

REVIEW ARTICLE

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

Supplementary Files

Table S1. Basis for each domain-level risk-of-bias judgment (Cochrane Risk of Bias 2 tool)

Study	D1	D2	D3	D4	D5	Overall
Schernhammer <i>et al.</i> ¹	Some concerns: randomized, double-blind allocation reported; method of sequence generation and allocation concealment not described in full.	Low: placebo-controlled double-blind design with adherence monitoring; no evidence of deviation from the intended intervention.	Low: outcome data available for a high proportion of randomized participants.	Low: objective laboratory biomarkers assessed independently of treatment allocation.	Some concerns: no prospectively registered analysis plan identified for the reported biomarker outcomes.	S
Palmer <i>et al.</i> ²	Low: randomized, double-blind, placebo-controlled allocation reported.	Low: identical placebo and double blinding of participants and assessors.	Low: outcome data reported for essentially all randomized participants.	Low: validated neuropsychological instruments applied by blinded assessors.	Low: prespecified primary and secondary outcomes reported.	L
Sedighi Pashaki <i>et al.</i> ³	Some concerns: randomization stated but sequence generation and allocation concealment not described.	Some concerns: blinding of participants and personnel not fully described for the parallel-group design.	Low: fatigue outcome data reported for both groups at the planned time points.	Some concerns: BFI is a subjective, patient-reported instrument and blinding was incompletely described.	Some concerns: no prospectively registered analysis plan identified.	S
Sedighi Pashaki <i>et al.</i> ⁴	Some concerns: randomization stated but sequence generation and allocation concealment not described.	Some concerns: blinding incompletely described over a multi-year intervention period.	Some concerns: attrition over two years of follow-up is incompletely described and not formally analyzed.	Some concerns: subjective patient-reported fatigue outcome with incompletely described blinding.	Some concerns: no prospectively registered analysis plan identified for the long-term outcomes.	S
Keshtpour Amlashi <i>et al.</i> ⁵	Some concerns: allocation described as controlled, but the randomization procedure is not fully reported.	Low: intervention and comparator delivered as intended over the follow-up period.	Some concerns: loss to follow-up over 3 years is incompletely described.	Low: EORTC QLQ-C30 is a validated instrument administered in a standardized manner.	Some concerns: no prospectively registered analysis plan identified for the reported quality-of-life outcomes.	S

(Cont'd...)

Table S1. (Continued)

Study	D1	D2	D3	D4	D5	Overall
Mukhopadhyay <i>et al.</i> ⁶	Low: phase III randomized, double-blind, placebo-controlled allocation with concealment reported.	Low: matched placebo and double blinding maintained throughout.	Low: outcome data available for 78 of 79 randomized participants.	Low: validated patient-reported instruments applied under double-blind conditions.	Low: prespecified primary endpoint reported in accordance with the trial protocol.	L
Nimee <i>et al.</i> ⁷	Some concerns: randomization and double blinding stated but sequence generation and allocation concealment not described.	Low: both groups received identical dietary advice and a matched placebo.	Low: outcome data reported for both groups at the planned time points.	Low: FACIT-fatigue administered under double-blind conditions.	Some concerns: within-group and between-group analyses reported without a prospectively registered analysis plan.	S
Vaziri <i>et al.</i> ⁸	Low: randomized, double-blind, placebo-controlled allocation reported.	Low: matched placebo with blinding of participants and investigators.	Low: outcome data reported for both groups at the planned time points.	Low: validated instruments (PSQI, CES-D, POMS) applied under double-blind conditions.	Low: prespecified sleep and mood outcomes reported.	L
Sadeghi Yazdankhah <i>et al.</i> ⁹	Low: randomized, triple-blind allocation with concealment reported.	Low: triple blinding of participants, personnel and assessors.	Low: outcome data reported for both groups at the planned time points.	Low: validated instruments (MFI, BAI, BDI) applied under triple-blind conditions.	Low: prespecified outcomes reported.	L
Sattari <i>et al.</i> ¹⁰	Some concerns: randomization and double blinding stated, but sequence generation and allocation concealment not described.	Low: matched placebo with blinding of participants and investigators.	Low: outcome data reported for both groups over the 4-week intervention.	Low: validated instruments (MENQOL, FSFI) applied under double-blind conditions.	Some concerns: multiple symptom outcomes reported without a prospectively registered analysis plan.	S
Celorio San Miguel <i>et al.</i> ¹¹	Some concerns: randomized allocation in a very small sample ($n = 20$) with the procedure incompletely described.	Some concerns: single-blind design with exercise as a co-intervention that may itself influence the outcome.	Low: outcome data reported for both groups over the 10-week intervention.	Some concerns: several outcomes are subjective, and the design was single-blind.	Some concerns: multiple physical, quality-of-life and hormonal outcomes reported without a prospectively registered analysis plan.	S

Notes: 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.

Abbreviations: BAI: Beck Anxiety Inventory; BDI: Beck Depression Inventory; BFI: Brief Fatigue Inventory; CES-D: Center for Epidemiologic Studies Depression Scale; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; FACIT: Functional Assessment of Chronic Illness Therapy; FSFI: Female Sexual Function Index; MENQOL: Menopause-Specific Quality of Life questionnaire; MFI: Multidimensional Fatigue Inventory; POMS: Profile of Mood States; PSQI: Pittsburgh Sleep Quality Index.

Table S2. Full search strategies

Database	Date searched	Search string
PubMed	May 15, 2026	(((((breast cancer[Title/Abstract]) AND melatonin[Title/Abstract]) AND English[Language]))) NOT REVIEW[Publication Type] AND (Intervention Studies OR intervention OR controlled trial OR “randomized” OR “randomised” OR “random” OR “randomly” OR “placebo” OR “assignment”)
Web of Science	May 15, 2026	TS=(“breast cancer”) AND TS=(“melatonin”) AND Document Types=(Article) AND TS=(“intervention” OR “intervention studies” OR “controlled trial” OR “randomized” OR “random” OR “randomly” OR “placebo” OR “assignment”)
Cochrane Library	May 15, 2026	(“breast cancer”:ti,ab,kw AND melatonin:ti,ab,kw) AND (intervention:ti,ab,kw OR “controlled trial”:ti,ab,kw OR randomized:ti,ab,kw OR random:ti,ab,kw OR randomly:ti,ab,kw OR placebo:ti,ab,kw OR assignment:ti,ab,kw)

Notes: All three databases were searched from inception to May 15, 2026, with no restriction on publication year; together, the three searches retrieved 378 records, of which 40 were duplicates (Figure 1).

References

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