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# Effect of melatonin supplementation on oxidative stress parameters: A systematic review and meta-analysis

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ABSTRACT

*Background:* Oxidative stress, defined as an imbalance between pro-oxidants and neutralizing antioxidants within the body, is a growing public health concern. Oxidative stress is involved in the progression of nearly all chronic diseases. Melatonin has been suggested to reduce oxidative stress by its potential radical scavenging properties.
*Objective:* To determine the efficacy and safety of melatonin as a therapy for the improvement of oxidative stress parameters in randomized controlled trials.
*Methods:* A systematic database search using Scopus, PubMed/Medline, EMBASE, Web of Science, the Cochrane Controlled Register of Trials and clinicaltrials.gov (https://clinicaltrials.gov) for studies published up to July 2020 was conducted. We included studies which investigated the effect of supplemental melatonin compared to placebo on oxidative stress parameters in unhealthy patients. Quantitative data synthesis was conducted using a random-effects model with standard mean difference (SMD) and 95 % confidence intervals (CI). Cochrane's Q and $I^2$ values were used to evaluate heterogeneity.
*Results:* A total of 12 randomized controlled trials (RCTs) were eligible. The meta-analysis indicated an association between melatonin intake and a significant increase in total antioxidant capacity (TAC) (SMD: 0.76; 95 % CI: 0.30, 1.21; $I^2 = 80.1$ %), glutathione (GSH) levels (SMD: 0.57; 95 % CI: 0.32, 0.83; $I^2 = 15.1$ %), superoxide dismutase (SOD) (SMD: 1.38; 95 % CI: 0.13, 2.62; $I^2 = 86.9$ %), glutathione peroxidase (GPx) (SMD: 1.36; 95 % CI: 0.46, 2.30; $I^2 = 89.3$ %), glutathione reductase (GR) (SMD: 1.21; 95 % CI: 0.65, 1.77; $I^2 = 00.0$ %) activities, and a significant reduction in malondialdehyde (MDA) levels (SMD: -0.79; 95 % CI: -1.19, -0.39; $I^2 = 73.1$ %). Melatonin intake was not shown to significantly affect nitric oxide (NO) levels (SMD: -0.24; 95 % CI: -0.61, 0.14; $I^2 = 00.0$ %) or catalase (CAT) activity (SMD: -1.38; 95 % CI: -1.42, 4.18; $I^2 = 96.6$ %).
*Conclusion:* Melatonin intake was shown to have a significant impact on improving Oxidative stress parameters. However, future research through large, well-designed randomized controlled trials are required to determine the effect of melatonin on oxidative stress parameters in different age groups and different disease types.

*Abbreviations:* BMI, body mass index; CAT, catalase; CI, confidence intervals; G6PD, glucose 6-phosphate dehydrogenase; GPx, glutathione peroxidase; GR, glutathione reductase; GSH, glutathione; IQR, interquartile range; MDA, malondialdehyde; MMT, methadone maintenance treatment; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NO, nitric oxide; Nrf2, nuclear factor E2-related factor 2; OS, oxidative stress; PCOS, polycystic ovary syndrome; PI3K, phosphoinositide 3-kinases; RCTs, randomized controlled trials; RNS, reactive nitrogen species; ROS, reactive oxygen sepsis; SDs, standard deviations; SE, standard error; SMD, standardized mean difference; SOD, superoxide dismutase; TAC, total antioxidant capacity.

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## 1. Introduction

Oxidative stress (OS) is a state that occurs when there is an excess of free radicals and a deficiency of enzymatic and non-enzymatic antioxidants, leading to many deleterious effects on various biomolecules, including lipids, proteins and DNA [1,2]. Free radicals, such as reactive oxygen species (ROS), which are very reactive and short-lived, are generated by oxygen metabolism. Although ROS have a crucial physiological role in signal transduction and immunological responses, they are also considered to be harmful [3,4]. However, so long as the antioxidant defense system can sufficiently scavenge the reactive species, the increased production of ROS or reactive nitrogen species (RNS) does not cause pathological injuries [5]. Consequently, chronic OS is involved in several diseases, including neurodegenerative disorders, diabetes mellitus, rheumatoid arthritis, cardiovascular diseases, respiratory diseases and various cancers [6,7]. Due to its prominent role in the etiology of many chronic diseases, OS has become a widely studied phenomenon and researchers are constantly looking for an ideal, safe and effective antioxidant to combat it. Melatonin is one of these compounds that has been widely considered as an effective antioxidant for the treatment of OS [8].

Melatonin, or n-acetyl-5-methoxytryptamine, is an indole-derived hormone produced in many organisms, such as fungi, bacteria, plants, and animals. It is the only hormone produced and secreted by the pineal gland in vertebrates [9,10] and is involved in the regulation of circadian rhythm with peak secretion in the middle of the night [11]. Melatonin is involved in several biological functions, namely glycemic status [12], lipid profile [13], inflammatory parameters [14] and anti-oxidative status [15]. Melatonin administration has been shown to be effective in controlling diseases, such as cancers [16,17], diabetes [18], obesity [19] and cardiovascular diseases [20]. Randomized controlled trials (RCTs) that have evaluated the impact of melatonin intake for OS have led to inconsistent results thus far. Some researchers have reported beneficial impacts of melatonin intake for OS [21–23], but there are also other reports that failed to find beneficial effects [24,25]. The discrepancies among the current studies might be due to the differences in population, melatonin dosage, duration of intervention, and the study design. Thus, it is important to evaluate whether the supplementation of melatonin can potentially improve OS status. According to previous database searches, there was no comprehensive systematic review and meta-analysis investigating this topic. The aim of this systematic review and meta-analysis was to answer the question, "Is melatonin effective in improving oxidant and antioxidant parameters?" The most common OS parameters including total antioxidant capacity (TAC); as an indicator of the oxidative defense system of body, glutathione (GSH) as an antioxidant; superoxide dismutase (SOD), glutathione reductase activity (GR), catalase activity (CAT), glutathione peroxidase activity (GPx); as main antioxidant enzymes, malondialdehyde (MDA) as the indicator of lipid peroxidation, and nitric oxide (NO) as the modulator of endothelial function.

## 2. Methods

### 2.1. Data sources and search strategy

This systematic review and meta-analysis was performed according to a pre-specified protocol consistent with the Cochrane Collaboration [26]. Electronic databases including PubMed/MEDLINE, EMBASE, Scopus, Web of Science, Cochrane and clinicaltrials.gov (https://clinicaltrials.gov) were systematically searched without language restrictions for RCTs published from the beginning of time up to July 2020. Reference lists of related reviews and potentially included articles were also searched for additional trials. The following terms were used for searching the databases: "Melatonin OR Pineal hormone AND Glutathione Reductase OR Glutathione Peroxidase OR Superoxide Dismutase OR Oxidative Stress OR Total Antioxidant Capacity OR Total Antioxidant Status OR antioxidant OR Oxidant OR reactive oxygen species OR Catalase OR Oxygen Radical Absorbance OR reactive nitrogen species OR lipid peroxide OR Total Radical Trapping Antioxidant Parameter OR Malondialdehyde OR Nitric oxide OR thiobarbituric acid reactive substances." Complete search strategy keywords and syntaxes for each individual database is presented in **Appendix 1** in Supplementary materials.

