REVIEW ARTICLE

Melatonin as a circadian-lifestyle interface in cancer care: biological mechanisms, clinical evidence, and future directions for integrative oncology

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Abstract

Melatonin is an endogenous circadian hormone with pleiotropic antioxidant, immunomodulatory, and oncostatic properties that offers a promising adjunct in cancer therapy. This review summarizes current mechanistic and clinical evidence supporting its role in oncology. Produced from L-tryptophan under circadian control, melatonin acts through MT1/MT2 receptors and receptor-independent antioxidant mechanisms to regulate hallmarks of cancer. It preserves mitochondrial function in normal tissues, suppresses PI3K/AKT and MAPK signaling, inhibits angiogenesis through VEGF and HIF-1α downregulation, reduces epithelial–mesenchymal transition and matrix metalloproteinase activity, and modulates estrogen. While clinical evidence remains inconsistent, most meta-analyses report modest improvements in cancer-related fatigue and quality of life; however, individual breast cancer trials have shown conflicting findings, emphasizing the need for large, independent, multicenter studies with standardized dosing and longer follow-up. Beyond symptom control, melatonin may counteract circadian disruption, inflammation, and mitochondrial dysfunction that contribute to cancer progression and treatment-related toxicity. Future research should integrate circadian phenotyping, biomarker-guided therapy, wearable monitoring, and immunotherapy to clarify its role as a safe, multitarget adjuvant in precision oncology.

Keywords: Melatonin, Lifestyle, Cancer care, Integrative oncology.

1. Introduction

Cancer remains a leading cause of morbidity and mortality worldwide, with breast cancer representing the most frequently diagnosed malignancy in women. Despite advances in multimodal therapies, treatment-related toxicities continue to significantly impair quality of life and survivorship outcomes (1-3). Among these toxicities, cancer-related fatigue (CRF) is one of the most prevalent and disabling symptoms, affecting the majority of patients undergoing active treatment and persisting into survivorship (4-6).

Cancer-related fatigue is a multifactorial syndrome involving inflammatory activation, mitochondrial dysfunction, hypothalamic–pituitary–adrenal axis dysregulation, and circadian rhythm disruption. Increasing evidence indicates that circadian disruption is not only a consequence of cancer but also a contributing etiological factor in tumorigenesis, particularly in hormone-dependent malignancies such as breast cancer (7-13).

Melatonin, the principal hormone regulating circadian rhythms, is secreted by the pineal gland in response to darkness and suppressed by light exposure (14). Beyond its chronobiological role, melatonin exhibits antioxidant, anti-inflammatory, immunomodulatory, and oncostatic properties (15, 16). Reduced melatonin secretion has been observed in cancer patients and is associated with worse clinical outcomes, including increased fatigue, sleep disturbance, and mood disorders (17-22).

This review synthesizes mechanistic and clinical evidence supporting melatonin as a circadian–lifestyle interface in oncology and explores its roles in cancer biology, symptom management, and the integration of lifestyle medicine.

2. Circadian biology and melatonin physiology

The indolamine melatonin (N-acetyl-5-methoxytryptamine) is biochemically derived from the amino acid L-tryptophan through a serotonin intermediate. This conversion is primarily governed by arylalkylamine N-acetyltransferase (AANAT), which serves as the rate-limiting enzyme in its biosynthetic pathway. Under physiological conditions, melatonin secretion exhibits a robust endogenous rhythmicity, orchestrated by the master circadian pacemaker located within the suprachiasmatic nucleus (SCN) of the hypothalamus (23-25).

The biological effects of melatonin are largely mediated through its interaction with two high-affinity G-protein-coupled receptors, MT1 and MT2. Activation of these receptors modulates intracellular cyclic AMP (cAMP) signaling cascades, thereby influencing downstream transcriptional programs that govern essential cellular processes, including mitogenesis, immunomodulation, and metabolic stability (15, 26, 27). Beyond these receptor-dependent mechanisms, melatonin functions as a potent, amphiphilic antioxidant. It acts both as a direct scavenger of reactive oxygen and nitrogen species and as a stimulator of endogenous antioxidant defense systems, specifically upregulating the activity of superoxide dismutase and glutathione peroxidase (28, 29).

