Influence of Dietary Sources of Melatonin on Sleep Quality: A Review

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Abstract: Sleep is an essential biological phenomenon, being a physiological and behavioral process necessary for quality of life. Melatonin is a circadian hormone produced at night by the pineal gland, regulated by the light/dark cycle, under the control of the suprachiasmatic nucleus. Melatonin is an indoleamine, synthesized from the essential amino acid tryptophan via serotonin. Melatonin is also found in plants, where it helps fight oxidative stress. To present a systematic review on the ability of food sources of melatonin to promote healthy sleep. A literature search was performed on the PubMed, Scopus, and ScienceDirect databases, including only randomized, placebo-controlled trials published in English between 2005 and 2019. The methodological quality of the trials was assessed by the Jadad scale. Of the 25 eligible articles, eight met the inclusion criteria. They addressed the intake of milk or cherry juice in children, adults, and elderly subjects and evaluated sleep quality by questionnaires, sleep diary, actigraphy, or polysomnography. The analysis of the studies presented limitations, including lack of homogeneity of treatment dosage and duration. Nonetheless, the results indicated that the consumption of milk and sour cherries, sources of melatonin, may improve sleep quality in humans. These results pointed out to the potential suitability of food sources of melatonin as adjuvants in the prevention and treatment of sleep disorders. Further studies are necessary to better ascertain the aspects relevant to their use.

Keywords: Food sources of melatonin, phytonutrients, antioxidant, anti-inflammatory, healthy sleep and sleep disorders

Introduction

Sleep is an essential biological phenomenon, being a physiological and behavioral process necessary for body regulation and quality of life at any age. In the modern world, sleep quality is often compromised, and sleep deprivation or restriction leads to several physiological and behavioral changes (Tufik, Andersen, Bittencourt, & Mello, 2009). A lack of sleep, in terms of either quantity or quality, can have many negative effects on health, such as metabolic dysfunction, hypertension, vascular disorders, and neurocognitive and cardiovascular diseases, leading to an increase in mortality (Cappuccio et al., 2008; Cappuccio, D'Elia, Strazzullo, & Miller, 2010; Hoevenaar-Blom, Spijkerman, Kromhout, Van den Berg, & Verschuren, 2011; Kripke, Garfinkel, Wingard, Klauber, & Marler, 2002).

Due to stressful working conditions and aging, it is estimated that one-third of the world population suffers from sleep disorders, mainly insomnia, and these disorders are more frequent in women and in the elderly (Miyamoto, 2009). Considering the numerous side effects related to insomnia medications (Glass, Lanctôt, Hermann, Sproule, & Busto, 2005), alternative therapies such as yoga, physical exercise, cognitive behavioral therapy, acupuncture, mindfulness, and nutritional therapy with functional foods, such as those that are sources of melatonin, have been proposed as non-pharmacological ways to promote better sleep quality (Tal, Suh, Dowdle, & Nowakowski, 2015).

A recent review found a potential reciprocal association between sleep and fruit and vegetables (FV) consumption. The authors reported that, although only a small number of studies evaluated this relationship in humans, the reviewed studies allowed the suggestion that the intake of FV sources of melatonin might improve sleep quality (Noorwali, Hardie, & Cade, 2019).

Melatonin is a circadian hormone produced by the pineal gland at night, with peak production around 02:00 a.m. in humans, and is regulated by the light/dark cycle, under the control of the suprachiasmatic nucleus (Daugaard et al., 2017).

The relationship between the sleep/wake cycle and the endogenous circadian system is important in promoting good health. The timing of the sleep/wake cycle follows the endogenous melatonin rhythm, and an association between the time of sleep onset and the initiation of melatonin synthesis has been demonstrated (Sletten, Vincenzi, Redman, Lockley, & Rajaratnam, 2010).

The endogenous levels of melatonin decrease with aging, possibly due to diminished perception of light by the vitreous body of the retina and/or by the decline in physiological activity of the pineal gland, leading to a higher incidence of sleep disorders (Amihaesei & Mungiu, 2012).

Besides circadian regulation and sleep improvement, melatonin bioactivities include antioxidant, anti-inflammatory and immune modulatory effects, memory improvement, neuroprotection, cardiovascular system modulation, bone homeostasis, lipid and glucose metabolism, and tumor inhibition (Kim, Kim, Bae, & Kim, 2017; Meng et al., 2017).

