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Effect of melatonin on Quality of life and symptoms in cancer patients: a systematic review and meta-analysis of randomized controlled trials

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Abstract

Objective The study was to systematically review the effect of the melatonin on quality of life and symptoms among cancer patients.

Design Systematic review and meta-analysis.

Methods Nine databases were systematically reviewed from inception to November 2021 for randomized controlled trials (RCTs). Two reviewers critically and independently assessed the risk of bias and extracted data using the designed form. All analyses were performed with Review Manager 5.3.

Results A total of 19 qualified studies that included 2101 cancer patients (melatonin: 1078, control: 1023) were included in the meta-analysis. Results indicated that melatonin had no significant effect on QoL [SMD = -0.01, 95% CI (-0.14, 0.11), P = 0.83], sleep quality [SMD = -0.35, 95% CI (-0.73, 0.03), P = 0.07], fatigue [SMD = 0.34, 95% CI (-0.73, 0.06), P = 0.10], pain [SMD = -0.34, 95% CI (-0.7, 0.02), P = 0.06] and severity of stomatitis [OR = 0.6, 95% CI (0.31, 1.16), P =0.13]. Melatonin had significant effect on incidence of stomatitis [OR = 0.49, 95% CI (0.35, 0.69), P < 0.001], but couldn't reduce the incidence of stomatitis among head and neck cancer patients [OR =1.17, 95% CI (0.57, 2.39), P = 0.67]. Meanwhile, melatonin could improve depression among patients who experienced intervention duration greater than 14 days [SMD = -0.14, 95% CI (-0.27, -0.01), P = 0.03] and those who under operation [SMD = -0.17, 95% CI (-0.32, -0.03), P = 0.02].

Conclusion Finding showed that melatonin couldn't improve the QoL, sleep quality, fatigue, pain and stomatitis severity among cancer patients. However, melatonin could decrease the incidence of stomatitis, though no effect on the head and neck cancer patients. Melatonin could decrease depression of cancer patients under operation and those received longer melatonin duration. Our review stressed the need for more high-quality RCTs.

PROSPERO registration number

CRD42021292855.

Strengths and limitations of this study

- As there are few meta-analyses and systematic review of melatonin on cancer patients. Our research tried to prove the effect of melatonin on QoL and symptoms (sleep, fatigue, pain, depression, stomatitis) in cancer patients, to provide a basis for future research.
- The significant results from subgroup analysis should be interpreted prudently due to the small number of the included studies.
- Differences in cancer diagnose, companied treatment and administration duration might be the main sources of heterogeneity in our study.

Introduction

Melatonin (MLT) is an important endogenous indoleamine that is synthesized and secreted into the systemic circulation and cerebrospinal fluid by the pineal gland, which has recognized anti-aging, anti-inflammatory, and anti-oxidant properties[1]. It also has a substantial role to regulate the circadian rhythm and sleep during the night. Recent studies proved the effect of melatonin on limiting skeletal muscle frailty, prolonging physical performance[2] and preventing bone loss[3]. In the oncology field, melatonin has significant apoptotic, angiogenic, oncostasis and anti-proliferative effects on various oncological cells[4]. It was proved that low levels of melatonin might be a risk factor for breast cancer[5]. Meanwhile, many studies have shown that melatonin's co-administration improves the sensitivity of cancers to inhibition by conventional drugs, and reduces the toxic consequences of anti-cancer drugs while increases their efficacy[6]. Once a meta-analysis revealed that MLT may benefit cancer patients who are also receiving chemotherapy, radiotherapy, supportive therapy, or palliative therapy by improving survival and ameliorating the side effects of chemotherapy[7]. Cancer patients commonly face various disturbing and substantial challenges, including physical symptoms brought by disease or anticancer treatment, psychological/spiritual distress, inadequate social support and information[8], lead to decreased quality of life. MLT has been shown to be associated with a wide variety of health outcomes in cancer patients[9], with less toxicity and side effects. Palmer et al showed that a neuroprotective effect of melatonin to counteract the adverse effects of chemotherapy on cognitive function, sleep quality and depressive symptoms in breast cancer patients[10]. Recent clinical trial proved the relationship between decreased levels of fatigue associated with the malignant condition and melatonin supply[11]. However, some of the recent findings published suggest the conflicting results[12 13] that melatonin intervention cannot improve the QoL or release the symptoms burden, or presented the uncertain results[14]. In addition, the relationship between the benefits of melatonin and the cancer type, duration, length, combined treatment is still unspecific and ambiguous. Thus, with accumulating evidence, we perform a systematic review and meta-analysis of randomized controlled trials (RCTs) to investigate the roles of melatonin, versus placebo, in the effectiveness of improving QoL and symptoms.

Methods

This review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (PRISMA) and the recommendations of the Cochrane

Collaboration. The study was registered in PROSPERO with a registration number of CRD42021292855.

Search strategy

A throughout search was conducted in Cochrane Library, PubMed, Embase, Web of Science, Medline, CINAHL, Scopus, ClinicalTrials.gov, and China Biology Medicine (CBM) from inception through November 2021 for randomized controlled trials (RCTs) without language restrictions. Sources of unpublished studies and gray literature to be searched through ProQuest and Open Gray. We used medical subject headings (MeSH) and text words to identify the potential interest studies (see supplemental file 1).

Eligibility criteria

Participants

Studies including adult patients (≥ 18 years) who were diagnosed with cancer, regardless of cancer type, cancer stage, and current treatment, were eligible.

Interventions and controls

All trials that reported and evaluated effects of melatonin were included. Literature excluded if they met the following criteria:(1) they were study design except RCT; (2) had studies the effects of melatonin along with other interventions (3) had lack of sufficient data for the interested outcomes.

Outcomes

Primary outcome was Quality of life. The scores of sleep quality, fatigue, depression, and pain, as well as the rate of stomatitis and its severity were the secondary outcome.

Studies

Only RCTs were eligible.

Data extraction

Two independent researchers (SiyuYang, Tongyu Wang) extracted the data, evaluated the quality of eligible studies, and performed double-checks. Any disagreements and differences were resolved by a third independent investigator (Xiaofan Bu). The following data from the full text of selected studies were extracted: first author's name, year of publication, the characteristics of the patients, the characteristics of the intervention and the control groups (study design, form of intervention, dose of melatonin supplementation, study duration), number of participants in each group and outcome results (means and standard deviations for continuous data; number of incidents for dichotomous data).

Risk of bias assessment

Two reviewers independently evaluated the risk of bias in the included RCTs using the Cochrane assessment tool, which consists of the following seven domains: "random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias". Each question can be rated as follows: yes (+), low risk of bias; unclear (?), unclear risk of bias; no (−), high risk of bias.

Data analysis

The meta-analysis was performed using Review Manager Software (version 5.3). The effect of

melatonin on scores of QOL and symptoms were estimated by mean difference (MD) when trials measured an outcome by using the same measurement method or scale. We used standard mean difference (SMD) when trials used different instruments to measure the same outcome. For dichotomous outcomes (such as stomatitis and its severity), we used odds ratio (OR). The effect size (ES) and the 95% confidence interval (CI) for primary and secondary outcomes were computed. The ES with scores of 0.2–0.5, 0.5–0.8, and > 0.8 were considered small, medium, and large effects, respectively. Forest plots were used to display the pooled ES, 95% CI, weight in percentage. If variability was presented by measures other than mean or SD, we used standard approaches for estimating data. If the studies did not report SD, we used the following formula to calculate missing SD: SD=√N×(Upper 95% CI－Lower 95% CI)/3.92. If a study provided medians and interquartile ranges (IQR), we transformed median and IQR to mean and SD by a method for non-normal data [15]. I^2 was used to measure the statistical heterogeneity among the trials in each analysis. If $P > 0.1$ and $I^2 < 50\%$, a fixed-effects model was adopted; if $P < 0.1$ and $I^2 \geqslant 50\%$, then a random-effects model was adopted. If heterogeneity was identified, subgroup analyses were conducted on different cancer type, dosage, and study duration if there were at least two studies on a stratum, considering that these variables might have influences on the outcomes. Sensitivity analysis was performed in light of the fact that some of the trials might impact the study results by removing studies with high or unclear risk of bias. Reporting and publication bias were investigated by visually examining the degree of asymmetry of a funnel plot.

Results

Literature search

The initial search identified 1670 publications through pubmed, embase, medline, scopus, sinomed, web of science, cochrane, and clinical trial. After excluding 501 duplicates, a total of 1161 studies were retrieved for title and abstract screening. After screening for title and abstract, 1111 articles were excluded and 50 papers were retrieved for full text review. Out of 50 retrieved papers, 1 article was excluded due to wrong langue[16], 6 articles were excluded without sufficient data, 14 articles were excluded without full text, 9 articles were excluded without target outcome, 1 article was excluded due to non-RCT study[17]. Therefore, a total of 19 articles were included in the final meta-analysis[18-36]. The flow chart of literature search is shown in Fig. 1.

Quality assessment

We used Cochrane scoring system to assess the quality of the included studies. The overall risk of bias as shown in Fig. 2 (in supplementary material) was moderate. Nearly all studies reported appropriate random sequence generation. Most studies reported completed data and had low risk of bias on the item ‘Selective reporting’. Almost a third of the studies did not report the blindness in outcome assessment. The individual risk of bias for each study is presented in Fig. 3 (in supplementary material).

Literature characteristics

The characteristics of the patients, interventions, controls, and outcome measures are shown in Table 1.

Table 1 The characteristics of the literature

Author	Year	Population	Mean age（intervention/control）	Study design	Time of duration	Administration time	Intervention group	Control group	Outcome	Intervention (Number)	Control (Number)
Palmer	2020	Breast cancer patients undergoing chemotherapy after lumpectomy or mastectomy	54.24/54.11	Randomized, double-blinded, placebo-controlled trial	10 days: three days prior to chemotherapy and seven following days	Approximately 1 hour before bedtime	Oral 20 mg melatonin	Placebo	Depressive symptoms (BDI-II), Sleep quality (PSQI), QOL (EORTC QLQ-C30)	18	18
Rasmussen	2015	Advanced cancer patients who reported significantly tired in palliative care unit	64/65	Double-blind placebo-controlled crossover trial	7 days	Each night	Oral 20 mg melatonin	Placebo	Fatigue (MFI-20), QOL (EORTC QLQ-C15-PAL), Insomnia (EORTC QLQ-C15-PAL)	21	23
Chen	2014	Breast cancer survivors	59/59	Randomized, placebo-controlled trial	4 months	Each night at 9 pm	3 mg oral melatonin	Placebo	Sleep (PSQI), depression (CES-D)	48	47
Pashaki	2021	Breast Cancer during adjuvant chemotherapy and radiotherapy	50.47/46.05	Randomized, Controlled, Parallel-Group trail	8weeks: from 1 week before until 1 month after the adjuvant radiotherapy	Every night approximately 1 hour before bedtime	Oral 18 mg melatonin	Placebo	Fatigue (BFI)	38	36
Madsen	2016	Patients undergoing breast cancer surgery	51/59	Randomized, Double-Blind, Placebo-Controlled Trial	2weeks: 3 days preoperatively until 2 weeks postoperatively	Approximately 1 h before bedtime	6mg oral melatonin	Placebo	Sleep (VAS, KSS), pain (VAS)	27	21
Hansen	2014	Patients undergoing breast cancer surgery	51/60	Randomized, double-blind, placebo-controlled trial	10days: 2 days preoperatively till 8 days postoperatively	Approximately 1 h before bedtime	6 mg oral melatonin	Placebo	Depression (MDI), Sleepiness (KSS, VAS), Fatigue (VAS), Pain (VAS)	28	26
Onseng	2017	Head and Neck Cancer Patients Receiving Concurrent Chemoradiation	47.3/49.6	Randomized, placebo-controlled trial	35days: 5 days a week throughout the 7 weeks of chemoradiation	At night after 21:00	10 mL of a 0.2% melatonin niosome oral gargle plus 20 mg oral dosage	placebo	QOL (FACT—H&N), Mucositis incidence rate, Mucositis severity (WHO-G)	19	20
Sookprasert	2014	NSCLC patients receiving chemotherapy	56.8/55.6	Randomized, double-blind, placebo-controlled trial	2 months: during chemotherapy for 2 months	At night after 21:00	10 mg melatonin or 20 mg melatonin	Placebo	QOL(FACT-L), Mucositis incidence rate	88	38
Seely	2021	Cancer patients following lung cancer resection	67.2/67.2	Randomized placebo controlled clinical trial	One year post-surgery	Approximately one hour before bedtime	20 mg oral melatonin	Placebo	Fatigue (MFI-20), QOL(QLQ-LC13), Sleep (MOS), Depression (BDI 2), Pain (BPI)	356	353
Shahrokhi	2021	Patients With Colorectal Cancer Undergoing Chemotherapy with sleep disorder	63.63/64.11	Randomized single-blind trail	4week of treatment	At bedtime	6 mg oral melatonin	10 mg zolpidem	Sleep (GSQS, PSQI), Depression (HRSD)	45	45

Grutsch	2021	NSCLC patients under chemotherapy	60.3/63	Randomized, double-blind, three-arm study	Each patient was followed until death.	At 8AM or at 8PM	Oral 20 mg melatonin	Placebo	QOL(QLQ-C30), Fatigue (QLQ-C30), Pain (QLQ-C30), Sleep (PSQI)	20	18
P. Lissoni	1999	Metastatic Solid Tumour Patients under Chemotherapy	53/56	Randomized controlled	7 days prior to chemotherapy, continued after chemotherapy interruption, until disease progression	Every night	Oral 20 mg melatonin	Placebo	Stomatitis incidence rate	124	126
Elsabagh H H	2019	Head and neck cancer (HNC) patients undergoing radiotherapy	57.8/55.9	Randomized clinical trial	Six weeks	30 minutes before sleeping	Oral 20 mg melatonin	Placebo	Oral mucositis severity (WHO-G), Stomatitis incidence rate, Pain (NRS)	20	20
P. Lissoni	2002	Untreated patients with metastatic solid tumors under chemotherapy	66/65	Randomized clinical trial	At least 2 months	During the dark period of the day	Oral 20 mg melatonin plus support care	Placebo plus support care	Stomatitis incidence rate	98	102
Borbalas	2021	Patients with head and neck cancer undergoing radiation therapy and chemical treatment	59/56	Randomized placebo-controlled phase II trial	5days lasting 7 weeks	Not clearly	3% MLT oral gel plus standard symptomatic treatment for OM	Placebo plus standard symptomatic treatment for OM	Oral mucositis severity (WHO-G), Stomatitis incidence rate	40	39
Yennurajalingam	2019	Patients with advanced cancer with poor sleep quality	Not clearly	Double-blind randomized factorial study design	14d	At bedtime	MLT 20mg plus bright white light therapy	Bright white light therapy alone	Sleep (PSQI), insomnia (ISI), fatigue (FACIT-F), depression (HADS), QOL(FACT)	6	8
Kurdi	2016	Cancer Patients with Insomnia	55.2/49.64	Randomized Double-Blind Placebo-Controlled Study	14 days	At 7 pm	Oral melatonin 3 mg	Placebo	Sleep (AIS)	25	25
P. Lissoni	1997	patients with metastatic solid tumors under chemotherapy	61/58	Randomized clinical trial	Until disease progression	At the evening of each day	Oral melatonin 20 mg	Placebo	Stomatitis incidence rate	39	40
Palmer	2019	Breast Cancer Patients Receiving Chemotherapy	54.24/54.11	Randomized, Double-Blinded, Placebo-Controlled Trial	10 days during treatment.	Approximately 1 h before bedtime	Oral melatonin 20 mg	Placebo	Pain (NRS), Sleep (PSQI), Depression (BDI)	18	18

BDI-II, Beck Depression Inventory; PSQI, Pittsburgh Sleep Quality Index; EORTC QLQ-C30, European Organization for Cancer Research and Treatment of Cancer Quality of Life Questionnaire; MFI-20, Multidimensional Fatigue Inventory; EORTC QLQ-C15-PAL, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 15 Palliative Version; CES-D, Center for Epidemiologic Studies-Depression; BFI: Brief Fatigue Inventory; VAS, Visual Analogue Scale; KSS, Karolinska Sleepiness Scale; MDI, Major Depression Inventory; FACT—H&N, Functional Assessment of Cancer Therapy—H&N Version 4; FACT-L, Functional Assessment of Cancer Therapy – Lung; QLQ-LC13, Lung Cancer-13 modules; BDI 2, Beck Depression Inventory 2; MOS, Medical Outcomes Study Sleep Survey; BPI, Brief Pain Inventory; GSQS, Sleep Quality Scale; HRSD, Hamilton Rating Scale for Depression; NRS, Numeric Rating Scales; ISI, Insomnia Severity Index; FACIT-F, Functional Assessment of Cancer Illness Therapy-Fatigue subscale; HADS, Hospital Anxiety and Depression Scale; FACT, Functional Assessment of Cancer Illness Therapy; AIS, Athens insomnia scale; WHO-G, WHO grading system

Participants

Publication dates ranged from 1997 to 2021. Among the 19 studies included in systematic review, the mean age of the participants ranged from 46.05 to 67.2 years. The sample size ranged from 14 to 709 participants. Regarding treatment trajectory, 12 studies were conducted in cancer patients with adjuvant chemotherapy and (or) radiotherapy [19 20 23-26 29-32 34 35]. One study was conducted in advanced cancer patients with fatigue[27]. One study was in breast cancer survivors[18]. 3 studies were in cancer patients with surgery[21 28 33]. 2 studies were in advanced cancer patients with poor sleep quality[22 36]. Regarding the cancer diagnose, 6 studies were in breast cancer[18 21 28 30-32]. 2 studies were in non-small cell lung cancer[20 33]. 3 studies were in head and neck cancer[19 26 29]. One was in colorectal cancer[34]. 7 studies were no restriction on cancer type but most in advanced cancer patients[22-25 27 35 36].

Intervention

The follow-up period ranged from seven days to one year. Melatonin dose varied between 3 and 20 mg. Types of melatonin administration, 17 were oral melatonin[18-25 27 28 30-33 37], one was melatonin oral gargle[26], and one was combined both[29]. Nearly all studies gave the melatonin at night, except one compared both in morning and night[20].

Instruments

All studies used standardized and validated tools. Quality of life was measured by four validated tools: European Organization for Cancer Research (EORTC QLQ-C30)[20 31], Treatment validated for the Brazilian population (QLQ-BR 23)[31], Functional Assessment of Cancer Therapy (FACT)[35 36], Ferrans and Powers Quality of Life Index (QLI)[20], European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 15 Palliative Version (EORTC QLQ-C15-PAL)[27], Lung Cancer-13 (QLQ-LC13)[33]. Sleep quality was measured by Pittsburgh Sleep Quality Index (PSQI)[18 20 30 31 34 36], Visual Analogue Scale (VAS)[21 28], Karolinska Sleepiness Scale (KSS)[21 28], Sleep Quality Scale (GSQS)[34], Athens insomnia scale[22], Medical Outcomes Study(MOS) Sleep Survey[33]. Depression was measured by Beck Depression Inventory (BDI-II)[31 33], Beck Depression Inventory (BDI)[30], Center for Epidemiologic Studies-Depression (CES-D)[18], Major Depression Inventory (MDI)[21], Hamilton Rating Scale for Depression (HRSD)[34], Hospital Anxiety and Depression Scale (HADS)[36]. Fatigue was measured by Multidimensional Fatigue Inventory (MFI-20)[27], EORTC QLQ-C15-PAL (fatigue domain)[27], Brief Fatigue Inventory (BFI)[32], VAS[21], Multidimensional Fatigue Index 20 questionnaire[33], QLQ-C30 (fatigue domain)[20], Functional Assessment of Cancer Illness Therapy-Fatigue subscale (FACIT-F)[36]. Pain was measured by VAS[21 28], Brief Pain Inventory (BPI)[33], QLQ-C30 (pain domain)[20], Numeric Rating Scales (NRS)[19 30]. The incidence of stomatitis was calculated by the ratio of occurrences number and the total number[19 23-26 29 35].

