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REVIEW

Melatonin supplementation and pro-inflammatory mediators: a systematic review and meta-analysis of clinical trials

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Abstract

Background Inflammatory processes are involved in chronic diseases. It has been suggested that melatonin reduces inflammation by its radical scavenging properties; however, the results of the previous studies are inconclusive. The objective of the present meta-analysis is to determine the direction and magnitude of melatonin supplementation effect on inflammatory biomarkers.

Methods Databases including PubMed, Scopus, Cochran Library, Embase, and Google Scholar were searched up to April 2019. Meta-analysis was performed using random-effect model. Subgroup analysis, sensitivity analysis, and meta-regression were also carried out.

Results Thirteen eligible studies with 22 datasets with total sample size of 749 participants were included in the meta-analysis. Melatonin supplementation significantly decreased TNF-α and IL-6 levels [(WMD = − 2.24 pg/ml; 95% CI − 3.45, − 1.03; $P < 0.001$; $I^2 = 96.7\%$, $P_{\text{heterogeneity}} < 0.001$) and (WMD = − 30.25 pg/ml; 95% CI − 41.45, − 19.06; $P < 0.001$, $I^2 = 99.0\%$; $P_{\text{heterogeneity}} < 0.001$)], respectively. The effect of melatonin on CRP levels was marginal (WMD = − 0.45 mg/L; 95% CI − 0.94, 0.03; $P = 0.06$; $I^2 = 96.6\%$, $P_{\text{heterogeneity}} < 0.001$).

Conclusion The results of the present meta-analysis support that melatonin supplementation could be effective on ameliorating of inflammatory mediators.

Keywords Melatonin · Inflammation · Tumor necrosis factor-α · C-Reactive protein · Interleukin-6 · Meta-analysis

Introduction

Interleukin 6 (IL-6), tumor necrosis factor alpha (TNF-α), and C-reactive protein (CRP) are the most noticeable inflammatory indicators that are released by adipocytes and are increased in chronic diseases [1, 2]. High circulating level of these inflammatory biomarkers is associated with cardiovascular complications, insulin resistance, anemia, hyperlipidemia, metabolic syndrome, type 2 diabetes, cancer, infertility, etc. [3]. It has been shown that antioxidants supplementation in humans decreases mediators of inflammation and oxidative stress such as IL-6 and TNF-α [4]. An improvement in the identification of different types of antioxidants and evaluating their direct and indirect effects on inflammation in chronic diseases can help practitioners to develop innovative approaches to treat the inflammation status.

Melatonin (*N*-acetyl-5-methoxytryptamine), an endogenous antioxidant, is a tryptophan derivative which is mostly produced by pineal gland and has a key role in the regulation of daily rhythms and physiological changes with alterations in day length [5, 6]. Exogenous intake of melatonin can directly reduce oxidative stress by negation of the hydroxyl radicals and also plays a key role in inhibition of cell proliferation, inflammation, and apoptosis. Furthermore, melatonin can improve the potential function of antioxidants enzymes such as glutathione (GSH), glutathione peroxidase,

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and superoxide dismutase (SOD) indirectly. In addition, melatonin reduces the translocation of nuclear factor-kB and production of pro-inflammatory mediators [5, 7]. Melatonin has been considered as a food supplement without any serious adverse effects or toxicities [8].

Thus, it is valuable to evaluate whether supplementation of this antioxidant would improve inflammation status. Former studies have suggested a positive impact of melatonin supplementation on improvement in inflammation biomarkers, however, there was no comprehensive systematic review and meta-analysis perusing the strength of the data that support this effect. Therefore, the present meta-analysis was conducted to assess the magnitude of melatonin supplementation effect on inflammatory biomarkers levels.

Methods

Search strategy

This study was undertaken according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and Cochrane handbook for systematic reviews of interventions [9, 10]. Two independent authors systematically searched literature in SCOPUS, PubMed, Cochrane Library, Embase, and Google scholar databases before April 11, 2019. The following search terms were used in the current study: Melatonin (including MeSH search using "Melatonin" and keyword search using word "Melatonin") and terms related to inflammation (including MeSH search using "C-Reactive Protein", "Tumor Necrosis Factor-alpha", "Interleukin-6", and keyword search using words "C-Reactive Protein", "CRP", "hs-CRP", "high sensitivity-CRP", "high sensitivity C-Reactive Protein", "Tumor Necrosis Factor-alpha", "TNF-alpha", "Tumor Necrosis Factor-α", "TNF-α", "Interleukin-6", "IL-6") and terms related to study design (including publication type search using "Randomized controlled trial", "Controlled Clinical Trial", and keyword search using words "Randomized", "Randomly", "Placebo", "Trial", "Groups"). The search was also completed by manual search of the references list of clinical trials and previous review articles to include other potentially eligible trials. Language restrictions were not applied for all search sections. Discrepancies were resolved through discussion between reviewers until consensus was reached.