While the pineal gland is the primary source of rhythmic circulating melatonin, evidence increasingly highlights significant extra-pineal synthesis in various compartments, including the mitochondria, gastrointestinal tract, and leukocytes. This suggests that melatonin also exerts vital autocrine and paracrine regulatory functions (30-32). Consequently, the chronic erosion of circadian hygiene, driven by nocturnal light

exposure, rotational shift work, or sleep fragmentation, precipitates a state of circadian disruption. This systemic desynchrony and subsequent suppression of melatonin production have been epidemiologically linked to elevated breast cancer incidence and diminished clinical outcomes (11, 12, 33).

3. Melatonin and the hallmarks of cancer

Melatonin functions as a highly pleiotropic molecule, exerting multi-level regulatory control over the fundamental hallmarks of cancer. Its ability to simultaneously modulate disparate signaling pathways positions it as a unique endogenous buffer against oncogenesis and tumor progression (16, 17, 34).

3.1. Redox homeostasis and mitochondrial bioenergetics

A defining feature of melatonin's bioactivity is its context-dependent modulation of oxidative stress. In healthy tissue, it preserves mitochondrial integrity by scavenging reactive oxygen species (ROS), stabilizing the mitochondrial membrane potential, and protecting mitochondrial DNA from oxidative lesions. Conversely, in the neoplastic environment, melatonin can selectively induce ROS-mediated apoptosis, particularly in cancer cells experiencing metabolic stress. By mitigating the Warburg effect and preventing metabolic reprogramming, melatonin effectively constrains the bioenergetic flexibility required for tumor survival (28, 35, 36).

3.2. Regulation of apoptosis and proliferative signaling

The pro-apoptotic influence of melatonin is characterized by the favorable modulation of the Bcl-2/Bax ratio, the activation of the caspase cascade, and the subsequent execution of programmed cell death. Simultaneously, melatonin antagonizes constitutive proliferative signaling. By inhibiting the phosphoinositide 3-kinase (PI3K)/AKT and mitogen-activated protein kinase (MAPK) axes, it induces cell cycle arrest, thereby limiting the uncontrolled expansion of malignant clones (37-40).

3.3. Angiogenesis and the metastatic cascade

Melatonin disrupts the transition from primary tumor growth to systemic dissemination by modifying the tumor microenvironment (TME). It suppresses neoangiogenesis through the downregulation of vascular endothelial growth factor (VEGF) and the inhibition of hypoxia-inducible factor 1-alpha (HIF-1α) signaling. Furthermore, melatonin mitigates the metastatic potential of cancer cells by suppressing the epithelial–mesenchymal transition (EMT) and reducing the proteolytic activity of matrix metalloproteinases (MMPs), which are essential for basement membrane degradation and tissue invasion (41-48).

3.4. Endocrine and epigenetic modulation

In hormone-dependent malignancies, specifically breast cancer, melatonin acts as a selective estrogen enzyme modulator (SEEM). It downregulates estrogen receptor alpha (ERα) expression, inhibits aromatase activity, and blunts estrogen-dependent transcriptional output. These oncostatic effects are further reinforced by melatonin's epigenetic influence; it modulates DNA methyltransferase activity and histone acetylation patterns, thereby restoring the expression of tumor suppressor genes and stabilizing the expression of core circadian clock genes (49-53).

4. Clinical evidence in oncology

Randomized controlled trials (RCTs) evaluating melatonin as an adjunctive therapy in oncology have yielded mixed results, particularly regarding its effects on cancer-related fatigue (CRF) and quality of life (QoL). While some studies, primarily in breast cancer populations, report benefits on fatigue, others, including larger or independent trials in broader or early-stage settings, show no statistically significant improvements in fatigue, global QoL, sleep, or other symptoms. Meta-analyses consistently highlight modest overall effects (e.g., SMD -0.23 to -0.45) accompanied by substantial heterogeneity (I^2 often 53-78%) due to variations in cancer types, disease stages, treatment regimens, dosing, treatment duration, baseline symptom burden, and outcome measures. This heterogeneity precludes strong, definitive recommendations in current evidence-based guidelines (20, 54, 55).