N-acetyl-5-methoxytryptamine, or melatonin, is an indoleamine synthesized from the essential amino acid tryptophan, via serotonin. As light is the main inhibitory environmental factor influencing melatonin production, hormone levels increase between 01:00 and 04:00 p.m. and are almost undetectable during the day (Scholtens, vanMunster, vanKempen, & de Rooij, 2016). Melatonin was originally identified in 1958, as a neurohormone in the pineal gland of cattle. In the late 1970s, it was identified in coffee. At the time, it was thought to be a by-product of the decaffeination process of coffee beans, but it is now known that coffee beans contain melatonin (Tan et al., 2012).

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However, in 1995, melatonin was also identified in plants (Erland, Chattopadhyay, Jones, & Saxena, 2016), where concentrations were higher than those found in animals (Wang, An, Shi, Luo, & He, 2017). As in animals, the biosynthesis of serotonin and melatonin in plants starts from tryptophan (Back, Tan, & Reiter, 2016).

Nowadays, it is well documented that melatonin exists in many foods, and its concentration ranges from picograms to milligrams/gram. The consumption of food sources of melatonin is associated with health benefits, significantly increasing serum concentrations and raising the antioxidant capacity in humans, being therefore considered a nutraceutical (Meng et al., 2017).

Among foods of animal origin, high concentrations of melatonin are found in eggs, fish, meat, animal and human milk (Karunanithi, Radhakrishna, Silvaraman, & Biju, 2014). Milk is already known to promote sleep because of its high levels of tryptophan that can be converted to melatonin (Milagres et al., 2014). Recent studies point to higher concentrations of melatonin in the milk extracted at night, presenting an advantage with respect to inducing sleep, in comparison to milk extracted during the day (Milagres et al., 2014). Fatty fish (fat content greater than 5%) is one of the main sources of vitamin D, omega 3 (HPA, DHA) and tryptophan, nutrients that play an important role in the prevention of physical and mental disorders, besides being important in the regulation of serotonin levels and sleep quality (Hansen et al., 2014).

The modern protein-abundant dietary pattern, rich in meat, poultry, fish, eggs, and milk, is associated with improved sleep quality, probably because of its high content of tryptophan and also of vitamin B12, which seems to aid in the regulation of sleep besides contributing to melatonin effects, being able to increase its synthesis and number of its brain receptors (Yu et al., 2017).

Melatonin has also been identified in many foods of plant origin, such as nuts, fruits, seeds, cereals, oils, coffee, wine, and beer (Tan, Zanghi, Manchester, & Reiter, 2014).

Some cereals such as wheat, oats, and barley have relatively high levels of melatonin (14.9 ng/g, 7.7 ng/g, and 6.0 ng/g, respectively) (Meng et al., 2017). With respect to melatonin in fruits, grapes and their derivatives (wine and juice), cherries, strawberries and kiwis have the highest concentrations. Among vegetables, the main sources of melatonin are peppers, tomatoes, and mushrooms (Kim et al., 2017; Lin, Tsai, Fang, & Liu, 2011; Meng et al., 2017).

After oral administration, melatonin is well absorbed, widely distributed and completely metabolized. It is able to pass the blood-brain barrier (Australian Goods Administration, 2009; Ng, Leong, Liang, & Paxinos, 2017). The intake of food sources of melatonin significantly increased its circulating levels in humans and presented positive effects on insomnia and other human pathologies (Gonzalez-Flores et al., 2012; Meng et al., 2017; Oba, Nakamura, Sahashi, Hattori, & Nagata, 2008; Reiter, Manchester, & Tan, 2005; Salehi et al., 2019).

It is noteworthy that glucose-rich food sources may also have a positive influence on sleep, as glucose favors tryptophan passage through the blood-brain barrier (Misra, Khor, Mitchell, Haque, & Benton, 2015).

The U.S. Dietary Supplemented Health and Education Act of 1994 (Natl. Inst. of Healthy—NIH, 1994) approved melatonin to be marketed as a dietary supplement, and the Natl. Sleep Foundation recommends for adults a dosage between 0.2 e 5mg 60 min before bedtime (National Sleep Foundation, 2019).