Study selection

Randomized controlled trials investigating the effect of melatonin supplementation on inflammation levels were included in the study. Human studies were included if they met the following criteria, including: (1) population: adults (age ≥ 18 years); (2) intervention: oral supplementation with melatonin compared to placebo group; (3) outcome: reporting enough data about intended outcomes (CRP, TNF-α, IL-6) at baseline and at the end of the study in each group; (4) study design: randomized clinical trial with either parallel or crossover design lasting at least for 4 weeks. Literature reviews, observational studies, case reports, republished data, and molecular and animal studies were excluded. After removal of duplicates, two reviewers independently screened studies by title, abstract, and full text as applicable for inclusion.

Data extraction and quality assessment

Two reviewers independently screened and extracted study characteristics from the original articles, including first author, country, year, study population, sex, sample size, melatonin dose, treatment duration, and outcome data. Moreover, mean and standard deviation (SD) of the inflammatory markers (CRP, TNF-α, IL-6) at baseline and end of intervention were extracted. Any disagreements were resolved by discussion with a third reviewer. The quality of included trials was assessed according to the parameters proposed by Jadad et al. [11]. Studies with scores greater than or equal to 3 were classified as "high" quality studies and less than or equal to 2 were classified as "low" quality studies. Also, Cochrane Collaboration criteria were used for evaluation of trials quality.

Statistical analysis

A random-effect model was used to compensate for the heterogeneity of studies in terms of demographic characteristics of included populations. Heterogeneity was evaluated using the I^2 index ($I^2 \geq 50\%$ indicates heterogeneous data and $I^2 < 50\%$ indicates non-heterogeneous data) [9]. Stata 14.0 (Stata Corporation, College Station, TX) was used for performing the analysis of this study. Effect size was defined as weighted mean difference (WMD) and 95% confidence interval (CI). Standard deviation was calculated when the information was reported as standard error of the mean (SEM) by multiplying SEM by the square root of the sample size. The effect sizes of meta-analysis were calculated based on mean differences and their corresponding standard deviations (SDs) of changes in inflammation markers for intervention and control groups [12]. To investigate the influence of each study on the overall effect size, sensitivity analysis was conducted using the leave-one-out method. To identify potential sources of heterogeneity, predefined subgroup analysis was conducted based on melatonin dosage, trial duration, and mean age of participants. In addition, we evaluated the presence of publication bias with the Begg's adjusted rank correlation and Egger's regression

asymmetry tests [13, 14]. Meta-regression analysis was done by a restricted maximum likelihood (REML) for potential confounders, including mean age of participants, trial duration, and melatonin dosage to investigate their relation to the estimated effect size for outcomes. This method corresponds to random-effects meta-regression comprising both withinstudy variances of treatment effects and the residual betweenstudy heterogeneity. Covariates for the meta-regression analysis were defined based on evidence-based knowledge. $P < 0.05$ was considered as significance level.

Results

Study characteristics

A total number of 694 articles were obtained from the electronic search of databases. After removing 167 duplicate citations, 527 articles went under evaluation by screening of titles and abstracts. Finally, the full text of 54 articles was assessed carefully, among which, 13 studies with 22 datasets fully met our specified inclusion criteria and were enrolled in the meta-analysis. The PRISMA flow chart of the study is shown in Fig. 1. Nine studies were on CRP, seven studies were on TNF-α, and six studies were on IL-6. Included trials were done during 1996–2018. All studies were randomized, double-blinded, and placebo-controlled with parallel design. Seven studies were performed in Iran [15–21], three in Poland [22–24], one in Italy [25], UK [26], and Mexico [27]. A total of 749 participants were enrolled in studies. Mean age in intervention group varied from 33 to 66 years. Intervention duration ranged from 4 to 60 weeks. All trials administered melatonin orally and the administration dose varied from 3 to 25 mg/day. Characteristics of the included studies are shown in Table 1.

Effect of melatonin on CRP

The results of random-effect analysis showed that melatonin supplementation has a marginal effect on CRP levels (WMD = − 0.45 mg/L; 95% CI − 0.94, 0.03; $P = 0.06$) (see Fig. 2). A remarkable between-study heterogeneity was observed ($I^2 = 96.6\%$, $P < 0.001$), which we were unable to find the source. The results of subgroup analysis indicated no significant difference, however, the results of sensitivity analysis after removing of studies by Forrest et al. [26] and Chojnachi et al. [23], which had outlier results, showed a significant decrease in CRP levels (WMD = − 0.41; 95% CI − 0.78, − 0.04, $P = 0.028$). In the meta-regression analysis, the effect of melatonin on CRP

