

REVIEW ARTICLE

Utility of exogenous melatonin in patients with breast cancer: A systematic review

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Abstract

Fatigue, sleep disturbance, menopausal symptoms and impaired quality of life remain common and poorly controlled in breast cancer. Exogenous melatonin is an inexpensive, plausible supportive-care option that has not yet been systematically appraised. PubMed, Web of Science and the Cochrane Library were searched to May 15, 2026 for controlled studies of oral melatonin in patients with breast cancer or survivors (full-text English only). Screening, extraction, and Cochrane Risk of Bias 2 assessment were performed in duplicate; results were synthesized narratively (Synthesis Without Meta-analysis), stratified by daily dose, with post hoc sensitivity analyses. Eleven trials (849 participants) were included, spanning chemotherapy, radiotherapy, endocrine therapy, adjuvant follow-up and survivorship rehabilitation, at 1–20 mg/day for 10 days to three years. Sleep quality was the most reproducible benefit: both trials assessing it reported improvement at low risk of bias. Benefit was also reported for endocrine therapy-related symptoms, sexual function, quality of life and fatigue (3 of 5 trials), although a phase III radiotherapy trial was negative. No effect was seen on estradiol or insulin-like growth factor-axis biomarkers, body composition, or fitness. Six Iranian trials formed two clusters with overlapping authors; their removal left the fatigue and quality-of-life signals unsupported, but the sleep signal persisted. Oral melatonin is well tolerated (no grade 3/4 toxicity) and reproducibly improves sleep quality (moderate certainty), with less certain signals for endocrine therapy-related symptoms, quality of life, and fatigue (low certainty), justifying adequately powered, symptom-stratified trials. It is not supported as an antitumor therapy or a routine adjunct to exercise-based rehabilitation.

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1. Introduction

1.1. Symptom burden during breast cancer treatment and survivorship

Advances in screening, surgery, radiotherapy, chemotherapy, and systemic endocrine therapy have substantially improved survival in breast cancer, and clinical priorities have correspondingly broadened from prolonging life to controlling long-term symptoms and preserving quality of life. Survivors nonetheless report poorer quality of life than cancer-free controls, most conspicuously in physical and emotional functioning, insomnia, and global health status.¹ Cancer-related fatigue is among the most frequent and persistent

of these problems, may persist for years after adjuvant chemotherapy has ended, and clusters with insomnia and depression to produce an additive decrement in health-related quality of life (HRQoL).²⁻⁷ Cognitive impairment affecting attention, memory and processing speed is also frequent and commonly coexists with anxiety, depression and pain⁸, while the hypo-estrogenic state induced by endocrine therapy adds hot flushes, menopause-like symptoms and sexual dysfunction that reduce treatment adherence and HRQoL.^{9,10} Patients therefore require not only effective antineoplastic treatment but also safe, low-toxicity and durable supportive-care strategies that improve patient-reported outcomes.¹¹

1.2. Biological rationale for melatonin supplementation

Melatonin is an endogenous indoleamine that regulates circadian rhythm and the sleep-wake cycle; its nocturnal peak synchronizes central and peripheral clocks, so exogenous supplementation may plausibly relieve difficulty initiating sleep, poor sleep quality, and other circadian-related symptoms.^{12,13} Melatonin also scavenges free radicals, reduces oxidative stress, protects mitochondrial function, and exerts anti-inflammatory and immunomodulatory effects.^{14,15} In breast cancer specifically, circadian disruption, light exposure at night, and attenuated melatonin signaling have been associated with tumor initiation and progression, and melatonin may act on estrogen-related pathways through melatonin, estrogen, and other nuclear receptors.^{16,17} Because melatonin is inexpensive, widely available, and generally well tolerated, it is a plausible supportive-care candidate whose clinical value warrants systematic appraisal.

1.3. Heterogeneity of the existing evidence and objective of this review

Clinical studies of melatonin in breast cancer span a wide range of treatment and rehabilitation settings but differ markedly in design, dose and duration, and their results conflict even within the same setting: two randomized trials of 20 mg/day melatonin during radiotherapy reached opposite conclusions about fatigue^{18,19}, while other trials have extended dosing from before adjuvant treatment until two years after its completion.²⁰ A topical melatonin cream has also been evaluated to prevent acute radiation dermatitis²¹; because topical application produces minimal systemic exposure, such studies are not comparable with systemic supplementation and were not eligible here (Section 2.3). Supplement trials in breast cancer more generally vary substantially in intervention type, dose, duration, route, control condition and outcomes.²²

Against this background, the present systematic review evaluates the clinical utility of exogenous oral melatonin in breast cancer. It synthesizes the effects of melatonin on treatment-related symptoms, HRQoL, biological outcomes and safety across chemotherapy, radiotherapy, endocrine therapy, long-term adjuvant follow-up and survivorship rehabilitation, and formally examines how robust the resulting conclusions are to risk of bias, to dose and to the concentration of the evidence within a small number of research groups.

2. Materials and methods

2.1. Reporting guidelines and protocol

This review was designed and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 statement²³, and the narrative synthesis was reported in accordance with the Synthesis Without Meta-analysis reporting guideline.²⁴ The review was not prospectively registered in the International Prospective Register of Systematic Reviews or in another systematic review registry; this omission is acknowledged as a limitation in Section 4.8.

2.2. Search strategy

PubMed, Web of Science, and the Cochrane Library were systematically searched to identify clinical studies of exogenous melatonin in patients with breast cancer. Each database was searched from inception to May 15, 2026, with no restriction on publication year. Search terms were constructed around three core concepts: breast cancer, melatonin, and clinical intervention or randomized controlled trial. The complete search string used in each database is reproduced in Table S2.

2.3. Eligibility criteria

Eligible populations were patients with breast cancer or breast cancer survivors. Eligible interventions were exogenous melatonin preparations; because the review addressed the systemic supportive-care effects of melatonin, only systemically administered (oral) melatonin was eligible, and studies of topical or other locally acting formulations were excluded on the grounds that local application yields minimal systemic exposure and is therefore not comparable with systemic supplementation. Studies had to include a placebo, usual-care, or other non-melatonin control group; report the melatonin dose and the timing or duration of administration; and report at least one extractable clinical or biomarker outcome. Randomized controlled trials, placebo-controlled trials, and other controlled clinical studies were eligible. No restriction was placed on treatment phase.

Only publications with full text available in English were eligible, and this restriction was additionally embedded in the PubMed search string. The restriction was applied because the review team had neither professional translation support nor reviewers able to screen and extract data reliably in additional languages, and because the three databases searched do not index the major non-English regional registries. The decision was therefore made explicit and applied consistently rather than left as an undocumented default. Its potential consequences for the findings, and the specific supplementary searches that would be required to remove it, are examined in Section 4.8.

2.4. Study selection and data extraction

All records were exported to EndNote (<https://www.myendnoteweb.com>; accessed May 15, 2026) for duplicate removal and manual verification. Two reviewers independently screened titles and abstracts, and potentially eligible articles were then assessed in full text against the criteria in Section 2.3. Data were extracted in duplicate using a standardized form covering country, sample size, study design, treatment setting and population, melatonin dose and route, duration of administration, outcome measures and principal findings. Disagreements at every stage were resolved by discussion. Reasons for exclusion at full-text stage were recorded, and the selection process is summarized in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 flow diagram.

2.5. Risk-of-bias assessment

Risk of bias was assessed with the Cochrane Risk of Bias 2 (RoB 2) tool²⁵ across five domains: the randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. Each domain was rated as low risk, some concerns, or high risk, and an overall judgment was then derived. Assessments were made independently by two reviewers, and disagreements were resolved by discussion. Domain-level and overall judgments are presented in tabular form and, following the conventions of the robvis visualization tool²⁶, as a study-level traffic-light plot and a domain-level summary plot. The explicit basis for every domain judgment is reported in Table S1.

2.6. Data synthesis, dose stratification, sensitivity analyses and appraisal of certainty

Since the included studies differed substantially in treatment setting, dose, duration and outcome instruments, and because several outcome domains were addressed by only one or two trials, quantitative pooling was not appropriate, and results were synthesized narratively by outcome

domain, tabulated by direction of effect (between-group benefit, within-group change only, or no difference) rather than by nominal statistical significance alone.