Healthy eating is one of the most important pillars for health and quality of life, and several epidemiological and methodological studies point to an association between healthy, balanced eating, and improved sleep quality. Based on the above considerations, the aim of this study is to present a systematic review of the functional properties of food sources of melatonin in promoting healthy sleep. Our study is, to the best of our knowledge, the first systematic review to investigate the influence of dietary sources of melatonin on sleep quality in humans.

Methodology

A systematic review was performed by searching the electronic databases of PubMed, Scopus databases and ScienceDirect, for English language articles published between 2005 and 2019. The study was conducted according to the PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analyses) guidelines (Peuhkuri, Sihvola, & Korpela, 2012; Tan et al., 2014) he following combinations of keywords: food (and) melatonin (and) sleep.

The articles were selected in two steps. In the first step, they were evaluated by title and abstract, according to the research objective and, in the second step, the full-texts of the articles were selected for data analysis. Only randomized double blind studies conducted in humans were selected, while observational or cross-sectional studies were excluded.

The Jadad scale was used to determine the quality of the study regarding double-blindness, randomization, and exclusions procedures, as well as description of losses. The total score allowed the classification of methodological quality as "null" (0), "very low" (1), "low" (2), "regular" (3), "good" (4), or "very good" (5) (Jadad et al., 1996). Only the articles presenting a score of at least 4 were included.

Results and Discussion

Selected studies and sample description

The flow chart of the selection of articles is shown in Figure 1. The application of the searching criteria recovered 90 articles in the ScienceDirect database and 175 in the PubMed database, of which 75 were cited in ScienceDirect as well. No articles were found in the Scopus database. Thus, a total of 190 articles were recovered. Of the 25 eligible articles, eight met the inclusion criteria. The selected articles were published from 2005 to 2017, showing that research associating food and sleep quality are recent. The studies adopted both short- and long-term treatment protocols (from 1 week to 4 months).

Assessment of the selected articles

Among the articles analyzed, all those selected were randomized, placebo-controlled and double blind studies (Table 1). According to the Jadad qualitative analysis scale, five articles (62.5%) received score of 4 and 3 (37.5%) received score of 5.

Sleep quality assessment

Tabel 1 shows that the first two articles used only questionnaires (subjective methods) to measure sleep quality. The first one used a subjective adapted questionnaire, which was filled by an observer (Valtonen, Niskanen, Kangas, & Koskinen, 2005), while the second one used the following questionnaires: insomnia severity index, Pittsburgh sleep quality index, Epworth sleepiness scale and sleep satisfaction scale (Bae, Jeong, & Jeon, 2016). Three studies used actigraphy combined with sleep diary. This method performs the recording of motor activity for 24 hr, allowing estimation of

Table 1–Summary of randomized double blind studies assessing the influence of dietary sources of melatonin on sleep quality in humans.

Study	Number of subjects (n)	Age (years)	Treatment	Results	Jadad	Instruments
Valtonen et al. (2005)	Study 1–Demented Subjects (62)	81.0 ± 9.0 (Mean ± SD)	**Study 1: S = Spring, T = 2 periods of 8 weeks separated by 1 week washout**	**Sleep Quality**		
			Group I: (N = 31): Night milk (period 1) compared with PLA (period 2)	Group I: ↔		
			Group II: (N = 31): PLA (period 1) compared with Night milk (period 2)	Group II: ↓		
	Study 2—Healthy Subjects (81)	82.8 ± 8.1 (Mean ± SD)	**Study 2: S = Winter, T = 2 periods of 8 weeks separated by 1 week washout**	**Sleep Quality**	4	Subjective assessment of sleep quality by an observer
			Group III: (N = 23): Night milk (period 1) compared with PLA (period 2)	Group III: ↑		
			Group IV: (N = 31): PLA (period 1) compared with Night milk (period 2)	Group IV: ↑		
			Group V: (N = 26): PLA (period 1) compared with PLA (period 2)	Group V: ↔		
Bae SM et al. (2016)	Single Study (91)	21 to 69	**T = 2 weeks**	**Sleep Satisfaction Scale**		SSS
				Group I and Group II: ↑		
				Epworth Sleepiness Scale		ESS
			Group I (N = 44): Melatonin-rich milk	Group I and Group 2: ↔	4	
			Group II (N = 47): PLA	**Insomnia Severity Index**		ISI
				Group I and Group II: ↓		
				Pittsburgh Sleep Quality Index		PSQI
				Group I and Group II: ↑		
Sekartini R et al. (2017)	Single study (115)	5 to 6	**T = 6 weeks**	**Wake After Sleep Onset (WASO)**		
				Group I, Group II and Group III: ↔		
			Group I (N = 39): Guar gum and starch-enriched milk	**Sleep Efficiency**		
			Group II (N = 37): α-casozepine, tryptophan-rich proteins, and maltodextrins-enriched milk	Group I, Group II and Group III: ↔	5	A + Sleep Diary
			Group III (N = 39): PLA	**Number of awakenings**		
				Group I: ↑		
				Group II and Group III: ↔		
Takada M et al. (2017)	Single study (94)	22.7 ± 0.2 (Mean ± SE)	**T = 11 weeks**	**Pittsburgh Sleep Quality Index**		PSQI
				Group I and Group II: ↔		
				Oguri-Shirakawa-Azumi Sleep Inventory		OSA

