MINI-REVIEW

The potential utility of melatonin in the treatment of childhood cancer

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Abstract
Childhood cancer management has improved considerably, with the overall objective of preventing early-life cancers completely. However, cancer remains a major cause of death in children, with the survivors developing anticancer treatment-specific health problems. Therefore, the anticancer treatment needs further improvement. Melatonin is a highly effective antioxidant and circadian pacemaker. Through multiple mechanisms, melatonin has significant positive effects on multitudes adult cancers by increasing survival and treatment response rates, and slowing disease progression. In addition, melatonin appears to be safe for children. As an appealing therapeutic agent, we herein address several key concerns regarding melatonin’s potential for treating children with cancer.

Keywords
antioxidant, childhood cancer, melatonin, therapeutic agent

1 | INTRODUCTION

Melatonin (N-acetyl-5-methoxy-tryptamine) is a phylogenetically old molecule which exhibits a very wide functional repertoire (Lerner, Case, Takahashi, Lee, & Mori, 1958). It is a highly effective antioxidant, and major circadian modulator (Burgess & Emens, 2018; Galano & Reiter, 2018; Han et al., 2017; Mayo et al., 2017; Reiter et al., 2017a). Melatonin also exhibits oncostatic properties against tumors during the progression (Ho et al., 2016; Quintana et al., 2016; Reiter et al., 2017b; Slominski et al., 2018; Su
et al., 2017). However, its application for treating childhood cancers has been sparingly investigated.

Survival rates of children with cancer have increased considerably and rapidly since the 1960s. Effective treatment of adolescents and children with cancer is a highly desirable goal of clinicians around the world. While the 5-year survival rate of young people with cancer is 80%, cancer still remains a major cause of death in children. Moreover, pediatric cancer survivors may have specific health problems associated with successful anticancer treatment (Long et al., 2018). Therefore, anticancer therapy requires further improvement. Because accumulating evidence suggests beneficial effects of melatonin as a treatment or co-treatment for many malignant and nonmalignant cancers in humans, we address several key concerns regarding its potential application in childhood cancer in this review.

2 | MELATONIN BIOSYNTHESIS AND ITS PHYSIOLOGICAL FUNCTION

Melatonin is synthesized from the tryptophan, primary in the pineal gland (Vijayalaxmi, Reiter, & Herman, 2002). Following an uptake of tryptophan into the pinealocyte, tryptophan can be converted to 5-hydroxytryptophan by tryptophan hydroxylase, which is subsequently decarboxylated to serotonin by 5-hydroxytryptophan decarboxylase (Figure 1). Serotonin is acetylated to N-acetylserotonin, and then N-acetylserotonin is converted to melatonin.

Melatonin is produced in a circadian manner in the pineal gland, after which it is released into the cerebrospinal fluid (CSF) and bloodstream after which it enters cells and other body fluids (Reiter, 1986). Melatonin secretions are controlled by the prevailing light-dark cycle through the retinohypothalamic tract (Kalsbeek, Perreau-Lenz, & Buijs, 2006) and peripheral sympathetic nervous systems; due to its circadian production, the CSF and blood have high levels in the night and low levels in the daytime. The relatively short half-life of melatonin in the blood of 30–57 min is due to its uptake into cells (Brown, Choe, Shanahan, & Czeisler, 1997; Iguchi, Kato, & Ibayashi, 1982; Mallo et al., 1990), and its rapid clearance through the liver by cytochrome P450 enzymes (Vijayalaxmi et al., 2002). Minor amounts of melatonin may be excreted in the urine (Wetterberg, 1999) with possibly large amounts being discharged into the bile (Tan et al., 1999).

In all vertebrates, including humans, the major source of melatonin synthesis is the pineal gland. In addition to the pineal gland, melatonin is produced in various tissue types, including the brain (Venegas et al., 2012), retina (Reiter, Richardson, Matthews, Lane, & Ferguson, 1983), lens (Alkozi, Wang, Perez de Lara, & Pintor, 2017), bone marrow (Conti et al., 2000), lymphocytes, skin (Slominski, Tobin, Zmijewski, Wortsman, & Paus, 2008), liver (Venegas et al., 2012), kidney (Sanchez-Hidalgo et al., 2009), pancreas (Soderquist, Hellstrom, & Cunningham, 2015), and gastrointestinal tract (Soderquist et al., 2015). Moreover, melatonin synthesized in other tissues is not released into the bloodstream in significant amounts and influences other functions through paracrine signaling (Pandi-Perumal et al., 2006).