Meta-analysis

Effect of melatonin on quality of life

Overall, 6 clinical trials evaluated the effect of melatonin on QOL. The results showed that there was no statistically significant difference between the intervention and control groups [SMD = -0.01, 95% CI (-0.14, 0.11), P = 0.83] with no heterogeneity (I^2=0%, P=0.42) (Fig. 4 was seen in supplementary material).

Effect of melatonin on sleep quality

Nine clinical trials evaluated the effect of melatonin on sleep quality (SQ). Pooled effect size from random effect model showed a significant lowering effect of melatonin on SQ [SMD = -0.78, 95% CI (-1.47, -0.10), P = 0.02]. There was significant heterogeneity between studies (I^2 = 94%, P <0.001). We deleted a study[34] with obvious heterogeneity and I^2 decreased to 79% [SMD = -0.35, 95% CI (-0.73, 0.03), P = 0.07] (Fig. 5 was seen in supplementary material). Subgroup analysis based on dose of melatonin, study duration, treatment, different combination of dosage and duration showed no significant differences between subgroups (Table 2).

Table 2 Subgroup analyses of melatonin supplementation on sleep quality

	N	WMD (95% CI)	Heterogeneity I^2 (P)	P within group
Overall effect	8	-0.35 (-0.73, 0.03)	79% (P<0.0001)	0.07
Dosage				
<10mg	4	-0.32 (-0.88, 0.23)	77% (P=0.005)	0.25
≧10mg	4	-0.42 (-1.16, 0.32)	84% (P=0.0004)	0.27
Duration				
<2 weeks	2	-0.01 (-0.33, 0.32)	0% (p=0.76)	0.96
≧2 weeks	6	-0.51 (-1.07, 0.05)	85% (p<0.00001)	0.08
Combination				
<10mg + ≧2 weeks	3	-0.46 (-1.18, 0.27)	83% (P=0.003)	0.22
>10mg + ≧2 weeks	3	-0.01 (-0.16, 0.13)	0% (P=1.00)	0.86
>10mg + <2 weeks	1	-1.75 (-2.54, -0.97)	-	<0.01
<10mg + <2 weeks	1	0.06 (-0.5, 0.62)	-	0.83
Combined treatment				
Under chemotherapy	2	-0.87 (-2.57, 0.82)	91% (P=0.0009)	0.31
Under surgery	3	-0.02 (-0.15, 0.12)	0% (P=0.89)	0.83
With insomnia				
Yes	2	-0.7 (-1.96, 0.57)	77% (P=0.04)	0.28
No	6	-0.23 (-0.58, 0.13)	73% (P=0.002)	0.21

N, number of the literatures

Effect of melatonin on fatigue

The overall ES of melatonin for fatigue alleviation was medium [SMD = 0.34, 95% CI (-0.73, 0.06), P = 0.10] with high heterogeneity among studies (P =0.002, I^2 = 74%), and there was no significant statistic difference. The study of Pashaki et al[32] showed a great heterogeneity for only this one proved a significant lower levels of fatigue in intervention group. We removed it and the heterogeneity decreased to 0 (Fig. 6 was seen in supplementary material).

Effect of melatonin on depression

Six clinical trials evaluated the effect of melatonin on depression. Only Palmer et al showed a significant effect on depression[31]. The overall treatment effect on depression showed there was no statistically significant difference between the intervention and control groups [SMD = -0.24, 95% CI (-0.53, 0.05), P = 0.10] with high heterogeneity among studies (P =0.03, I^2 = 60%). A sensitivity analysis was done by removing one study from the analysis[31] (Fig. 7 was seen in supplementary

material). Regarding subgroup analysis, a significant difference was observed on the study duration and treatment, Though, both showed a slight ES. Patients experienced intervention duration greater than 14 days had a significant lower depression [SMD = -0.14, 95% CI (-0.27, -0.01), P = 0.03] with low heterogeneity (P =0.4, I^2 = 0%). Meanwhile, melatonin seemed to alleviate depression in cancer patients under operation [SMD = -0.17, 95% CI (-0.32, -0.03), P = 0.02] with low heterogeneity (P =0.35, I^2 = 0%). No significant difference was observed among studies on the dosage (P = 0.43), cancer diagnose (P = 0.20), and combined chemotherapy (P = 0.13).

Effect of melatonin on pain

Five clinical trials evaluated the effect of melatonin on pain [SMD = -0.34, 95% CI (-0.7, 0.02), P = 0.06] with high heterogeneity among studies (P =0.03, I^2 = 62%). No significant difference was observed among studies on the cancer diagnose (P=0.27), combined treatment (P=0.37), duration (P=0.27) and dosage (P=0.16). Sensitivity analysis was done by removing one study[19] from the analysis and the heterogeneity decreased to 0% (Fig. 8 was seen in supplementary material).

Effect of melatonin on stomatitis

A for stomatitis, all the studies were conducted in cancer patients combined with radiation or chemical treatment. Seven clinical trials evaluated the effect of melatonin on the incidence of stomatitis showed moderate ES [OR = 0.49, 95% CI (0.35, 0.69), P < 0.001] (Fig. 9 was seen in supplementary material), however high heterogeneity (P =0.01, I^2 = 64%). All of the study duration were more than 2 weeks and patients all accept both melatonin or radiotherapy. Besides, nearly all these clinical trials gave the melatonin of 20mg, except one used 3% melatonin oral gel[26]. However, removing it or not caused little change to heterogeneity and ES. Further subgroup analysis showed that the difference in cancer type. Melatonin couldn't reduce the incidence of stomatitis among head and neck cancer patients under adjuvant chemotherapy or radiotherapy [OR =1.17, 95% CI (0.57, 2.39), P = 0.67] with low heterogeneity (P =0.5, I^2 = 0%), while had slight significant value in patients with metastatic solid tumor [OR =0.28, 95% CI (0.17, 0.44), P < 0.0001] with low heterogeneity (P =0.74, I^2 = 0%).

As for stomatitis severity, three clinical trials evaluated the effect of melatonin on the incidence of stomatitis severity, mainly in the effect on reducing 3-4 grades (severe) stomatitis according to WHO grade system. The overall treatment effect showed that the intervention has no statistically significant difference between the intervention and control groups [OR = 0.6, 95% CI (0.31, 1.16), P =0.13] with low heterogeneity (P =0.13, I^2 = 22%) (Fig.10 was seen in supplementary material).

Discussion

The aims of this systematic review were to determine the effectiveness of melatonin on the QoL, sleep quality, and other symptoms like fatigue, depression, pain and stomatitis of cancer patients. To the best of our knowledge, this study is the first meta-analysis that investigated the effect of melatonin on QoL and symptoms in cancer patients. Unfortunately, in the current study, we proved that melatonin didn't have beneficial effects on QoL, sleep quality, fatigue and pain. However, it had potential ability to improve depression and reduce the incidence of stomatitis, with small effect sizes in depression (ES=0.14-0.17) and moderate effect sizes in stomatitis (ES=0.49).

The clinical correlates of QoL in cancer patients include poor sleep quality, occurrence of

various symptoms like fatigue, depression, pain, and so on. Thus, the effect of melatonin on improving QoL might be achieved through relieving symptom suffering. However, multiple researches provided conflict results. A previous study reported beneficial short-term effects of melatonin on sleep but not QoL in haemodialysis patients[38]. Innominato et al revealed bedtime melatonin was associated with a significant improvement in sleep quality, fatigue severity, global quality of life, and social and cognitive functioning in advanced breast cancer patients[39]. In cachectic patients with advanced cancer, melatonin did not improve appetite, weight, or quality of life[40]. Our review included six trails regarded QoL of cancer patients as outcome. None of them proved a significant improvement in intervention group in QoL, though Grutsch et al[20] and Sookprasert et al[35] provided a trend for better QoL compared with baseline. However, improvement from baseline couldn't be the convincing evidence to confirm the certain effectiveness of melatonin on QoL, for both two research duration lasted a long time and existed various confounding factors. For the invalid effectiveness of melatonin on QoL, one of the possible interpretations might be the differences due to study population, interventions and measurements. Another explanation might be the multi-dimensional properties of QoL, which not only contained physical domain but covered the domains of psychology, spirit, and social. Thus, drugs may play a complementary role. Symptoms relief like sleep or fatigue alone seems to be difficult to effectively improve the QoL, especially for cancer patients who facing with a mass of disturbing from many aspects.

Due to the important role in regulating the circadian rhythm and sleep, many studies have conducted to verify the value of melatonin on sleep. A network meta-analysis support effectiveness of melatonin in improving sleep-onset difficulties[41]. A review about the influence of dietary sources of melatonin on sleep quality indicated that the sources of melatonin consumption of milk and sour cherries may improve sleep quality[42]. However, it seems melatonin has different effect on different study groups. Fatemeh et al found the significant effects of melatonin on sleep quality in patients with respiratory diseases, metabolic disorders, and sleep disorders, but not in mental disorders, neurodegenerative diseases and breast cancer [43]. Maria et al found a significant improvement of melatonin in mood and sleep quality in perimenopausal women [3], while a meta-analysis showed that melatonin treatment resulted in no benefits to sleep quality, general menopause symptoms and psychological issues like depression and anxiety in menopausal women[44]. It is unknown whether a higher dose or longer treatment duration would have affected these circadian parameters. Innominato et al found 5mg for two months has a positive effectiveness on sleep quality and QoL in advanced breast cancer patients[39]. Two studies that proved the significant impact on sleep in our review were the 20mg for 10 days in breast cancer patients under chemotherapy[31] and 3mg for 14 days in cancer patients with insomnia respectively[22]. Our review revealed significant large pooled effect size of melatonin on sleep, nevertheless with large heterogeneity. The subgroup analysis revealed the melatonin duration more than 2 weeks had a higher ES (ES=0.51) with a near significance (P=0.08). Unfortunately, there was no difference between dosage <10mg and ≧10mg (P=0.25-0.27), as well as different combination of dosage and duration (P=0.22-0.86), indicating the further research on the dosage and duration. As far as we know, the study on effectiveness of melatonin in cancer patients with insomnia is limited. Melatonin seems to have potential effect in cancer patients with insomnia[22], but the validity disappeared when in advanced cancer patients[36]. The type of melatonin is another point. It was found prolonged release melatonin formulation for 2 mg results in significant and clinically meaningful improvements in sleep quality, morning alertness, sleep onset latency and quality of life in primary insomnia patients[45] and in Parkinson's disease

patients with a poor sleep quality[46]. The availability of melatonin in patients with insomnia is still unknown. Combination of bright light and melatonin improved subjective daytime sleepiness, fatigue, and cognitive function in patients with delayed sleep phase disorder[47], similarly failed in advanced cancer patients with insomnia[36].

Melatonin may be an effective treatment for patients with chronic fatigue syndrome[48]. Nevertheless, in the current study, none of the study was showed to improve fatigue in cancer patients. Only a high quality trail proved a significant effect of melatonin on breast cancer patients undergoing adjuvant chemotherapy and radiotherapy[32], with melatonin 18 mg a day from 1 week before until 1 month after the adjuvant radiotherapy. The evidence supporting the usage of melatonin for cancer-related fatigue is limited. Short-term use of dexamethasone or methylprednisolone is recommended for the control of CRF in metastatic cancer patients according to ESMO Guidelines[49], while the use of eszopiclone, megestrol acetate and melatonin is not recommended for the control of CRF. However, the prevent effect of melatonin on cancer-related fatigue is still under study. Non-pharmaceutical interventions were recommended to manage fatigue[49]. Some non-pharmaceutical interventions like relaxation exercise, massage, cognitive-behavioural therapy, physical activity and so on were demonstrated to have moderate-to-large effect size[50]. Multimodal therapy, qigong, aerobic exercise, and cognitive-behavioural therapy might be the best chose for cancer-related fatigue[51].

Melatonin seems to be able to ease the pain, however, the results varied in different researches. Lee et al found the prophylactic administration of melatonin confers significant clinical benefits in reducing postoperative pain and opioid use and improved sensory recovery following orthognathic surgery[52]. Tunay et al found preoperative oral administration of melatonin led to a reduction in pain scores, total morphine consumption and supplemental analgesic requirement after surgery[53]. Melatonin could improve pain in females with primary dysmenorrhea[54]. But it couldn't release pain in critically ill patients at ICU and patients after total knee arthroplasty [55 56]. Some study demonstrated that melatonin did not show any analgesic, anti-hyperalgesic, or anti-inflammatory properties in the burn injury model[57]. As for cancer patients, the evidence is restricted. Our review revealed that there was no significant between melatonin group and control group. Only Elsabagh et al found the beneficial effect of melatonin on alleviating pain in head and neck cancer patients undergoing radiotherapy, with dosage of 20 mg for six weeks[19]. At the same time, Palme et al found a more drops of pain scores from baseline in melatonin group[30]. The minor role of melatonin on pain in cancer patients could be explained by the cancer-related pain is one of the most common and troublesome symptoms affecting cancer patients with high severity[58]. Thus, for such kind sever pain, effective analgesic like opioid is more helpful. In addition, despite the availability of effective treatments, cancer-related pain may be inadequately controlled in up to 50% of patients, thus the multidisciplinary interventions are required[59] and the effectiveness of single melatonin seems too weak.

Circadian rhythm disruption underlies the pathophysiology of psychiatric disorders, especially depression[60]. Melatonin as a pleiotropic regulator molecule and its analogues have been observed to resynchronize the circadian rhythm and to alleviate depressive symptoms[61]. However, duration of treatment and target population might affect the antidepressant effects of melatonin. Based on subgroup analysis, there were significant effects of melatonin supplementation on patients who experienced intervention duration greater than 14 days and patients under operation. Though, both showed a slight ES. The longer the duration is, the better antidepressant effects of melatonin might

be. Meanwhile, cancer patients under operation obtained more benefits from melatonin. Our assumption is that patients under operation means they tend to be in the early stages of the disease with lighter disease load, possibly companied slight depression. Antidepressant effect of melatonin of long drug duration in patients with not so serious disease were showed in some studies. For example, melatonin administration for 12 weeks had beneficial effects on decreasing depression in women with polycystic ovary syndrome[62], patients with Parkinson's disease[63] and diabetic hemodialysis patients[64], but had no prophylactic antidepressant effect on acute coronary syndrome[65] and patients with acute mania[66].

Oral Mucositis (OM) refers to inflammation and ulceration of the oral mucosa as a frequent side-effect of cancer therapy[67]. It is a significant toxicity of systemic high doses of chemotherapy (CT) for cancer or radiotherapy (RT) for head and neck (H&N) cancer [68]. Stomatitis can hamper oral nutrition resulting in malnutrition, reduce quality of life and introduce the need for dose reductions and interruption of chemotherapy[69], especially grade 3 or 4 mucositis[70]. Melatonin has the potential direct antitumor activity, which was proved to modulate the effects of cancer chemotherapy, by enhancing its therapeutic efficacy and reducing its toxicity[71]. Our review showed the overall pooling effect size of melatonin on OM was moderate (OR = 0.49). Further subgroup analysis showed that melatonin couldn't reduce the incidence of stomatitis among H&N cancer patients, while had slight significant effect in patients with metastatic solid tumor. Among the studies conducted in H&N cancer patients, Borbalas et al found that melatonin oral gel caused a consistent trend to lower incidence and shorter OM duration[26]. Onseng et al revealed that adjuvant melatonin could delay the onset of oral mucositis[29]. Elsabagh et al found the administration of melatonin could reduce severe oral mucositis development[19]. None of them proved the effect of melatonin on reducing the incidence of stomatitis. The possible interpretation was that compared with other cancer type under chemotherapy alone, most H&N cancer patients received the combination chemoradiotherapy, which further promoted the occurrence of stomatitis. We also found in melatonin group, the reported incidence of stomatitis was higher in H&N cancer patients (52.5%-90%) than other cancer population (5.12%-24%). Moreover, our review revealed that melatonin couldn't reduce the severity of stomatitis. A meta-analysis showed that probiotics might reduce the incidence and mitigate the severity of cancer therapy-induced OM[72]. Also, photobiomodulation (PBM) was recommended for the prevention of OM[73 74]. How the effect of them for H&N cancer patients under chemoradiotherapy are still unknown.

Conclusion

As far as we known, this study is the first meta-analysis that investigated the effect of melatonin on QoL and symptoms in cancer patients. Our review showed that melatonin couldn't improve the QoL, fatigue, and pain among cancer patients. However, melatonin has positive effects on decreasing the incidence of stomatitis, though no effect on the severity of stomatitis and the population of head and neck cancer patients. Melatonin had the beneficial effect on depression of cancer patients under operation and those who were administrated longer melatonin duration. Also, it showed the possible effect on sleep quality. Our review stressed the need for more high-quality RCTs to reduce the existing uncertainties. However, the main significant results were from subgroup analysis of the limited studies, thus the results should be interpreted prudently. Additionally, differences in cancer diagnose, companied treatment and administration duration might be the main sources of heterogeneity, indicating the need for more high-quality RCTs to

remove some uncertainty.

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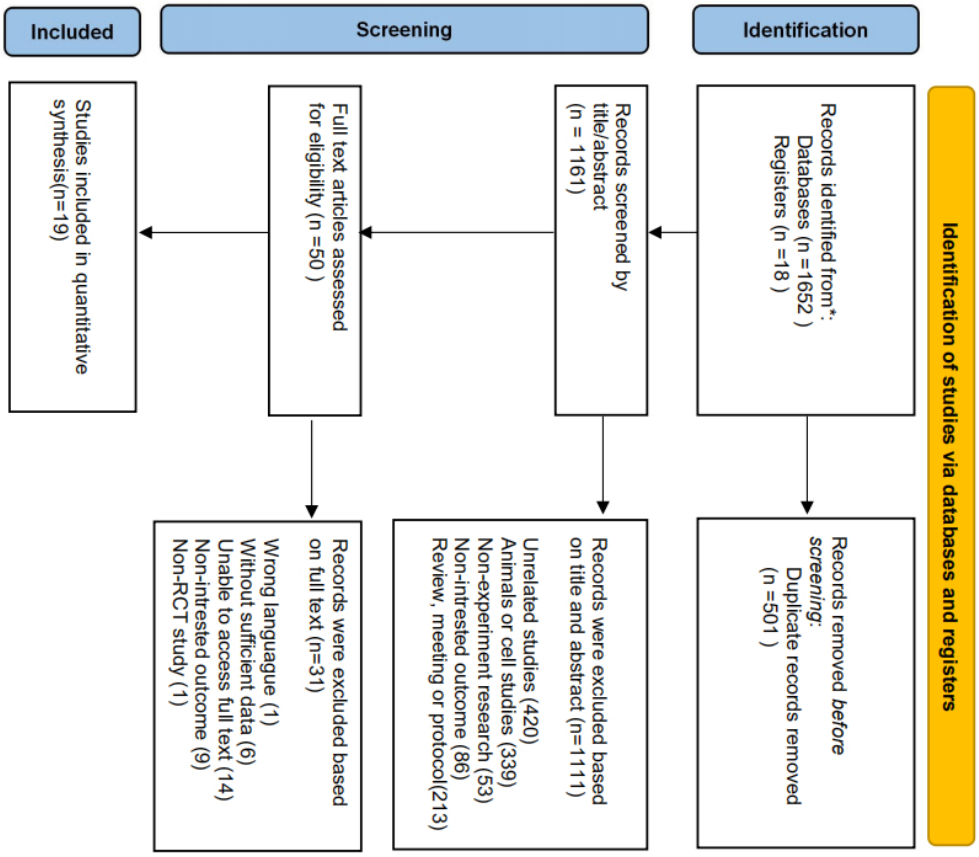

