Current Sleep Medicine Reports (2023) 9:225–233
https://doi.org/10.1007/s40675-023-00261-w

Too Sour to be True? Tart Cherries (*Prunus cerasus*) and Sleep: a Systematic Review and Meta-analysis

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Accepted: 26 June 2023 / Published online: 11 July 2023

Abstract

Purpose for Review Sleep deprivation and insomnia are associated with mortality and morbidity worldwide. A pharmacological agent that improves subjective and objective measures of sleep, without significant side effects, remains nebulous. However, initial randomised controlled trials suggest *Prunus cerasus* (tart cherry) ingestion may be beneficial. This systematic review and meta-analysis evaluates the effect of *Prunus cerasus* on objective and subjective measures of sleep.

Recent Findings We identified a total of 277 unique records, from which 8 studies of low-moderate methodological quality were included in the systematic review. Meta-analysis of subjectively recalled sleep efficiency (SE) and total sleep time (TST) were not significant. Objective SE, however, was significantly higher in the cherry cohort when compared to placebo with an effect size of 0.63 (95% CI 0.29–0.97, $P < 0.01$). There was low associated heterogeneity ($I^2 = 0\%$). Objective TST was significantly higher in the cherry cohorts, with a pooled effect size of 1.21 (95% CI 0.83–1.58, $P < 0.01$). There was high associated heterogeneity ($I^2 = 81.5\%$).

Summary Whilst individuals may not subjectively experience a benefit, there is evidence to support significant improvements to total sleep time and sleep efficiency with the ingestion of *Prunus cerasus* using objective measures. Tart cherry may be the next frontier of sleep medicine and warrants further research.

Keywords *Prunus cerasus* · Sleep · Cherry · Insomnia · Nutritherapeutics · Clinical nutrition

Introduction

Sleep deprivation is a global health problem with significant implications for individuals and society. Sleep deprivation may occur in the setting of conditions such as sleep apnoea which already have established management options. However, there are other causes for sleep deprivation such as poor sleep hygiene, circadian rhythm disturbances (such as shift work) and medications [1]. Whilst guidelines for duration of sleep differ according to age group, approximately 35% of adults and 70% of high school students do not obtain the recommended amount of sleep [1, 2]. Sleep is a complex process that supports many metabolic and physiological processes and serves as a major, modifiable behaviour that is intimately related to the health of an individual [3]. Sleep deprivation is associated with an increased risk of both all-cause mortality and many leading causes of death, namely cardiovascular disease, malignancy, cerebrovascular disease, metabolic and autoimmune diseases and neurodegenerative diseases [4]. Patients with sleep deprivation also report lower quality of life compared to population norms [5]. This association with negative outcomes is more direct than that observed with sleep excess, which is likely secondary to chronic health issues [6–9]. The ingestion of *Prunus cerasus* (tart cherry) has been purported to assist with sleep and possibly aid in ameliorating this issue.

Sleep deprivation also poses a larger community risk. Insufficient sleep confers more immediate risks by contributing to erratic, unsafe behaviours and impulsivity, impaired judgement and daytime somnolence/microsleeps [10, 11]. This translates to an increased risk of medical errors [12], traffic accidents [13] and workplace injuries [14] and

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reduced academic performance. Furthermore, those with significant sleep deprivation account for a disproportionately high utilisation of health care resources [15].

Sleep deprivation may be managed with pharmacological therapies; however, these medications are not without notable side effects. Caffeine is used by many to combat daytime somnolence and fatigue but negatively impacts the quality of sleep, creating a cycle of worsening fatigue and increased dependence [16–18]. Many sleep-promoting agents have significant adverse effects including sedation and psychomotor impairment. They also carry the risk of addiction and abuse [19]. Many individuals may turn to other therapies to improve their sleep quality, such as cognitive behavioural therapy for insomnia (CBT-I) which has its own limitations such as a paradoxical increase in daytime somnolence which persists for 3–4 weeks, often resulting in patient dropout [20]. Other complementary therapies include nutritional supplementation; however, the evidence regarding their effect is variable [21–23]. One nutritional supplement that has shown early promise is *Prunus cerasus* (*tart*, *sour*, *Montmorency cherry)* [20, 24].