To examine whether effects varied with dose, trials were stratified by total daily oral dose into three strata reflecting the natural clustering of the doses actually used: low (1–3 mg/day), intermediate (>3 to <18 mg/day) and high (18–20 mg/day). Because dose and duration were partly confounded across trials, the dose-stratified synthesis is presented alongside duration of administration (Section 3.8).

Two post hoc sensitivity analyses were conducted to test the robustness of the narrative conclusions. First, a leave-one-cluster-out analysis was performed in which trials sharing authorship, dose regimen, and recruitment context were treated as a single cluster rather than as independent studies, and each cluster was removed in turn. Second, a best-evidence analysis was performed in which the synthesis was repeated using only the trials rated at low overall risk of bias. Both analyses are reported in Section 3.9.

Because effect estimates were not pooled, formal Grading of Recommendations, Assessment, Development and Evaluations (GRADE) certainty ratings could not be generated. The strength of the evidence in each outcome domain was instead summarized using four explicit, GRADE-informed descriptors²⁷: moderate, when at least two controlled trials showed a consistent direction of effect and all or most were at low risk of bias; low, when trials were inconsistent, or when a single trial at low risk of bias had not been replicated; very low, when evidence came from a single small trial or from trials with important risk-of-bias concerns and inconsistent results; and insufficient, when no controlled data were available. No outcome domain met the criteria for high certainty.

3. Results

3.1. Study selection

Database searching and manual screening initially yielded 378 records. After removal of 40 duplicates using EndNote and manual verification, 338 records underwent title and abstract screening. Of these, 204 were excluded at first pass: 68 were off-topic, 68 were reviews, conference abstracts, or registry entries, 21 were animal studies, and 47 were cell or other *in vitro* studies. The remaining 134 reports were assessed in full text; 123 were excluded, chiefly because they were not randomized or controlled clinical studies, because they did not report complete or usable results, because data could not be extracted, or because they used a non-systemic (topical) route of administration. Eleven studies met all eligibility criteria and were included in

the narrative synthesis. The selection process is shown in Figure 1.

3.2. Characteristics of the included studies

Table 1 presents the main characteristics of the 11 included studies.^{18–20,28–35} All enrolled patients had breast cancer or were breast cancer survivors, and the studies evaluated exogenous melatonin, in most cases against placebo or usual care. The designs were predominantly randomized, double-blind, placebo-controlled trials, together with a small number of randomized supportive-care or survivorship rehabilitation studies with combined interventions. Trials were conducted in the United States, Brazil, Iran, Greece, and Spain, and individual sample sizes ranged from 20 to 184 participants (849 participants in total).

Dose, duration, and treatment setting varied considerably: oral melatonin doses ranged from 1 to 20 mg/day, and administration lasted from 10 days to 3 years, across chemotherapy, radiotherapy, adjuvant treatment and post-treatment follow-up, endocrine therapy, and exercise-based rehabilitation in survivors. Reported outcomes included cancer-related fatigue, sleep quality, cognitive function, anxiety and depression, HRQoL, endocrine therapy-related menopausal symptoms, sexual function, body composition, and estrogen- and insulin-like growth factor (IGF)-related biomarkers.

In terms of geographical and authorship clustering, 6 of the 11 trials were conducted in Iran^{19,20,30,31,33,34}, and these fall into two clusters with overlapping authors plus one apparently independent trial. Cluster A comprises three reports that evaluated 18 mg/day melatonin for adjuvant treatment-related fatigue or HRQoL and share authorship.^{20,30,31} Cluster B comprises two reports in endocrine therapy populations that share authorship, and that report an identical sample size ($n = 60$), the same total daily dose (6 mg/day) and the same treatment duration (four weeks) while reporting different outcome sets^{33,34}; the possibility that these are companion reports of a single trial rather than two independent trials cannot be excluded from the published information. The samples within each cluster should therefore not be added together, and the two clusters should not be treated as independent replications when the overall strength of the evidence is assessed. This clustering is examined quantitatively in the sensitivity analyses reported in Section 3.9.

3.3. Risk of bias in the included studies

Domain-level and overall RoB 2 assessments are shown in Table 2 and displayed graphically in Figures 2 and 3; the basis for each assessment is presented in Table S1. Four trials were rated at low overall risk of bias.^{18,19,29,33} The remaining seven raised some concerns, and no trial was judged to be at high overall risk of bias.

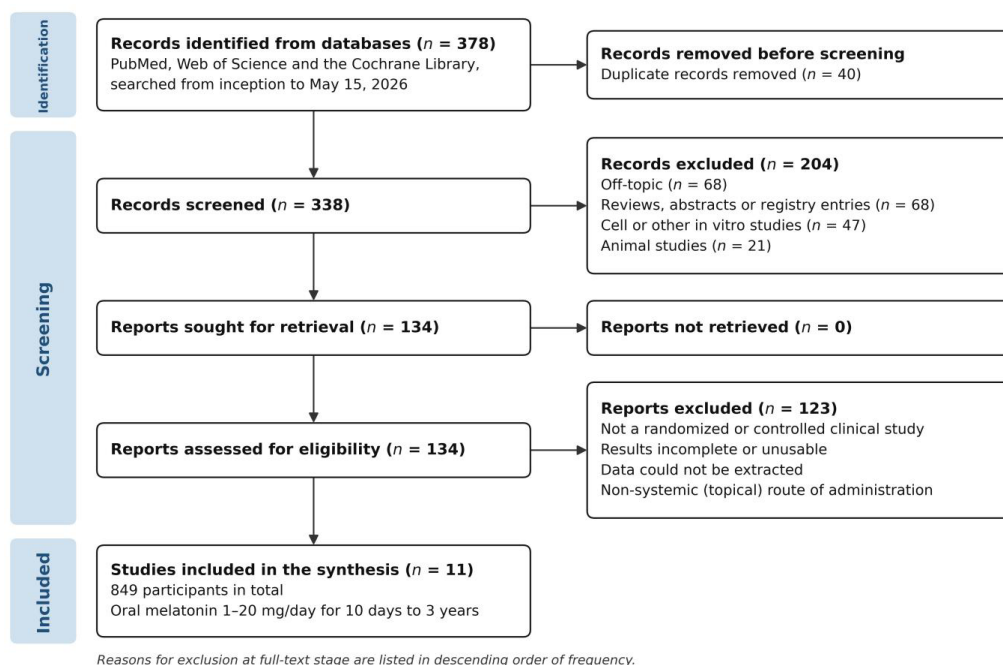


Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 flow diagram of study identification, screening and inclusion

Table 1. Main characteristics of the included studies

Study	Country	Sample size, total (melatonin/control)	Study design	Treatment setting/population	Melatonin dose (oral)	Duration	Main outcomes	Main findings
Schernhammer <i>et al.</i> ²⁸	United States	95 (48/47)	Double-blind, placebo-controlled randomized trial	Postmenopausal survivors of stage 0–III breast cancer who had completed active treatment	3 mg/day	Four months	Estradiol, IGF-1, IGFBP-3, adherence and safety	Adherence was high, and no grade 3/4 toxicity occurred. Short-term supplementation with 3 mg/day did not significantly change estradiol, IGF-1, or IGFBP-3 concentrations.
Palmer <i>et al.</i> ²⁹	Brazil	36	Randomized, double-blind, placebo-controlled trial	Patients with breast cancer receiving their first cycle of adjuvant chemotherapy	20 mg/day	10 days before and during the first chemotherapy cycle	Cognitive function, sleep quality, depressive symptoms, BDNF/TrkB	Executive function, episodic memory, recognition memory, and verbal fluency improved, indicating possible protection against chemotherapy-related cognitive, sleep, and mood symptoms.
Sedighi Pashaki <i>et al.</i> ³⁰	Iran	74 (37/37)	Randomized, controlled, parallel-group trial	Patients receiving adjuvant chemotherapy and radiotherapy	18 mg/day	From one week before adjuvant radiotherapy to one month after its completion	Cancer-related fatigue (BFI)	Post-intervention BFI scores were significantly lower in the melatonin group than in the placebo group, and severe fatigue was less frequent.
Sedighi Pashaki <i>et al.</i> ²⁰	Iran	92	Randomized, controlled, parallel-group clinical trial	Adjuvant treatment and long-term follow-up in patients with breast cancer	18 mg/day	From one week before adjuvant treatment to two years after its completion	Long-term cancer-related fatigue (BFI)	Groups were comparable at baseline. Post-intervention fatigue scores were lower in the melatonin group and declined more markedly over time.
Keshtpour Amlashi <i>et al.</i> ³¹	Iran	184 (93/91)	Controlled clinical study with long-term follow-up	Patients with non-metastatic breast cancer	18 mg/day	Three years	Health-related quality of life (EORTC QLQ-C30)	Global health-related quality of life improved over time and was significantly better than in the control group.
Mukhopadhyay <i>et al.</i> ¹⁸	United States	79 randomized; 78 treated	Phase III randomized, double-blind, placebo-controlled trial	Patients with early-stage breast cancer or DCIS receiving definitive radiotherapy	20 mg/day	From the night before radiotherapy to two weeks after its completion	FACIT-Fatigue, FACIT subscales, ESAS, PROMIS	No significant between-group difference was observed in FACIT-Fatigue. Most secondary symptom outcomes were also unchanged, and tolerability was good.
Nimee <i>et al.</i> ³²	Greece	49 (23/26)	Randomized, double-blind, placebo-controlled study	Patients with breast cancer receiving chemotherapy; both groups received Mediterranean diet advice	1 mg/day	Three months	FACIT-Fatigue, body mass index, diet adherence	Fatigue improved from baseline in the melatonin group, but between-group differences were not significant, suggesting a possible benefit with limited evidence.