### 2.2. Selection criteria

Randomized, placebo-controlled trial or cross-over design studies that evaluated the effect of melatonin supplementation on oxidative stress in unhealthy subjects (mean age: 6.6–66.3 years old) were selected. Trials will be included if they administered melatonin alone or if they are in combination with other treatments and matched with an appropriate control group. Papers that reported sufficient data on oxidative stress at the beginning and end of the intervention in both melatonin and control groups comprised the difference in means with 95 % confidence intervals (95 % CI). OS parameters including TAC (mmol/L), GSH (μmol/L), SOD(U/L), GR(U/L), CAT(U/L), GPx (U/L), MDA (μmol/L), and NO (μmol/L).

Exclusion criteria were non-original publications, observational study designs (cross-sectional, case series, case studies, case-controls and cohort), articles that were non-randomized or without a control group, studies presented only as abstracts, review articles, letters to the editor, and *in vitro* and animal studies. Table 1 indicates the Cochrane PICO search criteria in this meta-analysis.

### 2.3. Data extraction and statistical analysis

The general characteristics extracted from the eligible studies included the first author's name, year of publication, country, number of patients, mean age, gender, BMI, the dose of melatonin, and main outcomes. The mean and standard deviation (SD) of the oxidative stress parameters were extracted from related articles for continuous and binary data. Standard error (SE), confidence interval, interquartile range (IQR), and the minimum-maximum value of each variable in both groups were converted to standard deviations (SD) to calculate the standardized mean difference (SMD) [27]. All statistical analysis was performed with a random effects model based on the inverse-variance method [28] using STATA software version 13 (STATA Corp, College Station, Texas) and statistical significance was considered at $p < 0.05$.

We assessed the heterogeneity of studies using the heterogeneity chi-squared test with p-value less than 0.1 and $I^2$ statistic over 50 % considered as significant heterogeneity. Sensitivity analysis was performed to evaluate the effect of each study or group on the overall effect. Funnel plot was used as a visual analysis to evaluate publication error. The symmetry of funnel plots was examined using Egger's regression asymmetry test and Begg's rank correlation. Risk of bias evaluation was performed independently by two researchers (SMN and ES) using the Cochrane risk-of-bias tool for assessing risk of bias [29].

**Table 1**
PICO inclusion criteria.

| Domain | Selection criteria |
|---|---|
| Subjects | Adults and children under oxidative stress |
| Interventions | Supplementation with any dose of melatonin |
| Comparators | Placebo<br>No intervention |
| Outcomes | Oxidative stress parameters, including SOD, MDA, TAC, NO, GR, GPx, and CAT |
| Study design | Randomized controlled trials (including parallel or crossover studies) |

*Abbreviations*: TAC: Total antioxidant capacity, SOD: Superoxide dismutase, MDA: Malondialdehyde, NO: Nitric oxide, GR: Glutathione reductase activity, CAT: Catalase activity, GPx: Glutathione peroxidase activity.

## 3. Results

### 3.1. Study selection

Details on the included studies is presented in Fig. 1. The initial computerized database search identified 2,551 unique records after duplicates were removed. After title and abstract assessment by two independent reviewers (MM and JH), 2,480 records were excluded and 71 studies remained for full text evaluation. Twelve articles [30–41] met the inclusion criteria. Fifty-nine records were excluded for reasons presented in **Appendix-1** in Supplementary materials.

### 3.2. Study characteristics

The main characteristics of the included studies are shown in Table 2. A total of 12 studies that enrolled 521 participants were included in the systematic review and meta-analysis. The number of participants in these trials ranged from 15 to 46. The included trials were published between 2004 and 2020 and were performed in Iran [30,32,35–37,39,40], India [33,34], Egypt [31], Poland [41] and China [38]. Duration of melatonin intake ranged from two to 12 weeks. The mean age of participants ranged from 6.6 to 66.3 years old. Patients' BMI ranged from 24.8 to 38.2 Kg/$m^2$. Three studies were performed on diabetic patients [36,39,40]. Two studies were performed on overweight or obese patients [30,41], two on epileptic subjects [33,34], one on cancer patients [31], one on Polycystic ovary syndrome (PCOS) women [35], one on methadone maintenance treatment (MMT) patients [32], one on orthognathic patients [38], and one on Parkinson patients [37].

### 3.3. Effect of melatonin on OS parameters

The overall effect of melatonin intake on oxidative stress parameters are presented in Table 3. The results of the random-effects analysis on eight included trials showed that melatonin supplementation significantly reduced MDA levels (SMD: -0.79; 95 % CI: -1.19, -0.39; $I^2 = 73.1$ %) (Fig. 2). A subgroup analysis by disease type was performed and found that melatonin intake reduced MDA in metabolic diseases more than in non-metabolic diseases (SMD: -0.92; 95 % CI: -1.44, -0.40; $I^2 =$ 76.9 %). However, the subgroup analysis on melatonin intake duration did not change the main effect size.

Fig. 3 presents the meta-analysis of eight included trials [30–32,35–37,39,40] on melatonin intake on TAC. The results indicated that melatonin intake significantly increased TAC (SMD: 0.76; 95 % CI: 0.30, 1.21; $I^2 = 80.1$ %). The subgroup analysis by disease type did not change the results. However, stratifying the results according to the duration of melatonin supplementation indicated that melatonin intake increased TAC more efficiently when given for at least 10 weeks (SMD: 1.05; 95 %