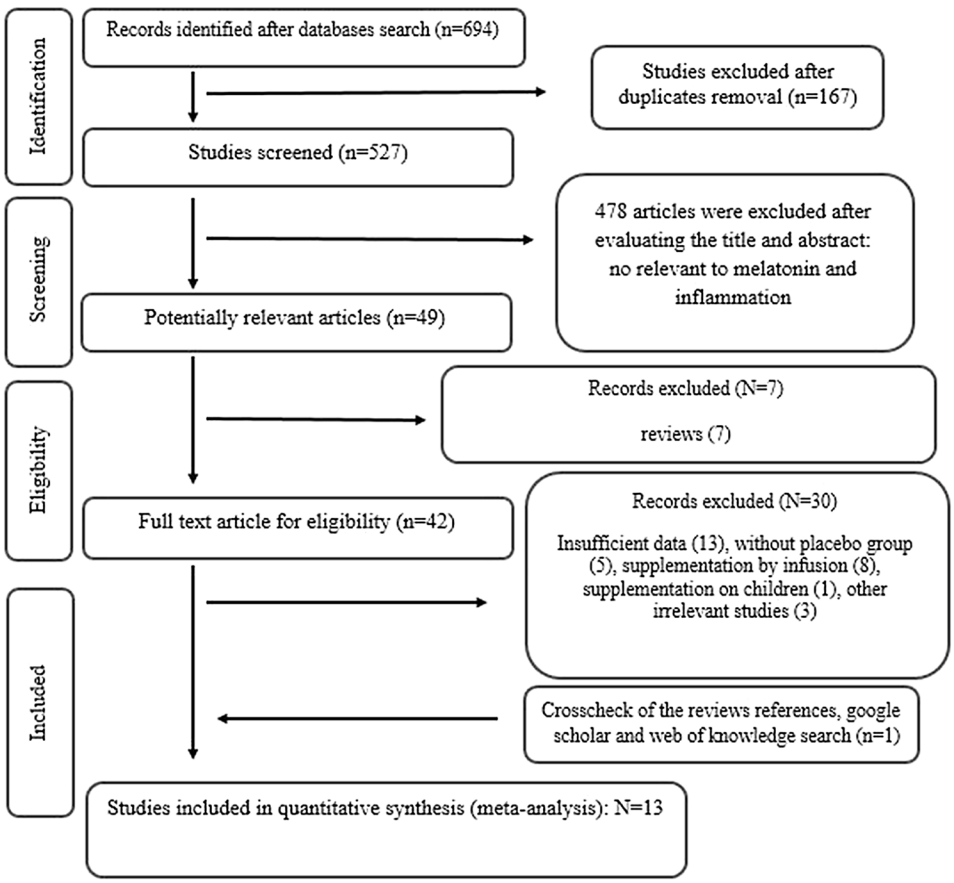

Fig. 1 The PRISMA flow chart of the study

Table 1 Characteristics and baseline measurements of included studies

Study	Lissoni P	Forrest CM	Cichoz-lach H	Chojnacki C	Mesri AN	Celinski K	Javanmard SH	Pakravan H	Raygan F	Bazyar H	Ghaderi A	Taghavi A	Sanchez-Lopez A
Location	Italy	UK	Poland	Poland	Iran	Poland	Iran	Iran	Iran	Iran	Iran	Iran	Mexico
Year	1996	2007	2010	2011	2014	2014	2016	2017	2017	2018	2018	2018	2018
Patient Features	Metastatic patients	RA	Steatohepatitis	UC	Obese women	NAFLD	CABG candidates	NAFLD	T2DM	T2DM	MMT patients	Children with AT	MS
Gender	Both	Both	Both	Both	Female	Both	Both	Both	Both	Both	Male	Both	Both
Sample size (*n*)	86	75	30	60	44	46	39	97	60	44	54	70	33
No. melatonin group	45	37	15	30	22	23	20	49	30	22	26	35	17
No. placebo group	41	38	15	30	22	23	19	48	30	22	28	35	16
Mean age (year)	66	65	35	35	33	36	60	42	65	51	42	9	51
Duration (week)	12	26	4	52	6	60	4	12	12	8	12	6	26
Melatonin dosage (g/day)	20	10	10	5	6	10	10	3	10	6	10	6	25
Baseline CRP (mg/L)													
Case	–	413.4 ± 69.5	–	34.9 ± 14.0	2.54 ± 0.49	–	2.02 ± 0.3	–	4.0 ± 2.3	2.53 ± 0.77	5.3 ± 2.4	1.5 ± 0.7	–
Control	–	281.7 ± 51.2	–	38.5 ± 12.9	2.37 ± 0.48	–	1.87 ± 0.24	–	3.6 ± 3.7	2.31 ± 0.96	6.3 ± 2.8	1.6 ± 0.8	–
Final CRP (mg/L)													
Case	–	340.2 ± 112.8	–	41.7 ± 21	1.67 ± 0.27	–	1.84 ± 0.26	–	NR	NR	4.3 ± 2	1.5 ± 0.6	–
Control	–	142.6 ± 36.6	–	131.3 ± 60.8	1.44 ± 0.21	–	1.99 ± 0.16	–	NR	NR	7 ± 4	1.5 ± 0.7	–
Baseline TNF (pg/ml)													
Case	43.16 ± 41.38	149.11 ± 37.28	2.43 ± 0.68	–	3.52 ± 0.72	2.56 ± 0.43	–	–	–	9.05 ± 3.56	–	–	40.5 ± 2.2
Control	38.88 ± 37.97	165.08 ± 71.01	2.82 ± 0.52	–	2.82 ± 0.52	2.68 ± 0.59	–	–	–	8.65 ± 3.87	–	–	40.9 ± 1.9
Final TNF (pg/ml)													
Case	18.99 ± 57.42	72.78 ± 37.27	1.52 ± 0.07	–	1.73 ± 0.07	1.38 ± 0.27	–	–	–	NR	–	–	33.2 ± 3.6
Control	50.34 ± 33.48	81.65 ± 33.73	2.01 ± 0.38	–	2.01 ± 0.38	2.25 ± 0.69	–	–	–	NR	–	–	41.7 ± 1.9
Baseline IL-6 (pg/ml)													
Case	–	8500.09 ± 1172.64	26.11 ± 6.32	–	27.12 ± 6.32	23.41 ± 6.38	–	–	–	2.0 ± 0.92	–	–	712.1 ± 43
Control	–	6618.18 ± 872.73	24.73 ± 6.50	–	24.73 ± 6.51	23.44 ± 6.78	–	–	–	2.16 ± 0.91	–	–	718.6 ± 58

