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Research Article

Efficacy of melatonin on mood disorders in cancer and cancer related diseases: A Systematic review and meta-analysis of randomized controlled trials

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ABSTRACT

The current meta-analysis sought to determine the efficacy of melatonin in improving mood disorders of patients with cancer and cancer-related illness. We included randomized controlled trials (RCTs) published in three electronic databases (EMBASE, PubMed and Cochrane) from inception to August 2022. Demographic data and mood outcomes such as depression (measured by Beck Depression Inventory Index (BDI) score) and emotional wellbeing outcome (measured by functional assessment of cancer therapy-Lung (FACT-L) scores) was extracted. The meta-analysis was conducted using a random effects model. A total of four RCTs with 966 participants were finally included for data analysis. Depression outcomes were found in three RCTs, and emotional wellbeing outcome was found in one RCT. For short term duration of treatment (<12 weeks), melatonin was associated with significantly reduced depression (WMD 3.67, 95% CI 1.41-5.98; p=0.002). However, long term duration of treatment (≥12 weeks) showed no difference in depression scores (WMD -0.072, 95% CI -0.42-0.28; p=0.68, I^2=32.4%). For emotional wellbeing, melatonin was associated with significantly reduced long term treatment in 3 months (mean difference 1.05, SD 0.22, 95% CI 0.63-1.47; p<0.001) and 7 months (mean difference 2.41, SD 0.22, 95% CI 1.97-2.85; p<0.001). Adding melatonin treatment among patients with cancer significantly improved mood disorders depending on the duration of treatment. Depression improvement significantly showed in short term treatment. However, emotional wellbeing was improved in long term treatment.

Keywords:
Melatonin, Cancer, Moods, Depression, Emotional-wellbeing

1. INTRODUCTION

Cancer is a major problem in public health. In 2021, new cases of cancer were reported by approximately two million patients in the US. Because of the early detection and progression of treatment, the cancer death rate declined by 2% yearly from 2015 through 2019. Cancer survival has improved for all the most common cancers since the mid1970s. The 5-year survival rate for all cancers was 67% between 2010 and 2016[1]. The prevalence of psychological distress among adult patients with cancer increased both at the time of diagnosis and upon disease recurrence[2-3].

Psychological distress among patients with cancer including anxiety, depression and hostility were reported[2,4]. Mood disorders in cancer involve multifactorial disorders. For instance, depression in cancer can be related to psychosocial, biological and even iatrogenic causes[5]. Related studies showed that disturbances of the circadian system can lead to mood disorders (depression and anxiety) among patients with cancer[6-7].

Exogenous melatonin acts like a hormone from the pineal gland to regulate the sleep-awake cycle. Dysregulation of these circadian cycles was the main feature of

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major depressive disorders[8]. The patterns of mood disorders showed periodic manifestation. Mood disorders such as major depressive disorders, bipolar disorders and seasonal affective disorders (SAD) would be associated with the dysregulation of circadian function from the alteration of melatonin secretion[9-11]. Therefore, supplementing exogenous melatonin might maintain physiologic responses. Moreover, melatonin can regulate dopamine signaling in the forebrain, and hypothalamic and hippocampal areas[12-13]. Regarding this, dopamine is not only the precursor of noradrenaline, but also is involved in the circadian regulation of melatonin production via activation of dopamine D4 receptors by noradrenergic signals[14-15]. According to the theory of depression regarding the neuroplastic hypothesis, melatonin may correct the imbalance of the glutamatergic system among patients with mood disorders and increase neuroplasticity in the central nervous system[16-17].