(Contd...)

Table 1. (Continued)

Study	Country	Sample size, total (melatonin/control)	Study design	Treatment setting/population	Melatonin dose (oral)	Duration	Main outcomes	Main findings
Vaziri <i>et al.</i> ³³	Iran	60 (34/26)	Randomized, double-blind, placebo-controlled trial	Patients receiving endocrine therapy who had sleep or mood problems	6 mg/day	Four weeks	PSQI, CES-D, POMS	Sleep quality, sleep latency, and sleep duration improved significantly, and sleep medication use decreased. Depression and mood scores did not improve significantly.
Sadeghi Yazdankhah <i>et al.</i> ¹⁹	Iran	100 (50/50)	Randomized, triple-blind, placebo-controlled trial	Patients receiving adjuvant radiotherapy	20 mg/day	Throughout radiotherapy until its completion	MFI fatigue, BAI anxiety, BDI depression	Post-intervention fatigue, anxiety, and depression scores were significantly lower in the melatonin group than in the placebo group.
Sattari <i>et al.</i> ³⁴	Iran	60	Randomized, double-blind, placebo-controlled trial	Hormone receptor-positive survivors receiving antihormonal therapy and experiencing menopausal symptoms	3 mg twice daily (6 mg/day)	Four weeks	Hot flushes, menopausal symptoms, MENQOL, FSFI	Hot-flush frequency and severity decreased, and menopausal symptoms, quality of life, and sexual function improved.
Celorrio San Miguel <i>et al.</i> ³⁵	Spain	20 (10/10)	Randomized, single-blind, placebo-controlled trial	Breast cancer survivors receiving an individualized exercise prescription	6 mg/day	10 weeks	Body composition, physical fitness, quality of life, hormonal response	Melatonin combined with exercise provided no additional significant improvement over placebo; between-group differences in quality of life, physical fitness, and hormonal markers were not significant.

Abbreviations: BAI: Beck Anxiety Inventory; BDI: Beck Depression Inventory; BDNF: Brain-derived neurotrophic factor; CES-D: Center for Epidemiologic Studies Depression Scale; DCIS: Ductal carcinoma *in situ*; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; ESAS: Edmonton Symptom Assessment System; FACIT: Functional Assessment of Chronic Illness Therapy; FSFI: Female Sexual Function Index; IGF-1: Insulin-like growth factor 1; IGFBP-3: Insulin-like growth factor binding protein 3; MENQOL: Menopause-Specific Quality of Life Questionnaire; MFI: Multidimensional Fatigue Inventory; POMS: Profile of Mood States; PROMIS: Patient-Reported Outcomes Measurement Information System; PSQI: Pittsburgh Sleep Quality Index; TrkB: tropomyosin receptor kinase B.

Table 2. Risk-of-bias assessment of the included studies using the Cochrane Risk of Bias 2 tool

Study	D1	D2	D3	D4	D5	Overall
Schernhammer <i>et al.</i> ²⁸	S	L	L	L	S	S
Palmer <i>et al.</i> ²⁹	L	L	L	L	L	L
Sedighi Pashaki <i>et al.</i> ³⁰	S	S	L	S	S	S
Sedighi Pashaki <i>et al.</i> ²⁰	S	S	S	S	S	S
Keshtpour Amlashi <i>et al.</i> ³¹	S	L	S	L	S	S
Mukhopadhyay <i>et al.</i> ¹⁸	L	L	L	L	L	L
Nimee <i>et al.</i> ³²	S	L	L	L	S	S
Vaziri <i>et al.</i> ³³	L	L	L	L	L	L
Sadeghi Yazdankhah <i>et al.</i> ¹⁹	L	L	L	L	L	L
Sattari <i>et al.</i> ³⁴	S	L	L	L	S	S
Celorrio San Miguel <i>et al.</i> ³⁵	S	S	L	S	S	S

Abbreviations: D1: Randomization process; D2: Deviations from intended interventions; D3: Missing outcome data; D4: Measurement of the outcome; D5: Selection of the reported result. H: High risk of bias; L: Low risk of bias; S: Some concerns.

Concerns arose most often in the randomization domain, where allocation was described as random but the method of sequence generation or allocation concealment was not reported, and in the selection of the reported result domain, where no prospectively registered protocol or statistical analysis plan was identified. Additional concerns included potential limitations in outcome measurement, as most primary outcomes were subjective and patient-reported and therefore potentially sensitive to imperfect blinding, as well as incomplete reporting of missing data in the trials with the longest follow-up.^{20,31} The trial by Celorrio San Miguel *et al.*³⁵ was a randomized controlled trial but enrolled only 20 participants, used a single-blind design, and delivered melatonin on top of an individualized exercise prescription, so that the co-intervention may itself shape the observed effect; it was accordingly rated as raising some concerns.

3.4. Cancer-related fatigue

Fatigue was the outcome assessed most frequently, in five trials. Sedighi Pashaki *et al.*³⁰ administered 18 mg/day melatonin during adjuvant chemotherapy and radiotherapy, and post-intervention Brief Fatigue Inventory scores were significantly lower than with placebo, with severe fatigue less frequent. A subsequent study from the same group,

in which dosing extended from before adjuvant treatment until two years after its completion, reported that fatigue scores remained below those of the control group and declined more markedly over time.²⁰ Nimee *et al.*³² administered a much lower dose of 1 mg/day melatonin for three months during chemotherapy and observed improvement from baseline that did not reach statistical significance between groups.

Findings in the radiotherapy setting were discordant. In the phase III double-blind placebo-controlled trial of Mukhopadhyay *et al.*¹⁸, 20 mg/day melatonin given from the night before radiotherapy until two weeks after its completion produced no between-group difference in Functional Assessment of Chronic Illness Therapy-fatigue. By contrast, Sadeghi Yazdankhah *et al.*¹⁹ administered 20 mg/day melatonin throughout adjuvant radiotherapy and reported significantly lower post-intervention fatigue than placebo. Differences in sample size, fatigue instrument, radiotherapy technique, study population and statistical handling may account for the discrepancy, and the effect of melatonin on radiotherapy-related fatigue therefore remains uncertain.

3.5. Sleep, cognitive function and psychological symptoms

Two trials assessed sleep, and both reported benefit. Palmer *et al.*²⁹ administered 20 mg/day melatonin for 10 days around the first cycle of adjuvant chemotherapy and reported improvement in executive function, episodic memory, recognition memory and verbal fluency, together with benefit for sleep and depressive symptoms. In patients receiving endocrine therapy who had sleep or mood complaints, Vaziri *et al.*³³ administered 6 mg/day melatonin for four weeks and reported significant improvement in Pittsburgh Sleep Quality Index (PSQI) global sleep quality, sleep latency and sleep duration, together with reduced use of sleep medication. Both trials were rated as having a low overall risk of bias.

Findings for mood were inconsistent. Sadeghi Yazdankhah *et al.*¹⁹ reported lower anxiety and depression scores with 20 mg/day during radiotherapy, whereas Vaziri *et al.*³³ found no significant improvement in depression severity or overall mood despite the sleep benefit in the same trial. Cognitive benefit rests on a single small trial.²⁹ Taken together, the available data support a sleep effect more consistently than any effect on depression, anxiety or cognition.