Table 1 (continued)

Study	Lissoni P	Forrest CM	Cichoz-lach H	Chojnacki C	Mesri AN	Celinski K	Javanmard SH	Pakravan H	Raygan F	Bazyar H	Ghaderi A	Taghavi A	Sanchez-Lopez A
Final IL-6 (pg/ml)													
Case	–	8000 ± 2036.4	17.32 ± 4.9	–	16.34 ± 6.32	18.01 ± 4.58	–	–	–	NR	–	–	465.1 ± 61
Control	–	9018.18 ± 1309.12	21.11 ± 5.9	–	21.11 ± 5.94	22.65 ± 6.72	–	–	–	NR	–	–	704.7 ± 38
Jadad score	1	4	1	2	3	1	4	5	5	5	5	5	5

Values are expressed as mean ± SD

RA rheumatoid arthritis, *UC* ulcerative colitis, *NAFLD* non-alcoholic fatty liver disease, *CABG* coronary artery bypass graft, *T2DM* type 2 diabetes mellitus, *NR* are not reported, the studies by Raygan et al. and Bazyar et al. did not report final mean ± SD for the variables, but reported mean changes (end – before) ± SD

levels was not modified by mean age, trial duration, and melatonin dosage (supplemental files 1–3). There was no publication bias either with Begg's ($P = 1.000$, $z = 0.00$) or with Egger's tests ($P = 0.997$, t = 0.0) (supplemental file 4).

Effect of melatonin on TNF-α

There was a significant reduction in TNF-α levels following melatonin supplementation using random-effect analysis (WMD = − 2.24 pg/ml; 95% CI − 3.45, − 1.03; $P < 0.001$) (see Fig. 3). A significant between-study heterogeneity was detected ($I^2 = 96.7\%$, $P < 0.001$). Subgroup analysis revealed that melatonin supplementation was more effective when intervention duration was ≥ 12 weeks (WMD = − 8.28 pg/ml; 95% CI − 15.01, − 1.55; $P = 0.01$). Moreover, melatonin supplementation was more efficient at the daily dosages of ≥ 10 mg than lower doses (WMD = − 3.56 pg/ml; 95% CI − 5.69, − 1.44; $P = 0.001$) (see Table 2). Also, the results were not significant in patients with age > 50 years ($P = 0.4$) in the sensitivity analysis, no single study remarkably affected on the effect size. In the meta-regression analysis, the effect of melatonin on TNF-α levels was not modified by mean age, trial duration, and melatonin dosage (supplemental files 5–7). No publication bias was detected with performing Begg's ($P = 1.00$, $z = -0.24$) and Egger's tests ($P = 0.237$, $t = -1.34$) (supplemental file 8).

Effect of melatonin on IL-6

Melatonin supplementation significantly decreases IL-6 levels using random-effect analysis which was accompanied with a high between-study heterogeneity (WMD = − 30.25 pg/ml; 95% CI − 41.45, − 19.06; $P < 0.001$, $I^2 = 99.0\%$; $P_{\text{heterogeneity}} < 0.001$) (see Fig. 4). The results of subgroup analysis demonstrated that melatonin supplementation is more impressive in patients with mean age of < 50 years (WMD = − 44.48 pg/ml; 95% CI − 61.01, − 27.95; $P < 0.001$). Moreover, intervention duration ≥ 12 weeks and melatonin dosage ≥ 10 mg/day had more potent effects [(WMD = − 551.27 pg/ml; 95% CI − 795.28, − 307.25; $P < 0.001$) and (WMD = − 83.74 pg/ml; 95% CI − 115.99, − 51.49; $P < 0.001$), respectively] (see Table 2). Sensitivity analysis indicated that after removing the Forrest study [26], the results were still significant (WMD = − 25.37 pg/ml; 95% CI − 35.10, − 15.64; $P < 0.001$). Meta-regression analysis showed no significant effects of mean age, trial duration, and melatonin dosage on the outcome (supplemental files 9–11). Publication bias was observed using Egger's test ($P = 0.023$, $t = -3.59$), but not with Begg's test ($P = 0.308$, $z = 1.02$) (supplemental file 12).