The roles of melatonin on circadian rhythms and psychotic symptoms including depression were discussed in recent studies[18-19]. Melatonin used in improving mood disorders among patients with cancer has limited outcomes. Furthermore, the effects of melatonin on mood scores demonstrated a variety of response due to the duration of treatment such as early response (1 to 4 weeks), acute phase response (6 to 12 weeks) and follow-up response (16 to 24 weeks)[20]. Although several studies showed benefits of melatonin in improving mood disorders, no related systematic study has summarized the magnitude of the effect of melatonin for such indications among patients with cancer. Thus, this meta-analysis sought to determine the efficacy of melatonin in improving mood disorders of patients with cancer and cancer-related illness in terms of depression symptom and emotional well-being in both short and long term treatment.

2. MATERIALS AND METHODS

2.1. Search strategy

This meta-analysis was registered at PROSPERO NO. CRD42023393024. PubMed, Embase and Cochrane Central Register of Controlled Trials were searched from inception until August 2022 using the following terms: ((cancer) OR (neoplastic) OR (neoplasm*) OR (tumor) OR (carcinoma*) OR (sarcoma*) OR (malignan*)) AND (melatonin)) AND ((mood) OR (depress*) OR (anxiet*)). The language was limited to English. The reference lists of reviews and the retrieved articles were also searched manually, while abstracts and unpublished reports were not considered.

2.2. Inclusion and exclusion criteria

Clinical randomized controlled trials (RCTs) of cancer and cancer-related patients (both adults and children) were included. The intervention of the included studies was melatonin while the comparator was placebo. The outcome indicators of each study had to include depression symptoms: Beck Depression Inventory index (BDI) and emotional well-being (EWD score). Interventions that were not coordinated or provided by a specialized team were excluded. Clinical record form (CRF) and quality of life (QOL) had to be evaluated by relevant questionnaires. CRF and QOL that were not assessed using standardized and validated questionnaires were also excluded. Cross-sectional and qualitative studies as well as pilot studies were excluded. When duplicate articles from the same institution were reported, either the better quality or most recent publication was included unless the endpoints were mutually exclusive or measured at different time intervals. Animal studies, lack of approval of the local ethics committee, incomplete outcome data and undetermined study type were excluded.

2.3. Study selection

Data were selected independently by four reviewers (JT, BS, PA and UP), who screened all titles, abstracts and full articles that were retrieved from the electronic databases. The full-text articles were obtained through the Chiang Mai University catalog and open sources. The reviewers read the full papers independently before they were included, and any disagreement was solved by discussion.

2.4. Data extraction and synthesis

Data were extracted independently by three of the authors (JT, PA and BS), who consulted each other to resolve any disagreements. The following data were extracted (the name of the first author, country and year of publication, intervention measures in the intervention group, numbers of patients, intervention measures in the control groups and length of follow-up). In addition, depression outcome measured by BDI score and emotional wellbeing outcome were extracted. Outcomes were classified in two levels according to treatment duration: less than 12 weeks (short term) and equal to or more than 12 weeks (long term).

2.5. Risk-of-bias assessment

The quality of the included studies was assessed using Version 2 of the Cochrane risk-of-bias tool for randomized trials (RoB 2). This tool contains five domains: 1) randomisation process, 2) deviation from intended interventions, 3) missing outcome data, 4) measurement of the outcomes and 5) selection of the reported results. Each domain is rated as 'high bias', 'low bias' or 'unclear'. Finally, the overall risk is rated as 'low risk', 'some concerns' and 'high risk'.

2.6. Data analysis

Statistical analyses were conducted following the recommendations of the Cochrane guidelines. For continuous data, the BDI scores were pooled in a meta-analysis. The *p*-value <0.05 indicated statistically significant differences. STATA® Software, Version 14.0 (license Pharmacy CMU serial number 301406219300) was employed to analyze and produce forest plots using a random-effects model due to clinical heterogeneity across the studies. The heterogeneity of the studies was assessed using I^2 and the *p*-value. Presenting an $I^2 \geq 50\%$ and *p*-value<0.05 identified a statistical heterogeneity. Mean difference and standard deviation were presented. Data were analysed according to time of outcome measures as short term (<12 week or ≥12 week of follow-up).