Melatonin participates in various physiological functions and affects a majority of the tissues and organs. It has vital antioxidant properties and can reduce oxidative stress. In addition to melatonin’s receptor independent actions (Reiter, Tan, & Galano, 2014), melatonin acts through MT1 and MT2 receptors expressed in several zones of the central nervous system (CNS) and peripheral tissues (Hardeland et al., 2011; Srinivasan et al., 2009). Because of a high receptor density in the circadian pacemaker, one of its most thoroughly described actions involves melatonin’s ability to phase circadian rhythms and enhance sleep promotion. Given its chronobiotic properties, melatonin has been used clinically in individuals with sleep disorders related to abnormal timing of the circadian system, such as totally blind people, night shift workers, and travelers with jetlag (Arendt & Skene, 2005; Armstrong, 1999; Sack & Lewy, 1997). In addition, other actions of melatonin may occur through the nuclear receptors and other binding sites (Hardeland et al., 2011).

3 | PROPOSED ANTITUMOR MECHANISMS OF MELATONIN

Using different carcinogenesis models, melatonin has been demonstrated to counteract tumor growth through multiple mechanisms (Blask, Sauer, & Dauchy, 2002; Ho et al., 2016; Hoang, Shaw, Pham, & Levine, 2007; Lu et al., 2018; Reiter et al., 2017b; Srinivasan, Spence, Pandi-Perumal, Trakht, & Cardinali, 2008; Su et al., 2017; Su, Reiter, Hsiao, Chung, & Yang, 2018; Yeh et al., 2016; Yeh et al., 2017; Figure 2). Numerous studies have suggested that oxidative stress-induced free radical damage is a primary contributing factor to cancer growth (Foss et al., 2017; Klaunig et al., 1998; Sholl, Barletta, & Hornick, 2017).

![Figure 1](Image 121x741 to 191x756) Biosynthesis of melatonin from the amino acid tryptophan.
Related to the widespread subcellular distribution and free radical scavenging actions, melatonin reduces oxidative damage in normal cells. However, in cancer cells, melatonin plays a role in inhibiting the cancer development (Blickenstaff, Brandstadter, Reddy, & Witt, 1994; Hardeland, 2005). This relates in part to its pro-oxidative actions in cancer cells (Bizzarri, Proietti, Cucina, & Reiter, 2013). Moreover, melatonin can act as a membrane-calming agent and modulates membrane excitability (Hoang et al., 2007).

The role of melatonin in inhibiting tumor proliferation has been documented (Reiter et al., 2017b). To regulate apoptosis, melatonin has directed proapoptotic on tumor cells (Cos, Mediavilla, Fernandez, Gonzalez-Lamuno, & Sanchez-Barcelo, 2002; Karasek & Pawlikowski, 1999; Riabykh, Nikolaeva, & Bodrova, 2000). Melatonin also limits the cellular uptake of key factors for tumor growth and their signaling molecules (Blask et al., 2005). Moreover, melatonin inhibits cell cycle kinetics and telomerase activity to restrain tumor cell growth (Leon-Blanco, Guerrero, Reiter, Calvo, & Pozo, 2003). As noted above, generally, melatonin is antiapoptotic in normal cells (Yu, Miller, & Osmond, 2000), but proapoptotic in cancer cells (Bizzarri et al., 2013). The actions of melatonin in cancer and in normal cells are obviously very different.

During cancer development and progression, angiogenesis is essential (Marme, 2018; Rajabi & Mousa, 2017). Melatonin reduces vascular endothelial growth factor secretion and plays a key inhibitory role in cancer metastasis (Lissoni et al., 2001). Moreover, it reduces the formation and release of endothelin-1 (Leon et al., 2014), which normally stimulates endothelial and perivascular cells and influences tumor angiogenesis. Moreover, accumulating evidence has linked the actions of melatonin to tumor metastasis within the tumor microenvironment, including the remodeling of the extracellular matrix, reorganization of the cytoskeleton, and epithelial–mesenchymal transition (EMT; Reiter et al., 2017b; Su et al., 2017). Through these actions, melatonin counteracts the angiogenic responses and thus reduces cancer cell invasion and metastasis.