3.6. Health-related quality of life, endocrine therapy-related symptoms and sexual function

Work on HRQoL centered on long-term adjuvant treatment and survivorship. Keshtpour Amlashi *et al.*³¹

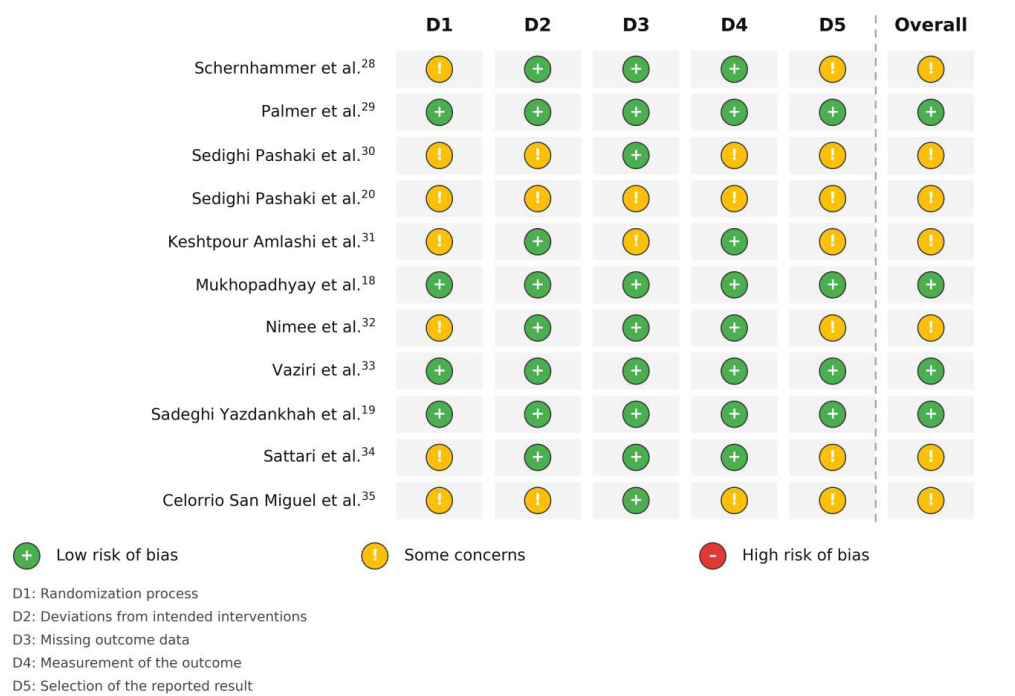


Figure 2. Study-level risk-of-bias traffic-light plot for the 11 included trials, based on the Cochrane Risk of Bias 2 tool

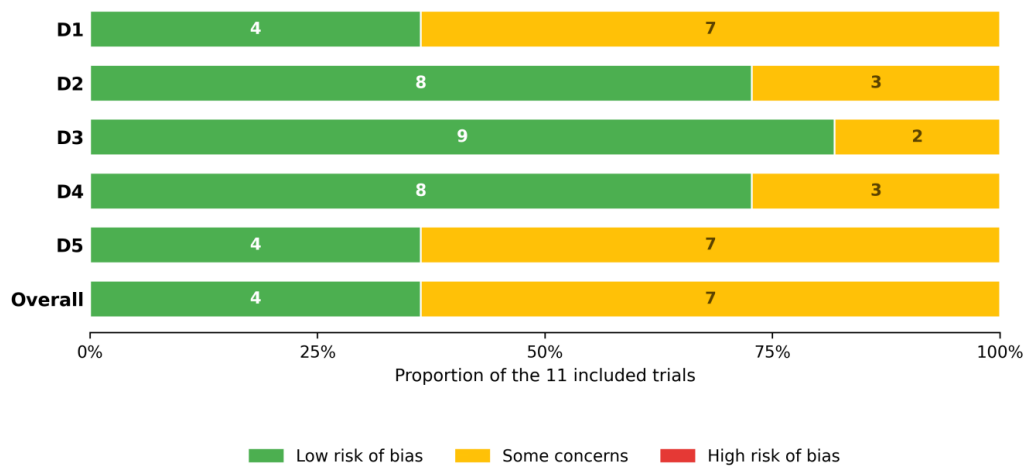


Figure 3. Domain-level summary of risk-of-bias judgments across the 11 included trials

included 184 patients with non-metastatic breast cancer and administered 18 mg/day for three years; global HRQoL on the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 improved over time and was better than in the control group. This supports a possible long-term HRQoL benefit, but the trial closely mirrors the fatigue work of the same

research cluster in dose, setting, and context, which must temper its interpretation (Section 3.9).

For endocrine therapy-related symptoms, Sattari *et al.*³⁴ reported that 3 mg melatonin twice daily for four weeks reduced the frequency and severity of hot flushes and improved menopausal symptom scores, HRQoL and sexual function. Vaziri *et al.*³³ likewise improved

endocrine therapy-related sleep disturbance with 6 mg/day, again without a clear effect on depression or overall mood. Together, these trials indicate a possible supportive-care role for melatonin in endocrine therapy-related sleep disturbance, vasomotor symptoms, and HRQoL, although both belong to the same cluster with overlapping authors.

3.7. Biomarkers, body composition and hormone-related outcomes

Biomarker data were sparse and uniformly negative. Schernhammer *et al.*²⁸ examined the effect of 3 mg/day melatonin on estradiol, IGF-1, IGF binding protein 3 (IGFBP-3) and the IGF-1/IGFBP-3 ratio in postmenopausal survivors; four months of this low dose left these markers essentially unchanged, although adherence was high and no grade 3/4 toxicity occurred. A low dose given over a relatively short period may have little effect on the estrogen and IGF axes, and any change may be difficult to detect against the low baseline estradiol concentrations of postmenopausal women.

Celorrio San Miguel *et al.*³⁵ tested 6 mg/day melatonin for 10 weeks alongside exercise-based rehabilitation, assessing body composition, physical fitness, HRQoL and hormonal response. Some measures of physical perception improved over time in both exercising groups, but melatonin conferred no additional benefit over placebo for body composition, HRQoL, fitness, or the testosterone/cortisol ratio. Based on the present evidence, adding melatonin to exercise-based rehabilitation does not produce further physical or hormonal gains.

3.8. Dose-stratified synthesis

Table 3 summarizes the included trials by total daily dose. In the low-dose stratum (1–3 mg/day melatonin, two trials), no between-group benefit was demonstrated for any outcome: 1 mg/day melatonin for three months produced within-group fatigue improvement only³², and 3 mg/day for four months did not alter estrogen- or IGF-axis biomarkers.²⁸ In the intermediate stratum (6 mg/day, three trials), results depended on the target

Table 3. Dose-stratified synthesis of melatonin effects in the included trials

Dose stratum	Study	Duration	Outcome domain assessed	Direction of effect	Setting
Low (1–3 mg/day)	Nimee <i>et al.</i> ³²	3 months	Cancer-related fatigue	(+)	Chemotherapy
	Schernhammer <i>et al.</i> ²⁸	4 months	Estradiol, IGF-1, IGFBP-3; safety	0 for biomarkers; good tolerability	Post-treatment survivorship
Intermediate (6 mg/day)	Vaziri <i>et al.</i> ³³	4 weeks	Sleep quality; depression and mood	+ for sleep; 0 for depression and mood	Endocrine therapy
	Sattari <i>et al.</i> ³⁴	4 weeks	Hot flushes, menopausal symptoms, HRQoL, sexual function	+ for all four domains	Endocrine therapy
	Celorrio San Miguel <i>et al.</i> ³⁵	10 weeks	Body composition, fitness, HRQoL, hormonal response	0 for all domains	Exercise-based rehabilitation
High (18–20 mg/day)	Sedighi Pashaki <i>et al.</i> ³⁰	≈ 2 months	Cancer-related fatigue	+	Adjuvant chemotherapy and radiotherapy
	Sedighi Pashaki <i>et al.</i> ²⁰	Up to 2 years	Long-term cancer-related fatigue	+	Adjuvant treatment and follow-up
	Keshtpour Amlashi <i>et al.</i> ³¹	3 years	Health-related quality of life	+	Non-metastatic disease, long-term follow-up
	Palmer <i>et al.</i> ²⁹	10 days	Cognition, sleep, depressive symptoms	+	First cycle of adjuvant chemotherapy
	Sadeghi Yazdankhah <i>et al.</i> ¹⁹	Duration of radiotherapy	Fatigue, anxiety, depression	+ for all three domains	Adjuvant radiotherapy
	Mukhopadhyay <i>et al.</i> ¹⁸	≈ 8 weeks	FACIT-fatigue and secondary symptom outcomes	0	Definitive radiotherapy