(Continued)

Table 1–Continued.

Study	Number of subjects (n)	Age (years)	Treatment	Results	Jadad	Instruments
			Group I (N = 48): Milk fermented with LcS Group II (N = 46): PLA	Group I and Group II: ↔ **Recovery in Sleepiness on Rising (by OSA scores)** Group I: ↑ Group II: ↔ **Sleep Length (by OSA scores)** Group I: ↑ Group II: ↔ **Sleep Latency (EEG)** Group I: ↓ Group II:↑ **N3 sleep percentage (EEG)** Group I: ↑ Group II: ↓ **Delta Power During First Sleep Cycle (EEG)** Group I: ↑ Group II: ↔	4	EEG
Pigeon W R et al. (2010)	Single study (15)	71.6 ± 5.4 (Mean ± SD)	**T = 4 periods of 2 weeks** Group I (N = 8): Baseline-Cherry juice-Washout-PLA Group II (N = 7): Baseline-PLA-Washout-Cherry juice	**Insomnia Severity Index** Group I and Group II: ↓ **Sleep latency (by Daily Sleep Diary -DSD)** Group I and Group II: ↓ **Wake after sleep onset – WASO (DSD)** Group I and Group II: ↓ **Total Sleep Time (DSD)** Group I and Group II: ↑ **Sleep Eficiency (DSD)** Group I and Group II: ↑	5	ISI DSD
Howatson G et al. (2012)	Single study (20)	26.6 ± 4.6 (Mean ± SD)	**T = 2 periods of 1 week separated by 2 weeks washout** Group I: Tart Cherry juice Group II: PLA	**Naps** (by Daily Sleep Diary -DSD) Group I: ↓ Group II: ↔ **Time in Bed** (by Actigraphy) Group I: ↑ Group II: ↔ **Total Sleep Time** (by Actigraphy) Group I: ↑ Group II: ↔ **Sleep Eficiency** (by Actigraphy) Group I: ↑		DSD A

(Continued)

Table 1–Continued.

Study	Number of subjects (n)	Age (years)	Treatment	Results	Jadad	Instruments
				Group II: ↔	4	
Garrido M et al. (2013)	Single study (30)	20 to 30 (n = 10)	**T = 2 periods of 5 days separated by 1 week washout**	**Actual Sleep Time and Immobility**		
		35 to 55 (n = 10)	Group I (young adults): Cherry juice Group II (young adults): PLA	Group I and Group III and Group V: ↑ Group II, Group IV and Group VI: ↔		
		65 to 85 (n = 10)	Group III (middle-age): Cherry juice Group IV (middle-age): PLA Group V (elderly): Cherry juice Group VI (elderly): PLA	**Number of Awakenings and Total Nocturnal Activity** Group I and Group III and Group V: ↓ Group II, Group IV and Group VI: ↔		
				Sleep Efficiency and Assumed Sleep Group I, Group II, Group III Group IV and Group VI: ↔ Group V: ↑ **Sleep Latency** Group I, Group II, Group IV and Group IV: ↔ Group III and Group V: ↓	5	A
Losso JN et al. (2017)	Single study (8)	≥50	**T = 2 weeks**	**Total Sleep Time** (by Polysomnography) Group I: ↑ Group II: ↔	4	PS
				Habitual Sleep Efficiency (by Pittsburgh Sleep Qualitity Index) Group I: ↑ Group II: ↔		PSQI
			Group I: Cherry Juice	**Insomnia Severity Index**		ISI
			Group II: PLA	Group I and Group II: ↔		
				Epworth Sleepness Scale Group I and Group II: ↔		ESS