Tart cherries contain multiple anti-inflammatory and antioxidative phytonutrients including phenolic acid (polyphenols) and flavonoids [25]. This capacity for tart cherries to reduce oxidative stress has been demonstrated to reduce exercise-induced inflammation and improve muscle recovery, and it is commonly used by athletes to improve their exercise recovery and performance [26–28]. In these studies, some athletes report an improvement in their sleep from tart cherry supplementation; however, there is no definitive synthesis of the available evidence to prove and support the general public and clinicians in utilising *Prunus cerasus* for its soporific effects. Accordingly, this systematic review and meta-analysis was conducted with the aim of evaluating studies that have examined the effect of *Prunus cerasus* ingestion on sleep.

Methods

The methodology for this systematic review was established within a protocol prior to its conduct. This study was prospectively registered with PROSPERO (CRD42021279145) and followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 (PRISMA 2020) and Meta-analyses Of Observational Studies in Epidemiology (MOOSE) reporting guidelines [29, 30].

Search Strategy and Selection Criteria

The population, intervention, comparator group, outcome (PICO) framework was used to formulate the research question and inclusion criteria. The population was individuals, with or without prior sleep diagnosis. The intervention was *Prunus cerasus* (tart/sour cherry) in whole, concentrated, or supplemental form. A comparator group was not required for inclusion. The primary outcome of interest was total sleep time (both objective assessment and subjective recall). Additional outcomes of interest were other sleep parameters, including objective and subjective measures of such, melatonin levels and measures of daytime fatigue/somnolence.

Data Extraction and Analysis

Two reviewers (BS and JK) independently screened titles and abstracts, reviewed full-texts and extracted data using a standardised form. Screening of titles and abstracts was via a web application (Rayyan, Qatar Computing Research Institute, Ar-Rayyan, Qatar) [31]. Extracted data included study design and setting, population characteristics, intervention characteristics, outcomes, methodological quality information and other information relevant to the review questions. Data relevant to study outcomes was summarised to determine effect sizes across the included studies.

The determination of whether studies met inclusion criteria was undertaken in duplicate using a standardised form. To be included in the systematic review, the following criteria had to be met: (1) published in English; (2) primary research article (reviews were excluded); (3) intervention was *Prunus cerasus*, in any form but as a sole constituent or main active ingredient; (4) total sleep time (subjective or objective); and (5) was available in full-text. Eligibility determination was undertaken in duplicate, and instances of disagreement were resolved through discussion between the reviewers and in the event of non-agreement, a third reviewer acted as arbiter. The Joanna Briggs Institute (JBI) Critical Appraisal Checklists for Randomised Controlled Trials were used to assess the risk of bias. This risk of bias analysis was performed in duplicate. Publications not reporting primary research data were excluded. Editorials, perspectives, letters and conference abstracts were excluded. PubMed (incorporating MEDLINE), Embase and CINAHL were searched from database inception to July 31, 2022. Key search terms included sleep, insomnia, somnolence, rest, cherry, prunus and cerasus. No publication restrictions were implemented. The individual search strings employed for each database are listed in Supplementary Information. Additionally, the reference lists of included articles and grey literature sources were searched for relevant studies.

Statistical Analysis

Statistical analysis was carried out using Stata® (Version 17.0, StataCorp, Texas, USA). Where appropriate, a meta-analysis of continuous data was performed using the *meta esize* function. A fixed effects model was utilised as studies

included in the meta-analysis largely incorporated a crossover randomised control trial design. Subjective and objective measures of sleep efficiency and total sleep time were intended for meta-analysis, a priori. Post hoc analysis of other results of interest was conducted according to data availability. Results were expressed as forest plots where appropriate, and effect size as the Hedges g statistic. $P<0.05$ denoted statistical significance for intergroup comparison. Heterogeneity was assessed using the I^2 test statistic. Low heterogeneity was denoted by $I^2<50\%$, moderate heterogeneity by I^2 50–74% and high heterogeneity by $I^2>75\%$. Due to the limited number of studies, meta-regression, subgroup analysis and publication bias were not assessed.