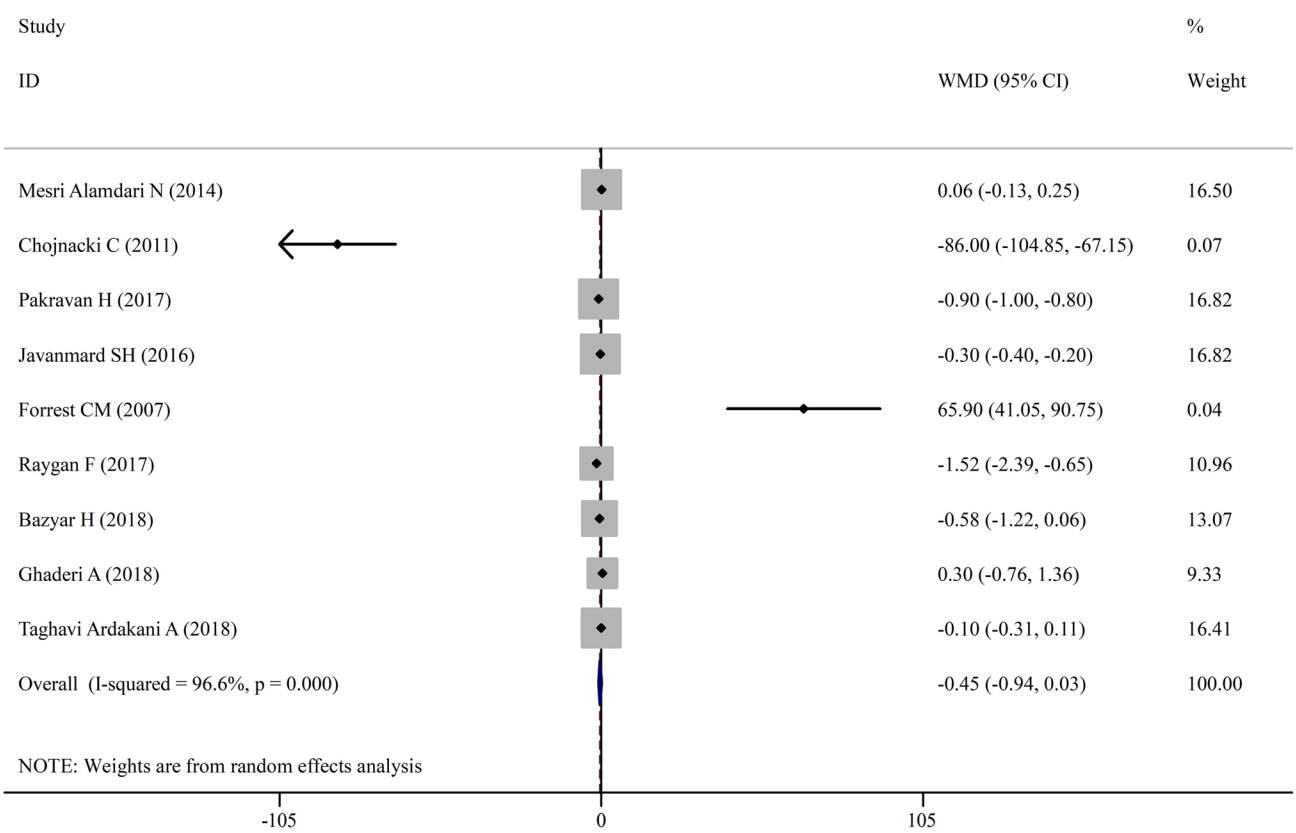

Fig. 2 The pooled effect of melatonin supplementation on CRP levels using random-effect analysis

Discussion

In the present systematic review and meta-analysis, we summarized available data from 13RCTs which examined the effect of melatonin supplementation on systematic inflammatory biomarkers as measured by pro-inflammatory agents (IL-6, TNF-α, CRP). The main result of this study was that, overall, melatonin supplementation significantly decreased TNF-α and IL-6 levels as compared the placebo group, however, CRP levels decreased marginally. Subgroup analysis showed that melatonin supplementation improved the levels of TNF-α and IL-6 more efficiently in studies which were carried out for ≥ 12 weeks and at a dosage ≥ 10 mg/day. Furthermore, there was a significant difference in CRP levels using sensitivity analysis.