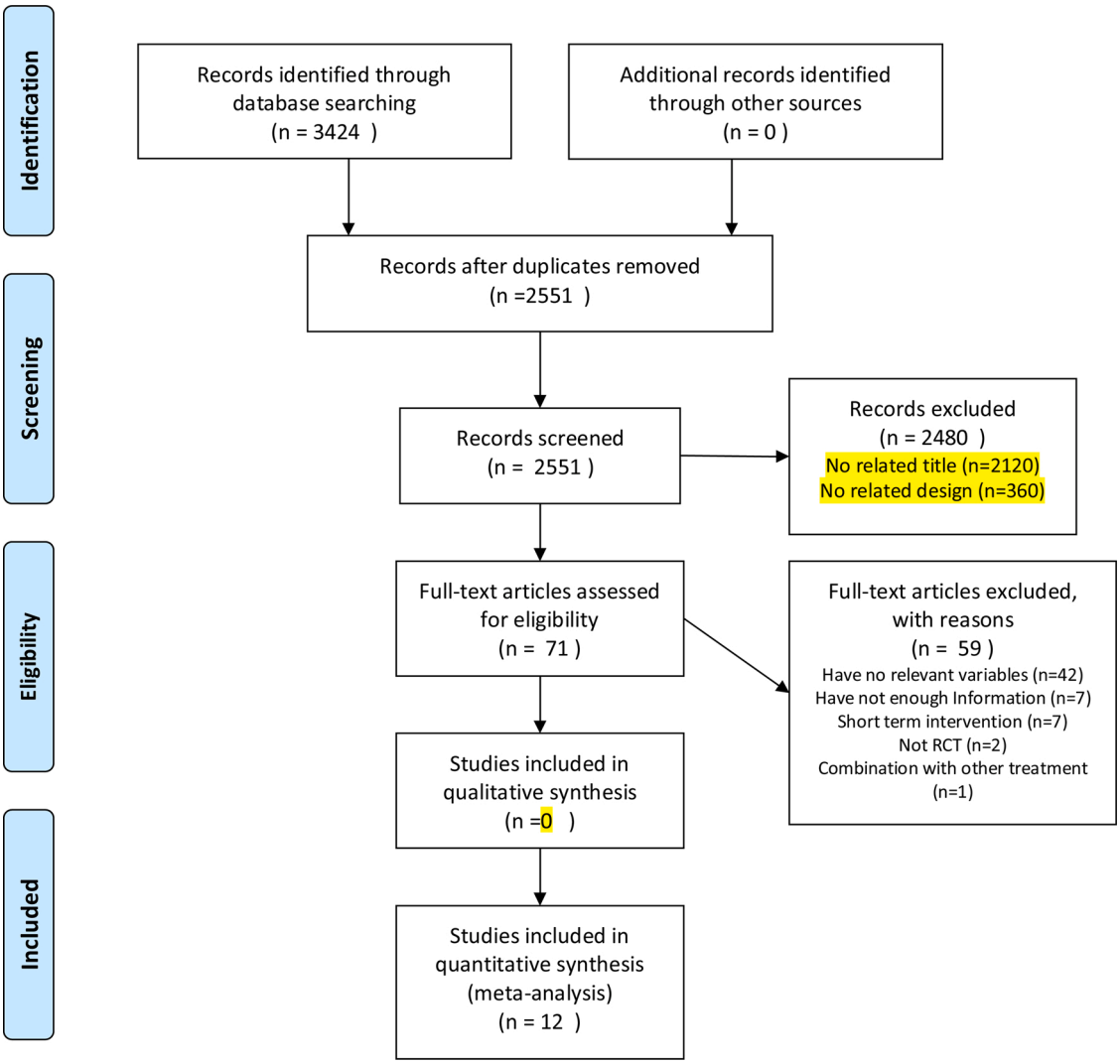



**Fig. 1.** Study selection diagram.

**Table 2**
Summary of randomized controlled trials to investigate the effects of melatonin supplementation on oxidative stress parameters.

| First author, year | Country | Population[¥] | Dose of melatonin (mg) | Sample size (including in analyses) | Duration (weeks) | Genders(n) | | Age (mean ± SD) | | BMI (mean ± SD) kg/m2 | | Main results[*] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Men | Women | Intervention group | Control group | Intervention group | Control group | |
| Esabagh et al, 2019 [31] | Egypt | Neck cancer (HNC) patients | 20 | 40 | 6 | 23 | 17 | 55.9 ± 11.01 | 57.80 ± 10.32 | – | – | ↑ TAC |
| Ghaderi et al, 2018 [32] | Iran | MMT patients | 10 | 54 | 12 | 54 | 0 | 42.5 ± 8.0 | 42.7 ± 9.9 | 24.8 ± 4.3 | 25.0 ± 4.1 | ↓ MDA |
| Gupta et al, 2004 [34] | India | Epileptic children | 3 | 29 | 2 | 18 | 11 | 7.4 ± 3.2 | 6.6 ± 3.9 | – | – | ↔ GPx, ↑GR |
| Gupta et al, 2004 [33] | India | Epileptic children | 6 for age<9<br>9 for age>9 | 28 | 2 | 21 | 7 | 8.1 ± 2.6 | 8.3 ± 3.1 | – | – | ↔ GPx, ↑GR |
| Jamilian et al, 2019 [35] | Iran | women with PCOS | 10 | 56 | 12 | 0 | 56 | 28.7 ± 2.1 | 28.3 ± 2.3 | 29.1 ± 4.6 | 29.2 ± 3.5 | ↓ MDA,↑ TAC, ↑ GSH |
| Javid et al, 2020 [36] | Iran | T2DM patients | 250 | 44 | 8 | 14 | 30 | 53.72 ± 6.68 | 51.45 ± 5.03 | 27.36 ± 2.1 | 27.21 ± 2.19 | ↔TAC, ↑SOD, ↑CAT, ↑ GPx, ↓ MDA |
| Daneshvar Kakhaki et al, 2020 [37] | Iran | PD patients | 10 | 51 | 12 | 32 | 19 | 64.4 ± 8.2 | 66.3 ± 9.3 | 25.1 ± 2.1 | 25.1 ± 3.0 | ↑ TAC, ↑ GSH, ↔MDA |
| Lee et al, 2019 [38] | China | Orthognathic patients | 10 | 30 | 3 | 10 | 20 | 25.2 ± 4.7 | 24.1 ± 4.6 | – | – | ↑CAT, ↑ GPx, ↓, ↑SOD |
| Mesri Alamdari et al, 2014 [30] | Iran | Obese women | 6 | 44 | 6 | 0 | 44 | 33.86 ± 6.94 | 34.76 ± 7.29 | 34.1 ± 3.25 | 35.7 ± 4.17 | ↔TAC, ↔ MDA |
| Ostadmohammadi et al, 2019 [39] | Iran | Diabetic HD patients | 10 | 53 | 12 | 38 | 15 | 65.6 6 13.1 | 64.1 6 8.2 | 26.4 6 4.7 | 26.4 6 5.9 | ↑ TAC, ↔GSH, ↓ MDA, ↑NO |
| Raygan et al, 2017 [40] | Iran | Diabetic patients with CHD | 10 | 60 | 12 | 27 | 33 | 67.7 ± 11.4 | 65.3 ± 10.1 | 30.4 ± 4.3 | 29.7 ± 4.4 | ↑ GSH, ↑NO, ↓ MDA, ↔TAC |
| Szewczyk-Golec et al, 2017 [41] | Poland | Obese patients | 10 | 30 | 4 | 20 | 10 | 37.7 ± 3.40 | 36.3 ± 4.18 | 37.8 ± 1.51 | 38.2 ± 1.94 | ↔ MDA, ↔ SOD, ↔ CAT, ↔ GPx |

[¥]T2DM: Type 2 diabetes mellitus, CP: Chronic periodontitis, NAFLD: Non-alcoholic fatty liver disease, HD: Hemodialysis, SOD: Superoxide dismutase, MDA: Malondialdehyde, TAC: Total antioxidant capacity, NO: Nitric oxide, GR: Glutathione reductase activity, CAT: Catalase activity, GPx: Glutathione peroxidase activity, PD: Parkinson's disease, CHD: Coronary heart disease, PCOS: Polycystic ovary syndrome, MMT: Methadone maintenance treatment.