3. RESULTS

3.1. Study characteristics

Of a total of 1,202 articles from the literature search, 430 articles were found from PubMed, 706 articles from Embase and 66 articles from Cochrane. After deleting the duplicate and excluding nonhuman research, 24 articles remained for full review. Articles involving protocol registration, incomplete trials and irrelevant results were excluded. The remaining four articles with 966 participants were included in the final analysis (Figure 1).

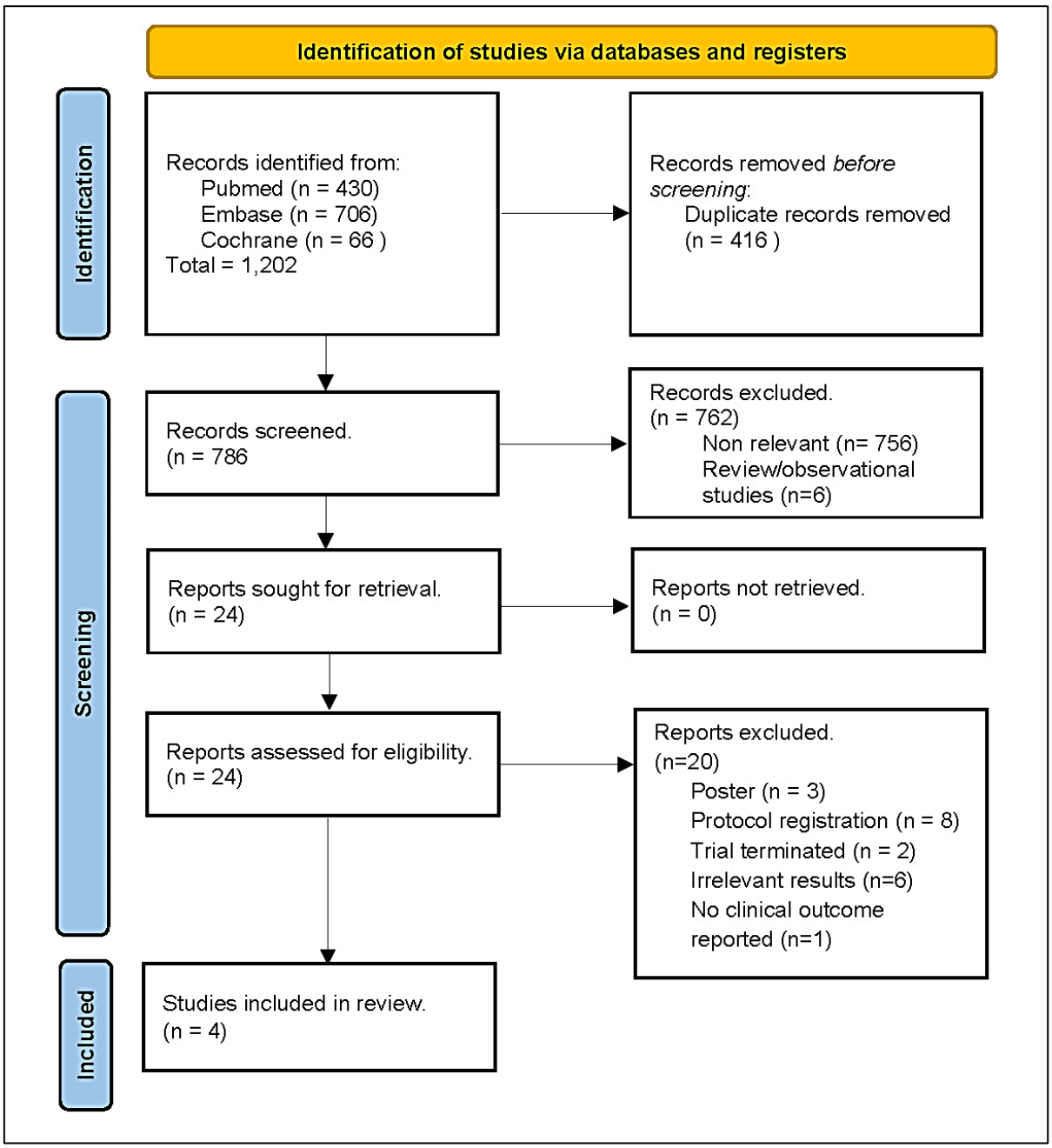

Figure 1. PRISMA flow diagram of the selection of studies to be included in the systematic review and meta-analysis.