Abbreviations:

A	Actigraphy	ISI	Insomnia severity index	PSQI	Pittsburgh sleep quality index	SE	Standard error of the mean
EEG	Electroencephalogram	LsC	Lactobacillus casei strain Shirota	PS	Polysomnography	SSS	Sleep satisfaction scale (1-10)
ESS	Epworth sleepness scale	OSA	Oguri-Shirakawa-Azumi Sleep Inventory	S	Season	T	Time of treatment
DSD	Daily sleep diary	PLA	Placebo group	SD	Standard deviation of the mean		

→ = No significant change; ↑ = Significant increase; ↓ = Significant decrease

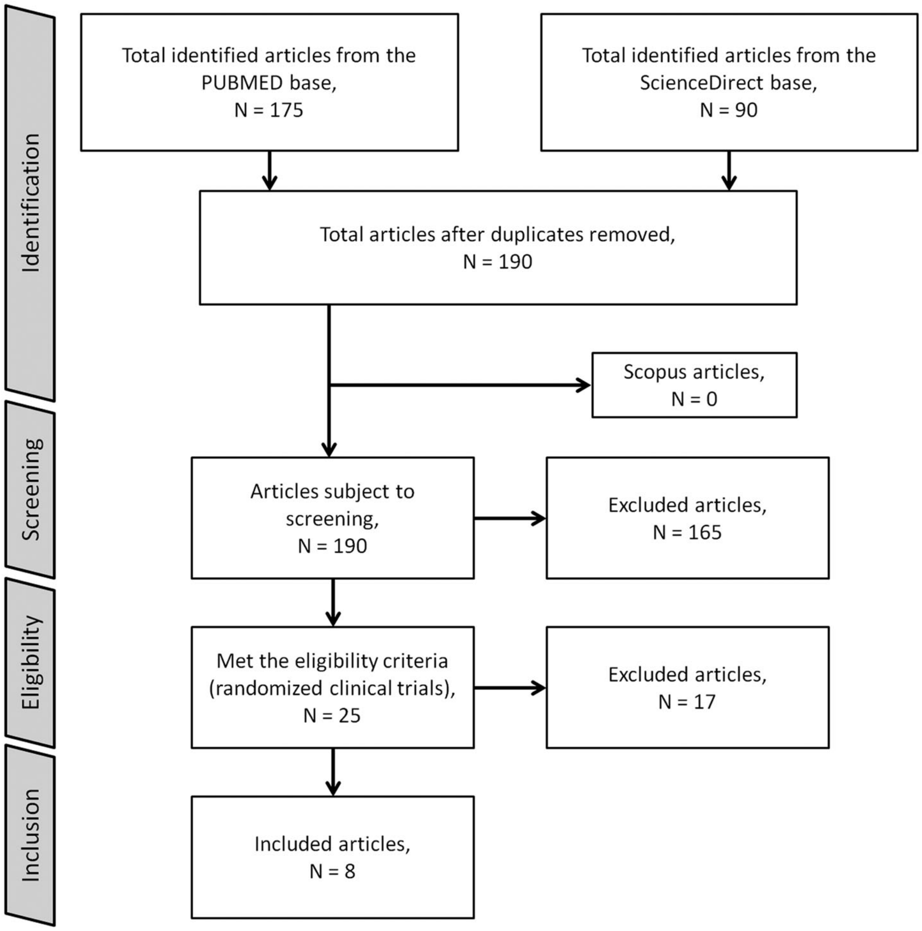

Figure 1–Flowchart of the selection of articles included in the study.

total sleep time, total time in wakefulness, and the number of awakenings (Howatson et al., 2012; Pigeon, Carr, Gorman, & Perlis, 2010; Sekartini et al., 2017). One of the selected studies used a distinct sleep inventory (Oguri-Shirakawa Azumi) combined with electroencephalography (Takada et al., 2017). The seventh study used only actigraphy (Garrido et al., 2013). Only one study used polysomnography (PSG) (Losso et al., 2017).