Mutated cells destined to develop into tumorous tissue can flourish in inflamed microenvironment (Bagnato & Spinella, 2003). Melatonin augments the immune response and alleviates immunodeficiency states (Maestroni, 1993), along with enhancing immunosurveillance by stimulating the activities of a multitude of immune cells, including T lymphocytes and B lymphocytes, monocytes, natural killer cells, and macrophages (Martins, Fernandes, Bartol, Cipolla-Neto, & Costa Rosa, 1998). Furthermore, melatonin stimulates the production of several cytokines, for example, interferon (IFN)-γ, interleukin (IL)-1, IL-2, IL-6, and TNF-α (García-Maurino et al., 1997). As a consequence of its immune-enhancing functions, its immunomodulatory potential may be of substantial value for the antitumor effects of melatonin.

4 | MELATONIN AS AN ANTITUMOR AGENT IN ADULTS

Given its broad spectrum of antitumor actions, melatonin has emerged as an appealing therapeutic agent. Many studies have
demonstrated that the coadministration of melatonin with conventional drugs leads to synergistic effects, thus increasing cancer cell inhibition (Bizzarri et al., 2013; Reiter et al., 2017b). Also importantly, melatonin renders chemotherapy-resistant cancer cells sensitive to chemotherapy (Casado-Zapico et al., 2010; Dauchy et al., 2014; Martin et al., 2010; Plaimee, Weerapreeyakul, Barusrux, & Johns, 2015). Combination of melatonin with conventional therapies has demonstrated a marked positive effect in treating human cancers including those of the brain, breast, gastrointestinal, blood, lung, kidney, liver, and pancreas cancer (Jung & Ahmad, 2006; Mills, Wu, Seely, & Guyatt, 2005; Reiter, Tan, Sainz, Mayo, & Lopez-Burillo, 2002; Seely et al., 2012). This treatment may increase the survival and treatment response rates, delay disease progression (Lissoni, Messina, Lissoni, & Franco, 2017).

The collateral toxicity and lethality of conventional chemotherapies and radiotherapy are serious concerns affecting their clinical application. Clinical trials have shown that melatonin efficiently mitigates cell damage from acute and chronic toxic drugs and other insults (Reiter et al., 2002). Melatonin coadministration reduced the toxicity of several chemotherapeutic agents (Rivara, Pala, Bedini, & Spadoni, 2015), including cisplatin, etoposide, 5-fluorouracil, and anthracyclines. A significant amelioration in treatment-related adverse events, such as cardiotoxicity, nephrotoxicity, myelosuppression, alopecia, and asthenia, has been reported. Moreover, current scientists have also used derivatives, analogs and new drug delivery systems (nanoparticle or liposome, etc.) to improve the poor solubility and bioavailability (Ma et al., 2018; Milan, Campmany, & Naveros, 2017; Shokrzadeh & Ghassemi-Barchi, 2018; Zhang, Ou, Ye, Song, & Luo, 2017).

5 | SAFETY PROFILES OF MELATONIN

Toxicological studies have documented a highly safe profile of melatonin, an essential requisite for its clinical application. In various animal species, melatonin was tested over very wide range of doses to determine its potential toxicity. Generally, no major unfavorable effects were informed (Andersen, Gogenur, Rosenberg, & Reiter, 2016; Vijayalaxmi et al., 2002). Even high doses of melatonin did not have adverse effects on fetal or maternal wellbeing in pregnant animal studies (Jahnke et al., 1999; Sadowsky, Yellon, Mitchell, & Nathanielsz, 1991).

In clinical practice, melatonin is frequently used in individuals with various diseases. Human studies have demonstrated that melatonin toxicities are low with no severe side effects even at high doses (Nordlund & Lerner, 1977; Papavasiliou et al., 1972; Seabra, Bignotto, Pinto, & Tufik, 2000). Minor negative reactions, such as vivid dreams, sleepiness, headache, and nausea, have been reported by a few patients receiving melatonin supplement, these usually do not exceed those seen in placebo-treated controls subjects.