Table 1. Characteristics of studies included in the meta-analysis.

Author	Country	Study design	Total number of patients	Characteristics of patients						
				Disease	Intervention (mg)	Number of patients using melatonin	Age (SD) (years)	Female (%)	Duration of intervention (weeks)	Time to follow-up (weeks)
Palmer ACS, et al. 2019[21]	Brazil	Randomized double blinded placebo-controlled trial	36	Breast cancer	Melatonin 20 mg	18	54.2 (10.6)	100.0	10 days	1, 2
Seely D, et al. 2021[22]	Canada	Randomized double blinded placebo-controlled trial	709	NSCLC eligible for complete surgical resection	Melatonin 20 mg for one year post-surgery	356	67.2 (8.5)	53.4	48	48, 96
Shabani A, et al. 2019[23]	Iran	Randomized, double-blind, placebo-controlled trial	60	PCOS	Melatonin 10 mg	30	26.5 (3.5)	100.0	12	12
Sookprasert A, et al. 2014[24]	Thailand	Randomized, double-blind, placebo-controlled trial	151	Advanced NSCLC received treatment	Melatonin 10 mg	51	56.8 (9.4)	31.7	24	8, 12, 28
					Melatonin 20 mg	53	56.3 (8.8)	39.6		

The characteristics of the included studies in this study are shown in Table 1. The patients' ages ranged from 23.0 to 75.7 years. Most patients were female. Type of diseases included breast cancer, nonsmall cell lung cancer (NSCLC) eligible for complete surgical resection, advanced NSCLC receiving treatment and polycystic ovary syndrome (PCOS). All studies used melatonin as depressive prevention. The duration of intervention ranged from 1.4 to 48 weeks. The time of follow-up ranged from 10 days to 96 weeks. Three studies (75%) were long term duration while one study involved short term duration (25%).

3.2. Quality of included studies

For quality assessment, each domain of all studies was rated as low bias. The overall risk of bias of all included studies was low risk. The summary of quality assessment is shown in Figure 2.