Results

Our search identified a total of 320 records. There were 277 studies after duplicate removal (Fig. 1). After the title and abstract screening, there were 27 articles reviewed in full text. Following full text review, references lists and grey literature were searched for additional articles, and one additional text was identified for inclusion. In total, eight studies were included in this systematic review. Characteristics of the included studies are detailed in Table 1. Study publication year ranged from 2009 to 2022. Five included studies were double-blind crossover design; two were prospective cohort studies; and one study was a placebo-controlled RCT without crossover design. The five crossover studies utilised a cherry supplement, with a washout period incorporated in the crossover design. Dose and timing varied between all studies but were commonly the equivalent of ~ 100 g of fresh cherries two times per day. Six studies assessed healthy patients, whereas two assessed patients with a history of insomnia. The age range of included participants varied significantly, but all age groups were included in at least four different trials. Objective measures of sleep were the most common outcome, four utilising actigraphic recordings, one using accelerometers and one using polysomnography. Only two studies used solely subjective recordings of sleep duration.

Risk of bias analysis of the included studies demonstrated that the majority of studies were of low to moderate risk of bias (see Supplementary Information).

Subjective Sleep Measures

Four studies assessed subjective measures of sleep [32–35].

Sleep Efficiency

Three studies assessed subjective sleep efficiency in cherry vs placebo, with a pooled effect size of 0.07 (95% CI − 0.28–0.42, $P=0.94$), and low associated heterogeneity ($I^2=0$) [32, 33, 35] (Fig. 2).

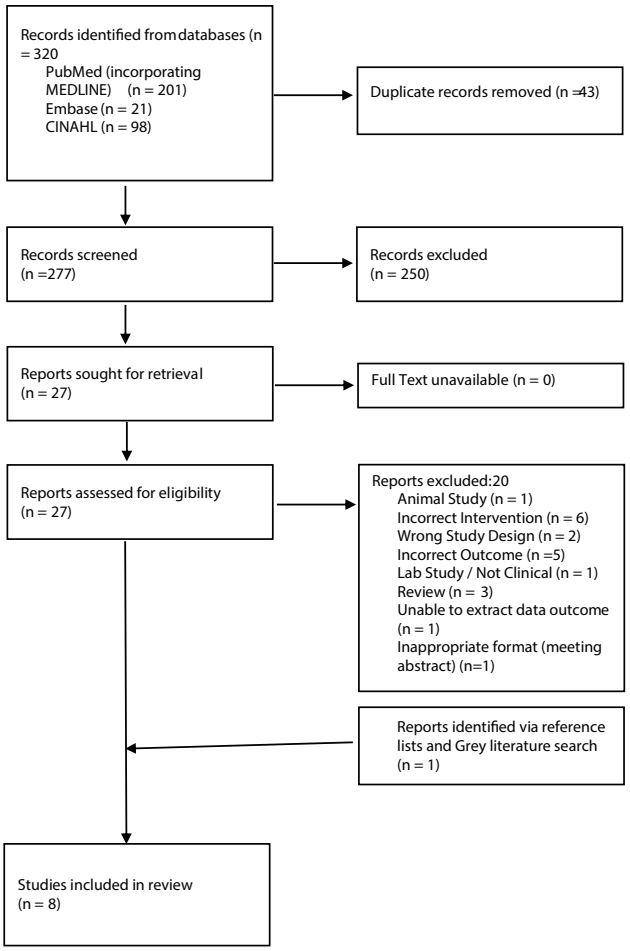

Fig. 1 Study selection

Total Sleep Time

Three studies reported subjective total sleep time in cherry vs placebo. With a pooled effect size of 0.14 (95% CI − 0.22–0.49, $P=0.79$). This result was associated with low heterogeneity ($I^2=0$) [32, 33, 35] (Fig. 3). The greatest difference between cherry and placebo for total sleep time was an additional 12 min (cherry group = 421 min vs placebo = 409 min; $P=0.197$), seen in healthy individuals [33]. The smallest observed difference between cherry and placebo for total sleep time was 1 min (cherry group = 475 min vs placebo = 476 min; $P=>0.05$), seen in healthy individuals [32]. Losso et al. reported subjective sleep measures as a standard mean difference and demonstrated a significant improvement in habitual sleep (sleep efficiency as measured by the Pittsburgh sleep quality index) ($0.5+/-0.5$, $P=0.0331$); however, a significant difference in sleep duration was not noted ($0.125+/-0.083$, $P=0.6845$) [34].