Safety data of melatonin in children derive mainly from its use in patients with neurologically disabling disorders for improving their sleep patterns (Gordon, 2000; Jan & Freeman, 2004). In general, no safety concerns were reported regarding severe adverse events or treatment-related comorbidity when children were treated using pharmacological doses. Only one report has described increased seizure activity in four neurologically disabled children receiving oral melatonin therapy (Sheldon, 1998). Even in premature infants, melatonin use has been shown to be effective and safe (Gitto et al., 2004a, 2004b, 2005).

6 | MELATONIN APPLICATION IN NEONATES AND CHILDREN

Because of its remarkably benign safety profile, melatonin has been used in children and neonates for a myriad of diverse diseases (Table 1). Children with neurodevelopmental disabilities have a higher risk of sleep disturbance. Due to the chronobiotic properties, melatonin was effective in improving sleep patterns in young patients with neurodevelopmental disabilities or autism (Dodge & Wilson, 2001; Garstang & Wallis, 2006; Wasdell et al., 2008). Melatonin in combination with conventional antiepileptic agents reduces seizure activity and improves quality of life in children with epilepsy (Gupta, Aneja, & Kohli, 2004; Peled, Shorer, Peled, & Pillar, 2001). In addition, melatonin can improve clinical outcomes in neonates with sepsis or asphyxia (Fulía et al., 2001; Gitto et al., 2001). With respiratory distress syndrome in premature infants, the beneficial effects of melatonin treatment were apparent in the reduction of inflammation (Gitto et al., 2004b, 2005). Moreover, melatonin was used as an alternative sedative for children receiving surgery or for examination of uncooperative children (Gitto et al., 2016; Johnson, Page, Williams, Wassemer, & Whitehouse, 2002). Melatonin therapy in children and neonates generally appears to be safe (Chen, Tain, Sheen, & Huang, 2012).

7 | POTENTIAL UTILITY OF MELATONIN FOR CHILDHOOD CANCER

In view of significant advances in childhood cancer management, the overall 5-year survival rate of these children is almost 80%. Survival rates in children with leukemia or lymphoma have continued to improve since 2010. By contrast, improvements in the survival of children with solid tumors have been only modest since the turn of the century (Smith et al., 2010). Thus, novel treatment strategies are necessary to improve outcomes. Through multiple mechanisms, the antiproliferative and oncostatic effects of melatonin have been established in a variety of adult cancers, of which most are solid tumors (Jung & Ahmad, 2006; Mills et al., 2005; Reiter et al., 2002; Seely et al., 2012). Melatonin may be a promising agent because of its acceptable safety profile in pediatric patients (Gordon, 2000), particularly those with refractory or resistant diseases.

To varying degrees, children with cancer experience numerous treatment-associated adverse outcomes. Conventional chemotherapeutic agents remain the basis of successful childhood cancer treatment,
# TABLE 1  Clinical reports regarding the use of melatonin in children