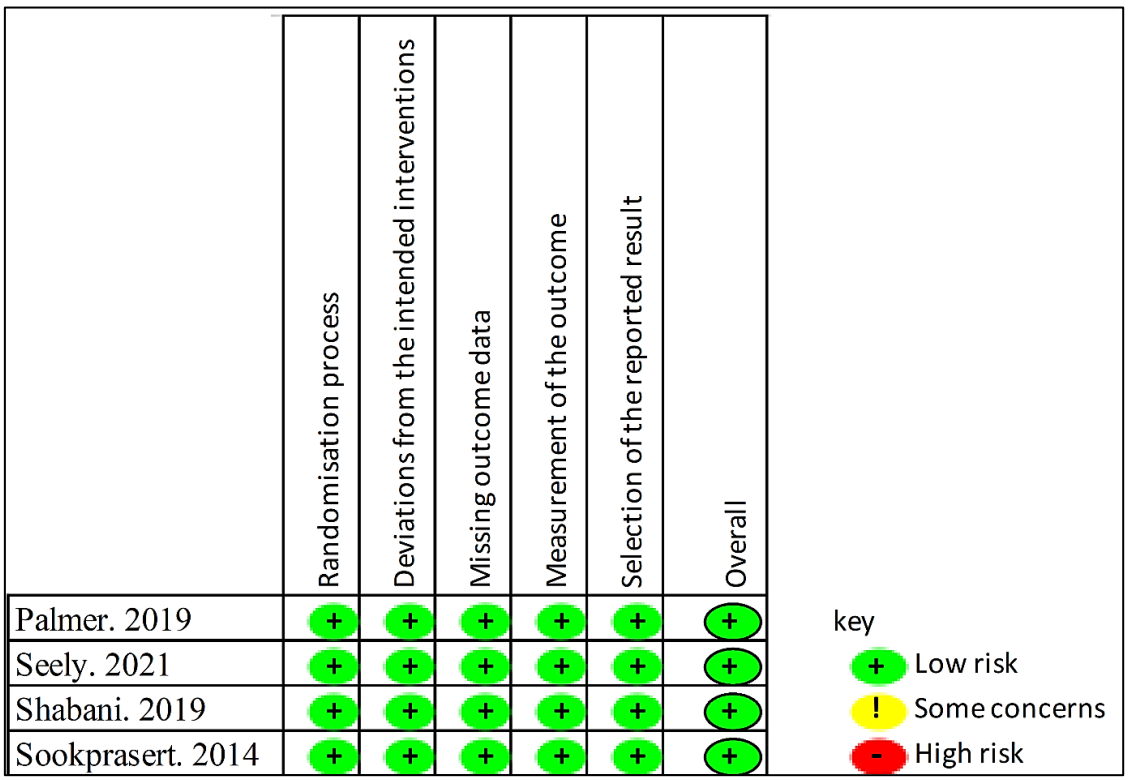

Figure 2. Risk of bias assessed using Version 2 of the Cochrane risk-of-bias tool for randomized trials (RoB 2).