Figure 1 Study flow diagram

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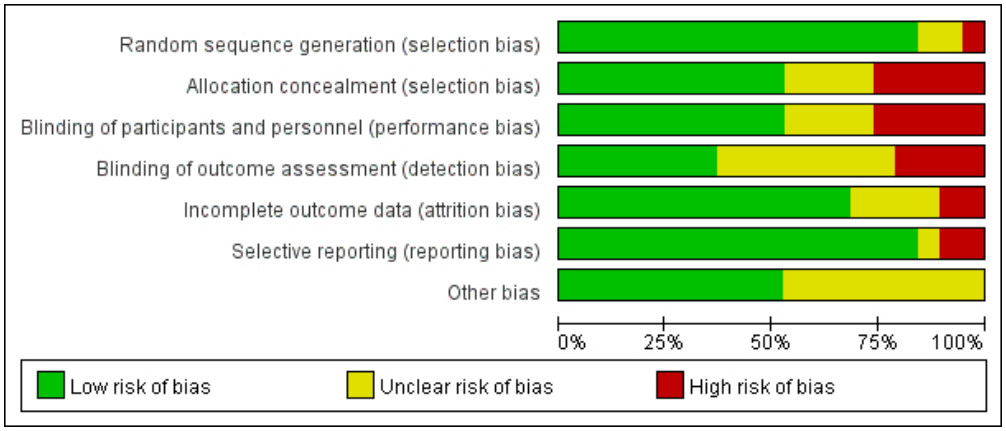

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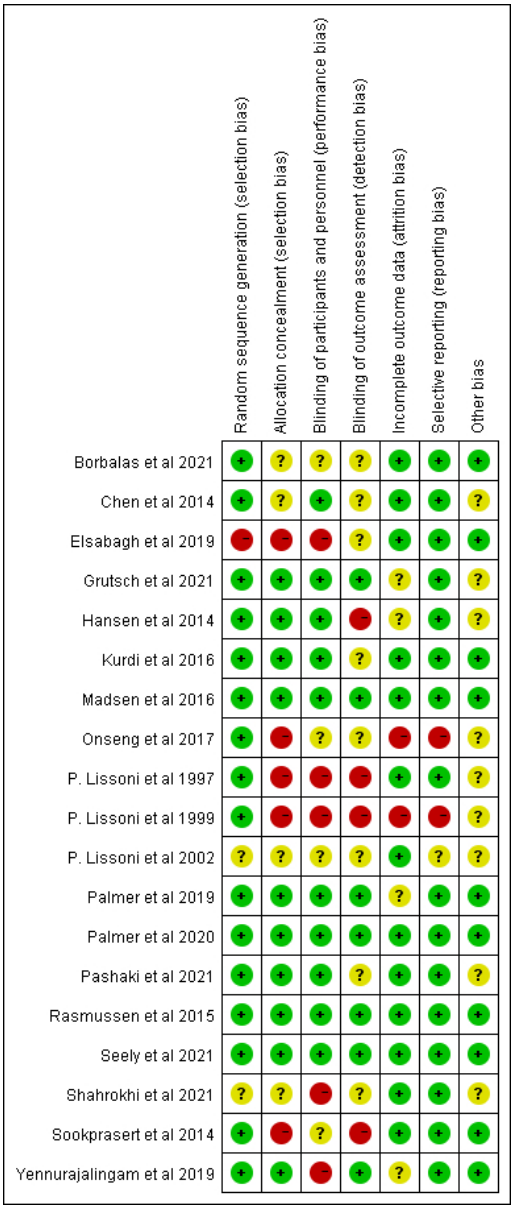

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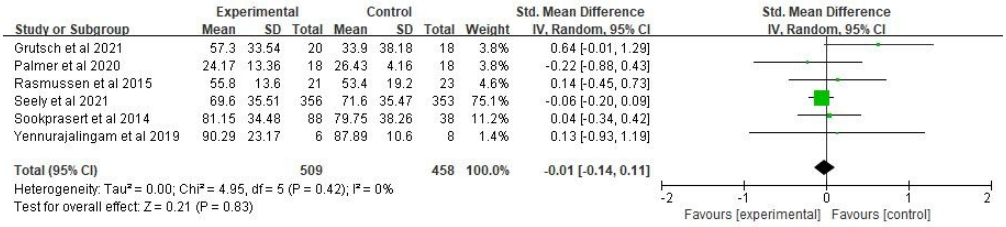

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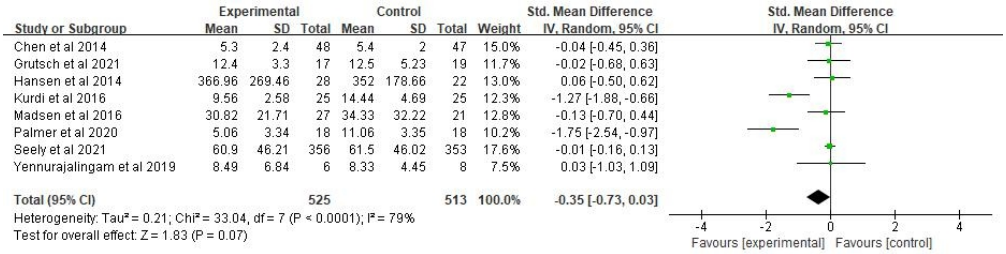

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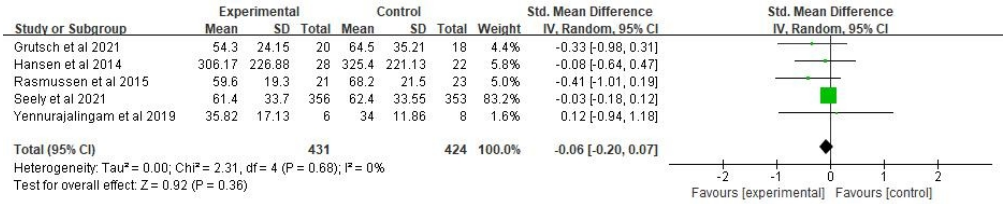

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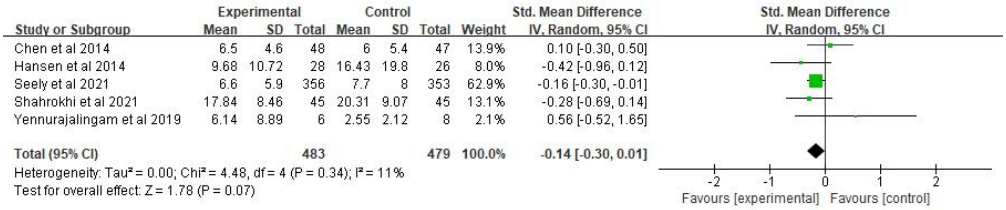

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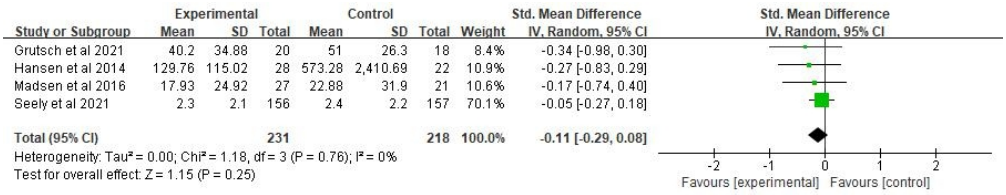

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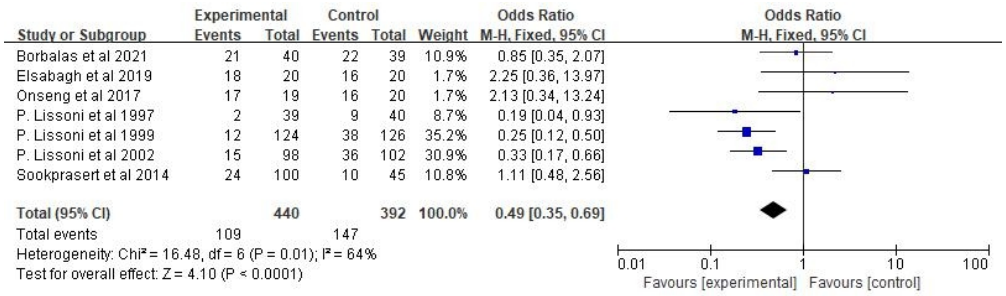

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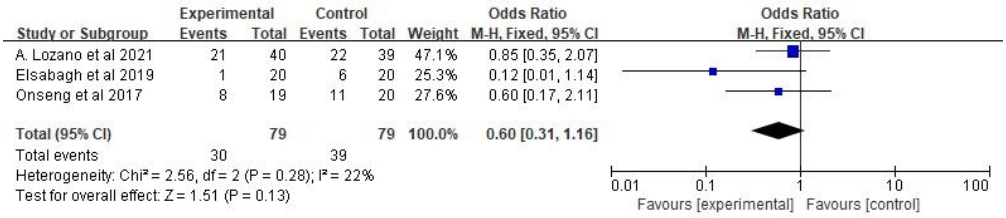

139x31mm (144 x 144 DPI)

Search strategy

#10 TS=(randomized controlled trial OR randomized OR placebo OR trial OR controlled)
#9 TS=(sleep disorder OR Insomnia OR sleep dysfunction OR Sleeplessness
#8 TS=(Quality of life OR Life Quality OR Health Related Quality Of Life OR HRQOL OR QOL)
#7 TS=(Appetite* OR Alteration*)
#6 TS=(Depression* OR Depressive)
#5 TS=(oral mucositis OR Mucositides OR stomatitis)
#4 TS=(fatigue OR Lassitude)
#3 TS=(Pain)
#2 TS=(melatonin)
#1 TS=(neoplasm OR Neoplasia* OR Tumor* OR Cancer* OR Malignancy OR Malignancies)
#11 ((((((#9) OR #8) OR #7) OR #6) OR #5) OR #4) OR #3
#12 (((#11) AND #10) AND #1) AND #2

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Page 1 in "Title"
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Page 1 in "Abstract"
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Page 2 in "Intruduction"
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Page 2 in "Intruduction"
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Page 3 in "Eligibility criteria"
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Page 3 in "Search strategy"
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Page 3 in "Search strategy"
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Page 3 in "Data extraction"
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Page 3 in "Data extraction"
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Page 3 in "Data extraction"
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Page 5-6 in "table 1"
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Page 4 in "Quality assessment"
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Page 3 in "Data analysis"
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Page 3 in "Data analysis"
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data	Page 3 in

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
		conversions.	"Data analysis"
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Page 3 in "Data analysis"
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Page 3 in "Data analysis"
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Page 3 in "Data analysis"
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Page 3 in "Data analysis"
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Page 3 in "Data analysis"
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Page 3 in "Risk of bias assessment"
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Page 4 in "Literature search"
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Page 4 in "Literature search"
Study characteristics	17	Cite each included study and present its characteristics.	Page 4 in "Literature characteristics"
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Page 4 in "Quality assessment"
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Page 4 in "Literature characteristics"
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Page 4 in "Quality assessment"
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Page 7-9
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Page 7-9
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Page 7-9
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Page 7-9
Certainty of	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Page 7-9

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
evidence			
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Page 9-12
	23b	Discuss any limitations of the evidence included in the review.	Page 9-12
	23c	Discuss any limitations of the review processes used.	Page 9-12
	23d	Discuss implications of the results for practice, policy, and future research.	Page 9-12
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Page 2 in "method"
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Page 2 in "method"
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	Page 2 in "method"
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Page 13 in "Footnotes"
Competing interests	26	Declare any competing interests of review authors.	Page 13 in "Footnotes"
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Page 13 in "Footnotes"

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

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BMJ Open

Effect of melatonin on quality of life and symptoms in patients with cancer: a systematic review and meta-analysis of randomized controlled trials

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Secondary Subject Heading:	Complementary medicine, Evidence based practice
Keywords:	Adult oncology < ONCOLOGY, Pharmacology < TROPICAL MEDICINE, CLINICAL PHARMACOLOGY

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Effect of melatonin on quality of life and symptoms in patients with cancer: a systematic review and meta-analysis of randomized controlled trials

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Abstract

Objective The study was to systematically review the effect of the melatonin on quality of life (QoL) and symptoms among cancer patients.

Design Systematic review and meta-analysis.

Data sources Cochrane Library, PubMed, Embase, Web of Science, Medline, CINAHL, Scopus, Clinical Trials.gov, China Biology Medicine (CBM), ProQuest and Open Gray were researched from inception through November 2021.

Eligibility criteria We included randomized controlled trials (RCTs) assessing the effects of melatonin on QoL, sleep quality, fatigue, depression, pain, rate of stomatitis and its severity in adult patients with cancer, without language restrictions. Researches that reported the effects of melatonin along with other interventions and lacked of interested data for meta-analytic synthesis

were excluded.

Data extraction and synthesis Two independent reviewers extracted data and another two reviewers assessed risk of bias. The mean difference or standard mean difference with 95% CIs was used in the computation of continuous variables to synthesis data. Odds ratio was used for dichotomous outcomes. Heterogeneity was assessed and quantified (I^2 statistic).

Results A total of 19 qualified studies that included 2101 cancer patients (melatonin: 1078, control: 1023) were included in the meta-analysis. Results indicated that melatonin had no significant effect on QoL [SMD = -0.01, 95% CI (-0.14, 0.11), P = 0.83], fatigue [SMD = -0.34, 95% CI (-0.73, 0.06), P = 0.10], pain [SMD = -0.34, 95% CI (-0.7, 0.02), P = 0.06], stomatitis incidence [OR = 0.59, 95% CI (0.31, 1.13), P = 0.11] and severity of stomatitis [OR = 0.6, 95% CI (0.31, 1.16), P =0.13]. MLT could reduce stomatitis rate among patients with metastatic solid tumor [OR =0.28, 95% CI (0.17, 0.44), P < 0.0001], while it failed in patients with head and neck cancer [OR =1.15, 95% CI (0.56, 2.4), P = 0.7]. MLT eased the depression in patients who received administration greater than 14 days [SMD = -0.14, 95% CI (-0.27, -0.01), P = 0.03] and those who underwent operation [SMD = -0.17, 95% CI (-0.32, -0.03), P = 0.02]. It improved sleep quality [SMD = -0.78, 95% CI (-1.47, -0.10), P = 0.02], though with large heterogeneity (I^2 = 94%, P <0.001).

Conclusion Finding showed that MLT could not improve the QoL, fatigue, pain and stomatitis severity among patients with cancer. However, it has limited effect on decreasing the stomatitis rate, easing the depression and improving sleep quality. Different treatments, duration and cancer types were the main source of heterogeneity. Further large-scale RCTs are urgently required. Besides, the effect of different combination of MLT dosage and duration, administration type and joint measures are worthy of further study.

PROSPERO registration number

CRD42021292855.

Strengths and limitations of this study

- This systematic review was registered a priori and conducted in line with Preferred Reporting Items for Systematic Reviews and Meta-Analysis and the recommendations of the Cochrane Collaboration.
- Most of the studies were of high quality with a low risk of bias, which could further lend confidence to the current pooled results.
- We widely explored the effectiveness of MLT in different population, treatment, dosage,

duration, administration time in subgroup analysis.

- For every dimension of MLT including QoL, sleep, fatigue, depression, pain and stomatitis, the literatures are limited, which limits the generality of the conclusion.
- The main significant results were from subgroup analysis of the limited studies and the results should be interpreted prudently

Key words: cancer patients, symptoms, QoL, melatonin, meta-analysis

Introduction

Melatonin (MLT) is an important endogenous indolamine that is synthesized and secreted into the systemic circulation and cerebrospinal fluid by the pineal gland, which has recognized anti-aging, anti-inflammatory, and anti-oxidant properties.[1] As a strong anti-fibrotic activity,[2] MLT can be used as a desired preconditioning agent in cell-based therapy.[3 4] It also has a substantial role to regulate the circadian rhythm and sleep during the night.[5 6] Recent studies proved the effect of MLT on limiting skeletal muscle frailty, prolonging physical performance,[7] and preventing bone loss.[8] In the oncology field, MLT has significant apoptotic, angiogenic, oncostasis, and anti-proliferative effects on various oncological cells.[9] It was proved that low levels of MLT might be a risk factor for breast cancer.[10] Meanwhile, MLT's co-administration improves the sensitivity of cancers to inhibition by conventional drugs, and reduces the toxic consequences of anti-cancer drugs while increases their efficacy.[11] There is major concern about the symptoms induced by cancer and cancer treatment that patients encounter, including physical symptoms and psychological/spiritual distress,[12] leading to decreased QoL. Equally, MLT play an important role in enhancing QoL through improving survival and decreasing symptoms.[13] The positive association between MLT and various health outcomes in cancer patients were be shown in some researches.[14] A recent meta-analysis revealed that MLT may benefit cancer patients by improving survival and ameliorating the side effects of chemotherapy.[15] Palmer et al showed the neuroprotective effect of MLT to counteract the adverse effects of chemotherapy on cognitive function, sleep quality and depressive symptoms in breast cancer patients.[16] A recent clinical trial drawn a conclusion that MLT supply decreased the levels of fatigue in patients with breast cancer.[17] However, some of the recent findings published suggest the conflicting results[18 19] that MLT intervention cannot improve the QoL, release the symptoms burden, or presented the uncertain results.[20] We are not aware of any systematic reviews and meta-analyses that have synthesized the evidence of the function of MLT on cancer patients. The real effect of MLT on health outcomes in cancer group remains unspecific and ambiguous. Thus, with accumulating evidence, we perform a systematic review and meta-analysis of RCTs to investigate the roles of

MLT in improving QoL and symptoms in patients with cancer.

Methods

This review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (PRISMA) and the recommendations of the Cochrane Collaboration. The study was registered in PROSPERO with a registration number of CRD42021292855.

Search strategy

A throughout search was conducted in Cochrane Library, PubMed, Embase, Web of Science, Medline, CINAHL, Scopus, ClinicalTrials.gov, and China Biology Medicine (CBM) from inception through November 2021 for RCTs without language restrictions. Sources of unpublished studies and gray literature to be searched through ProQuest and Open Gray. We used medical subject headings (MeSH) and text words to identify the potential interest studies. Search strategies were provided in supplemental file 1.

Eligibility criteria

Participants

Studies including adult patients (≥ 18 years) who were diagnosed with cancer according to National Cancer Institute codes, regardless of cancer type, cancer stage (early, middle or advanced), and current treatment (radiation therapy, chemotherapy, surgery, targeted therapy, immunotherapy and so on, combination of any above treatment, or without any treatment), were eligible.

Interventions and controls

All trials that reported and evaluated effects of MLT were included. Literature excluded if they met the following criteria:(1) they were not RCTs; (2) studied the effects of MLT along with other interventions (3) lacked of sufficient data on interested outcomes.

Outcomes

Primary outcome was QoL. The scores of sleep quality, fatigue, depression, and pain, rate of stomatitis and its severity were the secondary outcome.

Studies

Only RCTs were eligible.

Data extraction

Two independent researchers (SiyuYang, Tongyu Wang) extracted the data, evaluated the quality of eligible studies, and performed double-checks. Any disagreements and differences were resolved by a third independent investigator (Xiaofan Bu). The following data from the full text of selected studies were extracted: first author's name, year of publication, the characteristics of the patients, the characteristics of the intervention and the control groups (study design, form of intervention, dose of melatonin supplementation, study duration), number of participants in each group and outcome results (means and standard deviations for continuous data; number of incidents for dichotomous data).

Risk of bias assessment

Two reviewers (Yan Tan, Hongyun Chen) independently evaluated the risk of bias for each eligible study using the Cochrane assessment tool, which consists of the following seven domains: "random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias". Each question can be rated as follows: yes (+), low risk of bias; unclear (?), unclear risk of bias; no (−), high risk of bias. Any disagreement between the reviewers was resolved by discussion until consensus was reached.

Data analysis

The meta-analysis was performed using Review Manager Software (version 5.3). The effect of MLT on scores of QoL and symptoms were estimated by mean difference (MD) when trials measured an outcome using the same measurement method or scale. We used standard mean difference (SMD) when trials used different instruments to measure the same outcome. For dichotomous outcomes (such as stomatitis and its severity), we used odds ratio (OR). The effect size (ES) and the 95% confidence interval (CI) for primary and secondary outcomes were computed. The ES with scores of 0.2–0.5, 0.5–0.8, and > 0.8 were considered small, medium, and large effects, respectively. Forest plots were used to display the pooled ES, 95% CI, weight in percentage. If variability was presented by measures other than mean or SD, we used standard approaches for estimating data. If the studies

did not report SD, we used the following formula to calculate missing SD: SD=√N×(Upper 95% CI −Lower 95% CI)/3.92. If a study provided medians and interquartile ranges (IQR), we transformed median and IQR to mean and SD by a method for non-normal data.[21] I^2 was used to measure the statistical heterogeneity among the trials in each analysis. If $P > 0.1$ and $I^2 < 50\%$, a fixed-effects model was adopted; if $P < 0.1$ and $I^2 \geqslant 50\%$, then a random-effects model was adopted. If heterogeneity was identified, subgroup analyses were conducted on different cancer type, treatment, dosage, administration time and duration. In subgroup analyses, considering that these variables might have influences on the outcomes if there were at least two studies on a stratum. Sensitivity analysis was performed in light of the fact that some of the trials might impact the study results by removing studies with high or unclear risk of bias. Reporting and publication bias were investigated by visually examining the degree of asymmetry of a funnel plot.