Adipocytokines are types of bioactive molecules (including IL-6, TNF-α) which are mainly produced and secreted by adipose tissue [28]. CRP is a potent and dynamic systemic marker of low-grade inflammation produced in the liver [29, 30]. It should be noted that increased levels of IL-6, TNF-α, and CRP are thought to cause the development of many diseases such as insulin resistance, T2DM, and CVD [31, 32]. The use of drugs for improving chronic systemic inflammation can give avoidable side effects, while, nutraceuticals such as melatonin have been confirmed to be a beneficial approach to improve inflammation, because of their high tolerability and safety [33]. Accordingly, our findings might be important for clinicians to improve the clinical course of illnesses which have an inflammatory etiology. Melatonin is known as an anti-oxidant and immunomodulatory factor, plays a protecting role in different physiological and pathological procedures [34]. Several studies have demonstrated the potential anti-inflammatory role of melatonin. However, the mechanism of its effect is still unknown. Several probable mechanisms may explain it. It has been demonstrated that melatonin might have a potential role in the inhibition of prostaglandins production, synthesis of adhesion molecules [35, 36], and decreased concentrations of cyclooxygenase 2 expression in macrophages of leukocyte-endothelial bond and of leukocyte trans-endothelial cell migration [37–39] along with the decrease in the polymorphonuclear cell accumulation in the inflammatory location [36, 40]. In addition, excessive reactive oxygen production (ROS) contributes significantly to inflammation [41, 42]. Melatonin, due to its essential antioxidant characteristics by scavenging free radicals and activating endogenous antioxidant defense, could prevent inflammatory processes [43, 44].

Gut microbiota has been shown to influence the host inflammation and metabolic diseases [45], and some metabolic disorders are originated from the disruption in

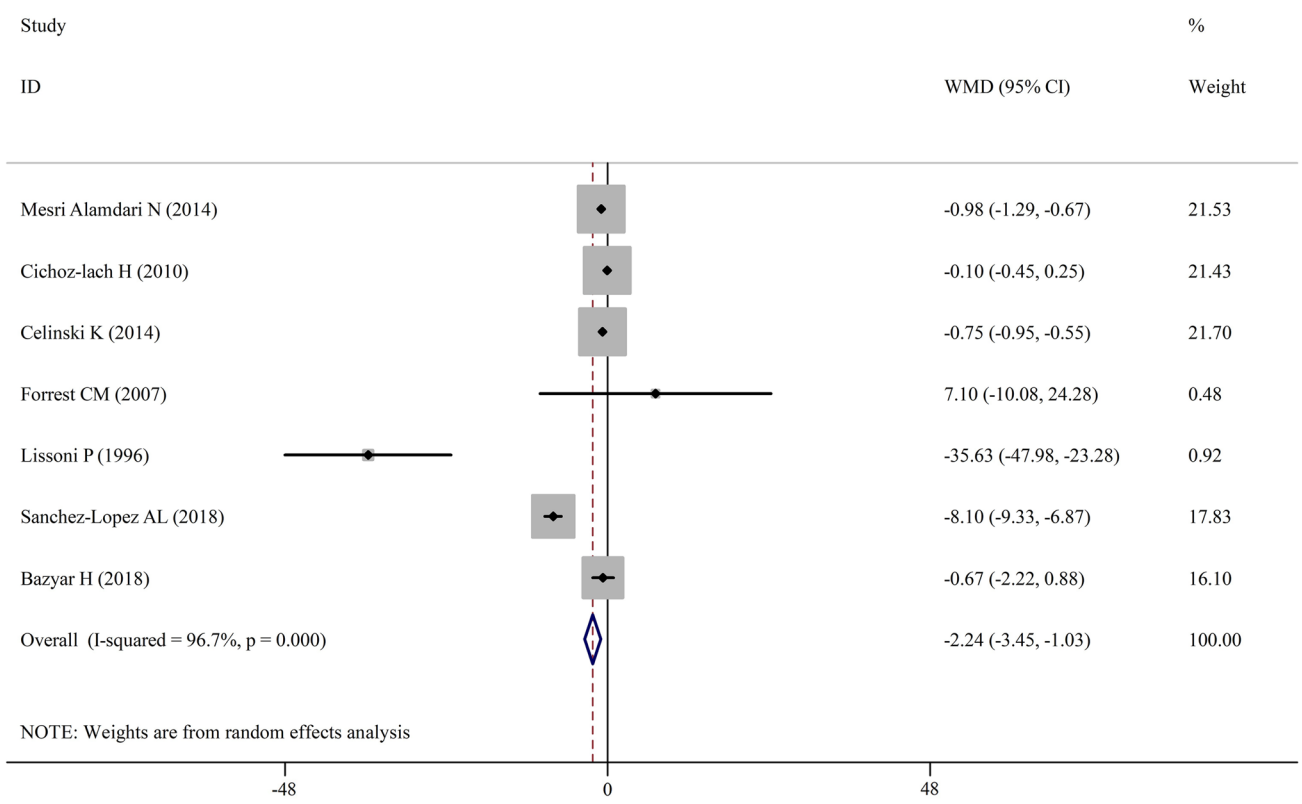

Fig. 3 The pooled effect of melatonin supplementation on TNF-α levels using random-effect analysis