[*] ↓ This symbol is a sign of decreasing variables in the intervention group, ↑ This symbol is a sign of increasing variables in the intervention group, ↔ This sign indicates that there is no difference between the two groups. NR: not reported.

**Table 3**
Main pooled effects of melatonin intake on oxidative stress parameters.

| Oxidative stress parameters | Number of included studies | Main pooled effect size (SMD) | 95 % CI | $I^2$ | P for heterogeneity |
|---|---|---|---|---|---|
| MDA | 8 | **−0.79** | **−0.19, -0.39*** | 73.1 % | **0.001** |
| TAC | 8 | **0.76** | **0.30, 1.21*** | 80.1 % | **0.000** |
| SOD activity | 3 | **1.38** | **0.13, 2.62*** | 86.9 % | **0.000** |
| NO | 2 | 0.24 | −0.61, 0.14 | 00.0 % | 0.941 |
| GSH | 5 | **0.57** | **0.32, 0.83*** | 15.1 % | 0.319 |
| GR | 2 | **1.21** | **0.65, 1.77*** | 00.0 % | 0.679 |
| Gpx | 5 | **1.36** | **0.46, 2.30*** | 89.3 % | **0.000** |
| CAT activity | 3 | 1.38 | −1.42, 4.18 | 96.6 % | **0.000** |

MDA: Malondialdehyde, TAC: Total Antioxidant Capacity, SOD: Superoxide dismutase, GSH: Glutathione, NO: Nitric Oxide, GR: Glutathione reductase, Gpx: Glutathione peroxidase, CAT: Catalase, SMD: Standard mean difference, CI: confidence interval.
* Statistically significant.

CI: 0.42, 1.67; $I^2$ = 83.9 %). The results also indicated that melatonin intake significantly increased SOD activity (SMD: 1.38; 95 % CI: 0.13, 2.62; $I^2$ = 86.9 %) (Fig. 4). In addition, the meta-analysis of two included trials showed that melatonin intake did not have any significant effect on NO levels (SMD: -0.24; 95 % CI: -0.61, 0.14; $I^2$ = 00.0 %) (Fig. 5). Five included trials assessed the effect of melatonin on GSH levels. The pooled effect size of this meta-analysis indicated that melatonin supplementation significantly increased GSH levels (SMD: 0.57; 95 % CI: 0.32, 0.83; $I^2$ = 15.1 %) (Fig. 6). A significant increase in GR activity after melatonin intake was also observed (SMD: 1.21; 95 % CI: 0.65, 1.77; $I^2$ = 00.0 %) (Fig. 7). Further, the pooled effect size of six included treatment arms indicated that melatonin intake significantly increased GPx activity (SMD: 1.36; 95 % CI: 0.46, 2.30; $I^2$ = 89.3 %) (Fig. 8). Finally, the meta-analysis results indicated that melatonin supplementation had no effect on CAT activity (SMD: -1.38; 95 % CI: -1.42, 4.18; $I^2$ = 96.6 %) (Fig. 9).

### 3.4. Publication bias, sensitivity analysis and quality appraisal

The funnel plot did not show significant asymmetry, which suggested that there was no potential publication bias (Appendix 3 in Supplementary materials). A sensitivity analysis was also performed to investigate the effect of individual trials on the pooled effect size, and there was no significant change after the drop out of each study. The results of the quality appraisal are presented in Appendix A.

## 4. Discussion

To the best of our knowledge, this is the first systematic review and meta-analysis that investigates the effect of melatonin intake on OS parameters. Previous systematic reviews evaluated the effect of melatonin intake on blood pressure [42,43], glycemic control [44], renal function [45], inflammatory mediators [46] and cardiovascular risk factors [47]. Evidence was collected from twelve trials that evaluated the impact of supplemental melatonin on OS biomarkers (MDA, TAC, GSH, GR, GPx, NO, SOD and CAT). The main outcome of this meta-analysis indicated that melatonin intake significantly increased TAC, GSH levels and GPx, GR, and SOD activity. Melatonin intake was also shown to significantly decrease MDA levels, however the small number of included trials and large heterogeneity between them should be considered and the results should be viewed with caution.

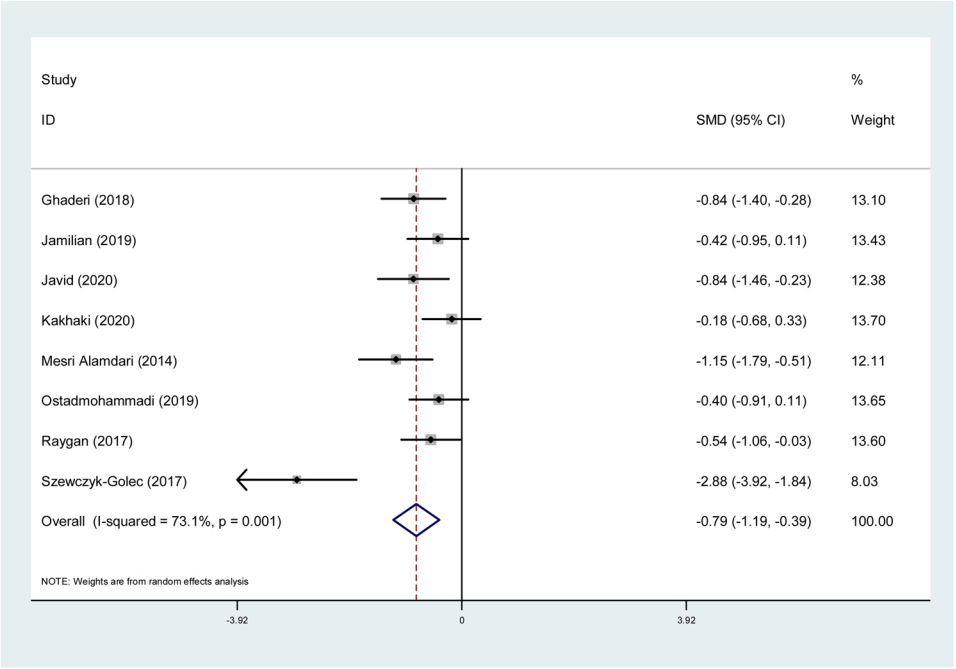
To date, no systematic reviews have evaluated the effect of melatonin on MDA levels, however primary and experimental studies indicate that melatonin improves MDA levels [48–50]. Several mechanisms have been suggested to explain the effect of melatonin on decreasing MDA, namely that melatonin is a direct free radical scavenger and indirect antioxidant, [51] it detoxifies a vast number of free radicals, such as the peroxynitrite anion [52] and the hydroxyl radical [53], and it detoxifies the precursor of hydrogen peroxide, the hydroxyl radical [54], and scavenges other oxidizing particles, such as peroxynitrous acid [55], nitric oxide [56] and singlet oxygen [57], which typically increase MDA through the elevation of lipid peroxidation [58]. Thus, melatonin could decrease MDA through its effect on detoxifying these radicals.