Patient and public involvement

No patient was involved.

Results

Literature search

The initial search identified 1670 publications through Pubmed, Embase, Medline, Scopus, Sinomed, Web of science, Cochrane, and clinical trial. After excluding 501 duplicates, a total of 1161 studies were retrieved for title and abstract screening. After screening for title and abstract, 1111 articles were excluded and 50 papers were retrieved for full text review. Out of 50 retrieved papers, 1 article was excluded due to wrong langue,[22] 6 articles were excluded without sufficient data, 14 articles were excluded without full text, 9 articles were excluded without target outcome, 1 article was excluded due to non-RCT study.[23] Therefore, a total of 19 articles were included in the final meta-analysis.[24-42] The flow chart of literature search is shown in Fig. 1.

Quality assessment

We used Cochrane scoring system to assess the quality of the included studies. Two reviewers had different opinions on bias in one article in “incomplete outcome data”, one article in “selective reporting”. Through the discussion, final consensus was achieved. The overall risk of bias as shown was moderate (Fig. 2). Nearly all studies reported appropriate random sequence generation. Most studies reported completed data and had low risk of bias on the item ‘Selective reporting’. Almost

a third of the studies did not report the blindness in outcome assessment. The individual risk of bias for each study is presented in Fig. 3.

Literature characteristics

The characteristics of the patients, interventions, controls, and outcome measures are shown in Table 1.

Table 1 The characteristics of the literature

Author	Year	Population	Mean age (intervention/ control)	Study design	Time of duration	Administration time	Intervention group	Control group	Outcome	Intervention (N)	Control (N)
P. Lissoni[31]	1997	Patients with metastatic solid tumors under chemotherapy	61/58	RCTs	Every day without a break until disease progression	At the evening of each day	20 mg oral MLT	Placebo	Stomatitis rate	39	40
P. Lissoni[30]	1999	Patients with metastatic solid tumour under chemotherapy	53/56	RCTs	7 days prior to chemotherapy, continued after chemotherapy interruption, until disease progression	Every night	20 mg oral MLT	Placebo	Stomatitis rate	124	126
P. Lissoni[29]	2002	Untreated patients with metastatic solid tumors under chemotherapy	66/65	RCTs	At least 2 months	At the evening of each day	20 mg oral MLT plus support care	Placebo plus support care	Stomatitis rate	98	102
Hansen[27]	2014	Patients undergoing breast cancer surgery	51/60	RCTs	10days: 2 days preoperatively till 8 days postoperatively	One hour before bedtime	6 mg oral MLT	Placebo	Depression (MDI), Sleepiness (KSS, VAS), Fatigue (VAS), Pain (VAS)	28	26
Chen[24]	2014	Breast cancer survivors	59/59	RCTs	4 months	Each night at 9 pm	3 mg oral MLT	Placebo	Sleep (PSQI), depression (CES-D)	48	47
Sookprasert[41]	2014	Patients with non-small cell lung cancer receiving chemotherapy	56.8/55.6	RCTs	2 months: during chemotherapy for 2 months	At night after 21:00	10 mg or 20mg oral MLT	Placebo	QOL(FACT-L), Mucositis rate	88	38
Rasmussen[33]	2015	Advanced cancer patients who reported significantly tired in palliative care unit	64/65	RCTs	7 days	Each night	20 mg oral MLT	Placebo	Fatigue (MFI-20), QOL (EORTC QLQ-C15-PAL), Insomnia (EORTC QLQ-C15-PAL)	21	23
Madsen[34]	2016	Patients undergoing breast cancer surgery	51/59	RCTs	2weeks: 3 days preoperatively until 2 weeks postoperatively	One hour before bedtime	6 mg oral MLT	Placebo	Sleep (VAS, KSS), pain (VAS)	27	21
Kurdi[28]	2016	Cancer Patients with Insomnia	55.2/49.64	RCTs	14 days	At 7 pm	3mg oral MLT	Placebo	Sleep (AIS)	25	25

Onseng[35]	2017	Patients with head and neck cancer receiving concurrent chemoradiation	47.3/49.6	RCTs	35days: 5 days a week throughout the 7 weeks of chemoradiation	At night after 21:00	10 mL of a 0.2% MLT niosome oral gargle plus 20 mg oral dosage	placebo	QOL (FACT—H&N), Mucositis rate, Mucositis severity (WHO-G)	19	20
Elsabagh H H[25]	2019	Patients with head and neck cancer undergoing radiotherapy	57.8/55.9	RCTs	Six weeks	30 minutes before sleeping	20 mg oral MLT	Placebo	Stomatitis severity (WHO-G), Stomatitis rate, Pain (NRS)	20	20
Palmer[36]	2019	Patients with breast cancer receiving chemotherapy	54.24/54.11	RCTs	10 days during treatment.	One hour before bedtime	20 mg oral MLT	Placebo	Pain (NRS), Sleep (PSQI), Depression (BDI)	18	18
Yennurajalingam[42]	2019	Patients with advanced cancer with poor sleep quality	Not clearly	RCTs	14d	At bedtime	20mg oral MLT plus bright white light therapy	Bright white light therapy alone	Sleep (PSQI), insomnia (ISI), fatigue (FACIT-F), depression (HADS), QOL(FACT)	6	8
Palmer[37]	2020	Patients with breast cancer undergoing chemotherapy after lumpectomy or mastectomy	54.24/54.11	RCTs	10 days: three days prior to chemotherapy and seven following days	Approximately 1 hour before bedtime	20 mg oral MLT	Placebo	Depressive symptoms (BDI-II), Sleep quality (PSQI), QOL (EORTC QLQ-C30)	18	18
Pashaki[38]	2021	Patients with breast cancer during adjuvant chemotherapy and radiotherapy	50.47/46.05	RCTs	8weeks: from 1 week before until 1 month after the adjuvant radiotherapy	Every night approximately 1 hour before bedtime	18 mg oral MLT	Placebo	Fatigue (BFI)	38	36
Seely[39]	2021	Cancer patients following lung cancer resection	67.2/67.2	RCTs	One year after surgery	One hour before bedtime	20 mg oral MLT	Placebo	Fatigue (MFI-20), QOL(QLQ-LC13), Sleep (MOS), Depression (BDI 2), Pain (BPI)	356	353
Shahrokhi[40]	2021	Patients with colorectal cancer undergoing chemotherapy with sleep disorder	63.63/64.11	RCTs	4week of treatment	At bedtime	6 mg oral MLT	10 mg zolpidem	Sleep (GSQS, PSQI), Depression (HRSD)	45	45
Grutsch[26]	2021	NSCLC patients under chemotherapy	60.3/63	RCTs	From intervention to death	At 8AM or at 8PM	20 mg oral MLT	Placebo	QOL(QLQ-C30), Fatigue (QLQ-C30), Pain (QLQ-C30), Sleep (PSQI)	20	18
Borbalas[32]	2021	Patients with head and neck cancer undergoing radiation therapy and chemical treatment	59/56	RCTs	5days lasting 7 weeks	Not clearly	3% oral MLT gel plus standard symptomatic treatment for stomatitis	Placebo plus standard symptomatic treatment for stomatitis	Stomatitis severity (WHO-G), Stomatitis rate	40	39

N, number; Randomized controlled trials, RCTs; Melatonin, MLT; BDI-II, Beck Depression Inventory; PSQI, Pittsburgh Sleep Quality Index; EORTC QLQ-C30, European Organization for Cancer Research and Treatment of Cancer Quality of Life Questionnaire; MFI-20, Multidimensional Fatigue Inventory; EORTC QLQ-C15-PAL, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 15 Palliative Version; CES-D, Center for Epidemiologic Studies-Depression; BFI: Brief Fatigue Inventory; VAS, Visual Analogue Scale; KSS, Karolinska Sleepiness Scale; MDI, Major Depression Inventory; FACT—H&N, Functional Assessment of Cancer Therapy—H&N Version 4; FACT-L, Functional Assessment of Cancer Therapy – Lung; QLQ-LC13, Lung Cancer-13 modules; BDI 2, Beck Depression Inventory 2; MOS, Medical Outcomes Study Sleep Survey; BPI, Brief Pain Inventory; GSQS, Sleep Quality Scale; HRSD, Hamilton Rating Scale for Depression; NRS, Numeric Rating Scales; ISI, Insomnia Severity Index; FACIT-F, Functional Assessment of Cancer Illness Therapy-Fatigue subscale; HADS, Hospital Anxiety and Depression Scale; FACT, Functional Assessment of Cancer Illness Therapy; AIS, Athens insomnia scale; WHO-G, WHO grading system

Participants

Publication dates ranged from 1997 to 2021. Among the 19 studies included in systematic review, the mean age of the participants ranged from 46.05 to 67.2. The sample size ranged from 14 to 709

participants. Regarding treatment trajectory, 12 studies were conducted in cancer patients with adjuvant chemotherapy and (or) radiotherapy,[25 26 29-32 35-38 40 41] 1 was in advanced cancer patients with fatigue,[33] 1 was in breast cancer survivors,[24] 3 were in cancer patients with surgery,[27 34 39] and 2 were in advanced cancer patients with poor sleep quality.[28 42] Regarding the cancer diagnose, 6 studies were in breast cancer,[24 27 34 36-38] 2 were in non-small cell lung cancer,[26 39] 3 were in head and neck cancer,[25 32 35] 1 was in colorectal cancer,[40] and 7 studies were no restriction on cancer type but most in advanced cancer patients.[28-31 33 41 42]

Intervention

The follow-up period ranged from seven days to one year. MLT dosage varied between 3 and 20 mg. As for types of MLT administration, 17 were oral MLT,[24-31 33 34 36-42] 1 was MLT oral gargle,[32] and 1 was combined both.[35] Nearly all studies gave the MLT at night, except one compared both in morning and night[26].

Instruments

All studies used standardized and validated tools. QoL was measured by four validated tools: European Organization for Cancer Research (EORTC QLQ-C30),[26 37] Treatment validated for the Brazilian population (QLQ-BR 23),[37] Functional Assessment of Cancer Therapy (FACT),[41 42] Ferrans and Powers Quality of Life Index (QLI)[26], European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 15 Palliative Version (EORTC QLQ-C15-PAL),[33] Lung Cancer-13 (QLQ-LC13).[39] Sleep quality was measured by Pittsburgh Sleep Quality Index (PSQI),[24 26 36 37 40 42] Visual Analogue Scale (VAS),[27 34] Karolinska Sleepiness Scale (KSS),[27 34] Sleep Quality Scale (GSQS),[40] Athens insomnia scale,[28] Medical Outcomes Study(MOS) Sleep Survey.[39] Depression was measured by Beck Depression Inventory (BDI-II),[37 39] Beck Depression Inventory (BDI),[36] Center for Epidemiologic Studies-Depression (CES-D),[24] Major Depression Inventory (MDI),[27] Hamilton Rating Scale for Depression (HRSD),[40] Hospital Anxiety and Depression Scale (HADS).[42] Fatigue was measured by Multidimensional Fatigue Inventory (MFI-20),[33] EORTC QLQ-C15-PAL (fatigue domain),[33] Brief Fatigue Inventory (BFI),[38] VAS,[27] Multidimensional Fatigue Index 20 questionnaire,[39] QLQ-C30 (fatigue domain),[26] Functional Assessment of Cancer Illness Therapy-Fatigue subscale (FACIT-F).[42] Pain was measured by VAS,[27 34] Brief Pain Inventory (BPI),[39] QLQ-C30 (pain domain),[26] Numeric Rating Scales (NRS).[25 36] The incidence of stomatitis was calculated by the ratio of occurrences number and the total number.[25 29-32 35 41]

Meta-analysis

Effect of MLT on QoL

Overall, 6 clinical trials evaluated the effect of MLT on QOL. The results showed that there was no statistically significant difference between the intervention and control groups [SMD = -0.01, 95% CI (-0.14, 0.11), P = 0.83] with no heterogeneity (I^2=0%, P=0.42) (Fig. 4). All these 6 studies used 20mg MLT dosage. Subgroup analysis based on study duration (P=0.65-0.92), treatment type(P=0.45-0.6) showed no significant differences.

Effect of MLT on sleep quality

Nine clinical trials evaluated the effect of MLT on sleep quality. Pooled ES from random effect model showed a significant lowering effect on sleep quality [SMD = -0.78, 95% CI (-1.47, -0.10), P = 0.02]. There was significant heterogeneity between studies (I^2 = 94%, P <0.001). We deleted a study[40] with obvious heterogeneity and I^2 decreased to 79% [SMD = -0.35, 95% CI (-0.73, 0.03), P = 0.07] (Fig. 5). Subgroup analysis based on dose, study duration, treatment, different combination of dosage and duration showed no significant differences between subgroups (Table 2).

Table 2 Subgroup analyses of melatonin supplementation on sleep quality

	N	WMD (95% CI)	Heterogeneity I^2 (P)	P within group
Overall effect	8	-0.35 (-0.73, 0.03)	79% (P<0.0001)	0.07
Dosage				
<10mg	4	-0.32 (-0.88, 0.23)	77% (P=0.005)	0.25
≧10mg	4	-0.42 (-1.16, 0.32)	84% (P=0.0004)	0.27
Duration				
<2 weeks	2	-0.01 (-0.33, 0.32)	0% (p=0.76)	0.96
≧2 weeks	6	-0.51 (-1.07, 0.05)	85% (p<0.00001)	0.08
Combination				
<10mg + ≧2 weeks	3	-0.46 (-1.18, 0.27)	83% (P=0.003)	0.22
>10mg + ≧2 weeks	3	-0.01 (-0.16, 0.13)	0% (P=1.00)	0.86
>10mg + <2 weeks	1	-1.75 (-2.54, -0.97)	-	<0.01

<10mg + <2 weeks	1	0.06 (-0.5, 0.62)	-	0.83
Combined treatment				
Under chemotherapy	2	-0.87 (-2.57, 0.82)	91% (P=0.0009)	0.31
Under surgery	3	-0.02 (-0.15, 0.12)	0% (P=0.89)	0.83
With insomnia				
Yes	2	-0.7 (-1.96, 0.57)	77% (P=0.04)	0.28
No	6	-0.23 (-0.58, 0.13)	73% (P=0.002)	0.21

N, number of the literatures

Effect of MLT on fatigue

The overall ES of MLT for fatigue alleviation was medium [SMD = -0.34, 95% CI (-0.73, 0.06), P = 0.10] with high heterogeneity among studies (P =0.002, I^2 = 74%), and there was no significant statistic difference. The study of Pashaki et al[38] showed a great heterogeneity for only this one proved a significant lower levels of fatigue in intervention group. We removed it and the heterogeneity decreased to 0 (Fig. 6).

Effect of MLT on depression

Six clinical trials evaluated the effect of MLT on depression. Only Palmer et al showed the significant effect on depression.[37] The overall treatment effect on depression showed there was no statistically significant difference between the intervention and control groups [SMD = -0.24, 95% CI (-0.53, 0.05), P = 0.10] with high heterogeneity among studies (P =0.03, I^2 = 60%). A sensitivity analysis was done by removing one study from the analysis (Fig. 7).[37] Regarding subgroup analysis, a significant difference was observed on the study duration and treatment, though both showed a slight ES. Patients who received intervention duration greater than 14 days had a significant lower depression [SMD = -0.14, 95% CI (-0.27, -0.01), P = 0.03] with low heterogeneity (P =0.4, I^2 = 0%). Meanwhile, MLT seemed to alleviate depression in cancer patients who underwent operation [SMD = -0.17, 95% CI (-0.32, -0.03), P = 0.02] with low heterogeneity (P =0.35, I^2 = 0%), compared to those received chemotherapy. No significant difference was observed among studies on the dosage (P = 0.27-0.43), cancer diagnose (P = 0.20), and combined chemotherapy (P = 0.13-0.42).

Effect of MLT on pain

Five clinical trials evaluated the effect of MLT on pain [SMD = -0.34, 95% CI (-0.7, 0.02), P = 0.06] with high heterogeneity among studies (P =0.03, I^2 = 62%). No significant difference was observed among studies on the cancer diagnose (P=0.27-0.47), combined treatment (P=0.37), duration (P=0.11) and dosage (P=0.16-0.27). Sensitivity analysis was done by removing one study[25] and the heterogeneity decreased to 0% (Fig. 8).

Effect of MLT on stomatitis

As for stomatitis, seven clinical trials evaluated the effect of MLT on the incidence of stomatitis showed moderate ES [OR = 0.59, 95% CI (0.31, 1.13), P = 0.11] (Fig. 9) with high heterogeneity (P =0.01, I^2 = 64%). All of the study duration were more than 2 weeks and patients all accepted chemotherapy or radiotherapy. Besides, nearly all these clinical trials gave the MLT of 20 mg, except one used 3% MLT oral gel.[32] However, removing it or not caused little change to heterogeneity and ES. Further subgroup analysis showed that the cancer type might be the main heterogeneity sources. MLT could not reduce the incidence of stomatitis among patients with head and neck cancer under adjuvant chemotherapy or radiotherapy [OR =1.15, 95% CI (0.56, 2.4), P = 0.7], with low heterogeneity (P =0.5, I^2 = 0%). However, it had slight significant value in patients with metastatic solid tumor [OR =0.28, 95% CI (0.17, 0.44), P < 0.0001] with low heterogeneity (P =0.74, I^2 = 0%).

As for stomatitis severity, three clinical trials evaluated the effect of MLT on reducing 3-4 grades (severe) stomatitis according to WHO grade system.[43] The overall treatment effect showed that the intervention has no statistically significant difference between the intervention and control groups [OR = 0.59, 95% CI (0.26, 1.36), P =0.22] with low heterogeneity (P =0.28, I^2 = 22%) (Fig.10).

Discussion

To the best of our knowledge, this study is the first meta-analysis that investigated the effect of MLT on the QoL, sleep quality, and other symptoms like fatigue, depression, pain and stomatitis in cancer patients. Unfortunately, in the current study, we did not prove the beneficial effect of MLT on QoL, sleep quality, fatigue and pain. However, it had potential ability to improve depression and reduce the incidence of stomatitis with small ES.

Most of the suffering that cancer patients now facing comes from disturbing symptoms like poor sleep, fatigue, depression, pain and so on. Effective symptoms controlling greatly improves QoL. Thus, the effect of MLT on QoL might be achieved through relieving symptom. Innominato et al revealed bedtime MLT was associated with a significant improvement in sleep quality, fatigue severity, QoL, social and cognitive function in advanced breast cancer patients.[44] However, contradictory conclusion revealed that MLT did not improve appetite, weight, or QoL in cachectic patients with advanced cancer.[45] Besides, a previous study reported beneficial short-term effects of MLT on sleep but not QoL.[46] Our review included six trails regarded QoL of cancer patients as health outcome. None of them proved a significant improvement in QoL in intervention group, though Grutsch et al[26] and Sookprasert et al[41] provided a trend for better QoL compared with baseline. However, the conclusion could not be the convincing evidence to support the certain effectiveness of MLT on QoL, for both them lasted a long duration and various potential confounding factors existed. For such invalid effectiveness, one of the possible interpretations might be the differences due to study population, interventions and measurements. Another explanation might be the multi-dimensional properties of QoL, which not only contained physical domain but covered the domains of psychology, spirit, and social. Thus, mere elimination of symptoms like sleep or fatigue through drug seems to be difficult to effectively improve the QoL, especially for cancer patients who were faced with a mass of disturbing from many other aspects.