Table 2 The result of subgroup analysis by age, intervention duration, and dosage

Biomarker	Subgroups		No. of studies	WMD (95% CI)	*P* value	*P* heterogeneity	I^2 (%)
CRP (mg/L)	Total		9	− 0.45 (− 0.94, 0.03)	0.06	< 0.001	96.6
	Mean age (year)	≥ 50	4	− 0.60 (− 1.86, 0.66)	0.35	< 0.001	91.5
		< 50	5	− 0.36 (− 1.17, 0.45)	0.38	< 0.001	97.8
	Intervention duration (week)	≥ 12	5	− 1.70 (− 4.56, 1.16)	0.24	< 0.001	96.5
		< 12	4	− 0.17 (− 0.38, 0.05)	0.13	0.005	76.4
	Melatonin dosage (g/day)	≥ 10	4	− 0.22 (− 1.87, 1.42)	0.79	< 0.001	91.7
		< 10	5	− 0.52 (− 1.29, 0.25)	0.18	< 0.001	97.8
TNF-α (pg/ml)	Total		7	− 2.24 (− 3.45, − 1.03)	< 0.001	< 0.001	96.7
	Mean age (year)	≥ 50	3	− 9.88 (− 33.23, 13.47)	0.40	< 0.001	93.6
		< 50	4	− 2.20 (− 3.44, − 0.96)	0.001	< 0.001	98.0
	Intervention duration (week)	≥ 12	4	− 8.28 (− 15.01, − 1.55)	0.01	< 0.001	98.2
		< 12	3	− 0.56 (− 1.31, 0.18)	0.13	0.001	85.2
	Melatonin dosage (g/day	≥ 10	5	− 3.56 (− 5.69, − 1.44)	0.001	< 0.001	97.8
		< 10	2	− 0.97 (− 1.27, − 0.67)	< 0.001	0.70	0.0
IL-6 (pg/ml)	Total		6	− 30.25 (− 41.45, − 19.06)	< 0.001	< 0.001	99.0
	Mean age (year)	≥ 50	2	− 1439.41 (− 4278.14, 1399.31)	0.32	< 0.001	99.3
		< 50	4	− 44.48 (− 61.01, − 27.95)	< 0.001	< 0.001	99.1
	Intervention duration (week)	≥ 12	3	− 551.27 (− 795.28, − 307.25)	< 0.001	< 0.001	99.6
		< 12	3	− 4.17 (− 8.88, 0.55)	0.08	< 0.001	94.8
	Melatonin dosage (g/day)	≥ 10	4	− 83.74 (− 115.99, − 51.49)	< 0.001	< 0.001	99.3
		< 10	2	− 3.73 (− 10.24, 2.78)	0.26	< 0.001	96.6