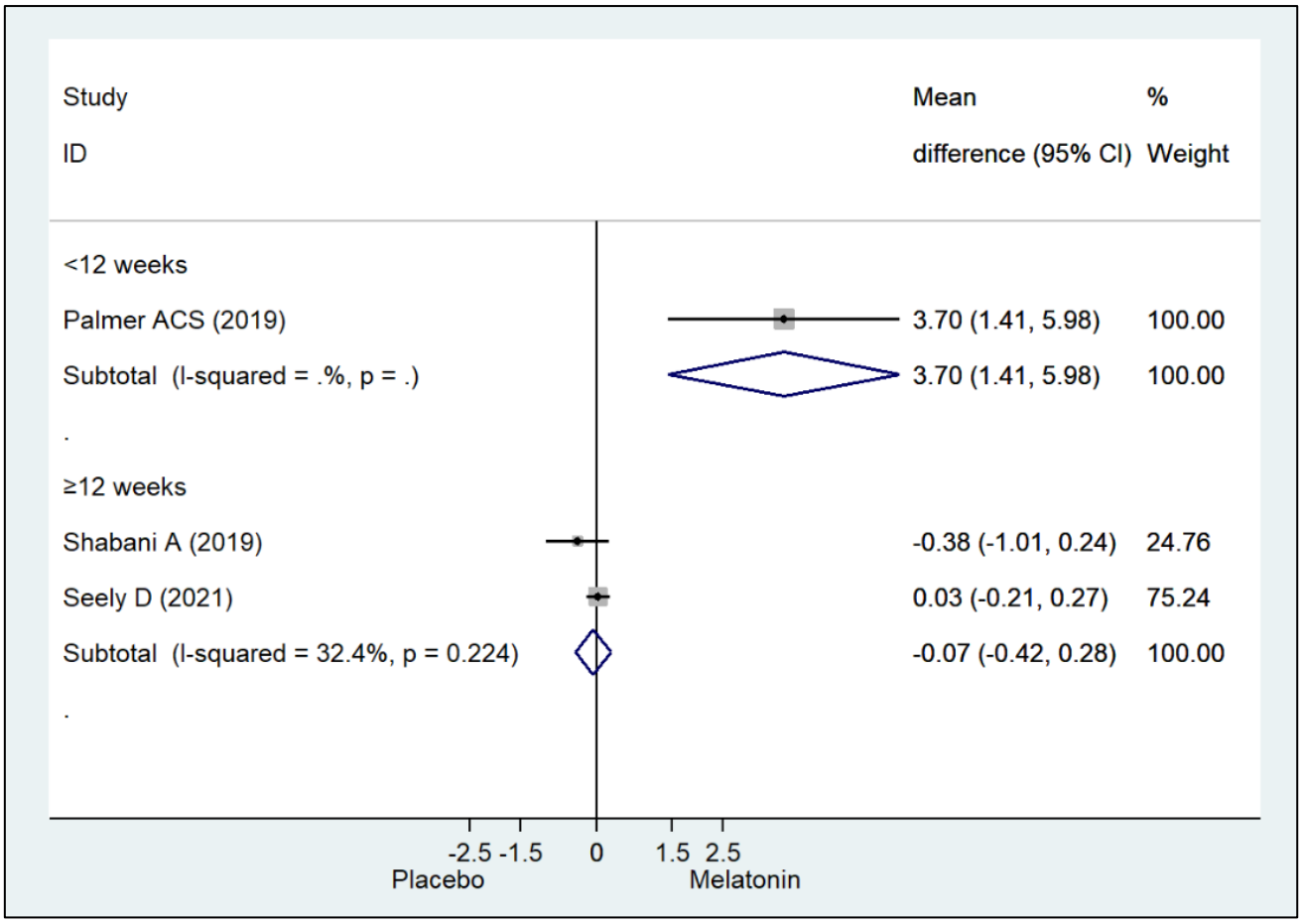

Figure 3. Forest plot of depression outcomes in mean difference (95% CI).