Due to the important role in regulating the circadian rhythm and sleep, many studies have been conducted to verify the value of MLT on sleep. MLT may be preferable to traditional hypnotics in management of insomnia.[47] A network meta-analysis support effectiveness of MLT in improving sleep-onset difficulties.[48] A review about the influence of dietary sources of MLT on sleep quality indicated that the sources of MLT consumption of milk and sour cherries may improve sleep quality.[49] There are many conflicting studies, no matter in population, dosage and duration. Fatemeh et al found the significant effects of MLT on sleep quality in patients with respiratory diseases, metabolic disorders, and sleep disorders, but not in mental disorders, neurodegenerative diseases and breast cancer.[50] Under the condition of using the Pittsburgh sleep quality index as unified measurement tool, 20mg MLT for 10 days in breast cancer patients under chemotherapy showed a positive sleeping improving,[37] while same dosage for at least 28 days revealed a meaningless result in patients with lung cancer.[51] Meanwhile, it remains unknown the optimal combination of dosage and duration. Innominato et al found 5mg for two months has a positive effectiveness on sleep quality and QoL in advanced breast cancer patients.[44] Similarly, in advanced cancer patients, combination of 14-day 20 mg MLT plus bright white light therapy did not improve the sleep quality.[42] Under fewer doses, 14-day 3mg MLT actually improved the sleep in cancer patients with insomnia.[28] Our review revealed MLT could improve the sleep with large heterogeneity. The subgroup analysis did not find the significant difference in different MLT duration, dosage, as well as combination of dosage and duration. The finding indicated the optimal combination of dosage

and duration in improving sleep for patients with cancer worthy of further exploration. The administration type is another point. It was found 2 mg prolonged release MLT formulation for 14 days results in significant and clinically meaningful improvements in sleep quality, morning alertness, sleep onset latency and quality of life in primary insomnia patients[52] and in Parkinson's disease patients with a poor sleep quality.[53] However, most of the researches were the oral MLT. How the administration type effect the effect on sleep in cancer patients remains to be studied. The effectiveness of the combination of bright light and MLT remains controversial. Yennurajalingam et al proved it could not work in advanced cancer patients with insomnia,[42] while it could improve subjective daytime sleepiness in patients with delayed sleep phase disorder.[54]

MLT may be an effective treatment for patients with chronic fatigue syndrome.[55] Nevertheless, in the current study, none of the study was showed to improve fatigue in cancer patients. Only a high quality trail proved a significant effect of melatonin on breast cancer patients undergoing adjuvant chemotherapy and radiotherapy,[38] with melatonin 18 mg a day from 1 week before until 1 month after the adjuvant radiotherapy. The evidence supporting the usage of melatonin for cancer-related fatigue is limited. Short-term use of dexamethasone or methylprednisolone is recommended for the control of cancer-related fatigue (CRF) in metastatic cancer patients according to European Society for Medical Oncology (ESMO) guideline,[56] while the use of eszopiclone, megestrol acetate and MLT is not recommended for the control of CRF. However, the preventive effect of MLT on cancer-related fatigue is still under study. Non-pharmaceutical interventions were also recommended,[56] like relaxation exercise, massage, cognitive-behavioural therapy, physical activity and so on were demonstrated to have moderate-to-large effect size.[57] Multimodal therapy, qigong, aerobic exercise, and cognitive-behavioural therapy might be the best chose for cancer-related fatigue.[58]

MLT seems to be able to ease the pain, however, the results varied in different researches. Lee et al found the prophylactic administration of MLT confers significant clinical benefits in reducing postoperative pain and opioid use, as well as improved sensory recovery following orthognathic surgery.[59] Tunay et al found preoperative oral MLT led to a reduction in pain scores, total morphine consumption and supplemental analgesic requirement after surgery.[60] MLT could also improve pain in females with primary dysmenorrhea.[61] However, the evidence was limited in critically ill patients at ICU and patients after total knee arthroplasty.[62 63] As for cancer patients, the evidence is also restricted. Our review revealed MLT had no effect on pain relief. Only Elsabagh et al found the beneficial effect of MLT on alleviating pain in head and neck cancer patients undergoing radiotherapy, with dosage of 20 mg for six weeks.[25] At the same time, Palme et al found a drops of pain scores from baseline in intervention group.[36] The minor role of MLT on pain in cancer patients could be explained by the cancer-related pain is one of the most common and troublesome symptoms affecting cancer patients with high severity.[64] For such kind sever pain, effective

analgesic like opioid is more helpful. In addition, despite the availability of effective treatments, cancer-related pain may be inadequately controlled in up to 50% of patients. Thus, the multidisciplinary interventions are required[65] and the single MLT seems too weak for cancer pain.

Circadian rhythm disruption underlies the pathophysiology of psychiatric disorders, especially depression.[6] MLT as a pleiotropic regulator molecule and its analogues have been observed to resynchronize the circadian rhythm and to alleviate depressive symptoms.[66] However, duration and treatment might affect the antidepressant effects of MLT, both showed a slight ES. We found MLT supplementation played significant effect in patients who received more than 14 days administration and those who underwent operation. Our assumption is that patients under operation means they tend to be in the early stages of the disease with lighter disease load and slight depression. Antidepressant effect of long MLT duration in patients with not so serious disease were showed in some studies. For example, MLT for 12 weeks had beneficial effects on decreasing depression in women with polycystic ovary syndrome,[67] patients with Parkinson's disease[68] and diabetic hemodialysis patients.[69] Nevertheless, it had no prophylactic antidepressant effect on acute coronary syndrome[70] and patients with acute mania.[71]

Oral mucositis refers to inflammation and ulceration of the oral mucosa, which is a frequent side-effect of cancer therapy.[72] Stomatitis especially the grade 3 or 4 mucositis[73] can hamper oral nutrition, resulting in malnutrition, reduce QoL and introduce the need for dose reductions and interruption of chemotherapy.[74] Melatonin has the potential direct antitumor activity, which was proved to modulate the effects of cancer chemotherapy, by enhancing its therapeutic efficacy and reducing its toxicity.[75] Our review showed MLT played no effect on mucositis. Further subgroup analysis showed the cancer type was the major source of heterogeneity. MLT couldn't reduce the stomatitis rate among head and neck cancer patients, while had slight significant effect in patients with metastatic solid tumor. Among the studies conducted in head and neck cancer patients, Borbalas et al found that oral MLT gel caused a consistent trend to lower incidence and shorter mucositis duration.[32] Onseng et al revealed that adjuvant MLT delayed the onset of oral mucositis.[35] Elsabagh et al found the MLT reduced severe oral mucositis development.[25] None of them proved the MLT on reducing the incidence of stomatitis. The possible interpretation was the significant toxicity of systemic high doses of chemotherapy or radiotherapy for head and neck cancer.[76] Compared to other cancer patients who only received chemotherapy or radiotherapy, most head and neck cancer patients received the combined chemoradiotherapy. In addition, radiation in head and neck adds the odds of stomatitis occurrence. We also found in MLT group, the reported incidence of stomatitis was higher in head and neck cancer patients (52.5%-90%) than other cancer population (5.12%-24%). Moreover, our review revealed that MLT could not reduce the severity of stomatitis. A meta-analysis showed that probiotics might reduce the incidence and mitigate the severity of cancer therapy-induced mucositis.[77] Also, photobiomodulation (PBM) was recommended for the

prevention of mucositis.[78 79] However, how the effect of them for patients with head and neck cancer under chemoradiotherapy are still unknown.

Strengths and limitations

This systematic review was registered a priori and conducted in line with Preferred Reporting Items for Systematic Reviews and Meta-Analysis and the recommendations of the Cochrane Collaboration.

Eleven databases were widely searched for eligible studies. Risk of bias analysis was conducted independently by two reviewers using the validated Cochrane assessment tool. Trials quality were generally in moderate level with most studies were in low risk of bias, which could further lend confidence to the current pooled results. In subgroup analysis, we also widely explored the effectiveness of MLT in different population, treatment, dosage, duration, administration time. There are some limitations. First is the insufficient literature. We reviewed many aspects of MLT, like QoL, sleep, fatigue, depression, pain and stomatitis. Though the total of 19 articles were included in the final meta-analysis. However, for every dimension the literatures are limited, from only 5-9. It is mostly resulted by the lacked RCTs of MLT on cancer patients, insufficient data used for synthesis and 14 excluded articles without full text, which limits the generality of the conclusion. Meanwhile, the assessment of publication bias is not allowed for no dimension has more than 10 references. Furthermore, the main significant results were from subgroup analysis of the limited studies. Thus, the results should be interpreted prudently.

Conclusion

Due to the nontoxic property and beneficial effects,[80 81] MLT is more and more used as adjuvant medicine in anticancer treatment. As far as we known, this study is the first meta-analysis that investigated the effect of MLT on QoL and symptoms in cancer patients. We included the moderate number of trials with varied populations and examined the effectiveness of MLT on cancer patients to provide evidence-based evidence in using MLT in real clinical setting. Our review showed that MLT couldn't improve the QoL, fatigue, and pain among cancer patients. It is partly due to the limited literatures. Besides, compared with other patients, cancer patients might have more severe symptoms and psychological suffering caused by disease and its treatment. Thus, MLT play a limited role in cancer population. MLT has positive effects on decreasing the stomatitis incidence and depression, which may make it a reasonable option to use for stomatitis and depression prevention in clinical. However, due to the large heterogeneity, we still could not verify therapeutic effects of MLT on sleep quality. Further large-scale RCTs are urgently required. Besides, the effect of

different combination of MLT dosage and duration, administration type and joint measures are worthy of further study.

Supplementary Material

Fig.1 Study flow diagram

Fig.2 The overall risk of bias

Fig.3 The individual risk of bias for each study

Fig.4 Forest plot of random effects model of the effect of MLT on QoL of cancer patients

Fig.5 Forest plot of random effects model of the effect of MLT on sleep quality of cancer patients

Fig.6 Forest plot of random effects model of the effect of MLT on fatigue of cancer patients

Fig.7 Forest plot of random effects model of the effect of MLT on depression of cancer patients

Fig.8 Forest plot of random effects model of the effect of MLT on pain of cancer patients

Fig.9 Forest plot of random effects model of the effect of MLT on stomatitis rate of cancer patients

Fig.10 Forest plot of random effects model of the effect of MLT on stomatitis severity of cancer patients

Footnotes

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Data availability statement:

All data relevant to the study are included in the article or uploaded as supplementary information. No additional data are available.

Authors' contributions:

All authors had contributed to this study. Xuying Li and Rongrong Fan conceived and designed the original study protocol. Rongrong Fan and Xiaofan Bu performed literature search and and literature screening. Siyu Yang and Tongyu Wang takes responsibility for the integrity of the data and the data analysis. Xuying Li interpreted the results. Yan Tan and Hongyun Chen assessed the risk of bias of the studies. Rongrong Fan was responsible for writting the first draft of the paper and revision of the manuscript. Xuying Li is responsible for the overall content as guarantor. All authors ccritically reviewed and approved the final manuscript.

Ethics approval:

This is a meta-analysis. The Hunan Cancer Hospital Research Ethics Committee has confirmed that no ethical approval is required.

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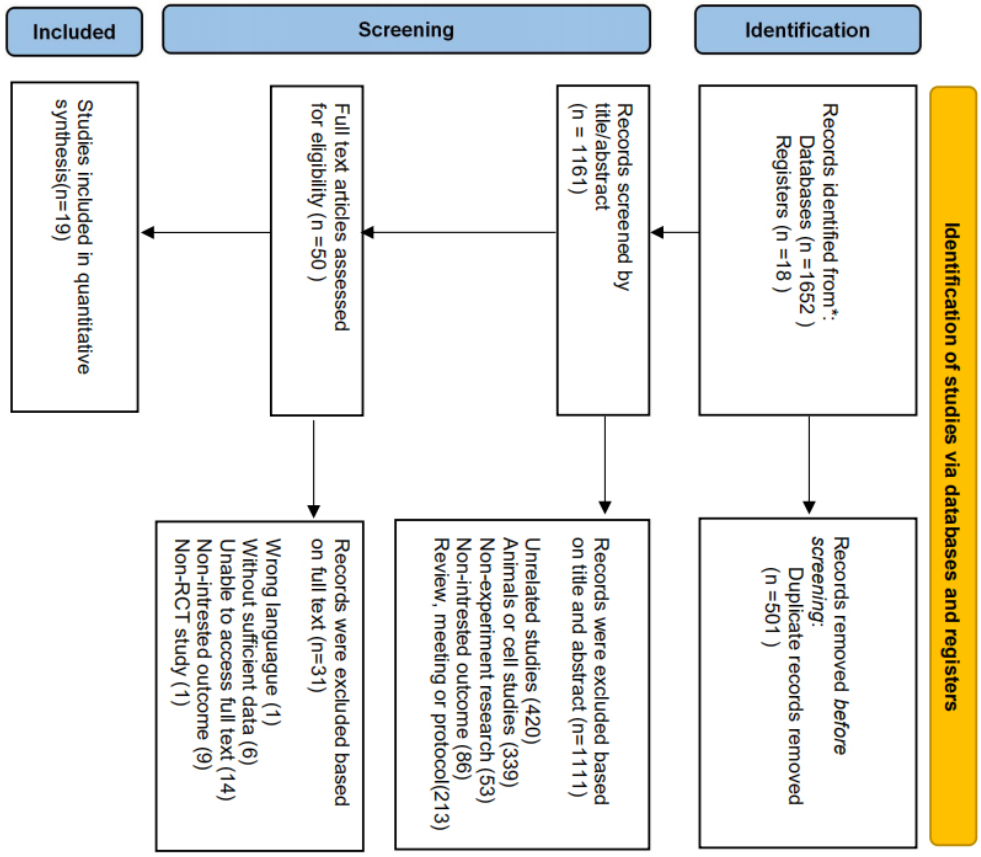

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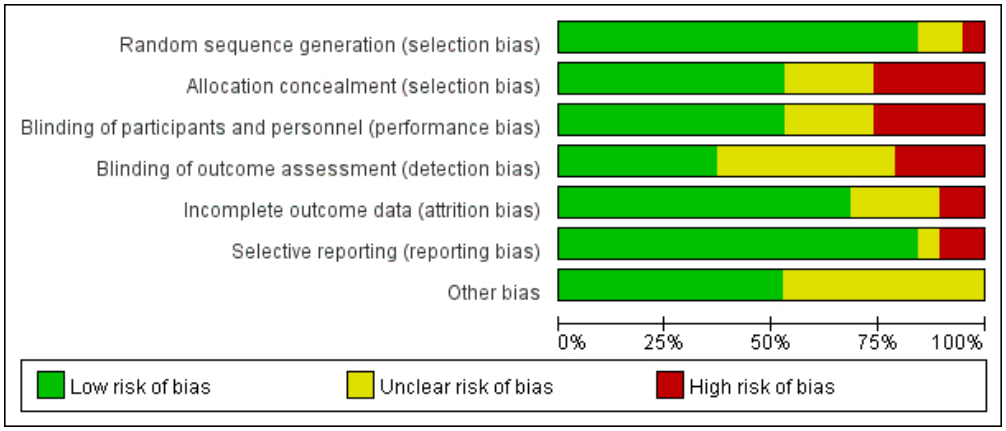

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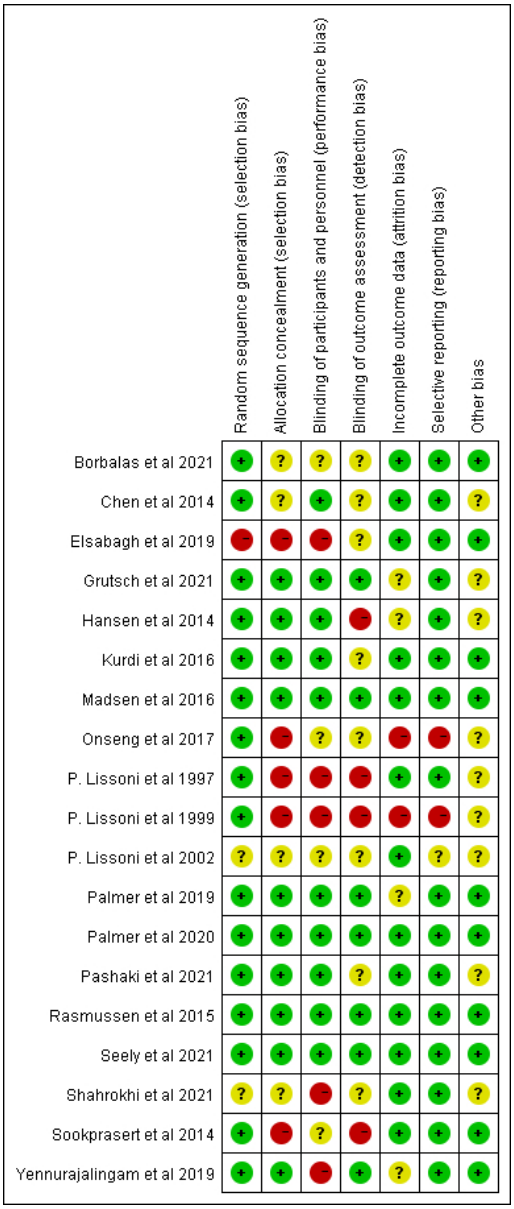

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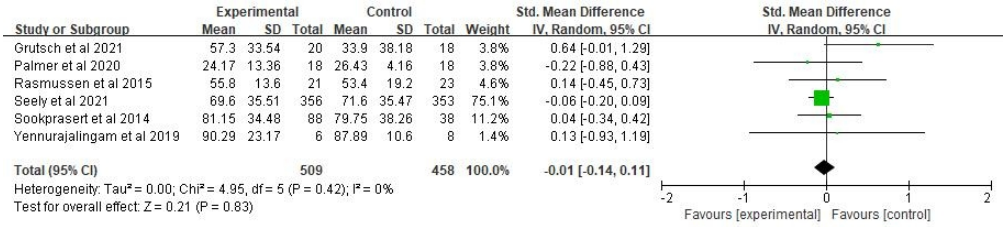

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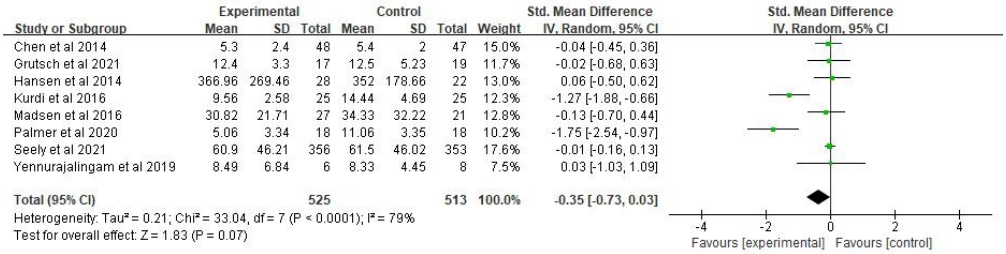

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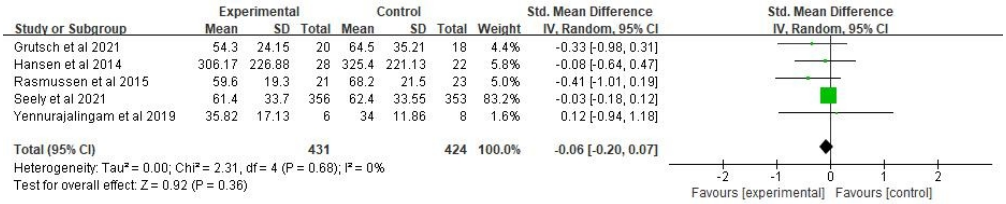

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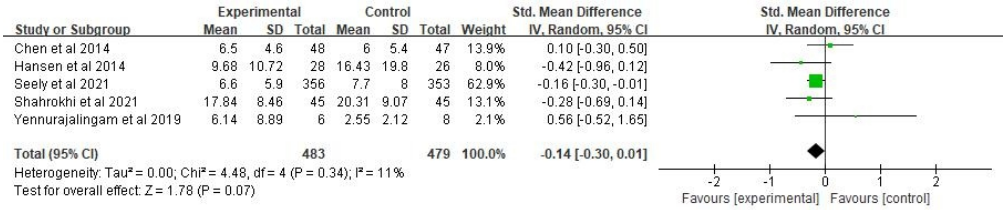