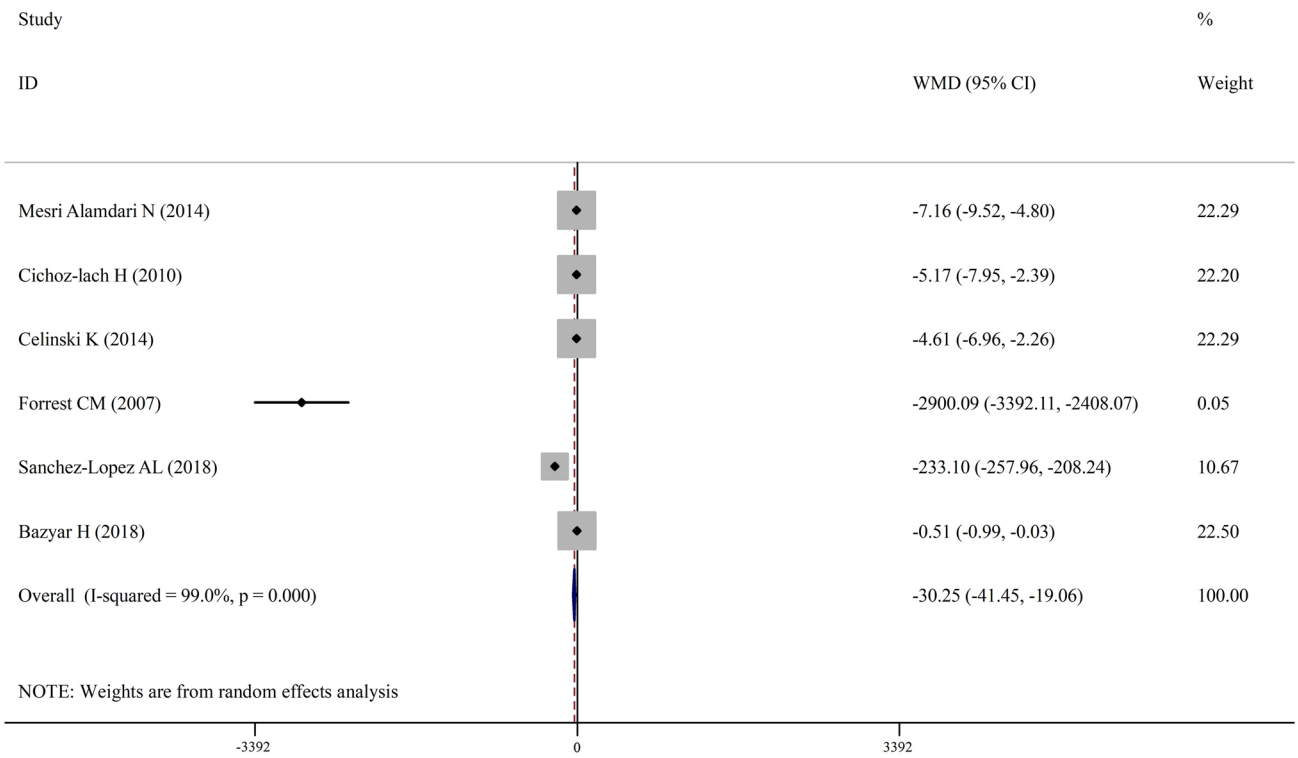

Fig. 4 The pooled effect of melatonin supplementation on IL-6 levels using random-effect analysis

gut–brain axis [46]. The intestinal microbiota undergoes diurnal compositional and functional oscillations that affect metabolic homeostasis [47]. Studies have identified that the microbiota regulates some aspect of host metabolism through the circadian transcription factor NFIL3 [48]. Because disruption of the circadian clock was shown to affect the dynamics of the intestinal microbiota and unfavorable change in microbiota is related to inflammation, a strong association between melatonin and the gut flora and inflammation has recently recognized [49]. Melatonin mediates the crosstalk between the central nervous system, microbiota, and intestinal immune system. Melatonin signalling not only activates the function of immune cells by modulating the release of cytokines, but also plays a vital role in regulating the rhythm of intestinal microbiota and microbial metabolites, meanwhile, the bacteria can also function in melatonin synthesis [49]. In this line, some studies have reported that melatonin has potential antimicrobiotic actions on many bacteria such as the *E. coli* and Bacteriodates class, which are increased in dysbiosis [50, 51]. Accordingly, as an alternative mechanism, the observed anti-inflammatory impacts of melatonin might, at least to some extent, be mediated by improving circadian clock and gut flora.

There was a significant reducing effect of melatonin supplementation on serum concentrations of TNF-α and IL-6. The findings of the studies on the effect of melatonin on serum IL-6 and TNF-α concentrations are conflicting. Most of the included trials have reported a significant reduction in serum IL-6 and TNF-α concentrations after melatonin administration compared with the placebo group [20, 24, 25, 27, 52], except two studies that did not find such a significant effect [20, 22, 53]. Prior studies demonstrated that serum concentrations of CRP, IL-6, and melatonin might be affected by age, dosage, and duration of treatment [54]. Our findings indicated that intervention for ≥ 12 weeks and at dosage ≥ 10 mg/day are more efficacious in amending IL-6 and TNF-α levels, showing that long-term interventions with high doses of melatonin are required to effectively reduce inflammation.

In a recent meta-analysis, Akbari et al. in contrary with our results showed that melatonin supplementation significantly decreased CRP and IL-6 levels with four and three trials, respectively. There was no significant effect of melatonin on TNF-α levels [55]. Moreover, in another meta-analysis, Henderson and et al. revealed that melatonin adjunctive therapy in neonatal sepsis significantly decreased CRP serum levels [56]. Our results showed that the melatonin supplementation significantly decreased TNF-α and IL-6 levels and had marginal effect on CRP levels. Akbari and et al. limited their study to the studies investigating on metabolic syndrome and related diseases [55], while we conducted this meta-analysis among all target populations. Furthermore, the number of included

trials in our study was more than other studies (Thirteen vs. six [55] and three [56] studies).

The present study is the most comprehensive meta-analysis exploring the effect of melatonin supplementation on circulating levels of inflammatory biomarkers, although, this study had some limitations. First, most of the trials included in this meta-analysis had few participants and the total number of included studies was low. Also, this limitation could theoretically cause to unstable estimates of treatment effects. Second, the amount of heterogeneity was remarkable in studies on all inflammatory biomarkers, which limits the generalizability of our findings. Third, included trials had low score on Jadad scale, which might affect the reliability of the results of the present study. Fourth, there was evidence for publication bias in studies on IL-6 using Egger's test.

Conclusion

The present meta-analysis showed that the supplementation with melatonin significantly reduced TNF-α and IL-6 levels. Also, melatonin supplementation might be beneficial in improving CRP levels. The result of this study suggests that melatonin supplementation has favorable properties in ameliorating of inflammatory biomarkers.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

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