Notes: Direction of effect: +: Significant between-group benefit; (+): Within-group improvement only, without a significant between-group difference; 0: No significant between-group difference. Abbreviations: HRQoL, health-related quality of life; IGF, insulin-like growth factor; FACIT: Functional Assessment of Chronic Illness Therapy; IGFBP-3: Insulin-like growth factor binding protein 3.

symptom: sleep quality³³ and endocrine therapy-related menopausal symptoms, HRQoL and sexual function³⁴ improved, whereas 6 mg/day melatonin added to an exercise prescription produced no additional benefit for body composition, fitness or HRQoL.³⁵ In the high-dose stratum (18–20 mg/day, six trials), five reported benefit for fatigue, HRQoL, cognition or mood^{19,20,29–31} and one, the largest radiotherapy trial, was negative.¹⁸

Three caveats constrain any dose-response inference. First, no included trial compared two or more melatonin doses head-to-head, so the apparent gradient rests entirely on between-trial comparison. Second, dose was confounded with the outcome assessed: the low-dose trials targeted biomarkers and fatigue, whereas the high-dose trials targeted fatigue, cognition, and HRQoL. Third, dose was confounded with authorship and geography, since three of the six high-dose trials belong to a single cluster with overlapping authors using an identical 18 mg/day regimen. The dose-stratified pattern is therefore best read as a hypothesis for prospective dose-finding work rather than as evidence of a true dose-response relationship.

3.9. Sensitivity analyses

For leave-one-cluster-out analysis, when Cluster A^{20,30,31} was removed, the evidence for a benefit of melatonin on cancer-related fatigue reduced to one positive radiotherapy trial¹⁹ set against one negative phase III radiotherapy trial¹⁸ and one trial showing within-group change only³², and the only trial supporting a long-term HRQoL benefit was lost. When Cluster B^{33,34} was removed, all evidence for benefit in endocrine therapy-related sleep disturbance, vasomotor symptoms and sexual function was lost, and support for a sleep benefit reduced to the single small trial of Palmer *et al.*²⁹ When both clusters were removed simultaneously, leaving the five trials conducted outside Iran^{18,28,29,32,35}, the remaining evidence comprised one small positive trial of cognition, sleep and mood during chemotherapy²⁹ and four trials showing no significant between-group benefit for fatigue, HRQoL, body composition or biomarkers.^{18,28,32,35}

Best-evidence analysis restricted to trials at low risk of bias. When the synthesis was restricted to the four trials at low overall risk of bias^{18,19,29,33}, the sleep signal was retained and was supported by both trials that measured sleep^{29,33}; fatigue remained discordant, with one positive¹⁹ and one negative¹⁸ radiotherapy trial; anxiety and depression remained inconsistent^{19,33}; and no low-risk trial addressed HRQoL, menopausal symptoms or biomarkers.

These analyses converge on three conclusions: (i) The improvement in sleep quality is the most robust finding, because it survives both restriction to low-risk-of-bias trials and, in attenuated form, removal of the clusters

with overlapping authors. (ii) The evidence for benefit on cancer-related fatigue and on long-term HRQoL is substantially dependent on a single research cluster and should not be regarded as independently replicated. (iii) The uniformly negative biomarker, body composition and fitness findings are unaffected by either analysis, since all the relevant trials lie outside the two clusters.

3.10. Safety and tolerability

Tolerability was consistently good. Schernhammer *et al.*²⁸ recorded high adherence to 3 mg/day melatonin over four months with no grade 3/4 toxicity. The phase III radiotherapy trial of Mukhopadhyay *et al.*¹⁸ likewise found 20 mg/day to be well tolerated, with no grade 3/4 events and headache, drowsiness, and abdominal pain as the most frequent complaints. No other included trial reported a serious safety concern attributable to melatonin. Short-term safety therefore appears reassuring across the full 1–20 mg/day dose range. However, no included trial systematically reported concomitant medication or supplement use, and none was designed or powered to detect interactions with chemotherapy, radiotherapy or endocrine therapy; long-term high-dose safety remains uncharacterized. These issues are examined further in Section 4.6.

3.11. Summary of evidence by outcome domain

Table 4 summarizes the direction of findings and the strength of the evidence in each outcome domain. Overall, controlled trials of melatonin in breast cancer have addressed supportive-care outcomes rather than hard oncological endpoints such as recurrence or overall survival.^{18–20,28–35} The evidence indicates a reproducible benefit for sleep quality, together with promising but less certain signals for cancer-related fatigue, endocrine therapy-related menopausal symptoms, sexual function and HRQoL, and consistently negative findings for estrogen- and IGF-related biomarkers, body composition and hormonal response.

4. Discussion

4.1. Principal findings

This review appraised the clinical utility of exogenous oral melatonin in breast cancer and survivorship. Whereas earlier reviews focused on chemotherapy-related toxicity or on adjuvant anticancer effects, the present synthesis spans chemotherapy, radiotherapy, endocrine therapy, long-term follow-up after adjuvant treatment and survivorship rehabilitation, and covers fatigue, sleep, cognition, mood, HRQoL, menopausal symptoms, sexual function, biomarkers and safety. Across 11 controlled trials, melatonin was consistently well tolerated and improved

Table 4. Summary of evidence and strength of evidence by outcome domain

Outcome domain	Trials (n)	Direction of findings	Effect of sensitivity analyses	Strength of evidence
Sleep quality	2	Both trials reported improvement in sleep outcomes. ^{29,33}	Retained in the low-risk-of-bias analysis (both trials were rated low risk); attenuated but not abolished by removal of Cluster B.	Moderate
Cancer-related fatigue	5	Benefit in three trials ^{19,20,30} ; no between-group effect in one phase III trial ¹⁸ ; within-group improvement only in one. ³²	Not supported after removal of Cluster A; remains discordant in the low-risk-of-bias analysis.	Low
Endocrine therapy-related menopausal symptoms and sexual function	1	Hot-flush frequency and severity, menopausal symptom scores, HRQoL and sexual function improved. ³⁴	Lost entirely on removal of Cluster B; no low-risk-of-bias trial addressed this domain.	Low
Health-related quality of life	3	Improvement in two trials ^{31,34} ; no additional benefit over exercise alone in one. ³⁵	Lost on removal of Clusters A and B; no low-risk-of-bias trial addressed this domain.	Low
Cognitive function	1	Executive function, memory and verbal fluency improved. ²⁹	Retained in the low-risk-of-bias analysis but unreplicated.	Very low
Anxiety and depression	3	Improvement in one trial ¹⁹ ; no improvement in depression or mood in another ³³ ; depressive symptoms assessed as a secondary outcome in a third. ²⁹	Remains inconsistent in every analysis.	Very low
Estrogen- and IGF-axis biomarkers, hormonal response	2	No significant change in estradiol, IGF-1 or IGFBP-3 ³⁸ ; no significant between-group hormonal response. ³⁵	Unaffected: both trials lie outside the two clusters.	Low
Body composition and physical fitness	1	No additional benefit over exercise alone. ³⁵	Unaffected: the trial lies outside the two clusters.	Very low
Safety and short-term tolerability	11	Tolerability was good, and no grade 3/4 toxicity was reported in any trial.	Unaffected by either analysis.	Moderate (short term only)

Notes: Strength of evidence was assigned using the Grading of Recommendations, Assessment, Development and Evaluations-informed descriptors defined in Section 2.6; no outcome domain achieved high certainty.

Abbreviations: HRQoL: Health-related quality of life; IGF: Insulin-like growth factor; IGFBP-3: Insulin-like growth factor binding protein 3.

several patient-reported outcomes, most reproducibly sleep quality and, less certainly, cancer-related fatigue, endocrine therapy-related symptoms, and HRQoL.

Two findings qualify these positive signals without negating them. First, the sleep-quality benefit was the only symptom effect to survive both sensitivity analyses, and it is the outcome most closely aligned with melatonin's established pharmacology. Second, the apparently strong evidence for fatigue and long-term HRQoL rests substantially on one research cluster with overlapping authors using a single 18 mg/day regimen, so that the number of independent replications is smaller than the number of published trials implies. What the evidence does not support is melatonin as an antitumor treatment, as a means of modifying estrogen or IGF-axis biomarkers, or as a general adjunct to exercise-based rehabilitation.