<table>
<thead>
<tr>
<th>Clinical conditions</th>
<th>Study design</th>
<th>N</th>
<th>Effects of melatonin use</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children with developmental disabilities and sleep</td>
<td>A randomized, double-blind, placebo-controlled study</td>
<td>20</td>
<td>A decrease in sleep latency and an increase in sleep duration</td>
<td>Dodge and Wilson (2001)</td>
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<td>disorders</td>
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<tr>
<td>Children with neurodevelopmental disabilities and</td>
<td>A randomized double-blind, placebo-controlled study</td>
<td>51</td>
<td>Improvement in total night-time sleep, sleep latency, and sleep efficiency</td>
<td>Wasdell et al. (2008)</td>
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<td>sleep disorders</td>
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<td>Children with autistic spectrum disorders and sleep</td>
<td>A randomized, placebo-controlled double-blind crossover study</td>
<td>11</td>
<td>A decrease in sleep latency and in waking per night, and an increase in sleep duration</td>
<td>Garstang and Wallis (2006)</td>
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<td>difficulties</td>
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<tr>
<td>Children with autism and sleep disorders</td>
<td>An open-label study</td>
<td>25</td>
<td>Improved sleep patterns evaluated by Children's Sleep Habits Questionnaire and sleep diaries</td>
<td>Giannotti, Cortesi, Cerquiglini, and Bernabei (2006)</td>
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<tr>
<td>Children with severe neurologic deficit disorders</td>
<td>A case-controlled study</td>
<td>6</td>
<td>A significant clinical improvement in seizure activity, particularly during the night</td>
<td>Peled, Shorer, Peled, and Pillar (2001)</td>
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<tr>
<td>Asphyxiated newborns</td>
<td>A comparative study</td>
<td>20</td>
<td>Significant reductions in serum malondialdehyde and nitrite/nitrate levels, and survival benefits</td>
<td>Fulia et al. (2001)</td>
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<tr>
<td>Septic newborns</td>
<td>A comparative study</td>
<td>20</td>
<td>Significant reductions in serum levels of lipid peroxidation products, and improvement of sepsis-related serum parameters</td>
<td>Gitto et al. (2001)</td>
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<tr>
<td>Preterm newborns with grade III or IV respiratory</td>
<td>A comparative study</td>
<td>74</td>
<td>Decreased plasma concentrations of interleukin-6, interleukin-8, tumor necrosis factor alpha, and nitrite/nitrate</td>
<td>Gitto et al. (2004b)</td>
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<td>distress syndrome</td>
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<tr>
<td>Preterm newborns with respiratory distress syndrome</td>
<td>A comparative study</td>
<td>110</td>
<td>Reduced pro-inflammatory cytokines in tracheobronchial aspirate and improved clinical outcomes</td>
<td>Gitto et al. (2005)</td>
</tr>
<tr>
<td>Sedation for children receiving elective surgery</td>
<td>A prospective, randomized, double-blind study</td>
<td>92</td>
<td>Significantly reduced doses of propofol required for induction of anesthesia, compared with midazolam</td>
<td>Gitto et al. (2016)</td>
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but specific classes of cytotoxic agents are associated with diverse side effects. Radiotherapy remains an essential treatment for many childhood malignancies, and younger patients are prone to severe injury, such as neurocognitive impairments. By mitigating damage to normal tissues, melatonin can efficiently reduce the toxicities of radiotherapy and chemotherapy in adult patients (Rivara et al., 2015). Accordingly, we speculate that melatonin may be also useful in ameliorating treatment-related adverse events in children with cancer.

Childhood cancer affects the patients and the family’s emotional and spiritual wellbeing. Despite the favorable survival outcome for childhood cancer, emotional distress continues to influence the survivors overall quality of life for months, years, or even decades after the treatment. For instance, sleep disturbance remains a serious problem for treated children for the long term. Same of the most effectively described actions of melatonin are phasing of circadian rhythms and sleep promotion. For example, melatonin is widely used in adults with sleep problems (Arendt & Skene, 2005; Armstrong, 1999; Sack & Lewy, 1997). Many studies have established that melatonin improved sleep patterns in children with high risk of sleep disturbance (Dodge & Wilson, 2001; Garstang & Wallis, 2006; Giannotti, Cortesi, Cerquiglini, & Bernabei, 2006; Wasdell et al., 2008). Taken together results, melatonin may be useful for ameliorating emotional distress, at least for sleep improvement, in children treated for cancer and for their parents.

8 | CONCLUSIONS

Melatonin is considered a valuable agent that can be administered for treating a variety of human diseases, even in pediatric patients. With multiple antitumor mechanisms, benefits of melatonin to the treatment efficacy of adult cancers have been demonstrated. However, there are no reports regarding its use in pediatric patients with malignancies. In combination with traditional chemotherapy and radiotherapy, melatonin can be greatly beneficial for their outcomes. For those with solid tumor or refractory disease, melatonin could be an alternative therapeutic agent with potential antitumor effects. In addition, melatonin has been demonstrated to ameliorate treatment-related adverse effects in adults with cancers. It can improve sleep quality in both adults and children. Therefore, we speculate that melatonin can be beneficial for improving the quality of life in pediatric patients receiving antitumor therapy, both physically and mentally. As a potential agent with a reliable safety profile for treating childhood cancers, additional studies should be necessary before its widespread use. We anticipate that the number of patients, both adults and children, benefiting from melatonin treatment will increase markedly in the future.

AUTHOR CONTRIBUTION

Yu-Hua Chao, Kang-Hsi Wu, Russel J. Reiter, and Shun-Fa Yang reviewed the state on the topic and wrote and revised the article. Chia-Ming Yeh and Shih-Chi Su involved in the searching suitable papers used in the manuscript. All the authors studied and approved the final manuscript.

CONFLICT OF INTERESTS

Authors declare that they have no conflict of interests.

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