The results also show that melatonin intake significantly increases TAC, which is supported by several primary and experimental studies [59,60]. Antioxidants, such as GSH, and antioxidant enzymatic activity, such as CAT, SOD, GPx and GR activity, are the main contributors of TAC in human plasma [61]. Melatonin intake was shown to significantly improve GSH levels and GR, GPx and SOD activity, indicating that melatonin intake may increase TAC through impacting the antioxidants and enzymatic activity related to TAC. Higher activities of antioxidant enzymes, levels and mRNA expression of SOD and GPx in cell lines in response to melatonin treatment demonstrated that melatonin potentially elevates antioxidant defense system levels, leading to less accumulation of ROS and higher level of TAC [62,63]. In addition, melatonin has been shown to increase TAC and exert its antioxidant properties through affecting several transcriptional regulation factors [64]. There are specific receptors for melatonin that have been characterized in mammalian cell types [65], namely MT1 and MT2, which are a subgroup of G-protein-coupled receptors [66,67]. Melatonin has been shown to affect transcriptional regulation factors through activating these receptors [68].

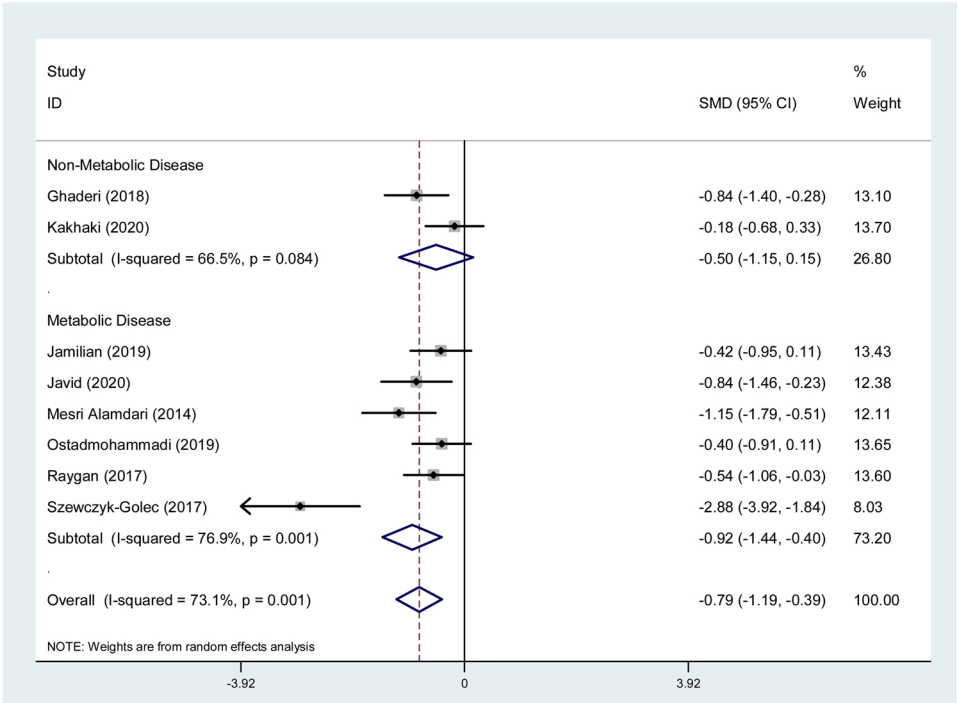
When bodily cells are faced with OS, the ROS produced function as second messengers and lead to the regulation of gene expression of inflammatory mediators. Nuclear factor kappa-light-chain-enhancer of activated B cells (NF-$\kappa$ B) is a transcription factor involved in up-regulation of these inflammatory mediators [69,70], and is regulated by the inhibitory subunit, I-$\kappa$ B, which keeps it inactive in the cytoplasm [71]. OS is one of the main conditions that induces NF-$\kappa$ B activation [72,73], through the phosphorylation of I-$\kappa$ B, leading to the translocation of NF-$\kappa$ B into the nucleus [74], where it attaches to the $\kappa$ B response region of its related target genes. I-κ B is then degraded by proteasomes [75]. Melatonin is proposed to suppress I-κ B degradation and also inhibit the nuclear translocation of NF-$\kappa$ B [76,77].

Melatonin intake was also shown to significantly increase GSH levels and GPx, GR and SOD activity. The beneficial effects of melatonin on GSH levels have also been confirmed in primary and experimental studies [35,37,78], and are explained through the direct antioxidant and scavenging effect of melatonin which has been shown to be more effective than any other endogenous scavengers in increasing GSH levels [79]. Melatonin has also been demonstrated to improve the function and increase the activity of the main antioxidative defense enzymes [80] through stimulation of their mRNA levels [81]. GPx, one of the most critical enzymes of GSH metabolism, is a major antioxidative defense enzyme. Interventional doses of melatonin have been demonstrated to increase the function of GPx in the brain in humans [82] and in the stomach and liver of rats [83]. Melatonin is also proposed to increase the activity of the glucose 6-phosphate dehydrogenase (G6PD) enzyme [84] in both the brain and the liver [85]. G6PD provides NADPH for the cells, which is essential for GR activity and producing reduced GSH from oxidized GSH [34]. Melatonin supplementation can thus lead to diminished cell and DNA damage through increasing the activity of the aforementioned enzymes and increasing the scavenging of ROS through high levels of GSH [86].

SOD activity was also shown to increase with melatonin supplementation through increasing mRNA gene expression for both Mn-SOD