Table 1 Study Characteristic

First author	Year	Design	Cohort	Age (years)	Total cohort size	Male/females (%)	Intervention	Duration of intervention	Sleep measures
Garrido, M	2009	Prospective cohort	Healthy	Young (20–30) middle-aged (45–55) elderly (65–70)	18	Not reported	27.85 g powdered freeze-dried cherries (equivalent to 141 g fresh cherries) BD	3 days	Actigraphic (sleep efficiency, actual sleep time, number of awakenings, total nocturnal activity, sleep latency, assumed sleep, and immobility)
Garrido, M	2010	Prospective cohort	Healthy	Middle-aged (35–55) elderly (65–85)	12	Not reported	200 g fresh cherries BD	3 days	Actigraphic (sleep efficiency, actual sleep time, number of awakenings, total nocturnal activity, sleep latency, assumed sleep, immobility
Garrido, M	2013	Double blind, randomised, crossover trial	Healthy	Young (20–30) middle-aged (35–55) elderly (65–85)	30	50/50	18.85 g of pitted, freeze-dried cherries (equivalent to 141 g fresh cherries) BD	5 days	Actigraphic (sleep efficiency, number of awakenings, total nocturnal activity, sleep latency, assumed sleep, actual sleep time, immobility
Howatson, G	2012	Double blind, randomised, crossover trial	Healthy	18–40	20	Not reported	30 ml cherry juice concentrate (equivalent to 100 cherries) BD	7 days	Actigraphic (sleep efficiency, sleep onset latency, time in bed, fragmentation index, total sleep time Online subjective sleep diaries
Kimble, R	2022	Placebo-controlled RCT without a crossover design	Healthy	Mean 48 +/− 6	50	32/68	30 ml cherry juice concentrate BD	3 months	Pittsburgh sleep quality inventory (PSQI)
Losso, J	2019	Double blind, randomised, crossover trial	Insomnia	Mean 68 +/− 9.2	8	37.5/62.5	240 ml cherry juice nocte	14 days	Over-night polysomnographic sleep study (number of awakenings, wake time after sleep onset, sleep onset latency, total sleep time, sleep efficiency, stage REM latency) Pittsburgh sleep quality inventory (PSQI)
Pigeon, W	2010	Double blind, randomised, crossover trial	Insomnia	Mean 71.6 +/− 5.4	15	53/47	240 ml blend of cherry and apple juice BD	14 days	Sleep diaries
Simper, T	2019	Double blind, randomised, crossover trial	Healthy	Mean 21 +/− 1	16	55/45	"Night time recharge," 1000 mg of cherry active nocte	7 days	Accelerometer (sleep efficiency, sleep latency, time in bed and total duration of sleep)

BD, twice per day; *Nocte*, night time

Three studies assessed subjective total sleep time in pre- and post-cherry supplementation, with a pooled effect size of 0.27 (95% CI − 0.27–0.80, $P = 0.11$). This finding was associated with moderate heterogeneity ($I^2 = 0.12$, 54.36%) [32, 33, 35] (Fig. 4). The greatest difference between baseline and cherry for total sleep time was an additional 29.3 min (baseline = 388.3 min vs cherry group = 417.6 min; $P < 0.01$), seen in individuals with insomnia [35].

Sleep Onset Latency and Naps

Not included in the meta-analysis, due to insufficient cohort data, was subjective sleep onset latency, which demonstrated variable results across the three studies. The greatest difference in sleep onset latency between placebo and cherry was a reduction of 5.3 min (cherry group = 34.2 min vs placebo = 39.5 min; $P > 0.05$), seen in healthy individuals [32]. In two studies, there was a trend toward reduced sleep onset latency, whilst the opposite effect was observed in the third; however, none of these observations were statistically significant ($P > 0.05$) [32, 35].

The only study to record subjective daytime naps demonstrated significantly less napping time in the cherry juice trial compared to baseline and the placebo trials ($P = 0.031$; 95% CI = 0.7–13.6 and 0.7–11.1 min, respectively) [32]. This finding was made in the absence of any significant differences in subjective sleep efficiency, sleep onset latency, wake up after sleep or total sleep times. There was, however,