4.2. Comparison with previous systematic reviews and the incremental contribution of this review

Several previous syntheses have addressed melatonin in oncology, and the incremental contribution of the present review is best understood by comparison with them (Table 5). Ramos *et al.*³⁶ reviewed the potential of melatonin to counteract chemotherapy-induced toxicity in breast cancer, but with a chemotherapy-centered scope. Scafuri *et al.*²² examined dietary supplements in breast cancer broadly and emphasized how widely such trials differ in intervention, dose, duration and outcome. The Cochrane review of melatonin in cancer treatment³⁷ spans tumor types and treatment settings and underscores that conclusions depend on cancer type, setting, outcome and evidence quality.

The closest quantitative comparator is the systematic review and meta-analysis of Fan *et al.*³⁸, which pooled 19 randomized controlled trials and 2,101 patients across mixed cancer types and found no significant overall effect of melatonin on quality of life, sleep quality, fatigue, pain or stomatitis severity; the only benefits were a lower incidence of treatment-induced stomatitis outside head and neck cancer, and a modest reduction in depression when melatonin was given for more than 14 days or after surgery. A breast cancer-specific synthesis remains justified for four reasons. First, restricting the population to breast cancer brings disease-specific contexts into view, notably endocrine therapy, vasomotor symptoms and sexual function, which a mixed-cancer meta-analysis cannot address. Second, searching to May 2026 captures the trials published after the November 2021 cutoff of Fan *et al.*³⁸, which include the majority of those reviewed here. Third, the outcome set is broader, extending to cognitive function and to estrogen- and IGF-axis biomarkers. Fourth, and specific to this revision, the present review formally tests the robustness of its own conclusions through dose stratification and through sensitivity analyses that account for authorship clustering, which no previous synthesis in this field has done.

The direction of the present conclusions is consistent with, rather than contradicted by, this prior work. The largely null pooled estimates of Fan *et al.*³⁸ fit the observation reported here that promising single-trial signals in breast cancer become fragile once clustering and risk of bias are taken into account. Conversely, the discrepancy between the null sleep result of Fan *et al.*³⁸ and the improvement reported in the breast cancer-specific meta-analysis of Seo *et al.*³⁹ supports the value of confining the evidence base to a single tumor type, and is concordant with sleep being the most robust signal in the present review. Pontinen and Lemke⁴⁰ similarly concluded that melatonin for fatigue in breast cancer remains an evidence-generating proposition that cannot yet be strongly recommended.

4.3. Interpretation of the symptom-related findings

Cancer-related fatigue attracted the most study attention but produced the least consistent picture. The positive results at 18 mg/day^{20,30} and the parallel HRQoL gain at the same dose³¹ arise from one research cluster; the two radiotherapy trials using 20 mg/day disagree^{18,19}; and 1 mg/day produced within-group change only.³² This variation is consistent with a fatigue effect that depends on dose, duration, treatment phase, baseline severity and the measurement instrument, and it is the principal reason for rating the certainty of the evidence for fatigue as low in **Table 4**, despite three positive trials.

Sleep has both the firmest theoretical foundation and the most robust empirical support. Improvement in PSQI sleep quality, latency and duration with 6 mg/day, accompanied by reduced use of sleep medication³³, is concordant with the breast cancer-specific meta-analysis of Seo *et al.*³⁹ and with the sleep benefit reported during chemotherapy.²⁹ Cognitive and psychological effects remain uncertain: the cognitive gains reported after 20 mg/day around the first chemotherapy cycle²⁹ are unreplicated, and the anxiety and depression benefits reported during radiotherapy¹⁹ are not corroborated in the endocrine therapy setting.³³ As Martella *et al.*⁴¹ observed, insomnia in women surviving breast and gynecological cancers reflects hormonal change, treatment-related symptoms and psychological factors simultaneously, which may explain why the effects on sleep appear more consistent than any effect on mood or cognition.

In terms of HRQoL, menopausal symptoms and sexual function represent the principal extension beyond earlier toxicity-focused reviews. In hormone receptor-positive survivors receiving antihormonal therapy, 3 mg twice daily for four weeks reduced hot-flush frequency and severity and improved menopausal symptoms, HRQoL and sexual function.³⁴ Because supplement use is common in this population and melatonin is among the natural products patients take⁴², clinicians should ask about it directly. By contrast, adding 6 mg/day to an exercise prescription produced no additional benefit³⁵, suggesting that melatonin suits specific symptom clusters better than a general role as a rehabilitation adjunct.

4.4. Biological plausibility and the biomarker gap

The biological rationale for melatonin in breast cancer supportive care is coherent. As a regulator of circadian rhythm, melatonin acts through melatonin receptors 1 and 2 on central and peripheral clocks and on sleep, immunity, metabolism and mood^{43,44}, and its antioxidant, anti-inflammatory and mitochondrial-protective actions could plausibly attenuate treatment-related tissue damage.⁴⁵ Breast cancer risk itself has been linked to circadian disruption, light at night and suppressed endogenous melatonin^{46–51}, and experimental studies indicate that melatonin can influence breast cancer cell proliferation, apoptosis, migration and treatment sensitivity, potentially acting synergistically with several anticancer agents.^{52–59} This literature is, however, almost entirely preclinical and cannot be read as evidence of clinical efficacy.

The clinical biomarker evidence lags conspicuously behind this mechanistic account. Neither 3 mg/day for four months in postmenopausal survivors²⁸ nor 6 mg/day for 10 weeks in an exercise setting³⁵ altered the biomarkers

Table 5. Comparison with previous systematic reviews and meta-analyses of melatonin in oncology

Review	Population and scope	Design and search cutoff	Main conclusions	Relation to the present review
Fan <i>et al.</i> ³⁸	Mixed cancer types; 19 RCTs, 2,101 patients	Systematic review and meta-analysis; November 2021	No significant overall effect on QoL, sleep quality, fatigue, pain or stomatitis severity. Lower incidence of treatment-induced stomatitis outside head and neck cancer, and a modest reduction in depression when melatonin was given for more than 14 days or after surgery.	Closest quantitative comparator. The present review is breast cancer-specific, extends the search to May 2026 (capturing most included trials), adds cognitive and biomarker outcomes, and adds cluster-based sensitivity analysis.
Seo <i>et al.</i> ³⁹	Breast cancer; sleep quality only	Systematic review and meta-analysis	Melatonin supplementation improved sleep quality, based on few studies with varied protocols and outcomes.	Concordant with the present finding that sleep is the most robust signal; the present review places that finding in the context of all other outcome domains and of risk of bias.
Ramos <i>et al.</i> ³⁶	Breast cancer; chemotherapy-induced toxicity	Systematic review	Melatonin has potential to counteract chemotherapy-induced toxicity.	Chemotherapy-centered. The present review adds radiotherapy, endocrine therapy, long-term follow-up and survivorship rehabilitation.
Scafuri <i>et al.</i> ²²	Breast cancer; dietary supplements generally	Systematic review	Supplement trials in breast cancer differ widely in intervention type, dose, duration, route and outcomes.	Provides the methodological context for the present review, which is confined to a single agent and formally quantifies that heterogeneity by dose stratum.
Yu <i>et al.</i> ³⁷	All cancers; melatonin in cancer treatment	Cochrane systematic review	Conclusions depend on cancer type, treatment setting, outcome type and the quality of the available evidence.	Supports the rationale for a tumor-type-specific synthesis and for the explicit strength-of-evidence appraisal used here.
Pontinen and Lemke ⁴⁰	Breast cancer; cancer-related fatigue	Integrative review	Melatonin for fatigue in breast cancer remains evidence-generating and cannot yet be strongly recommended.	Concordant with the low-certainty rating assigned to fatigue here; the present review additionally identifies the authorship clustering that underlies that uncertainty.

Abbreviations: QoL: Quality of life; RCT: Randomized controlled trial.

measured, including estradiol, IGF-1, IGFBP-3 and the testosterone/cortisol ratio. Symptom benefit in the positive trials may therefore depend more on sleep and circadian regulation, subjective symptom relief, or inflammatory and oxidative pathways than on short-term change in circulating estrogen or IGF markers. Closing this gap will require trials that pair patient-reported outcomes with objective measures.