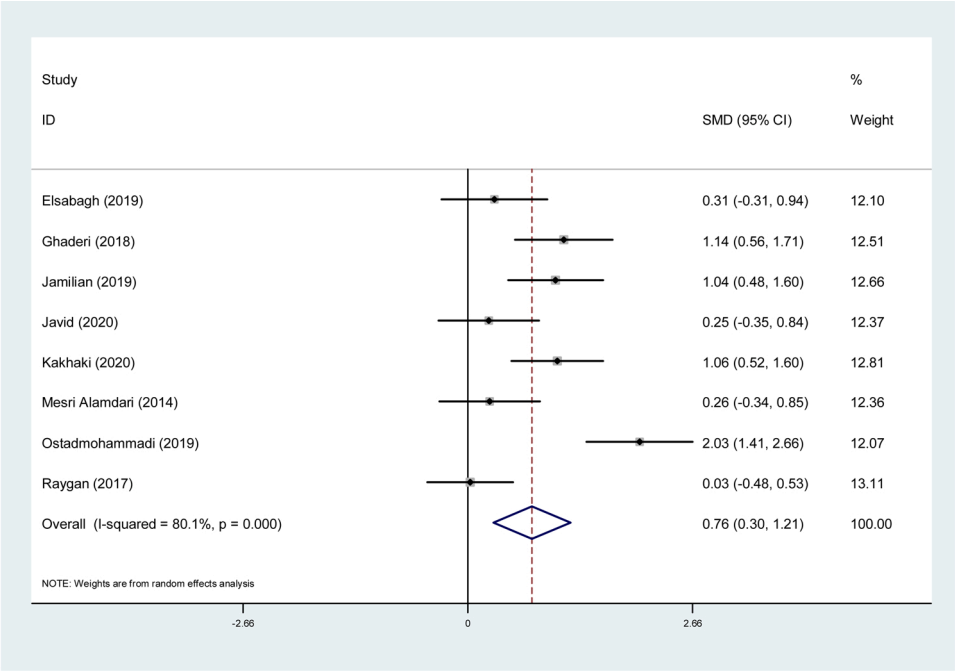



A

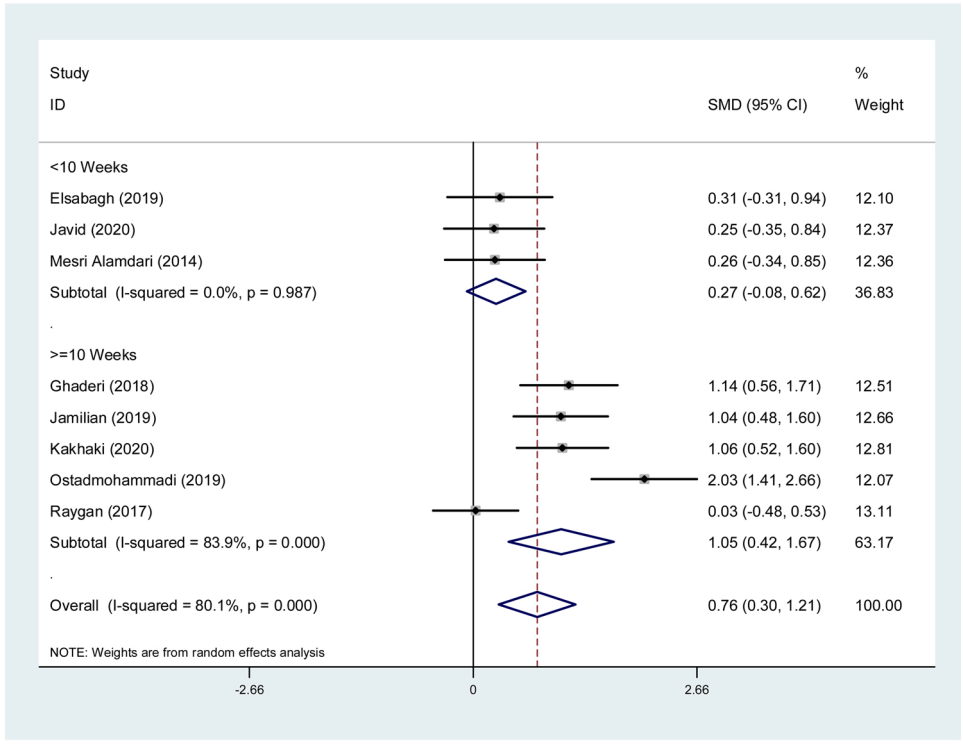



B

**Fig. 2.** Forest plot detailing standard mean difference and 95 % confidence intervals for the effect of melatonin on MDA levels.
A: Overall effect of melatonin on MDA.
B: Effect of melatonin on MDA, stratified by disease type.




A




B

**Fig. 3.** Forest plot detailing standard mean difference and 95 % confidence intervals for the effect of melatonin on the TAC.
A: Overall effect of melatonin on TAC.
B: Effect of melatonin on TAC, stratified by duration.

and Zn-Cu-SOD [87,88]. SOD has been shown to preserve and protect the mitochondrial membrane from oxidative damage [89,90] and melatonin has demonstrated to increased mitochondrial membrane protection and decrease calcium overload [91]. Melatonin also has a pivotal role in mitochondrial physiology through its impact on the genetic expression of SOD and high recycling of GSH [87,92]. In addition, it has been shown that melatonin preserves membrane integrity through its effects on reducing caspase-3 activity and activating the PI3K/AKT pathway [93–95]. Activation of the PI3K/AKT pathway can increase the expression of several genes that play a crucial role in the

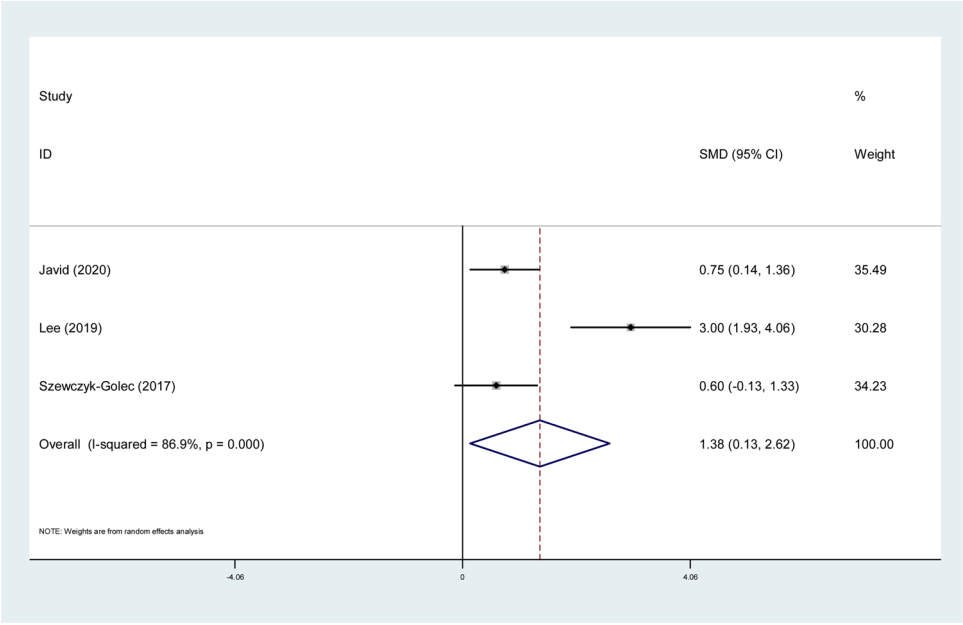



**Fig. 4.** Forest plot detailing standard mean difference and 95 % confidence intervals for the effect of melatonin on SOD activity.