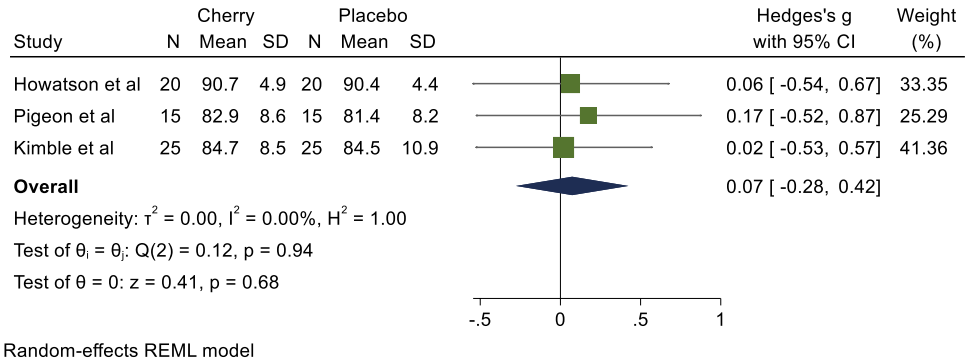

Fig. 2 Subjective sleep efficiency, placebo vs cherry. Left favour placebo, right favours cherry

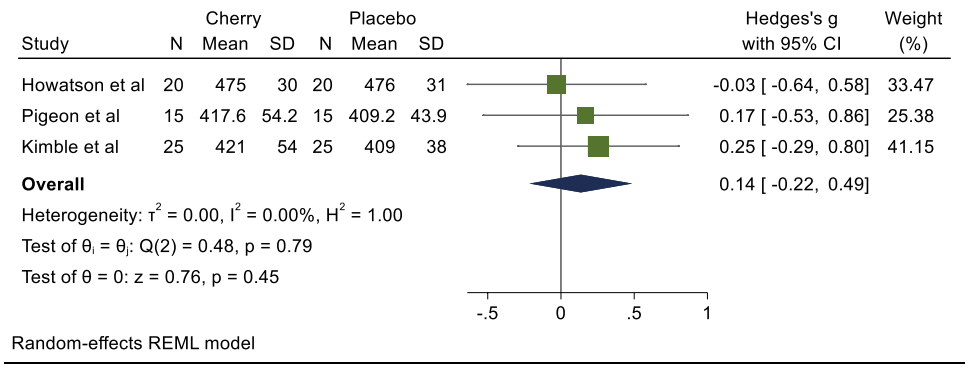

Fig. 3 Subjective total sleep time, placebo vs cherry. Left favours placebo, right favours cherry

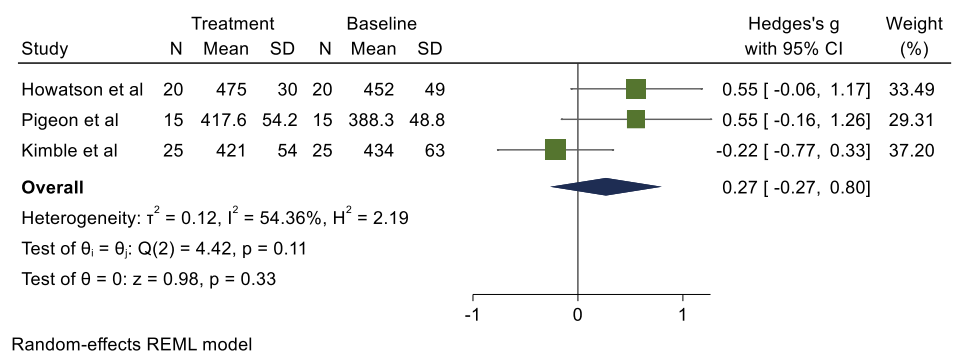

Fig. 4 Subjective total sleep time, pre- and post-cherry supplementation. Left favours baseline, right favours cherry

a significant increase in objective total sleep time in the cherry juice group vs baseline and placebo ($P < 0.003$; 95% CI = 15.2–39.7, 14.7–63.6, respectively).

Objective Sleep Measures

Six studies reported objective sleep measures, either utilising accelerometry, actigraphy or polysomnography [32, 34, 36–39].

Sleep Efficiency

Three studies uniformly reported sleep efficiency and, therefore, were included in a meta-analysis [32, 38, 39]. Sleep efficiency was significantly higher in the cherry cohort when compared to placebo with an effect size of 0.63 (95% CI 0.29–0.97, $P < 0.01$) (Fig. 5). There was low associated heterogeneity ($I^2 = 0\%$).