Although PSG is considered the gold standard method for the diagnosis of sleep disorders, such as apnea, a recent review pointed that the perfect sleep assessment method does not exist, and suggests that different methods should be combined to achieve a better understanding of sleep quality. Several studies have shown that subjective methods, such as questionnaires and sleep diaries, present sensitivity between 73% and 97.7%, while specificity ranges between 50% and 96%. The actigraphy, an objective method, have sensibility higher than 90% (Ibáñez, Silva & Cauli, 2018).

Effect of melatonin food sources on sleep quality

Although several foods are a source of melatonin, there are few controlled-placebo randomized studies assessing this subject. Our review identified only eight studies, four looking at milk as the source or melatonin and the other four looking at cherries. Milk is known to contain several proteins and essential amino acids, including tryptophan. As previously mentioned, tryptophan is converted to serotonin and melatonin, inducing relaxation and increasing somnolence (dela Perla et al., 2015).

The first paper analyzed the effects of melatonin intake from night-extracted milk in demented (study 1) and healthy (study 2) elderly subjects (Valtonen et al., 2005). Milk extracted at night showed increased melatonin levels (10 to 40 ng/L) when compared to standard milk. Each of the two studies included two periods of 8 weeks separated by a washout period of 1 week. During each period of 8 weeks, the volunteers received half a liter of either night-harvested or standard milk per day. In the first study, in which all the 62 elderly patients were diagnosed with dementia, trained nurses subjectively evaluated their sleep quality. In the second study, 81 healthy elderly had their sleep quality subjectively graded by the caregivers from their rest-homes.

The first study was held during spring. No significant changes in sleep quality was detected in the group of demented elderlies receiving night milk followed by normal milk (group I, $n = 31$). Contrastingly, the group receiving normal milk followed by night milk (group II, $n = 31$), subjectively-assessed sleep quality even decreased. The authors found a significant effect of season, as the study was performed during a period of shortened dark period. However, they observed an effect on daytime and evening activity in some of the elderlies who consumed night-extracted milk (Valtonen et al., 2005).

The second study was held in the winter, and the 81 volunteers were divided into three distinct groups. The group that consumed night-milk for 8 weeks, followed by a 1-week washout period, and then ingested standard milk for 8 weeks was called group III ($n = 23$). Group IV ($n = 26$) started with standard milk for 8 weeks, followed by a 1-week washout period, and then ingested night-milk for 8 weeks. The group V (n = 32) consumed standard milk throughout the study, and was considered as the control group (Valtonen et al., 2005).

The results of Study 2 indicated, in the second period of the study, a better score of sleep quality in group III ($P < 0.001$), IV ($P < 0.001$), and also in the control group ($P < 0.05$), demonstrating once more the seasonal effect on sleep quality, and confirming that the human sleep rhythm responds to changes related to day length. In addition, it was observed that Group IV had an improvement in the performance of its activities during the day ($P < 0.001$) and in the evening ($P < 0.01$) (Valtonen et al., 2005).

The study concluded that night-extracted milk was not able to increase serum levels of melatonin and sleep quality. However, even very low doses of melatonin may benefit the elderly by increasing their daytime activity (Valtonen et al., 2005).

The second article analyzed included 91 adults with mild insomnia, aged 21 to 69 years (Bae et al., 2016). The study evaluated the effects of the consumption of 1 cup of melatonin-rich milk before bedtime, ingested for 2 weeks (n = 44), compared to standard milk placebo (n = 47), with the objective of evaluating possible improvements in sleep quality. The melatonin-rich milk powder consumed by the study group was a hydrolyzed nonfat dry milk (CJ Night Milk®, 12.5 g/sachet) containing 1 ng of melatonin per sachet and 58.24 mg of tryptophan per sachet, while the placebo group consumed an usual milk (general hydrolyzed nonfat dry milk, 12.5 g/sachet) containing 0.1 ng/sachet of melatonin and 46.9 mg of tryptophan. The instruments used to assess sleep quality were the Insomnia Severity Index, the Epworth Sleepiness Scale, the Sleep Satisfaction Scale, and the Pittsburgh Sleep Quality Index. According to the results, the changes observed in the melatonin-rich milk group were not statistically different as compared to the placebo group, as both groups had significant improvements in sleep satisfaction, Pittsburgh Sleep Quality Index and Insomnia Severity Index scores (Bae et al., 2016).