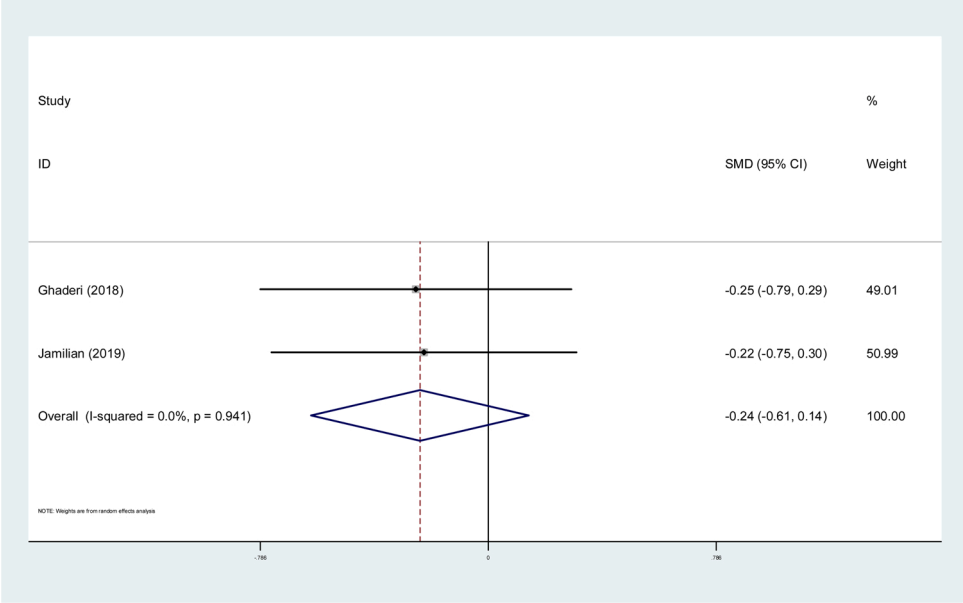



**Fig. 5.** Forest plot detailing standard mean difference and 95 % confidence intervals for the effect of melatonin on NO levels.

antioxidant defense system [96], namely nuclear factor E2-related factor 2 (Nrf2) gene expression through the activation of the PI3K/AKT pathway by melatonin [97]. Nrf2 is a redox-sensing transcription factor and is a main inducers of antioxidant enzyme gene expression such as SOD, GPx and GR [98]. It has also been shown that the activation of the PI3K/AKT pathway can increase transcriptional regulation of the antioxidant enzyme, heme oxygenase-1 (HO-1). HO-1 is another detoxifying enzyme that protect cells against diverse effects of oxidative stress and toxins [99].

Our results show that melatonin intake did not affect CAT activity, however, only having a limited number of included studies may be the reason for this result. CAT is one of the most critical enzymes associated with oxidative stress [100] and *in vitro* studies have shown that melatonin intake can both increase CAT activity [101] and prevent the effect of oxidants in reducing CAT activity [102]. This may be due to excessive production of peroxide radical causing the inactivation of the CAT enzyme. Peroxide radical has been demonstrated to be the leading cause of damage to the heme part of catalase, and melatonin has been shown to prevent these damages by reducing the levels of peroxide radicals as mentioned above [103].

This systematic review has some limitations. The first is the variation in the included trials when considering the patient age and disease background, which may have affected the results through introducing significant heterogeneity between studies. Secondly, the small number of included studies evaluating the most of the variables did not allow for a subgroup analysis to draw a more resolute conclusion in each of the individual variables. For example, gender may make a difference in the results of oxidative stress outcomes and a subgroup analysis based on gender may help us better clarify the effect of melatonin as an antioxidant. Thirdly, the majority of the included trials were performed in

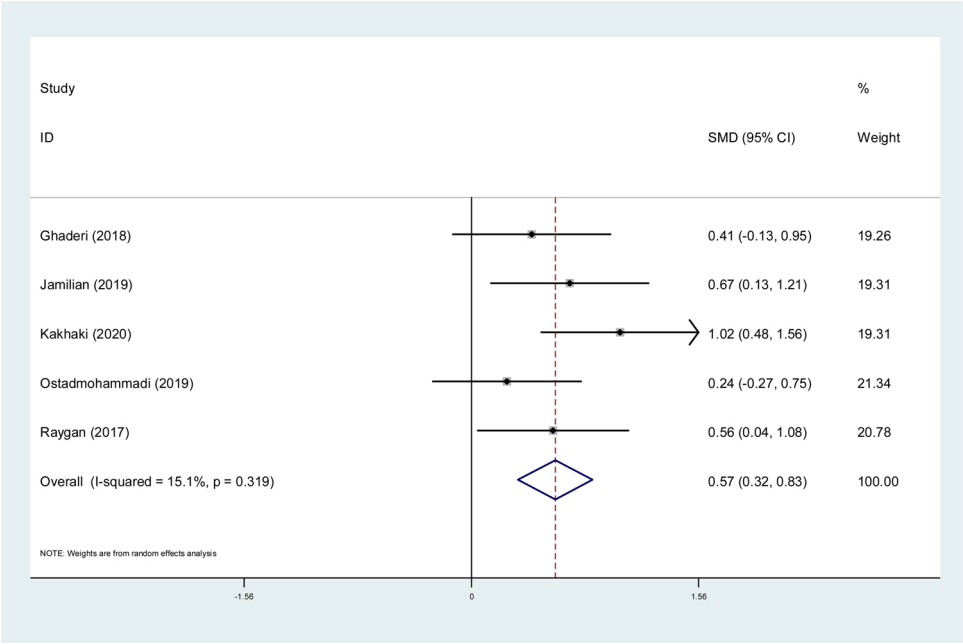



**Fig. 6.** Forest plot detailing standard mean difference and 95 % confidence intervals for the effect of melatonin on GSH levels.

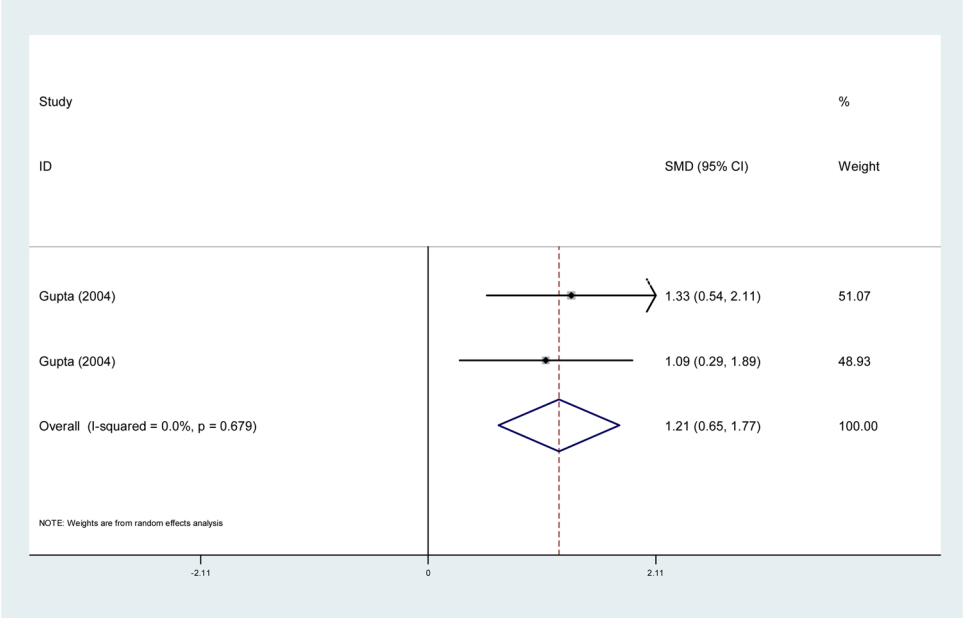



**Fig. 7.** Forest plot detailing standard mean difference and 95 % confidence intervals for the effect of melatonin on GR activity.

eastern countries that maybe weaken generalizability. Finally, there were major faults within the individual studies, namely the lack of critical analysis which reflected an unfamiliarity with the best practices for the measurement of oxidative stress endpoints in humans. For example, the analysis of MDA in serum or plasma is error-prone as serum MDA is a by-product of thromboxane A2 activity after blood-clotting and is thus not considered a valid OS marker. MDA is preferably measured spectrophotometrically or fluorimetrically, which was done in most of the papers included.

