.

This review underscores the potential of melatonin as a complementary therapy in cancer treatment. Its low toxicity profile, combined with its efficacy in regulating key cellular processes involved in tumorigenesis, might make it a compelling candidate for integration into existing cancer treatment protocols. Moreover, melatonin's ability to mitigate the side effects of traditional therapies may significantly improve treatment adherence and patient well-being. Future research should focus on optimizing dosing regimens, understanding the pharmacokinetics of melatonin in brain tumor patients, and exploring the molecular mechanisms underlying its anticancer effects. Investigating the genetic and molecular predictors of response to melatonin could potentially enable personalized therapeutic strategies that maximize efficacy and minimize side effects.

CONCLUSION

In conclusion, melatonin presents a promising adjunct to traditional brain tumor therapies. Its broad spectrum of biological activities, combined with its low toxicity, offers hope for improved treatment outcomes and quality of life for patients.

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