Total Sleep Time

Both the largest and smallest differences in placebo vs treatment (cherry) were observed in a patient cohort of similar characteristics (young, 20–30-year-old, healthy individuals). The greatest difference between cherry and placebo for total sleep time was an additional 67 min (cherry group = 425.52 min vs placebo = 358.54 min; P value not calculated) [38]. The smallest observed difference between cherry and placebo for total sleep time was an additional 22.2 min (cherry group = 408 min vs placebo = 385.8 min, $P = 0.244$) was reported [39]. Three studies uniformly reported total sleep time; therefore, they were included in a meta-analysis [32, 38, 39]. Total sleep time was significantly higher in the cherry cohorts, with a pooled effect size of 1.21 (95% CI 0.83–1.58, $P < 0.01$) (Fig. 6). This was associated with high heterogeneity ($I^2 = 81.5$).

The greatest difference between baseline and cherry for total sleep time was an additional 47.8 min (baseline = 398 min vs cherry group = 445.8 min; $P < 0.05$) in healthy middle-aged volunteers [38]. There were also some notable and significant improvements in total sleep time and sleep efficiency in the study by Garrido et al. (2010); however, values are reported as a 'fold' increase over baseline, so actual numbers of minutes are unknown. Losso et al. were the only study to assess objective sleep measures in patients with insomnia and reported no significant difference between cherry and placebo across sleep efficiency, sleep onset latency, REM latency, wake after sleep onset and number of awakenings. However, a significant increase in total sleep time was observed, with an increase of 84 min ± 61.7 ($P = 0.0182$) [34]. Similarly, Garrido et al. (2009) demonstrated statistically significant improvements in actual sleep time with cherry over baseline in the young (12.3% +/− 0.5: $P < 0.05$), middle-aged (10% +/− 0.2: $P < 0.05$) and elderly (18.2% +/− 1.6: $P < 0.05$) [36]. Garrido et al. (2010) echo these results with improvements in actual sleep time over baseline in middle-aged and elderly volunteers, the degree of which differing based on the strain of cherry used (range

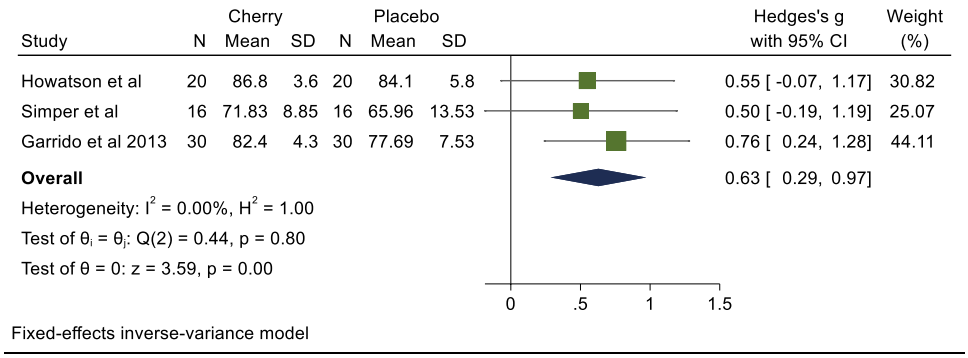

Fig. 5 Objective sleep efficiency. Left favours placebo, right favours cherry

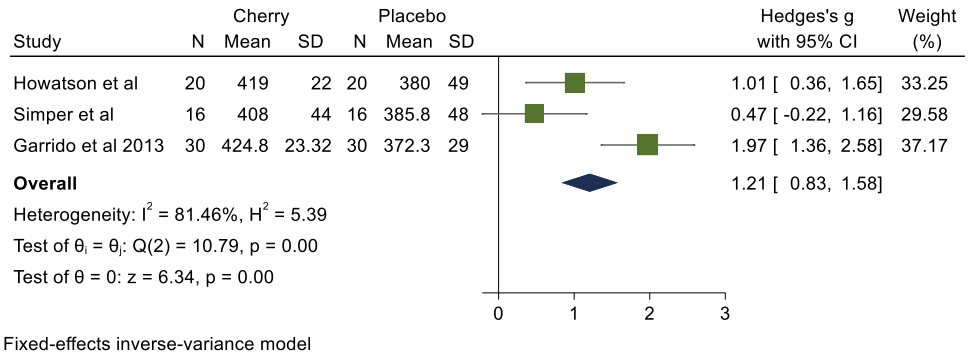

Fig. 6 Objective total sleep time. Left favours placebo, right favours cherry

from 1.15 + / − 0.05 fold increase for Pico Limón cherries to 1.45 + / − 0.07 fold increase for Pico Negro cherries ($P < 0.05$)) [37].