A notable cluster of positive findings comes from a series of double-blind, randomized, parallel-group trials conducted by the same Iranian research group (Sedighi Pashaki et al.). These studies involved women with stage I-III breast cancer undergoing adjuvant chemoradiotherapy. They administered oral melatonin (doses typically 6-18 mg nightly), initiated one week before treatment and continued for months to years. The trials reported clinically meaningful reductions in fatigue severity (e.g., on the Brief Fatigue Inventory or similar scales) compared with placebo, with sustained benefits observed during long-term follow-up (56-58).

However, these findings have not been uniformly replicated by independent investigators. For example, a phase III double-blind placebo-controlled trial in patients with early-stage breast cancer receiving radiotherapy found no benefit of melatonin (20 mg nightly) on CRF or other symptoms, leading to early termination for futility (59). Other trials in mixed solid-tumor populations or with shorter durations have similarly reported neutral effects on global QoL, sleep quality, pain, and fatigue. Systematic reviews and meta-analyses integrating these data describe the pooled impact on patient-reported outcomes as modest at best and highly context-dependent (20, 54, 55, 60).

The concentration of strongly positive results within one research group raises the possibility of center-specific effects, population characteristics, or publication bias, underscoring the need for independent replication across diverse healthcare settings, patient demographics, and treatment contexts before broad generalization. Table 1 summarizes selected key RCTs in this area.

These discrepancies likely stem from differences in cancer stage (e.g., early vs. more symptomatic adjuvant settings), concurrent therapies, baseline circadian disruption and symptom burden, melatonin dosing regimens, treatment duration, and the sensitivity of chosen endpoints. Longer-duration interventions in patients with higher baseline fatigue appear more likely to detect benefits, whereas shorter trials in lower-burden populations often do not.

In summary, while melatonin shows promise as a low-risk adjunct for mitigating cancer-related fatigue in select breast cancer contexts, particularly with prolonged use, the evidence remains heterogeneous and preliminary. Independent, multicenter RCTs with standardized dosing, longer follow-up, and rigorous controls for bias are essential to clarify its role in integrative oncology care. Future studies should also explore biomarkers of response (e.g., circadian alignment) to enable personalized application.

Table 1. Summary of selected studies evaluating melatonin supplementation for cancer-related fatigue

Study (Year)	Design and Population	Intervention (Dose, Duration)	Key Outcomes	Main Findings	Limitations
Pashaki et al. (2021/2023 series) (56, 57)	Double-blind RCT; Stage I–III breast cancer, adjuvant chemoradiotherapy (Iran)	6–18 mg oral nightly; initiated pre-treatment, continued months	Fatigue (BFI), QoL, IL-6	Significant reductions in fatigue severity; sustained long-term benefits vs. placebo	Single research group; potential center effects; specific population
Mukhopadhyay et al. (2024) (59)	Phase III double-blind RCT; Early-stage breast cancer on radiotherapy (US)	20 mg nightly during Radiotherapy + 2 weeks post	FACIT-Fatigue, ESAS, PROMIS	No significant benefit on fatigue or most symptoms; trial stopped early	Early-stage/low-burden; shorter duration; demographic homogeneity
Nimee et al. (2024) (22)	Double-blind RCT; Breast cancer on chemotherapy	1 mg/day + Mediterranean diet; 3 months	FACIT-Fatigue, well-being	Improvement in melatonin arm (within-group); limited between-group superiority	Small sample; combined diet intervention; modest dose
Yazdankhah et al. (2025) (61)	RCT; Breast cancer on radiotherapy	Melatonin during Radiotherapy	Fatigue, anxiety, depression	Significant alleviation of fatigue, anxiety, depression	Recent; details on blinding/sample pending full verification in context

Brief fatigue inventory = BFI; Quality of life = QoL; Functional assessment of chronic illness therapy – fatigue scale = FACIT-Fatigue; Edmonton symptom assessment system = ESAS; Patient-reported outcomes measurement information system = PROMIS

5. Cancer-related fatigue and psychoneuroimmunology

Cancer-related fatigue is a multidimensional syndrome rooted in a complex interplay of systemic inflammation, mitochondrial bioenergetic failure, and the desynchronization of endogenous circadian rhythms (8, 9, 62). The pathogenesis of Cancer-related fatigue is largely driven by the chronic elevation of pro-inflammatory cytokines, specifically interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), which impair neural signaling and metabolic efficiency (7, 63, 64). Melatonin serves as a potent immunomodulatory agent within the psychoneuroimmunological framework, attenuating these inflammatory cascades and mitigating oxidative stress (17, 28, 65). By stabilizing the architecture of the sleep-wake cycle and restoring circadian rhythmicity, melatonin addresses the physiological underpinnings of fatigue (54, 55). Furthermore, its ability to modulate serotonergic signaling and reinforce circadian stability contributes to the alleviation of comorbid psychological distress, including anxiety and depressive symptoms often observed in oncological cohorts (60, 66, 67).