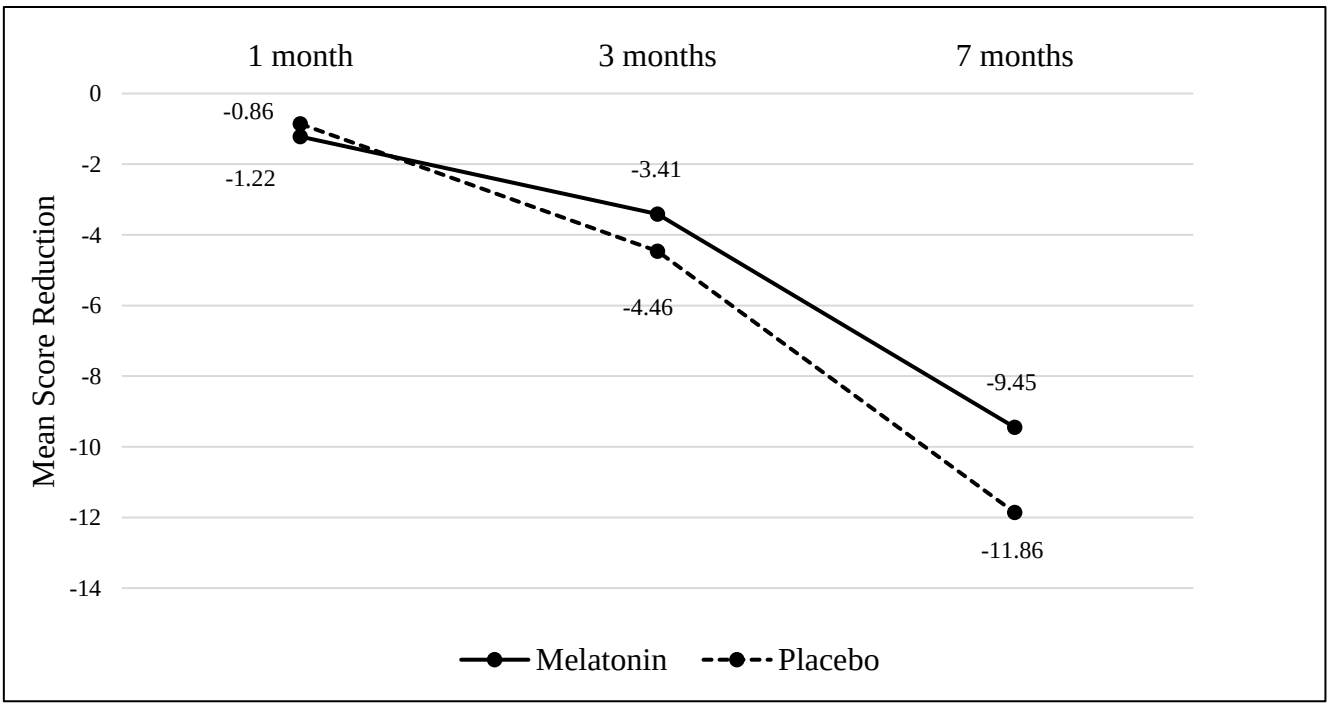

Figure 4. Mean score difference of emotional wellbeing outcomes.

3.3. Outcomes

3.3.1. Depression outcome

Depression outcome in terms of BDI score was reported in three RCTs. The score was classified in two groups based on treatment duration: less than 12 weeks (short term) and equal to or more than 12 weeks (long term). One study was classified as short term treatment duration. The result showed that melatonin was associated with significantly reduced depression (WMD 3.67, 95% CI 1.41 to 5.98; p=0.002). However, two studied of long term treatment duration showed no difference in depression scores (WMD -0.072, 95% CI -0.42 to 0.28; p=0.68, I^2=32.4%) (Figure 3).

3.3.2. Emotional wellbeing outcome

The study of Sookprasert A, et al. reported data on emotional wellbeing outcomes measured by one domain using the Functional Assessment of Cancer Therapy-Lung (FACT-L). This outcome was classified in two groups according to treatment duration: short and long term. The melatonin group indicated a greater significantly reduced lower mean score in emotional wellbeing than that of the placebo group regarding the long term treatment duration at three months (mean difference 1.05, SD 0.22, 95% CI 0.63 to 1.47; p<0.001) and seven months (mean difference 2.41, SD 0.22, 95% CI 1.97 to 2.85; p<0.001). However, the effect of melatonin on emotional wellbeing did not show in the short term duration compared with placebo (mean difference -0.36, SD 0.19, 95% CI -0.73 to 0.01). All results are shown in Figure 4.

4. DISCUSSION

Our findings indicated adding exogenous melatonin to patients with cancer and cancer-related diseases could improve depression and emotional wellbeing. The subgroup analysis by duration of melatonin use among patients with cancer and cancer-related diseases was demonstrated in this study. Melatonin treatment for depression appeared effective when used for a brief period (<12 weeks). In addition, long term (≥12 weeks) administration of melatonin could enhance the emotional health of these patients.

Rao W, et al. reported that psychological distress is frequently reported in chronic diseases including patients with cancer and cancer-related diseases (20%). Patients with cancer were more likely to experience psychological distress than those with chronic diseases because of the aggressive medical treatment and higher morbidity rate; this carries more psychological pressure than less lethal chronic diseases[25]. The different types or stages of cancer and duration of treatment might affect depression and mood disorder[3,5]. BDI-II is a self-report measurement of depressive symptoms, which is reliable but not specific to patients with cancer and cancer-related diseases. Although this tool is not specific to cancer, it has been used by various oncology studies in a variety of settings[25]. We found three studies reporting depression outcome using BDI score. The validity test of BDI score among patients with cancer at an outpatient neuropsychiatric unit showed sensitivity of 87% and specificity of 73%. These values are acceptable for screening and monitoring depression symptoms in both nononcology and oncology patients[26]. The study recommends a duration treatment of melatonin in insomnia until 13 weeks in elderly populations aged >55 years[27]. The suggested duration of melatonin treatment is adequate to demonstrate the significant effect of depression improvement in cancer and cancer related diseases. Several clinical trials have proven that exogenous melatonin reveals antidepressant properties up to 12 weeks[28-30]. However, the study of Chen WY, et al. employing a lower dose of melatonin, 3 mg, was assessed using the Center for Epidemiologic Studies-Depression (CES-D) scale on mood in postmenopausal breast cancer. It indicated that the use of melatonin at four months didn't improve depression[31].