Studies in animals have also shown that night-extracted milk had a sleep enhancing effect (dela Perla et al., 2015). In addition, the high concentrations of casein that is found in all milk, is responsible for the release of opioids, which may positively influence sleep quality (dela Perla et al., 2015, 2016).

The third study assessed for this review was conducted with 115 children (aged between 5 and 6 years) with decreased sleep efficiency, and aimed to evaluate the influence of drinking milk on sleep and memory efficiency (Sekartini et al., 2017). Children were allocated in three groups. The first group received beverages enriched with guar gum and starch (denominated satiety group, n = 39), the second group received milk enriched with α-casozepine, tryptophan-rich proteins and maltodextrins (relax group, n = 37), and the third group consumed standard milk (control group, n = 39). Each group received 200 mL of the drink for breakfast and another serving 15 min before bed, for 6 weeks. The results showed no differences in total sleep time and sleep efficiency among the three groups. In the satiety group, the number of nocturnal awakenings increased ($P = 0.021$) at the end of the study, indicating that the consumption of starch drink was negatively associated with sleep efficiency. Regarding memory, at the end of the study, the satiety group presented significant worsening in remembering words ($P < 0.001$). The article concluded that the composition of milk influences memory recall, sleep parameters, and growth (Sekartini et al., 2017).

The fourth article evaluated 94 medical students who were under psychological stress (Takada et al., 2017). The study evaluated the effects of the daily intake, for 11 weeks, of 100 mL of milk fermented with Shirota strain of *lactobacillus casei* (LcS) (n = 48) in comparison to the placebo group (n = 46), which received milk added with lactic acid to match the flavor of the fermented milk. The results showed an improvement in sleep latency ($P < 0.05$), N3 sleep percentage ($P < 0.01$), and delta power during the first sleep cycle ($P < 0.05$), parameters assessed by electroencephalography (EEG) recordings of a single channel. Moreover, sleep latency increased in the placebo group and was reduced in the group that consumed the fermented milk. The fermented milk was also able to improve recovery in sleepiness on rising ($P < 0.01$) and sleep length scores ($P < 0.05$), both measured by the Oguri-Shirakawa Azumi questionnaire, which contributed to higher satisfaction about sleep quality in the same questionnaire. The study therefore concluded that the daily consumption of LcS was able to ameliorate sleep quality during a period of stress (Takada et al., 2017).

The study did not measure the quantity of melatonin and/or tryptophan presented in the fermented milk and concluded that the mechanisms of action of LsC in the improvement of sleep quality remain unknown (Takada et al., 2017). It is well known that the consumption of probiotics, such as fermented milk with LcS, improves the gut microbiota (Martín-Cabrejas, Aguilera, Benítez, & Reiter, 2017). The intestinal microbiota maintains a bidirectional neurohumoral communication between the intestine and the brain, influencing the metabolism of tryptophan and the biosynthesis of serotonin and a healthy microbiota has been shown to exert a positive effect on sleep (Kato-Kataoka et al., 2016; O'Mahony, Clarke, Borre, Dinan, & Gryan, 2015). A study evaluating the intake of fermented beverage with lactobacilli Helveticus twice a day for 3 weeks, also showed an improvement in sleep quality of healthy elderly (Yamamura et al., 2009).

Another important source of melatonin is the sour cherry or Montmorency cherry (*Prunus cerasus*), which has numerous health benefits, including the regulation of sleep. These benefits have been attributed to the high concentrations of phytonutrients, including phenolic acids, chlorogenic acid, caffeic acid, ellagic acid, and flavonoids, such as quercetin, catechin, and epicatechin (Burkhardt, Tan, Manchester, Hardeland, & Reiter, 2001). In addition, sour cherries contain high concentrations of tryptophan, serotonin, melatonin and antioxidants, improving sleep quality and reducing oxidative damage (Darshan, Yuriko & Laugero, 2018; Howatson et al., 2012). The sour cherry contains a higher concentration of melatonin (13.46 ± 1.10 ng/g) than the sweet cherry (2.06 ± 0.17 ng/g) (Burkhardt et al., 2001).

The remaining four studies investigated cherries as a food source of melatonin and consequently, as a sleep quality promoter.