6. Integrative lifestyle medicine and chronobiology

Melatonin functions as a critical molecular interface between environmental lifestyle factors and host biological homeostasis (15, 68, 69). The modern 24-hour society frequently induces circadian misalignment; specifically, nocturnal light exposure acutely suppresses pineal melatonin secretion, an endocrine disruption epidemiologically linked to increased oncogenic risk (11, 12, 70). Conversely, the implementation of stringent sleep hygiene and environmental circadian anchoring facilitates the restoration of physiological rhythms (71).

Within the realm of lifestyle medicine, chrononutrition, the strategic timing of nutrient intake, further enhances circadian

robustness and metabolic regulation (72, 73). These behavioral interventions are complemented by chronotherapy, which optimizes the timing of pharmacological agents to align with biological rhythms, thereby maximizing anti-tumor efficacy while minimizing systemic toxicity. In this context, melatonin emerges as a dual-purpose tool: it acts as a direct therapeutic adjuvant and serves as a sensitive proxy biomarker for assessing the integrity of the patient's underlying circadian health (41, 74, 75).

7. Survivorship and longitudinal clinical outcomes

The transition into cancer survivorship is frequently burdened by a constellation of lingering sequelae, including persistent fatigue, chemobrain (cognitive impairment), and a diminished quality of life. These long-term challenges are often symptomatic of a protracted state of neuroendocrine disequilibrium and circadian fragility (62, 76). Melatonin supplementation offers a promising rehabilitative strategy by promoting the re-establishment of robust circadian oscillations and restoring neuroendocrine balance (17, 77). By addressing these foundational regulatory systems, melatonin may facilitate more comprehensive long-term recovery, improving functional status and psychological well-being in the post-treatment phase (20, 78).

8. Future directions in precision circadian oncology

The trajectory of future research must pivot toward the realization of precision circadian oncology. This paradigm shift necessitates the development of sophisticated circadian phenotyping to identify individual variations in chronobiological status, allowing for biomarker-guided therapeutic strategies (79-81). A particularly compelling frontier lies in the synergy between melatonin and immunotherapy; understanding how melatonin-mediated immune modulation influences the efficacy of checkpoint inhibitors could revolutionize current treatment protocols (17, 82-84).

Furthermore, the integration of wearable biosensors and digital health monitoring offers a transformative opportunity for real-time, longitudinal tracking of circadian rhythms (85-89). Such data-driven approaches will enable the personalization of melatonin-based interventions, optimizing dosage and timing according to a patient's unique chronotype (90-94). Continued investigation into the epigenetic modifications and TME alterations induced by melatonin remains essential to fully elucidate its role as a multifaceted oncostatic agent (41, 48, 52).

9. Conclusion

Melatonin functions as a pivotal circadian–endocrine–metabolic rheostat, bridging the gap between lifestyle-induced environmental signals and the molecular landscape of tumor biology. Its extensive pleiotropic profile, encompassing the regulation of oxidative stress, immunomodulation, the antagonism of estrogen signaling, and the maintenance of circadian homeostasis, highlights its systemic importance in oncology. Accumulating clinical evidence underscores its efficacy in mitigating cancer-related fatigue and enhancing patient-reported quality of life, with particularly robust findings in breast cancer populations.

In the broader context of lifestyle medicine, melatonin serves as a vital translational bridge connecting environmental exposures and behavioral modifications to clinical oncological outcomes. By stabilizing the biological infrastructure that is often compromised by modern environmental

stressors, melatonin represents a cornerstone of integrative cancer care. Its potential as a non-toxic, multi-target adjuvant therapy warrants its formal incorporation into comprehensive strategies aimed at improving both the survival and the functional well-being of cancer patients.

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