Sleep Onset Latency and Naps

The greatest difference in sleep onset latency between placebo and cherry was a reduction of 10 min (placebo = 19 min vs cherry group = 9 min; $P < 0.001$) in young healthy individuals [39]. No objective measures of daytime naps were undertaken.

Discussion

This systematic review is the first to synthesise the potential benefits of *Prunus cerasus* on sleep. *Prunus cerasus* use may provide an objective and clinically significant improvement in total sleep time and sleep efficiency. This objective improvement in sleep was not reflected in the participants subjective recall of total sleep time or sleep efficiency. However, the subjective meta-analysis included more participants with insomnia, a condition which is known to cause extreme deviations between subjective and objective measures of sleep [40]. Importantly, the objective meta-analysis included studies that together cover a wide age range, suggesting benefit is not restricted to a certain age group. This is also one of the rare instances where a study has performed a meta-analysis on objective measures of sleep for a supplement.

The dose of *Prunus cerasus* is of relevance when interpreting the present study's findings. Generally, effective dose of cherry supplementation was derived from ~ 100 g of cherries. This amount of fresh fruit contains ~ 0.135 µg of melatonin and 9 mg of tryptophan. The clinical dosing recommendations for these compounds are actually 0.5–5 mg for melatonin and 1.2–2.4 g for tryptophan, suggesting neither of these is the direct mechanism of tart cherry's benefits [34]. However, significant elevations in urinary melatonin metabolites [32, 37, 38] and a reduced degradation of tryptophan have been observed in the included studies [34]. Additionally, significant elevations in interleukin 1B, 8 and Tumour Necrosis Factor alpha have been demonstrated with cherry consumption which are all somnogenic cytokines [38]. The exact mechanism, however, remains unclear, and further studies may reveal a target for a new, safe and effective sleep pharmacotherapeutic agent.

Although none of the studies specifically studied *Prunus cerasus* supplementation in hospital inpatients, the potential for benefit from *Prunus cerasus* supplementation could extend beyond an outpatient, community setting and improve inpatient hospital outcomes. Currently, hospital systems pose difficulties to the achievement of healthy sleep in such a way that may potentially adversely affect patient outcomes [41, 42]. There is increased attention toward low-risk, supplementary regimens to improve patient outcomes [43]. Particularly in the absence of proven pharmacological interventions to improve sleep in hospitalised adults, *Prunus cerasus* supplementation may assist in patient sleep and recovery [44]. It may also be considered in hospital staff to improve sleep and, therefore, their decision-making, mood disturbances and burnout [45, 46]. However, firm evidence on its effectiveness in hospital settings is required before it's integration into hospital care systems [47].

This review has several limitations that should be acknowledged, including the exclusion of non-English articles. The small sample size of the included studies, further confounded by the small sample sizes observed in the included studies, is another limitation. Additionally, the trials are only short-term, and there is no evidence on long-term response, so the possibility of tachyphylaxis or tolerance has not been addressed. This precludes the ability to comment on the potential for better outcomes secondary to improved sleep in long-term users.

Conclusion

This systematic review is the first to synthesise the potential benefits of *Prunus cerasus* (tart cherries) on sleep. Whilst individuals may subjectively not experience a benefit, objectively, there is evidence to support significant improvements to total sleep time and sleep efficiency. Notably, the benefits were observed across all age groups. This review demonstrates the therapeutic benefit of tart cherries and their potential for the reduction of sleep deprivation-related morbidity and mortality worldwide. Further research is required to ascertain whether the benefits are retained after long-term supplementation and the exact mechanism of action.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40675-023-00261-w.

Funding Open Access funding enabled and organized by CAUL and its Member Institutions

Data Availability All data was sourced from existing literature and can be accessed by reviewing the appropriate referenced material.

Declarations

Conflict of Interest The authors declare no competing interests.

Human and Animal Rights and Informed Consent Formal ethical approval was not required or sought as this study does not involve the primary testing or humans or animals. This study does not involve any human or animal testing.

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