4.5. Dose, duration, timing and treatment context

Differences in dose, duration and setting help explain the inconsistent conclusions, but they do not, by themselves, establish a dose-response relationship (Section 3.8). A higher dose did not guarantee greater efficacy: the largest trial in the high-dose stratum was negative¹⁸, whereas 6

mg/day was sufficient to improve sleep and vasomotor symptoms in endocrine therapy populations.^{33,34} Timing and formulation are likely to matter as much as total dose, since sustained-release and immediate-release capsules produce distinct plasma profiles⁶⁰ and the sleep effect of exogenous melatonin varies across populations and types of sleep complaint.⁶¹ Future trials should state the time of administration explicitly, the formulation, whether dosing occurs at bedtime and whether it is synchronized with radiotherapy or chemotherapy cycles.

Treatment setting and outcome measurement further shape interpretation. Chemotherapy is associated with fatigue, cognitive decline, sleep disturbance and distress; radiotherapy with fatigue and local symptoms; endocrine

therapy with hot flushes, insomnia and sexual dysfunction; and survivorship with reduced fitness, pain and persistent sleep problems, so the same dose may act through different mechanisms in different phases.^{62–64} Outcomes were correspondingly heterogeneous: fatigue was assessed with the Brief Fatigue Inventory, Functional Assessment of Chronic Illness Therapy-fatigue or Multidimensional Fatigue Inventory; sleep predominantly with the PSQI; psychological symptoms with the Center for Epidemiologic Studies Depression Scale, Profile of Mood States, Beck Anxiety Inventory or Beck Depression Inventory; and HRQoL with the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 or Menopause-Specific Quality of Life questionnaire. These instruments capture different constructs, which frustrates direct comparison; as a network meta-analysis of insomnia treatments has shown, drug type, dose, follow-up duration and outcome selection can all shift efficacy estimates even in a well-defined condition.⁶⁵ Future trials should stratify by treatment phase and dominant symptom and prespecify standardized, clinically meaningful primary outcomes.

4.6. Safety, tolerability and potential drug interactions

No included trial reported a severe adverse event attributable to melatonin, and tolerability was good at doses up to 20 mg/day.^{18,19,28,33–35} This is consistent with the broader clinical literature, in which the adverse events most commonly associated with oral melatonin are mild and self-limiting, chiefly daytime somnolence, headache, dizziness and nausea⁶⁵, and with safety data from other conditions.^{61,66,67} Nevertheless, the absence of reported harm in 11 small, short trials that did not systematically record concomitant medication is weak evidence of safety in the polypharmacy context that characterizes breast cancer care, in which a patient may simultaneously receive cytotoxic chemotherapy, radiotherapy, endocrine therapy, targeted agents, analgesics, antidepressants, hypnotics and multiple supplements.⁴² The following considerations, summarized in Table 6, should therefore inform both practice and future trial design.

- Pharmacokinetic interactions: Exogenous melatonin undergoes extensive first-pass metabolism, principally by cytochrome P450 family 1 subfamily A member 2 (CYP1A2), so drugs that modulate this enzyme markedly alter melatonin exposure.⁶⁸ Fluvoxamine, a potent CYP1A2 inhibitor, strongly inhibits melatonin biotransformation and can raise plasma concentrations several-fold, whereas other antidepressants have much weaker effects⁶⁹; this is directly relevant to breast cancer care, in which selective serotonin and serotonin-noradrenaline

reuptake inhibitors are widely used both for depression and for vasomotor symptoms. Conversely, CYP1A2 inducers such as carbamazepine, omeprazole and tobacco smoke may reduce exposure and thereby efficacy.⁶⁸ Melatonin is not an established inhibitor of cytochrome P450 family 2 subfamily D member 6 (CYP2D6), the enzyme responsible for bioactivation of tamoxifen to endoxifen, so a clinically important interaction with tamoxifen is not expected on current knowledge, although this has not been tested directly and concomitant strong CYP2D6 inhibitors remain a separate, well-recognized concern.⁷⁰

- Pharmacodynamic and treatment-related interactions: The cytotoxicity of anthracyclines, alkylating agents and ionizing radiation depends in part on reactive oxygen species, raising a theoretical concern that a potent antioxidant given concurrently could attenuate antitumor efficacy. Observational data from a cooperative group trial found that antioxidant supplements during adjuvant chemotherapy for breast cancer were associated with poorer recurrence-free and overall survival⁷¹, whereas preclinical work suggests that melatonin sensitizes tumor cells while protecting normal tissue.^{52,57} This tension is unresolved, and no included trial reported oncological endpoints, so unsupervised high-dose melatonin during curative-intent chemotherapy or radiotherapy is best avoided outside clinical trials. Melatonin also adds to the sedative effects of benzodiazepines, Z-drugs, opioids and sedating antidepressants^{66,68}, and acute administration impairs glucose tolerance in humans⁷², which is relevant to patients receiving corticosteroid antiemetic premedication.
- Product quality: Because melatonin is marketed as a dietary supplement in many jurisdictions, product content is inconsistently regulated: analysis of commercial preparations found melatonin content ranging from 83% below to 478% above the labeled dose, lot-to-lot variability within a single product of up to 465%, and serotonin in 26% of products tested.⁷³ Unlabeled serotonin is of particular concern in patients taking serotonergic antidepressants. Trials and clinical recommendations should therefore specify a pharmaceutical-grade, content-verified preparation.

4.7. Implications for clinical practice

The evidence summarized in Table 4 does not support routine use of melatonin as standard supportive care in breast cancer, but neither does it justify dismissing consistent positive signals. The following graded suggestions follow directly from the strength of evidence

Table 6. Potential interactions between melatonin and treatments commonly used in breast cancer

Agent or class	Proposed mechanism	Implication for breast cancer care
Fluvoxamine and other CYP1A2 inhibitors (e.g., ciprofloxacin, cimetidine, oral estrogen-containing preparations)	Inhibition of CYP1A2-mediated first-pass metabolism of melatonin, raising plasma concentrations several-fold ^{68,69}	Relevant because SSRIs and SNRIs are widely used for depression and vasomotor symptoms. Use the lowest effective melatonin dose and counsel about daytime somnolence.
CYP1A2 inducers (carbamazepine, rifampicin, omeprazole, tobacco smoke)	Increased melatonin clearance and reduced systemic exposure ⁶⁸	May account for apparent non-response. Smoking status and concomitant inducers should be recorded in trials.
Tamoxifen	Tamoxifen requires CYP2D6-mediated bioactivation to endoxifen; melatonin is not an established CYP2D6 inhibitor ⁷⁰	A clinically important interaction is not expected based on current knowledge but has not been tested directly. Strong CYP2D6 inhibitors remain a separate, well-recognized concern.
Aromatase inhibitors	No reported pharmacokinetic interaction; melatonin did not alter estradiol or IGF-axis biomarkers in the only trial to measure them ²⁸	No specific precaution identified, but endocrine-axis effects of long-term supplementation remain uncharacterized.
Anthracyclines, alkylating agents, taxanes and ionizing radiation	Cytotoxicity depends in part on ROS generation, which a potent antioxidant could theoretically attenuate; observational data link antioxidant supplement use during chemotherapy to poorer outcomes ⁷¹ , whereas preclinical data suggest melatonin sensitizes tumor cells while protecting normal tissue ^{45,52,57}	Unresolved. Avoid unsupervised high-dose melatonin during curative-intent chemotherapy or radiotherapy outside clinical trials; trials in this setting should collect oncological endpoints.
Benzodiazepines, Z-drugs, opioids, sedating antidepressants and antihistamines	Additive central nervous system depression ^{66,68}	Risk of excessive daytime somnolence and falls, particularly in older survivors and in patients on multiple symptom-control agents.
Antihypertensive agents	Melatonin may lower nocturnal blood pressure and may interact with calcium channel blockers ⁶⁸	Monitor blood pressure when melatonin is started in patients on antihypertensive treatment.
Corticosteroids and antidiabetic therapy	Acute melatonin administration impairs glucose tolerance in humans ⁷²	Relevant during chemotherapy cycles that include corticosteroid premedication and in patients with impaired glucose regulation.
Anticoagulants and antiplatelet agents	Possible potentiation of anticoagulant effect ^{66,68}	Consider closer monitoring when melatonin is added to anticoagulant therapy.
Product quality (all preparations)	Melatonin content of commercial supplements ranged from 83% below to 478% above the labeled dose, with lot-to-lot variability up to 465% and serotonin detected in 26% of products ⁷³	Unlabeled serotonin is of particular concern with serotonergic antidepressants. Specify a pharmaceutical-grade, content-verified preparation in practice and in trials.