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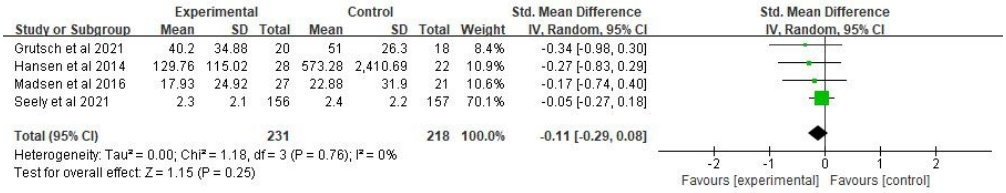

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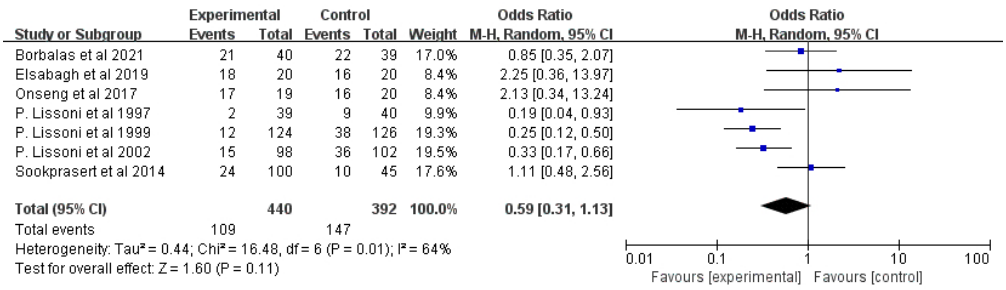

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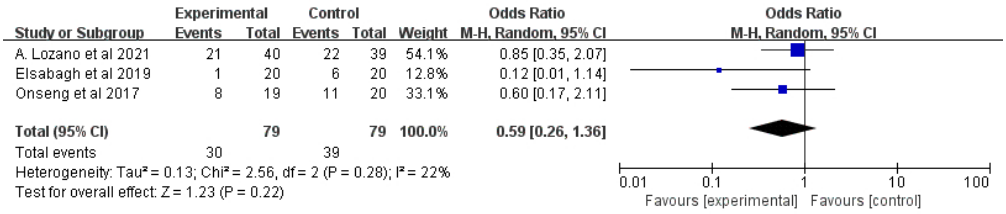

285x62mm (72 x 72 DPI)

Search strategy	
#1	TS=(neoplasm OR Neoplasia* OR Tumor* OR Cancer* OR Malignancy OR Malignancies)
#2	TS=(melatonin)
#3	TS=(Pain)
#4	TS=(fatigue OR lassitude)
#5	TS=(oral mucositis OR mucositides OR stomatitis)
#6	TS=(Depression* OR Depressive)
#7	TS=(Appetite* OR Alteration*)
#8	TS=(Quality of life OR Life Quality OR Health Related Quality Of Life OR HRQOL OR QOL)
#9	TS=(sleep disorder OR Insomnia OR sleep dysfunction OR Sleeplessness
#10	TS=(randomized controlled trial OR randomized OR placebo OR trial OR controlled)
#11	((((((#9) OR #8) OR #7) OR #6) OR #5) OR #4) OR #3
#12	(((#11) AND #10) AND #1) AND #2

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Page 1 in "Title"
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Page 1 in "Abstract"
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Page 2 in "Intruduction"
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Page 2 in "Intruduction"
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Page 3 in "Eligibility criteria"
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Page 3 in "Search strategy"
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Page 3 in "Search strategy"
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Page 3 in "Data extraction"
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Page 3 in "Data extraction"
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Page 3 in "Data extraction"
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Page 5-6 in "table 1"
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Page 4 in "Quality assessment"
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Page 3 in "Data analysis"
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Page 3 in "Data analysis"
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data	Page 3 in

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
		conversions.	"Data analysis"
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Page 3 in "Data analysis"
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Page 3 in "Data analysis"
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Page 3 in "Data analysis"
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Page 3 in "Data analysis"
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Page 3 in "Data analysis"
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Page 3 in "Risk of bias assessment"
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Page 4 in "Literature search"
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Page 4 in "Literature search"
Study characteristics	17	Cite each included study and present its characteristics.	Page 4 in "Literature characteristics"
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Page 4 in "Quality assessment"
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Page 4 in "Literature characteristics"
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Page 4 in "Quality assessment"
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Page 7-9
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Page 7-9
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Page 7-9
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Page 7-9
Certainty of	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Page 7-9

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
evidence			
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Page 9-12
	23b	Discuss any limitations of the evidence included in the review.	Page 9-12
	23c	Discuss any limitations of the review processes used.	Page 9-12
	23d	Discuss implications of the results for practice, policy, and future research.	Page 9-12
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Page 2 in "method"
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Page 2 in "method"
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	Page 2 in "method"
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Page 13 in "Footnotes"
Competing interests	26	Declare any competing interests of review authors.	Page 13 in "Footnotes"
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Page 13 in "Footnotes"

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

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Effect of melatonin on quality of life and symptoms in patients with cancer: a systematic review and meta-analysis of randomized controlled trials

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Primary Subject Heading:	Complementary medicine
Secondary Subject Heading:	Complementary medicine, Evidence based practice
Keywords:	Adult oncology < ONCOLOGY, Pharmacology < TROPICAL MEDICINE, CLINICAL PHARMACOLOGY

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Effect of melatonin on quality of life and symptoms in patients with cancer: a systematic review and meta-analysis of randomized controlled trials

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Abstract

Objective This study systematically reviewed the effect of melatonin on quality of life (QoL) and symptoms among cancer patients.

Design Systematic review and meta-analysis.

Data sources Cochrane Library, PubMed, Embase, Web of Science, Medline, CINAHL, Scopus, Clinical Trials.gov, China Biology Medicine (CBM), ProQuest and Open Gray, were searched from inception through November 2021.

Eligibility criteria We included randomized controlled trials (RCTs) assessing the effects of melatonin on QoL, sleep quality, fatigue, depression, pain, stomatitis rate and stomatitis severity in adult patients with cancer, without language restrictions. Studies that reported the effects of melatonin along with other interventions and had incomplete or absent outcome data were

excluded.

Data extraction and synthesis Two independent reviewers extracted data, and another two reviewers assessed the risk of bias. The risk of bias for each eligible study was assessed using the Cochrane assessment tool. The mean difference or standard mean difference with 95% CIs was used in the computation of continuous variables to synthesise data. The relative risk was used for dichotomous outcomes. Heterogeneity was assessed and quantified (I^2 statistic).

Results A total of 19 qualified studies that included 2101 cancer patients (melatonin: 1078, control: 1023) were included in the meta-analysis. The results indicated that melatonin had no significant effect on QoL [SMD = -0.01, 95% CI (-0.14, 0.11), P = 0.83], sleep quality [SMD = -0.18, 95% CI (-0.62, 0.26), P = 0.42], fatigue [SMD = -0.34, 95% CI (-0.73, 0.06), P = 0.10], pain [SMD = -0.34, 95% CI (-0.7, 0.02), P = 0.06] or stomatitis severity [RR = 0.78, 95% CI (0.47, 1.30), P =0.35]. MLT reduced stomatitis rate among patients with cancer [RR =0.47, 95% CI (0.26, 0.88), P = 0.02], except those with head and neck cancer [RR =1.09, 95% CI (0.92, 1.29), P = 0.35]. MLT eased depression in patients who received administration for more than 14 days [SMD = -0.14, 95% CI (-0.27, -0.01), P = 0.03], and those who underwent surgery [SMD = -0.17, 95% CI (-0.32, -0.03), P = 0.02].

Conclusion The findings showed that MLT did not improve the QoL, sleep quality, fatigue, pain or stomatitis severity among patients with cancer. It had a limited effect on decreasing the stomatitis rate and easing depression. Different treatments, durations and cancer types were the main sources of heterogeneity. Further large-scale RCTs are urgently needed. In addition, the effects of different combinations of MLT dosage and duration, administration types and joint measures are worthy of further study.

PROSPERO registration number

CRD42021292855.

Strengths and limitations of this study

- A strictsearch strategy was used in multiple databases.
- Most of the studies were of high quality with a low risk of bias, which could further lend confidence to the current pooled results.
- We widely explored the effectiveness of MLT in different populations, treatments, dosages, and durations in subgroup analysis.
- For every dimension of MLT, including QoL, sleep, fatigue, depression, pain and stomatitis, the literature is limited, which limits the generality of the conclusion.

- The main significant results were from subgroup analysis of the limited studies, and the results should be interpreted prudently.

Key words: cancer patients, symptoms, QoL, melatonin, meta-analysis

Introduction

Melatonin (MLT) is an important endogenous indolamine that is synthesized and secreted into the systemic circulation and cerebrospinal fluid by the pineal gland and has recognized antiaging, anti-inflammatory, and antioxidant properties.[1] As a strong antifibrotic agent,[2] MLT can be used as a desired preconditioning agent in cell-based therapy.[3 4] It also has a substantial role in regulating the circadian rhythm and sleep during the night.[5 6] Recent studies have proven the effect of MLT on limiting skeletal muscle frailty, prolonging physical performance,[7] and preventing bone loss.[8] In the oncology field, MLT has significantly apoptotic, angiogenic, oncostatic, and antiproliferative effects on various oncological cells.[9] It was proven that low levels of MLT might be a risk factor for breast cancer.[10] Meanwhile, MLT coadministration improves the sensitivity of cancers to inhibition by conventional drugs and reduces the toxic consequences of anticancer drugs while increasing their efficacy.[11] There is major concern about the symptoms induced by cancer and cancer treatment that patients encounter, including physical symptoms and psychological/spiritual distress,[12] leading to decreased QoL. Equally, MLT plays an important role in enhancing QoL by improving survival and decreasing symptoms.[13] The positive association between MLT and various health outcomes in cancer patients has been shown in some studies.[14] A recent meta-analysis revealed that MLT may benefit cancer patients by improving survival and ameliorating the side effects of chemotherapy.[15] Palmer et al, showed the neuroprotective effect of MLT to counteract the adverse effects of chemotherapy on cognitive function, sleep quality and depressive symptoms in breast cancer patients.[16] A recent clinical trial concluded that MLT supply decreased the levels of fatigue in patients with breast cancer.[17] However, some of the recent published findings suggest conflicting results[18 19] that MLT intervention cannot improve the QoL, reduce the symptom burden, or present the uncertain results.[20] We are not aware of any systematic reviews and meta-analyses that have synthesized the evidence of the function of MLT in cancer patients. The effect of MLT on health outcomes in the cancer group remains nonspecific and ambiguous. Thus, with accumulating evidence, we performed a systematic review and meta-analysis of RCTs to investigate the roles of MLT in improving QoL and symptoms in patients with cancer.

Materials and methods

Search strategy

A thorough search was conducted in the Cochrane Library, PubMed, Embase, Web of Science, Medline, CINAHL, Scopus, ClinicalTrials.gov, and China Biology Medicine (CBM) from inception through November 2021 for RCTs without language restrictions. Sources of unpublished studies and grey literature were searched through ProQuest and Open Grey. We used medical subject headings (MeSH) and text words to search the studies. The search strategies are provided in supplemental file 1.

Eligibility criteria

Participants

Studies including adult patients (≥ 18 years) who were diagnosed with cancer according to National Cancer Institute codes, regardless of cancer type, cancer stage (early, middle or advanced), and current treatment (such as radiation therapy, chemotherapy, surgery, targeted therapy, immunotherapy, combination of any of the above treatments, or without any treatment), were eligible.

Interventions and controls

All trials that reported and evaluated the effects of MLT were included. Literature were excluded if they met the following criteria: (1) they were not RCTs; (2) studied the effects of MLT along with other interventions; and (3) incomplete or absent outcome data.

Outcomes

The primary outcome was QoL. The scores of sleep quality, fatigue, depression, and pain, stomatitis rate and stomatitis severity were the secondary outcomes.

Studies

Only RCTs were eligible.

Data extraction

Two independent researchers (SiyuYang, Tongyu Wang) extracted the data of eligible studies and performed double-checks. Any disagreements and differences were resolved by a third investigator

(Xiaofan Bu). The following data from the full text of selected studies were extracted: first author's name, year of publication, the characteristics of the patients, the characteristics of the intervention and the control groups (study design, form of intervention, dose of melatonin supplementation, duration), number of participants in each group and outcome data (means and standard deviations for continuous data; number of incidents for dichotomous data).

Risk of bias assessment

Two reviewers (Yan Tan, Hongyun Chen) independently evaluated the risk of bias for each eligible study using the Cochrane assessment tool, which consists of the following seven domains: "random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias". Each question can be rated as follows: yes (+), low risk of bias; unclear (?), unclear risk of bias; no (−), high risk of bias. Any disagreement between the reviewers was resolved by discussion until consensus was reached.

Data analysis

The meta-analysis was performed using Review Manager Software (version 5.3). The scores of QoL and symptoms was estimated by the mean difference (MD) when trials measured an outcome using the same measurement method or scale. We used the standard mean difference (SMD) when different instruments were used to measure the same outcome. For dichotomous outcomes (such as stomatitis rate and stomatitis severity), we used relative risk (RR). The effect size (ES) and the 95% confidence interval (CI) were computed. ESs with scores of 0.2–0.5, 0.5–0.8, and > 0.8 were considered as small, medium, and large effects, respectively. Forest plots were used to display the pooled ES, 95% CI, weight in percentage. If variability was presented by measures other than the mean or SD, we used standard approaches for estimating data. If the studies did not report SD, we used the following formula to calculate missing SD: $SD=\sqrt{N}\times(\text{upper 95\% CI}-\text{lower 95\% CI})/3.92$. If a study provided medians and interquartile ranges (IQRs), we transformed the median and IQR to the mean and SD by a method for nonnormal data.[21] I^2 was used to measure the statistical heterogeneity among the trials in each analysis. If $P > 0.1$ and $I^2 < 50\%$, a fixed-effects model was adopted; if $P < 0.1$ and $I^2 \geqslant 50\%$, then a random-effects model was adopted. If heterogeneity was identified, subgroup analyses were conducted on different cancer types, treatments, dosages and durations. Sensitivity analysis was performed by removing studies with a high or unclear risk of bias. Reporting and publication bias were investigated by visually examining the degree of asymmetry of a funnel plot.

Patient and public involvement

No patients were involved.

Results

Literature search

The initial search identified 1670 publications through PubMed, Embase, Medline, Scopus, SinoMed, Web of Science, Cochrane, and Clinical Trials. After excluding 501 duplicates, a total of 1161 studies were retrieved for title and abstract screening. After screening the titles and abstracts, 1111 articles were excluded, and 50 papers were retrieved for full text review. Out of 50 retrieved papers, 1 article was excluded due to wrong languages,[22] 6 articles were excluded without complete data, 14 articles were excluded without full text, 9 articles were excluded without target outcome, and 1 article was excluded due to a non-RCT study.[23] Therefore, a total of 19 articles were included in the final meta-analysis.[24-42] The flow chart of the literature search is shown in Fig. 1.

Quality assessment

We used the Cochrane scoring system to assess the quality of the included studies. Two reviewers had different opinions on bias in one article in "incomplete outcome data", and one article in "selective reporting". Through the discussion, final consensus was achieved. The overall risk of bias as shown was moderate (Fig. 2). Nearly all studies reported appropriate random sequence generation. Most studies reported completed data and had low risk of bias on the item 'Selective reporting'. Almost one-third of the studies did not report blindness in the outcome assessment. The individual risk of bias for each study is presented in Fig. 3.

Literature characteristics

The characteristics of the patients, interventions, controls, and measures are shown in Table 1.

Table 1 The characteristics of the literature

Author	Year	Population	Mean age (interve	Study design	Time of duration	Administration time	Intervention group	Control group	Outcome	Intervention (N)	Control (N)

			ntion/ control）								
P. Lissoni[31]	1997	Patients with metastatic solid tumors under chemotherapy	61/58	RCTs	Every day without a break until disease progression	Every night	20 mg oral MLT	Placebo	Stomatitis rate	39	40
P. Lissoni[30]	1999	Patients with metastatic solid tumour under chemotherapy	53/56	RCTs	7 days prior to chemotherapy, continued after chemotherapy interruption, until disease progression	Every night	20 mg oral MLT	Placebo	Stomatitis rate	124	126
P. Lissoni[29]	2002	Untreated patients with metastatic solid tumors under chemotherapy	66/65	RCTs	At least 2 months	Every night	20 mg oral MLT plus support care	Placebo plus support care	Stomatitis rate	98	102
Hansen[27]	2014	Patients undergoing breast cancer surgery	51/60	RCTs	10days: 2 days preoperatively till 8 days postoperatively	One hour before bedtime	6 mg oral MLT	Placebo	Depression (MDI), Sleepiness (KSS, VAS), Fatigue (VAS), Pain (VAS)	28	26
Chen[24]	2014	Breast cancer survivors	59/59	RCTs	4 months	Each night at 9 pm	3 mg oral MLT	Placebo	Sleep (PSQI), depression (CES-D)	48	47
Sookprasert[41]	2014	Patients with non-small cell lung cancer receiving chemotherapy	56.8/55.6	RCTs	2 months: during chemotherapy	At night after 21:00	10 mg or 20mg oral MLT	Placebo	QOL(FACT-L), Mucositis rate	88	38
Rasmussen[33]	2015	Advanced cancer patients who reported significantly tired in palliative care unit	64/65	RCTs	7 days	Every night	20 mg oral MLT	Placebo	Fatigue (MFI-20), QOL (EORTC QLQ-C15-PAL), Insomnia (EORTC QLQ-C15-PAL)	21	23
Madsen[34]	2016	Patients undergoing breast cancer surgery	51/59	RCTs	2weeks: 3 days preoperatively until 2 weeks postoperatively	One hour before bedtime	6 mg oral MLT	Placebo	Sleep (VAS, KSS), pain (VAS)	27	21
Kurdi[28]	2016	Cancer Patients with Insomnia	55.2/49.64	RCTs	14 days	At 7 pm	3mg oral MLT	Placebo	Sleep (AIS)	25	25
Onseng[35]	2017	Patients with head and neck cancer receiving concurrent chemoradiation	47.3/49.6	RCTs	35days: 5 days a week throughout the 7 weeks of chemoradiation	At night after 21:00	10 mL of a 0.2% MLT niosome oral gargle plus 20 mg oral dosage	placebo	QOL (FACT—H&N), Mucositis rate, Mucositis severity (WHO-G)	19	20
Elsabagh H H[25]	2019	Patients with head and neck cancer undergoing radiotherapy	57.8/55.9	RCTs	Six weeks	30 minutes before sleeping	20 mg oral MLT	Placebo	Stomatitis severity (WHO-G), Stomatitis rate, Pain (NRS)	20	20
Palmer[36]	2019	Patients with breast cancer receiving chemotherapy	54.24/54.11	RCTs	10 days during treatment.	One hour before bedtime	20 mg oral MLT	Placebo	Pain (NRS), Sleep (PSQI), Depression (BDI)	18	18
Yennurajalingam[42]	2019	Patients with advanced cancer with poor sleep quality	Not clearly	RCTs	14d	At bedtime	20mg oral MLT plus bright white light therapy	Bright white light therapy alone	Sleep (PSQI), insomnia (ISI), fatigue (FACIT-F), depression (HADS), QOL(FACT)	6	8
Palmer[37]	2020	Patients with breast cancer undergoing chemotherapy after lumpectomy or mastectomy	54.24/54.11	RCTs	10 days: three days prior to chemotherapy and seven following days	One hour before bedtime	20 mg oral MLT	Placebo	Depressive symptoms (BDI-II), Sleep quality (PSQI), QOL (EORTC QLQ-C30)	18	18