The results indicated that supplemental melatonin can increase TAC and GSH levels, increase the activity of GPx, GR and SOD, and significantly decrease MDA levels. It has been suggested that melatonin could be used as an adjunct therapy to reduce OS parameters in chronic and high stress patients. However, large and well-designed clinical trials are required doing forward to determine the effect of melatonin on OS parameters in different age groups and different disease types.

## Authors' contribution

MM and JH: designed the study; SF, and FM: conducted the database search and data extraction; SMN, and ES: conducted the statistical analysis, evaluated and reported the results; SHA and EP: wrote the article's draft; and all authors: carefully evaluated the final draft of the manuscript and approved it.

## Declaration of Competing Interest

The authors report no declarations of interest.

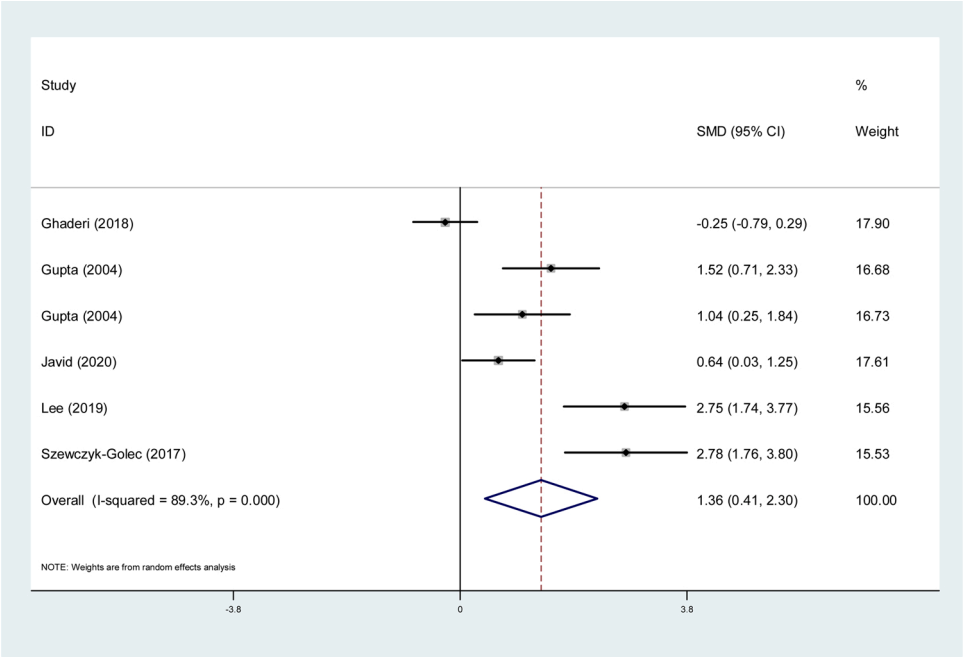



**Fig. 8.** Forest plot detailing standard mean difference and 95 % confidence intervals for the effect of melatonin on the GPx activity.

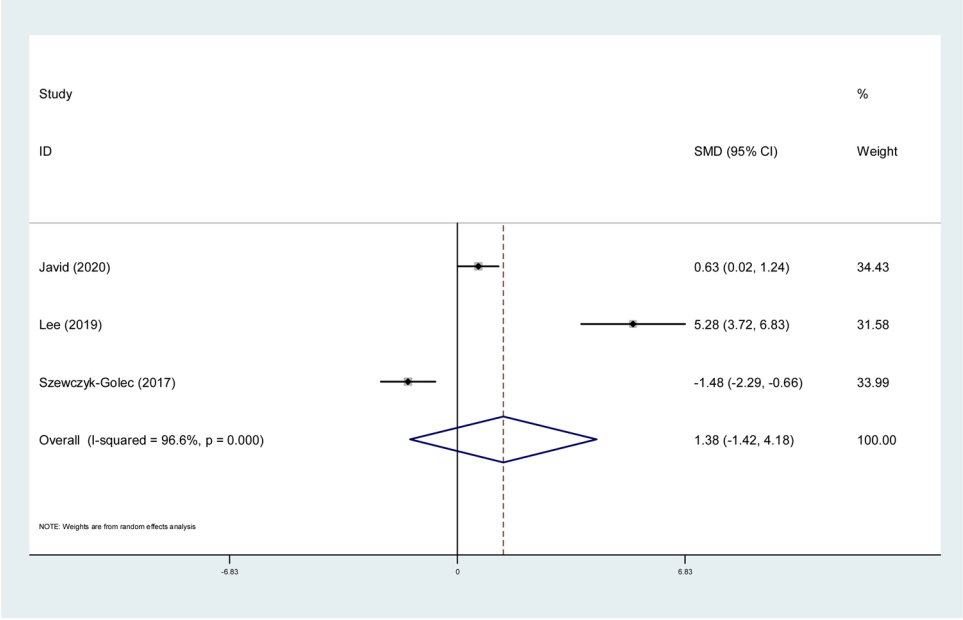



**Fig. 9.** Forest plot detailing standard mean difference and 95 % confidence intervals for the effect of melatonin on CAT activity.

## Appendix A. Assessment of the risk of bias in the included studies

: High risk,

: Low risk,

: Unclear.

| Author, year | Random sequence generation (selection bias) | Allocation concealment (selection bias) | Blinding of participants and personnel (performance bias) | Blinding of outcome assessment (detection bias) | Incomplete outcome data (attrition bias) | Selective reporting (reporting bias) | Other bias |
|---|---|---|---|---|---|---|---|
| Esabagh et al, 2019[31] | – | – | ? | + | ? | ? | – |
| Ghaderi et al, 2018[32] | – | – | – | – | ? | – | – |
| Gupta et al, 2004[34] | – | – | ? | ? | – | ? | – |
| Gupta et al, 2004[33] | – | – | ? | ? | – | ? | – |
| Jamilian et al, 2019[35] | – | – | ? | + | ? | – | – |
| Javid et al, 2020[36] | – | – | – | ? | – | + | – |
| Daneshvar Kakhaki et al, 2020[37] | – | ? | – | – | ? | ? | – |
| Lee et al, 2019[38] | – | ? | + | + | ? | ? | – |
| Mesri Alamdari et al, 2014[30] | – | – | – | – | + | ? | – |
| Ostadmohammadi et al, 2019[39] | – | – | – | – | – | – | – |
| Raygan et al, 2017[40] | – | – | – | ? | ? | – | – |
| Szewczyk-Golec et al, 2017[41] | – | ? | + | + | ? | ? | - |

## Appendix B. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.phrs.2020.105210.

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