Abbreviations: CYP1A2: Cytochrome P450 family 1 subfamily A member 2; CYP2D6: Cytochrome P450 family 2 subfamily D member 6; IGF: Insulin-like growth factor; ROS: Reactive oxygen species; SNRI: Serotonin-noradrenaline reuptake inhibitor; SSRI: Selective serotonin reuptake inhibitor.

in each domain and are offered to assist shared decision-making rather than as formal recommendations.

- Where melatonin may reasonably be discussed as an option (moderate certainty): For patients with breast cancer who have persistent treatment-related sleep disturbance, particularly during endocrine therapy, a time-limited trial of oral melatonin at 3–6 mg taken

at bedtime, with reassessment after about four weeks, is a reasonable option to discuss. Melatonin should complement rather than displace cognitive behavioral therapy for insomnia, which has the stronger evidence base in cancer survivors^{5,7} and should be reserved for patients in whom that therapy is unavailable, declined or insufficient.

- Where melatonin may be considered on an individual basis (low certainty): For endocrine therapy-related hot flushes, menopausal symptoms and sexual dysfunction, and for cancer-related fatigue that persists despite exercise and other first-line measures, melatonin may be considered within shared decision-making, with explicit acknowledgment that the supporting evidence comes from single trials or from a small number of related trials, that the optimal dose is undefined, and that participation in a clinical trial is preferable where one is available.
- Where melatonin is not currently supported (low to very low certainty): Melatonin should not be offered as an antitumor therapy, as a means of modifying estrogen or IGF-axis biomarkers, or as a routine adjunct to exercise-based rehabilitation intended to improve body composition or physical fitness, since controlled trials in these domains have been consistently negative.^{28,35}
- Practical safety guidance for all patients: Clinicians should ask directly about melatonin and other supplement use, since such use is common and frequently undisclosed⁴²; document the dose, timing and formulation; recommend a content-verified preparation⁷³; review concomitant medication for CYP1A2 inhibitors and additive sedatives (Table 6); and advise against unsupervised high-dose use during curative-intent chemotherapy or radiotherapy pending adequate data.

4.8. Limitations

Eligibility was restricted to publications with full text available in English (Section 2.3), which introduces the risk of language bias. Meta-epidemiological work indicates that excluding non-English publications rarely changes the conclusions of systematic reviews of interventions in most medical fields^{74,75}, which offers some reassurance. The risk is nonetheless more material here than average, for a reason evident in the present dataset: 6 of the 11 included trials were conducted in Iran, and further work from Iran and from other regions with active melatonin research such as Brazil, China and Spain may have been published in Persian, Portuguese, Chinese or Spanish and would have been missed. Because the geographical distribution of the evidence is already skewed, language restriction may have compounded rather than offset that skew. A language-unrestricted update is planned and would require supplementary searching of Embase, Scopus, Scientific Electronic Library Online, Latin American and Caribbean Health Sciences Literature, China National Knowledge Infrastructure, Wanfang, Scientific Information Database and Magiran, together with the World Health Organization

International Clinical Trials Registry Platform and Iranian Registry of Clinical Trials, and translation support for screening and extraction. Until then, the findings should be read as applying to the English-language evidence base.

As shown in Section 3.9, the included trials do not represent 11 independent tests of the same hypothesis. Two clusters with overlapping authors account for 5 of the 11 trials, and the fatigue and HRQoL conclusions depend heavily on one of them. Publication of related follow-up reports from overlapping cohorts may also inflate the apparent volume of evidence. Accordingly, a leave-one-cluster-out analysis was conducted, with its results reported alongside the main synthesis to assess the potential influence of overlapping cohorts on the overall findings.

The included trials were limited, and most were small single-center studies; heterogeneity in dose, duration, timing, setting, and outcome instruments precluded meta-analysis, so the strength-of-evidence descriptors used here are GRADE-informed rather than formal GRADE ratings. Most primary outcomes were subjective and patient-reported and are therefore vulnerable to imperfect blinding, placebo and expectancy effects and symptom fluctuation. Several trials reported randomization, allocation concealment, prospective registration or handling of missing data incompletely, which generated the some-concerns ratings in RoB 2. The review itself was not prospectively registered, and the dose stratification and sensitivity analyses were specified after the studies had been identified. Finally, the literature has concentrated on symptom relief and quality of life, leaving recurrence, disease-free survival, overall survival, treatment completion and long-term safety essentially unexamined.

4.9. Priorities for future research

The positive signals identified here define a clear next step rather than a reason for inaction. The field needs adequately powered, multicenter, prospectively registered, double-blind, placebo-controlled trials that stratify patients by treatment phase and by dominant symptom rather than by diagnosis alone. The highest-priority trial is one in which sleep disturbance is the primary endpoint in patients receiving endocrine therapy, since this is the domain with the most consistent signal and the clearest mechanistic rationale; trials in cancer-related fatigue and in endocrine therapy-related vasomotor symptoms are the logical parallel priorities. Such trials should incorporate design features the existing literature lacks. Doses should be compared head-to-head rather than chosen by convention, and the timing of administration relative to bedtime and to treatment cycles, together with the formulation used,

should be specified and reported. Fatigue trials should use validated instruments and prespecify a clinically meaningful minimum improvement; sleep trials should combine the PSQI with sleep diaries, actigraphy or wearable devices; and endocrine therapy trials should capture vasomotor symptoms, sexual function, treatment adherence and HRQoL together. Concomitant medication and supplement use should be recorded systematically so that the interactions discussed in Section 4.6 can be assessed, and a content-verified pharmaceutical-grade preparation should be used. Biomarker substudies should measure melatonin metabolites, cortisol rhythm, inflammatory cytokines, oxidative stress markers, clock-gene expression, estrogen- and IGF-axis markers and immune indices together, and trials conducted during curative-intent treatment should collect oncological endpoints so that the theoretical antioxidant concern can be addressed directly. Finally, replication outside the small number of centers that currently dominate this literature is essential if the fatigue and HRQoL signals are to be regarded as established.

5. Conclusion

Eleven controlled trials show that exogenous oral melatonin is safe and well tolerated in patients with breast cancer and survivors across a dose range of 1–20 mg/day, with no grade 3/4 toxicity reported. Within this evidence base, melatonin improved sleep quality consistently, an effect that persisted when analysis was restricted to trials at low risk of bias and that is supported by an independent breast cancer-specific meta-analysis. Positive signals were also observed for endocrine therapy-related hot flushes and menopausal symptoms, sexual function, health-related quality of life and cancer-related fatigue. Melatonin therefore has supportive-care potential in breast cancer, particularly for the sleep and endocrine therapy-related symptom clusters that remain inadequately managed in routine practice.

These findings should be interpreted with appropriate, but not dismissive, caution. The trials were few and mostly small; treatment settings and outcome instruments differed, and the fatigue and quality-of-life results depend substantially on a single research cluster with overlapping authors; findings for anxiety, depression, estrogen- and IGF-axis biomarkers, body composition and hormonal response were inconsistent or negative.^{18,19,28,35} The literature has also concentrated on symptom relief, leaving recurrence, disease-free survival, overall survival, treatment adherence and long-term safety largely unexamined.

The appropriate response to this evidence is not to set melatonin aside but to test it properly. Adequately powered,

multicenter, prospectively registered, double-blind, placebo-controlled trials, stratified by treatment phase and dominant symptom and using head-to-head dose comparison together with standardized patient-reported outcomes and objective biomarkers, are the logical next step; a trial with sleep disturbance during endocrine therapy as its primary endpoint is the most immediately justified. Pending such trials, melatonin is best regarded as a low-cost, accessible and generally safe supportive-care option that may reasonably be discussed with individual patients for sleep disturbance and endocrine therapy-related symptoms, but that cannot yet be recommended as routine care or as antitumor therapy in breast cancer.

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Conflict of interest

The authors declare that they have no competing interests.

Author contributions

Conceptualization: All authors

Data curation: Ji Yu

Investigation: Ji Yu

Methodology: Ji Yu, Junfei Xu

Supervision: Junfei Xu

Writing—original draft: Ji Yu

Writing—review & editing: Junfei Xu

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Consent for publication

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Availability of data

All data supporting the findings of this review are available in the cited published articles.

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