Pashaki[38]	2021	Patients with breast cancer during adjuvant chemotherapy and radiotherapy	50.47/46.05	RCTs	8weeks: from 1 week before until 1 month after the adjuvant radiotherapy	One hour before bedtime	18 mg oral MLT	Placebo	Fatigue (BFI)	38	36
Seely[39]	2021	Cancer patients following lung cancer resection	67.2/67.2	RCTs	One year after surgery	One hour before bedtime	20 mg oral MLT	Placebo	Fatigue (MFI-20), QOL(QLQ-LC13), Sleep (MOS), Depression (BDI 2), Pain (BPI)	356	353
Shahrokhi[40]	2021	Patients with colorectal cancer undergoing chemotherapy with sleep disorder	63.63/64.11	RCTs	4week of treatment	At bedtime	6 mg oral MLT	10 mg zolpidem	Sleep (GSQS, PSQI), Depression (HRSD)	45	45
Grutsch[26]	2021	NSCLC patients under chemotherapy	60.3/63	RCTs	From intervention to death	At 8am or at 8pm	20 mg oral MLT	Placebo	QOL(QLQ-C30), Fatigue (QLQ-C30), Pain (QLQ-C30), Sleep (PSQI)	20	18
Borbalas[32]	2021	Patients with head and neck cancer undergoing radiation therapy and chemical treatment	59/56	RCTs	5days a week, lasting 7 weeks	Not clearly	3% oral MLT gel plus standard symptomatic treatment for stomatitis	Placebo plus standard symptomatic treatment for stomatitis	Stomatitis severity (WHO-G), Stomatitis rate	40	39

N, number; Randomized controlled trials, RCTs; Melatonin, MLT; BDI-II, Beck Depression Inventory; PSQI, Pittsburgh Sleep Quality Index; EORTC QLQ-C30, European Organization for Cancer Research and Treatment of Cancer Quality of Life Questionnaire; MFI-20, Multidimensional Fatigue Inventory; EORTC QLQ-C15-PAL, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 15 Palliative Version; CES-D, Center for Epidemiologic Studies-Depression; BFI: Brief Fatigue Inventory; VAS, Visual Analogue Scale; KSS, Karolinska Sleepiness Scale; MDI, Major Depression Inventory; FACT—H&N, Functional Assessment of Cancer Therapy—H&N Version 4; FACT-L, Functional Assessment of Cancer Therapy – Lung; QLQ-LC13, Lung Cancer-13 modules; BDI 2, Beck Depression Inventory 2; MOS, Medical Outcomes Study Sleep Survey; BPI, Brief Pain Inventory; GSQS, Sleep Quality Scale; HRSD, Hamilton Rating Scale for Depression; NRS, Numeric Rating Scales; ISI, Insomnia Severity Index; FACIT-F, Functional Assessment of Cancer Illness Therapy-Fatigue subscale; HADS, Hospital Anxiety and Depression Scale; FACT, Functional Assessment of Cancer Illness Therapy; AIS, Athens insomnia scale; WHO-G, WHO grading system

Participants

The publication dates ranged from 1997 to 2021. Among the 19 studies included in the systematic review, the mean age of the participants ranged from 46.05 to 67.2. The sample size ranged from 14 to 709 participants. Regarding treatment trajectory, 12 studies were conducted in cancer patients with adjuvant chemotherapy and/or radiotherapy,[25 26 29-32 35-38 40 41] 1 was in advanced cancer patients with fatigue,[33] 1 was in breast cancer survivors,[24] 3 were in cancer patients with surgery,[27 34 39] and 2 were in advanced cancer patients with poor sleep quality.[28 42] Regarding cancer diagnosis, 6 studies were in breast cancer,[24 27 34 36-38] 2 were in non-small-cell lung cancer,[26 39] 3 were in head and neck cancer,[25 32 35] 1 was in colorectal cancer,[40] and 7 studies were not restricted to cancer type but were mostly in advanced cancer patients.[28-31 33 41 42]

Intervention

The follow-up period ranged from seven days to one year. The MLT dosage varied between 3 and 20 mg. Regarding the types of MLT administration, 17 involved oral MLT,[24-31 33 34 36-42] 1 involved MLT oral gargle,[32] and 1 was combined.[35] Nearly all studies gave the MLT at night, except one which compared dosage given both in the morning and at night[26].

Instruments

All studies used standardized and validated tools. QoL was measured by four validated tools: the European Organization for Cancer Research (EORTC QLQ-C30),[26 37] Treatment validated for the Brazilian population (QLQ-BR 23),[37] Functional Assessment of Cancer Therapy (FACT),[41 42] Ferrans and Powers Quality of Life Index (QLI)[26], European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 15 Palliative Version (EORTC QLQ-C15-PAL),[33] and Lung Cancer-13 (QLQ-LC13).[39] Sleep quality was measured by the Pittsburgh Sleep Quality Index (PSQI),[24 26 36 37 40 42] Visual Analogue Scale (VAS),[27 34] Karolinska Sleepiness Scale (KSS),[27 34] Sleep Quality Scale (GSQS),[40] Athens insomnia scale,[28] and Medical Outcomes Study (MOS) Sleep Survey.[39] Depression was measured by the Beck Depression Inventory (BDI-II),[37 39] Beck Depression Inventory (BDI),[36] Center for Epidemiologic Studies-Depression (CES-D),[24] Major Depression Inventory (MDI),[27] Hamilton Rating Scale for Depression (HRSD),[40] Hospital Anxiety and Depression Scale (HADS).[42] Fatigue was measured by the Multidimensional Fatigue Inventory (MFI-20),[33] EORTC QLQ-C15-PAL (fatigue domain),[33] Brief Fatigue Inventory (BFI),[38] VAS,[27] Multidimensional Fatigue Index 20 questionnaire,[39] QLQ-C30 (fatigue domain),[26] and Functional Assessment of Cancer Illness Therapy-Fatigue subscale (FACIT-F).[42] Pain was measured by VAS,[27 34] Brief Pain Inventory (BPI),[39] QLQ-C30 (pain domain),[26] and Numeric Rating Scales (NRS).[25 36] The incidence of stomatitis was calculated by the ratio of the occurrence number to the total number.[25 29-32 35 41]

Meta-analysis

Effect of MLT on QoL

Overall, 6 clinical trials evaluated the effect of MLT on QOL. The results showed that there was no statistically significant difference between the intervention and control groups [SMD = -0.01, 95% CI (-0.14, 0.11), P = 0.83] with no heterogeneity (I^2=0%, P=0.42) (Fig. 4). All 6 studies used a 20mg MLT dosage. Subgroup analysis based on study durations (P=0.65-0.92) and treatment types(P=0.45-0.6) showed no significant differences.

Effect of MLT on sleep quality

Nine clinical trials evaluated the effect of MLT on sleep quality. Pooled ES from the random effect model showed that there was no significant effect on sleep quality [SMD = -0.18, 95% CI (-0.62, 0.26), P = 0.42] (Fig. 5). There was significant heterogeneity between studies (I^2 = 87%, P <0.001). We deleted a study[40] with obvious heterogeneity and I^2 decreased to 79% [SMD = -0.35, 95% CI (-0.73, 0.03), P = 0.07]. Subgroup analysis based on dosage, study durations, treatments, different

combinations of dosage and duration showed no significant differences between subgroups (Table 2).

Table 2 Subgroup analyses of melatonin supplementation on sleep quality

	N	WMD (95% CI)	Heterogeneity I^2 (P)	P within group
Overall effect	8	-0.35 (-0.73, 0.03)	79% (P<0.0001)	0.07
Dosage				
<10mg	4	-0.32 (-0.88, 0.23)	77% (P=0.005)	0.25
≧10mg	4	-0.42 (-1.16, 0.32)	84% (P=0.0004)	0.27
Duration				
<2 weeks	2	-0.01 (-0.33, 0.32)	0% (p=0.76)	0.96
≧2 weeks	6	-0.51 (-1.07, 0.05)	85% (p<0.00001)	0.08
Combination				
<10mg + ≧2 weeks	3	-0.46 (-1.18, 0.27)	83% (P=0.003)	0.22
>10mg + ≧2 weeks	3	-0.01 (-0.16, 0.13)	0% (P=1.00)	0.86
>10mg + <2 weeks	1	-1.75 (-2.54, -0.97)	-	<0.01
<10mg + <2 weeks	1	0.06 (-0.5, 0.62)	-	0.83
Combined treatment				
Under chemotherapy	2	-0.87 (-2.57, 0.82)	91% (P=0.0009)	0.31
Under surgery	3	-0.02 (-0.15, 0.12)	0% (P=0.89)	0.83
With insomnia				
Yes	2	-0.7 (-1.96, 0.57)	77% (P=0.04)	0.28
No	6	-0.23 (-0.58, 0.13)	73% (P=0.002)	0.21

N, number of the literatures

Effect of MLT on fatigue

The overall ES of MLT for fatigue alleviation was medium [SMD = -0.34, 95% CI (-0.73, 0.06), P = 0.10] with high heterogeneity (P =0.002, I^2 = 74%). However, there was no significant difference. The study of Pashaki et al,[38] showed great heterogeneity because only this one proved a significantly lower level of fatigue in the intervention group. We removed it, and the heterogeneity decreased to 0% (Fig. 6).

Effect of MLT on depression

Six clinical trials evaluated the effect of MLT on depression. Only Palmer et al, showed a significant effect on depression.[37] The overall treatment effect on depression showed that there was no statistically significant difference between the intervention and control groups [SMD = -0.24, 95% CI (-0.53, 0.05), P = 0.10] with high heterogeneity (P =0.03, I^2 = 60%). A sensitivity analysis was performed by removing one study from the analysis (Fig. 7).[37] Regarding subgroup analysis, a significant difference was observed for different study durations and treatments, although both showed a slight ES. Patients who received an intervention duration greater than 14 days had significantly lower depression [SMD = -0.14, 95% CI (-0.27, -0.01), P = 0.03] with low heterogeneity (P =0.4, I^2 = 0%) (Fig. 8). Meanwhile, MLT alleviated depression in cancer patients who underwent surgery [SMD = -0.17, 95% CI (-0.32, -0.03), P = 0.02] with low heterogeneity (P =0.35, I^2 = 0%) compared to those received chemotherapy (Fig. 9). No significant difference was observed among studies on the different dosages (P = 0.27-0.43), cancer diagnosis (P = 0.20), and combined chemotherapy (P = 0.13-0.42).

Effect of MLT on pain

Five clinical trials evaluated the effect of MLT on pain [SMD = -0.34, 95% CI (-0.7, 0.02), P = 0.06] with high heterogeneity among studies (P =0.03, I^2 = 62%). No significant difference was observed among studies on the cancer diagnosis (P=0.27-0.47), combined treatments (P=0.37), durations (P=0.11) and dosages (P=0.16-0.27). Sensitivity analysis was performed by removing one study[25], and the heterogeneity decreased to 0% (Fig. 10).

Effect of MLT on stomatitis

Regarding stomatitis, seven clinical trials evaluated the effect of MLT on the incidence of stomatitis. The finding showed that there was no significant ES [RR = 0.71, 95% CI (0.45, 1.13), P = 0.15] (Fig. 11), with high heterogeneity (P < 0.001, I^2 = 86%). All of the study durations were more than 2 weeks, and all patients accepted chemotherapy or radiotherapy. In addition, nearly all these clinical trials gave an MLT of 20 mg, except one that used a 3% MLT oral gel.[32] However, removing it or not caused little change to heterogeneity and ES. Further subgroup analysis showed that the cancer type might be the main source of heterogeneity. MLT did not reduce the incidence of stomatitis among patients with head and neck cancer under adjuvant chemotherapy or radiotherapy [RR =1.09, 95% CI (0.92, 1.29), P = 0.35], with low heterogeneity (P =0.64, I^2 = 0%). However, it had significant value in patients with other kinds of tumours except head and neck cancer [RR =0.47, 95% CI (0.26, 0.88), P = 0.02] with high heterogeneity (P =0.03, I^2 = 66%) (Fig.12).

For stomatitis severity, three clinical trials evaluated the effect of MLT on reducing 3-4 grade (severe) stomatitis according to the WHO grading system.[43] The overall treatment effect showed that the intervention had no statistically significant difference between the intervention and control groups [RR = 0.78, 95% CI (0.47, 1.30), P =0.35] with low heterogeneity (P =0.22, I^2 = 35%) (Fig.13).

Discussion

To the best of our knowledge, this study is the first meta-analysis to investigate the effect of MLT on QoL, sleep quality, and other symptoms, such as fatigue, depression, pain and stomatitis, in cancer patients. Unfortunately, in the current study, we did not prove the beneficial effect of MLT on QoL, sleep quality, fatigue or pain. However, it has the potential to improve depression and reduce the incidence of stomatitis with small ESs.

Most of the suffering that cancer patients now face comes from disturbing symptoms, such as poor sleep, fatigue, depression, pain and so on. Effective symptom control greatly improves QoL. Thus, the effect of MLT on QoL might be achieved through relieving symptoms. Innominato et al, revealed that bedtime MLT was associated with a significant improvement in sleep quality, fatigue severity, QoL, and social and cognitive function in advanced breast cancer patients.[44] However, contradictory conclusions revealed that MLT did not improve appetite, weight, or QoL in cachectic patients with advanced cancer.[45] In addition, a previous study reported beneficial short-term effects of MLT on sleep but not QoL.[46] Our review included six trials that regarded the QoL of cancer patients as a health outcome. None of them proved a significant improvement in QoL in the intervention group, although Grutsch et al,[26] and Sookprasert et al,[41] provided a trend for better QoL compared with baseline. For such invalid effectiveness, one of the possible interpretations might be the differences due to the study population, interventions and measurements. Another explanation

might be the multidimensional properties of QoL, which contained domains of physical, psychology, spirit, and social. Thus, the mere elimination of symptoms played a limited role in improving the QoL, especially for cancer patients who were faced with many other disturbing aspects.

Due to the important role in regulating the circadian rhythm and sleep, many studies have been conducted to verify the value of MLT on sleep. MLT may be preferable to traditional hypnotics in the management of insomnia.[47] A network meta-analysis supports the effectiveness of MLT in improving sleep-onset difficulties.[48] A review of the influence of dietary sources of MLT on sleep quality indicated that the sources of MLT consumption of milk and sour cherries may improve sleep quality.[49] There are many conflicting studies regarding different populations, dosages and durations. Fatemeh et al, found the significant effects of MLT on sleep quality in patients with respiratory diseases, metabolic disorders, and sleep disorders but not in mental disorders, neurodegenerative diseases and breast cancer.[50] Under the condition of using the Pittsburgh Sleep Quality Index as a unified measurement tool, 20mg MLT for 10 days in breast cancer patients under chemotherapy showed a positive sleeping improvement,[37] while the same dosage for at least 28 days revealed a meaningless result in patients with lung cancer.[51] Meanwhile, the optimal combination of dosage and duration remains unknown. Innominato et al, found that 5mg for two months has a positive effect on sleep quality and QoL in advanced breast cancer patients.[44] Similarly, in advanced cancer patients, the combination of 14-Day 20 mg MLT plus bright white light therapy did not improve sleep quality.[42] Under fewer doses, 14-Day 3mg MLT actually improved sleep in cancer patients with insomnia.[28] Our review revealed that MLT could not improve sleep. The subgroup analysis did not find a significant difference in different MLT durations, dosages, or combinations of dosage and duration. The optimal combination of dosage and duration in improving sleep for patients warrants further exploration. The administration type is another factor. It was found that a 2 mg prolonged release MLT formulation for 14 days resulted in significant and clinically meaningful improvements in sleep quality, morning alertness, and sleep onset latency in primary insomnia patients[52] and in Parkinson's disease patients with a poor sleep quality.[53] However, most of the studies we included used oral MLT. How the administration type affects effect on sleep in cancer patients remains to be studied. The effectiveness of the combination of bright light and MLT remains controversial. Yennurajalingam et al, proved that it could not work in advanced cancer patients with insomnia,[42] while it could improve subjective daytime sleepiness in patients with delayed sleep phase disorder.[54]

MLT may be an effective treatment for patients with chronic fatigue syndrome.[55] Nevertheless, in the current study, none of the studies showed any improvement in fatigue in cancer patients. Only a high-quality trial proved a significant effect of MLT on breast cancer patients undergoing adjuvant chemotherapy and radiotherapy,[38] with MLT doses of 18 mg a day from 1 week before until 1 month after adjuvant radiotherapy. The evidence supporting the usage of melatonin for cancer-related fatigue is limited. Short-term use of dexamethasone or methylprednisolone is recommended for the

control of cancer-related fatigue (CRF) in metastatic cancer patients according to European Society for Medical Oncology (ESMO) guidelines,[56] while the use of eszopiclone, megestrol acetate and MLT is not recommended for the control of CRF. However, the preventive effect of MLT on cancer-related fatigue is still under study. Nonpharmaceutical interventions were also recommended,[56] such as relaxation exercise, massage, cognitive-behavioural therapy, and physical activity, which were demonstrated to have moderate-to-large ESs.[57] Multimodal therapy, qigong, aerobic exercise, and cognitive-behavioural therapy might be the best choices for cancer-related fatigue.[58]

MLT seems to be able to ease pain. However, the results have varied in different studies. Lee et al, found that the prophylactic administration of MLT conferred significant clinical benefits in reducing postoperative pain and opioid use, as well as improved sensory recovery following orthognathic surgery.[59] Tunay et al, found that preoperative oral MLT led to a reduction in pain scores, total morphine consumption and supplemental analgesic requirements after surgery.[60] MLT could also improve pain in females with primary dysmenorrhea.[61] However, the evidence was limited in critically ill patients in the ICU and patients after total knee arthroplasty.[62 63] For cancer patients, the evidence is also restricted. Our review revealed that MLT had no effect on pain relief. Only Elsabagh et al, found a beneficial effect of MLT on alleviating pain in head and neck cancer patients undergoing radiotherapy, with a dosage of 20 mg for six weeks.[25] At the same time, Palme et al, found a drop in pain scores from baseline in the intervention group.[36] The minor role of MLT on pain in cancer patients could be explained by the fact that cancer-related pain is one of the most common and troublesome symptoms affecting cancer patients with high severity.[64] For such sever pain, effective analgesics, such as opioids, are more helpful. In addition, despite the availability of effective treatments, cancer-related pain may be inadequately controlled in up to 50% of patients. Thus, multidisciplinary interventions are required[65], and single MLT seems too weak for cancer pain.

Circadian rhythm disruption underlies the pathophysiology of psychiatric disorders, especially depression.[6] MLT is a pleiotropic regulator molecule, and its analogues have been observed to resynchronize the circadian rhythm and to alleviate depressive symptoms.[66] However, duration and treatment might affect the antidepressant effects of MLT, and both showed a slight ES. We found that MLT supplementation had a significant effect in patients who received more than 14 days of treatments and those who underwent surgery. Our assumption is that patients under operation tend to be in the early stages of the disease with lighter disease load and slight depression. The antidepressant effect of a long MLT duration in patients with less serious disease was shown in some studies. For example, MLT for 12 weeks had beneficial effects on decreasing depression in women with polycystic ovary syndrome,[67] patients with Parkinson's disease[68] and diabetic haemodialysis patients.[69] Nevertheless, it had no prophylactic antidepressant effect on acute coronary syndrome[70] or patients with acute mania.[71]

Oral mucositis refers to inflammation and ulceration of the oral mucosa, which is a frequent side effect of cancer therapy.[72] Stomatitis, especially the grade 3 or 4 mucositis[73], can hamper oral nutrition, resulting in malnutrition, reduce QoL, and introduce the need for dose reductions and interruption of chemotherapy.[74] MLT has potential direct antitumor activity and has been proven to modulate the effects of cancer chemotherapy by enhancing therapeutic efficacy and reducing toxicity.[75] Our review showed that MLT had no effect on mucositis. Further subgroup analysis showed that the cancer type was the major source of heterogeneity. MLT could not reduce the stomatitis rate among head and neck cancer patients, while it had a slightly significant effect in patients with other tumours. Among the studies conducted in head and neck cancer patients, Borbalas et al, found that oral MLT gel demonstrated a consistent trend in lowering incidence and shortening mucositis duration.[32] Onseng et al, revealed that adjuvant MLT delayed the onset of oral mucositis.[35] Elsabagh et al, found that MLT reduced severe oral mucositis development.[25] None of them proved that MLT could reduce the incidence of stomatitis. The possible interpretation was the significant toxicity of systemic high doses of chemotherapy and radiotherapy for head and neck cancer.[76] Compared to other cancer patients who only received chemotherapy or radiotherapy, most head and neck cancer patients received the combined chemoradiotherapy. In addition, radiation in the head and neck increases the odds of stomatitis occurrence. We also found that in the MLT group, the reported incidence of stomatitis was higher in head and neck cancer patients (52.5%-90%) than in other cancer populations (5.12%-24%). Moreover, our review revealed that MLT could not reduce the severity of stomatitis. A meta-analysis showed that probiotics might reduce the incidence and mitigate the severity of cancer therapy-induced mucositis.[77] Additionally, photobiomodulation (PBM) was recommended for the prevention of mucositis.[78 79] However, how they affect patients with head and neck cancer under chemoradiotherapy is still unknown.