In addition to mood improvement, melatonin use yields better emotional wellbeing, performance status and quality of life[32]. The study of Maprasert W, et al. reported that adding melatonin to standard treatment can improve quality of life measured using the Thai Functional Assessment of Cancer Therapy-Hepatobiliary (FACT-HEP) scores among patients with nonresectable cholangiocarcinoma[33]. Our findings also showed that melatonin could improve emotional wellbeing of patients with cancer and cancer-related diseases in long term treatment. The study among consecutive untreated patients with metastatic NSCLC showed that patients treated with chemotherapy and melatonin exhibited better survival at 12 months. Three of 49 patients (6%) experienced a five-year survival[34]. Therefore, melatonin could improve quality of life because of prolonging the survival time of patients with cancer. Its biological and psychological properties could prevent cancer-related cachexia and synergize the efficacy of chemotherapy[35-36].

In addition to mood improvement, melatonin also provides additional benefits in cancer such as anti-inflammation, anti-oxidant, and anticancer effects[37-38]. The anticancer effects of melatonin have been studied in various types of cancers such as prostate cancer, NSCLC or leukaemia[37-40]. Melatonin showed differential regulation of the cell cycle, cell survival and metabolism in malignant cells in contrast to normal cells[39]. As it acts as a strong anti-oxidant, it scavenges free radicals, prevents cell proliferation and activates an apoptotic response. Moreover, *In vitro* experiments involving melatonin showed synergistic cytotoxicity in leukemia cells when combined with doxorubicin, everolimus or barasertib. Melatonin was accompanied by strong

induction of apoptosis and decreased ROS level in only leukemia cells, without affecting normal lymphocytes[38]. Those data suggested that melatonin constitutes a promising supplement in chemotherapy which might help increase anticancer efficacy and reduce or minimize their adverse reactions.

The study encountered several limitations. The instruments used to measure mood and depression varied among the three RCTs. The most common tools comprised BDI score, HADS score, HAMA or HAMD score or self-rating depression scales. Only BDI scores were reported for all three studies. BDI score was a self-reported assessment, so its reliability might not be comparable with physician assessment[41]. However, the trend of BDI score for all three studies was likely to indicate that melatonin could be used in the depression compared with the placebo group. Thus, BDI score could be used to represent the efficacy of melatonin on mood among patients with cancer. Next, cancer stage impacted depression and emotional wellbeing of patients[25]. All patients in included studies were under different stages and cancer types. Our findings could not conclude the appropriate time of initiating melatonin in the cancer treatment. Finally, the types of cancer and cancer-related diseases in all included studies were limited to only breast cancer, NSCLC and PCOS. Hence, our findings cannot be generalized to other types of patients with cancer and cancer-related diseases.

5. CONCLUSION

Adding melatonin treatment among patients with cancer and cancer-related diseases significantly improved mood disorders. The effects depended on melatonin treatment duration. Depression was significantly improved in short term treatment for breast cancer only, while emotional wellbeing was improved in long term treatment for NSCLC and PCOS. Moreover, additional clinical study is required to further confirm the benefit of melatonin.

6. ACKNOWLEDGEMENT

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Conflict of interest
They authors have none to declare.

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Author contribution
JT, BS and PA conceptualized, while JT, BS, PA and UP extracted the data. JT, PD and BS performed quality assessment, and UP, PD and BS conceived and designed the analysis. UP, PD and JY contributed analysis tools, while JT, UP and BS prepared original manuscript. JT and BS performed visualization and the table in Results section. JT, BS and UP discussed the results, and all authors have read and agreed to the final manuscript.

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