Strengths and limitations

To the best of our knowledge, this study is the first meta-analysis to investigate the effect of MLT on QoL and symptoms in cancer patients. Eleven databases were widely searched for eligible studies. Risk of bias analysis was conducted independently by two reviewers using the validated Cochrane assessment tool. The trial quality was generally moderate, with most studies having a low risk of bias, which could further lend confidence to the current pooled results. In the subgroup analysis, we also widely explored the effectiveness of MLT in different populations, treatments, dosages, and durations. There are some limitations. The first is the insufficient literature. We reviewed many aspects of MLT, such as QoL, sleep, fatigue, depression, pain and stomatitis. A total of 19 articles were included in the final meta-analysis. However, for every dimension, the literature is limited, from only 5-9. This is mostly the result of the lack of RCTs of MLT in cancer patients. Thus, insufficient data were used for synthesis. There were 14 excluded articles without full text, which

limits the generality of the conclusion. Meanwhile, the assessment of publication bias was not allowed because no dimension had more than 10 references. Furthermore, the main significant results were from subgroup analysis, and the results should be interpreted prudently.

Conclusion

Due to its nontoxic property and beneficial effects,[80 81] MLT is increasingly used as an adjuvant medicine in anticancer treatment. We included a moderate number of trials with varied populations and examined the effectiveness of MLT on cancer patients to provide evidence-based findings on using MLT in a real clinical setting. Our review showed that MLT did not improve QoL, sleep quality, fatigue, or pain among cancer patients. MLT has positive effects on decreasing the stomatitis incidence and depression, which may make it a reasonable option for stomatitis and depression prevention in the clinic. Even so, there are still many restrictions. Further large-scale RCTs are urgently needed. In addition, the effects of different combinations of MLT dosage and durations, administration types and joint measures are worthy of further study.

Supplementary Material

Fig.1 Study flow diagram

Fig.2 The overall risk of bias

Fig.3 The individual risk of bias for each study

Fig.4 Forest plot of the effect of MLT on QoL among patients with cancer

Fig.5 Forest plot of the effect of MLT on sleep quality among patients with cancer

Fig.6 Forest plot of the effect of MLT on fatigue among patients with cancer

Fig.7 Forest plot of the effect of MLT on depression among patients with cancer

Fig.8 Forest plot of longer MLT duration on depression among patients with cancer

Fig.9 Forest plot of MLT on depression among cancer patients underwent surgery

Fig. 10 Forest plot of the effect of MLT on pain among patients with cancer

Fig. 11 Forest plot of the effect of MLT on stomatitis incidence among patients with cancer

Fig. 12 Forest plot of the effect of MLT on stomatitis incidence among cancer patients except head

and neck cancer

Fig. 13 Forest plot of the effect of MLT on stomatitis severity among patients with cancer

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Authors' contributions:

All authors had contributed to this study. Xuying Li and Rongrong Fan conceived and designed the original study protocol. Rongrong Fan and Xiaofan Bu performed literature search and and literature screening. Siyu Yang and Tongyu Wang takes responsibility for the integrity of the data and the

data analysis. Xuying Li interpreted the results. Yan Tan and Hongyun Chen assessed the risk of bias of the studies. Rongrong Fan was responsible for writting the first draft of the paper and revision of the manuscript. Xuying Li is responsible for the overall content as guarantor. All authors ccritically reviewed and approved the final manuscript.

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This is a meta-analysis. The Hunan Cancer Hospital Research Ethics Committee has confirmed that no ethical approval is required.

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Not applicable.

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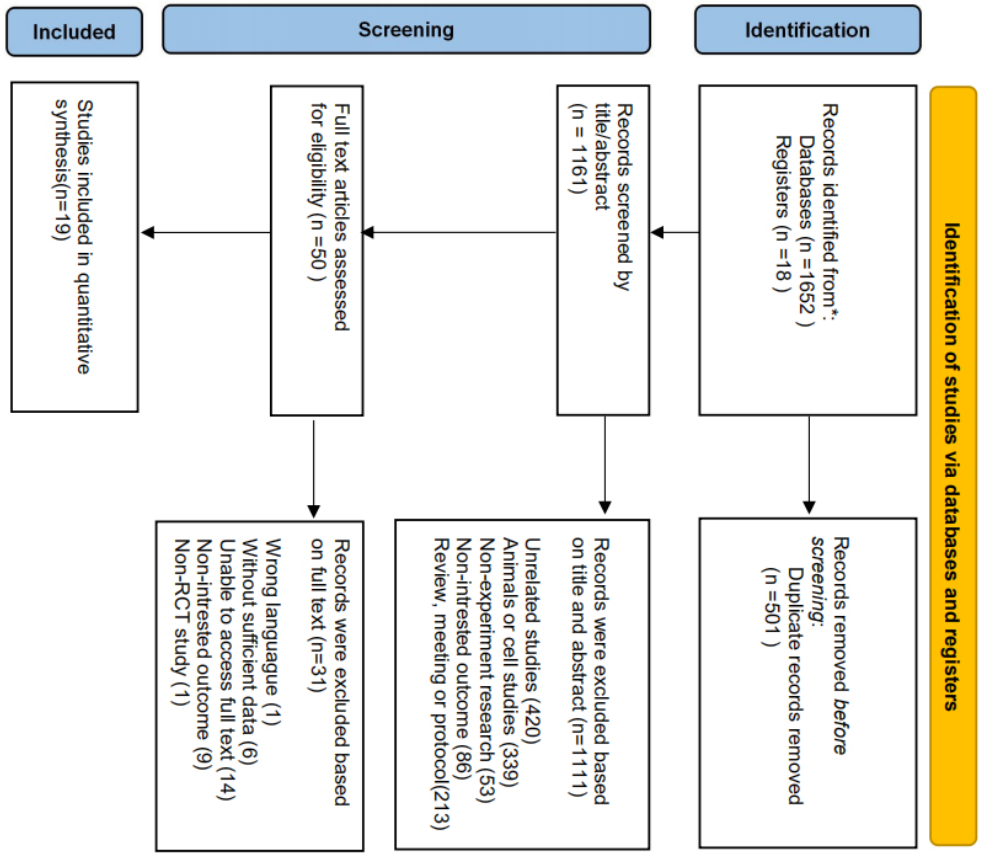

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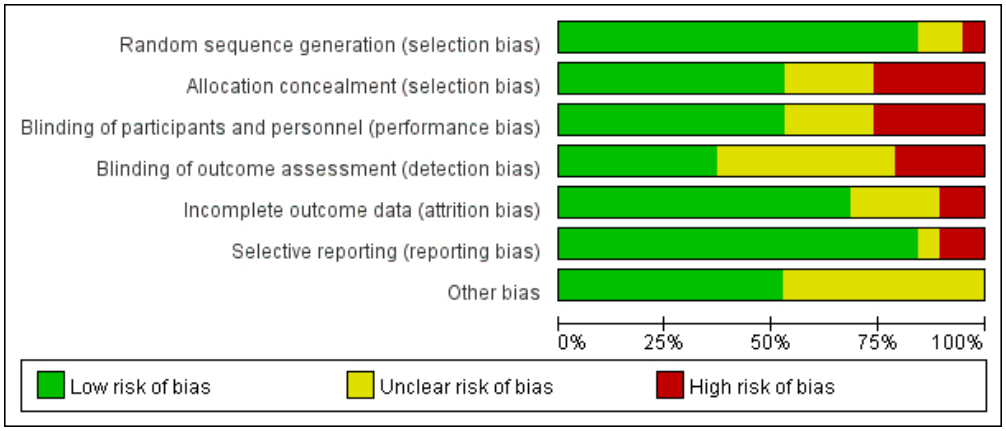

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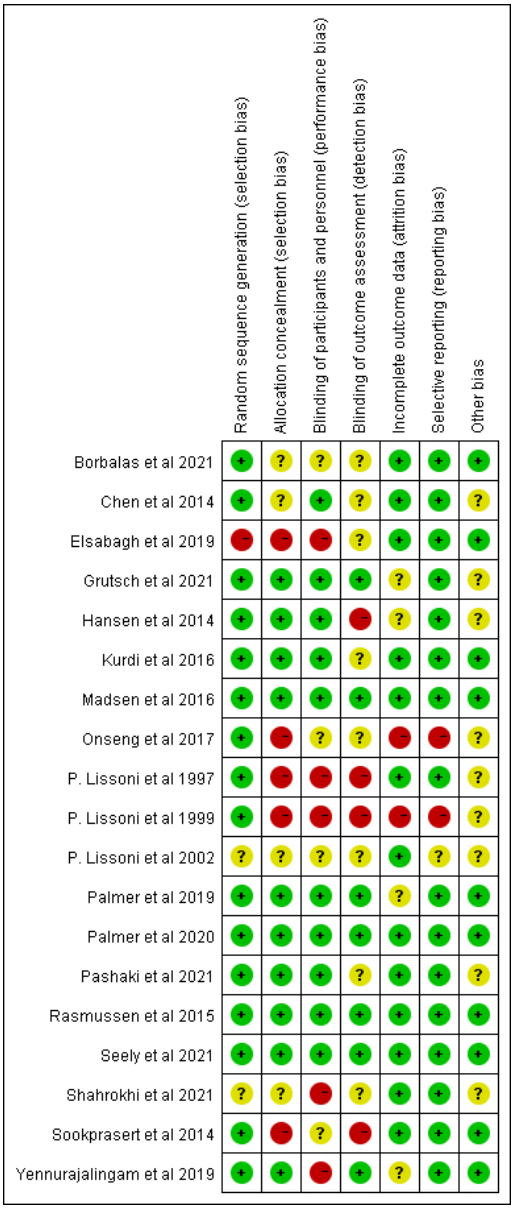

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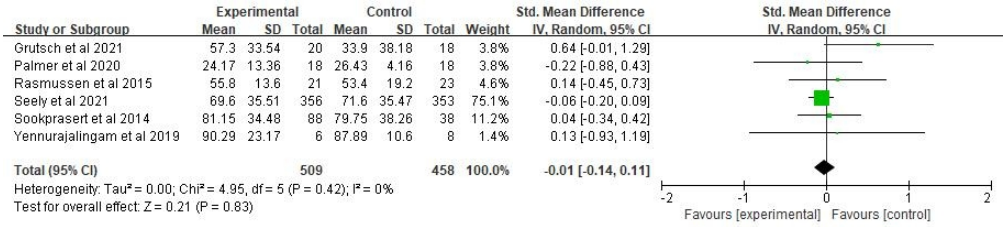

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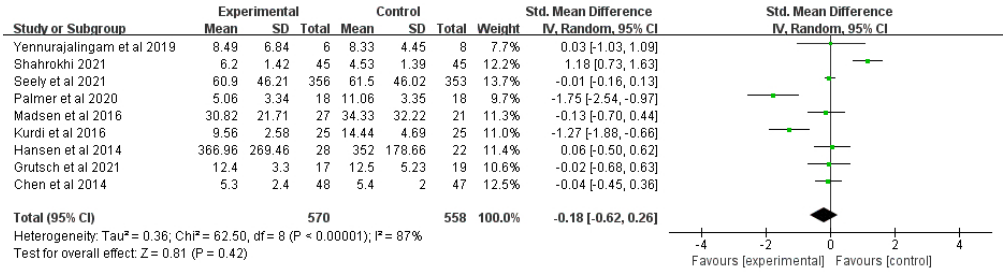

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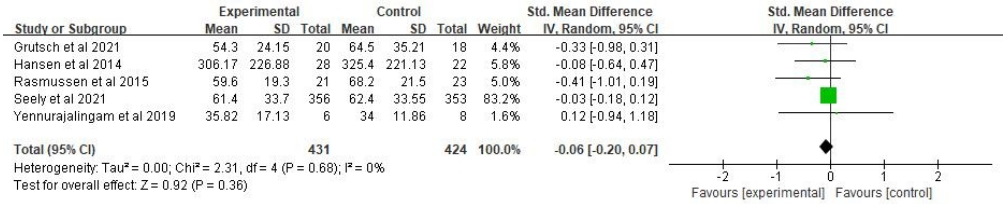

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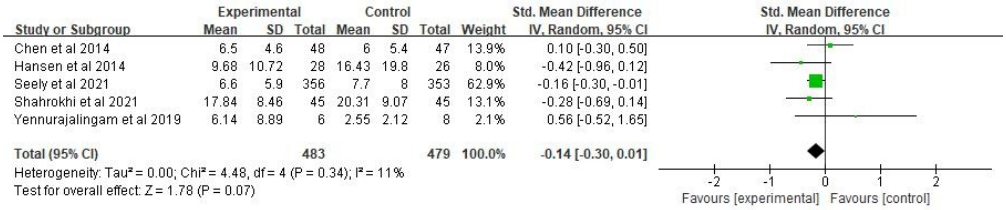

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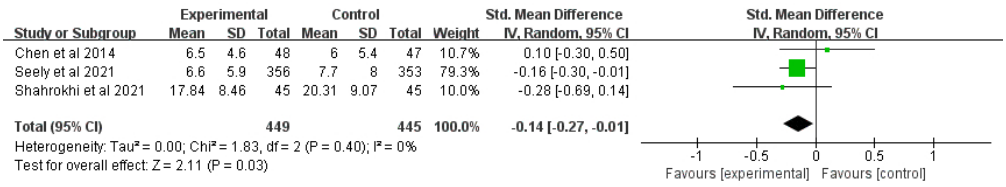

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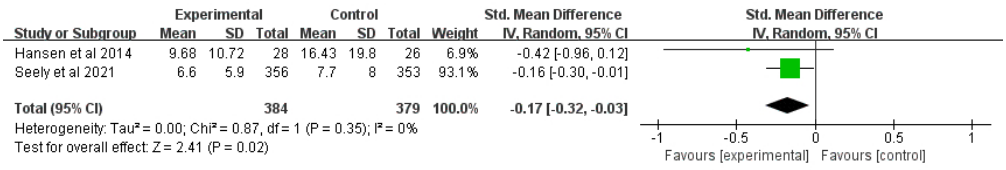

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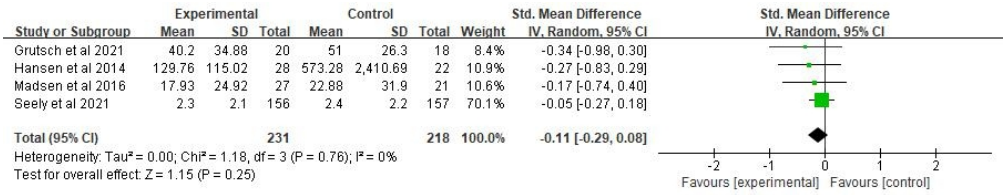

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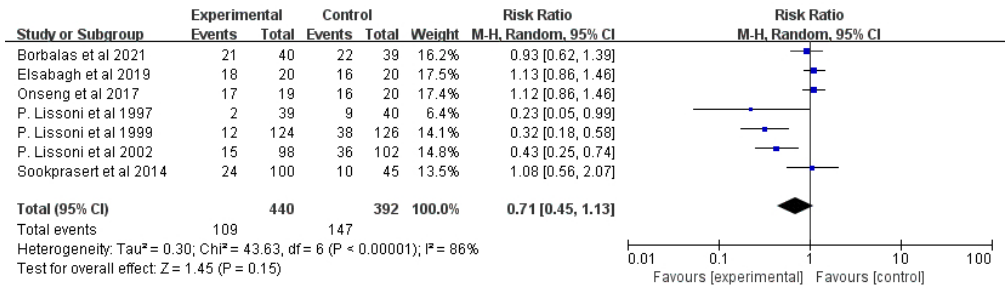

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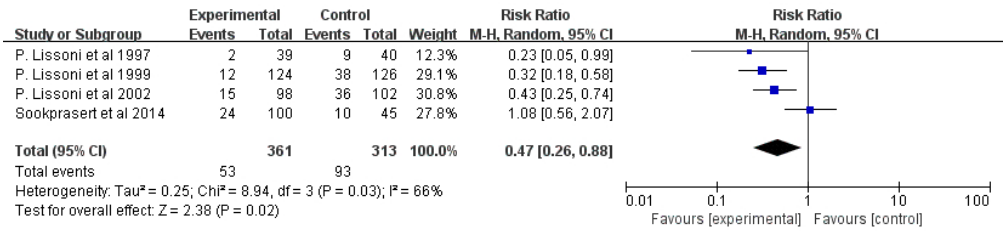

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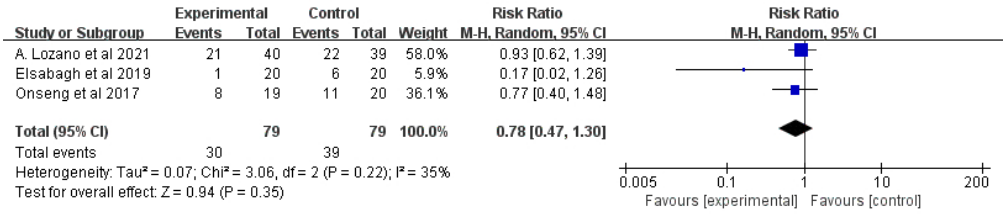

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Search strategy	
#1	TS=(neoplasm OR Neoplasia* OR Tumor* OR Cancer* OR Malignancy OR Malignancies)
#2	TS=(melatonin)
#3	TS=(Pain)
#4	TS=(fatigue OR lassitude)
#5	TS=(oral mucositis OR mucositides OR stomatitis)
#6	TS=(Depression* OR Depressive)
#7	TS=(Appetite* OR Alteration*)
#8	TS=(Quality of life OR Life Quality OR Health Related Quality Of Life OR HRQOL OR QOL)
#9	TS=(sleep disorder OR Insomnia OR sleep dysfunction OR Sleeplessness
#10	TS=(randomized controlled trial OR randomized OR placebo OR trial OR controlled)
#11	((((((#9) OR #8) OR #7) OR #6) OR #5) OR #4) OR #3
#12	(((#11) AND #10) AND #1) AND #2

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Page 1 in "Title"
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Page 1 in "Abstract"
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Page 2 in "Intruduction"
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Page 2 in "Intruduction"
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Page 3 in "Eligibility criteria"
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Page 3 in "Search strategy"
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Page 3 in "Search strategy"
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Page 3 in "Data extraction"
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Page 3 in "Data extraction"
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Page 3 in "Data extraction"
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Page 5-6 in "table 1"
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Page 4 in "Quality assessment"
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Page 3 in "Data analysis"
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Page 3 in "Data analysis"
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data	Page 3 in

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
		conversions.	"Data analysis"
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Page 3 in "Data analysis"
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Page 3 in "Data analysis"
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Page 3 in "Data analysis"
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Page 3 in "Data analysis"
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Page 3 in "Data analysis"
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Page 3 in "Risk of bias assessment"
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Page 4 in "Literature search"
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Page 4 in "Literature search"
Study characteristics	17	Cite each included study and present its characteristics.	Page 4 in "Literature characteristics"
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Page 4 in "Quality assessment"
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Page 4 in "Literature characteristics"
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Page 4 in "Quality assessment"
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Page 7-9
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Page 7-9
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Page 7-9
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Page 7-9
Certainty of	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Page 7-9

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
evidence			
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Page 9-12
	23b	Discuss any limitations of the evidence included in the review.	Page 9-12
	23c	Discuss any limitations of the review processes used.	Page 9-12
	23d	Discuss implications of the results for practice, policy, and future research.	Page 9-12
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Page 2 in "method"
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Page 2 in "method"
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	Page 2 in "method"
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Page 13 in "Footnotes"
Competing interests	26	Declare any competing interests of review authors.	Page 13 in "Footnotes"
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Page 13 in "Footnotes"

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

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