One study was conducted with 15 old adults (≥65 years of age) with chronic insomnia, who received both the treatment (Montmorency tart cherries juice, 240 mL, twice a day) and the placebo (beverage with similar sugar, acid and visual properties of the cherry juice, but without the phytonutrients), for 2 weeks, with 2 weeks washout between the treatments. Both the placebo and juice treatments were compared to a baseline period. The results showed that the consumption of cherry juice significantly improved the insomnia severity index ($P < 0.05$), decreased sleep latency ($P < 0.05$), and the number of awakenings (WASO–$P < 0.01$), consequently increasing total sleep time ($P < 0.01$) and sleep efficiency ($P < 0.05$). Interestingly, an improvement in the mean values of insomnia severity index, sleep latency, WASO, total sleep time and sleep efficiency was also observed in the placebo group, however, only the total sleep time was significantly increased by the consumption of the placebo ($P < 0.05$). These parameters were assessed by the Insomnia Severity Index and the Daily Sleep Diary. The study concluded that the pure cherry juice had beneficial effects in elderlies with insomnia (Pigeon et al., 2010).

Another selected study was conducted among 20 young and healthy adults (mean age of 26.6 years). The participants received tart Montmorency cherry juice or placebo for 7 days, followed by a washout period of 14 days, and then more 7 days consuming of juice or placebo. The concentration of melatonin on the cherry juice was 42.61g/30 mL, leading to the consumption of 85.2 g of melatonin per day. The placebo preparation was made with less than 5% of fruit, containing no melatonin or anthocyanin (Howatson et al., 2012). The supplementation with 30 mL of tart Montmorency cherry juice concentrate, ingested twice a day, was able to increase melatonin-circulating levels and ameliorate sleep quality by increasing time in bed ($P \leq 0.05$), total sleep time ($P \leq 0.05$), and sleep efficiency total ($P \leq 0.05$), while it reduced the number of naps ($P < 0.05$). Total sleep time increased 5% to 6%. The authors suggested that the consumption of tart Montmorency cherry juice can elevate melatonin circulating levels and may be helpful adjuvants for the treatment of sleep disturbances in healthy subjects with no reported sleep disorders (Howatson et al., 2012).

The seventh selected study evaluated the effect of the ingestion of cherries from the Jerte Valley on sleep quality, urinary concentrations of 6-sulfatoxymealtonine (aMT6-s) and serum concentrations of: interleukin 1B (IL-1B), tumor necrosis factor (TNF-α), and interleukin-8 (IL8). Ten young (20 to 30 years old), 10 middle-aged (35 to 55 years old), and 10 older adult (65 to 85 years old) volunteers with no diagnostic of sleep disorders were evaluated (Garrido et al., 2013). The study design consisted of two distinct treatment periods of 5 days each, when the volunteers received either placebo or the Jerte Valley cherry, separated by a washout period of 1 week. The drink consisted of a concentrate of 18.85 g of frozen cherries, equivalent to 141 g of fresh cherries, which has high levels of total phenolic compounds, tryptophan and melatonin. The preparation was lyophilized and then diluted in water (125 mL doses), and consumed twice a day as a dessert, after lunch and dinner. The drink offered as placebo was a commercial cherry-flavored soft drink (kool-aid®) (Garrido et al., 2013).

The study used actigraphy and showed that the consumption of Jerte Valley cherries improved ($P < 0.05$) sleep time and immobility, and reduced wakefulness, total nocturnal activity, and sleep latency ($P < 0.05$) in all groups that received the cherry juice. Reduction in sleep latency was observed in the middle-aged and older adult volunteers ($P < 0.05$), while the improvement of sleep efficiency ($P < 0.05$) and assumed sleep ($P < 0.05$) was detected only in the elderly group after ingestion of the cherry concentrate. The authors also found elevated urinary levels of 6-sulfatoxymelatonin and increased serum pro-somnogenic cytokines in all groups. Thus, the consumption of Jerte Valley cherries was able to establish a high-quality sleep, and the fruit can be used as a nutriceutical for a better sleep quality (Garrido et al., 2013).

The last research was performed with eight individuals over the age of 50, with a clinical diagnosis of insomnia (Losso et al., 2017). These volunteers ingested 240 mL of cherry juice or placebo juice in the morning and another serving 1 to 2 hr before bed, for 14 days. The placebo juice contained vapor-distilled water, fructose, dextrose, and lemon powder and had the appearance and taste of a cherry juice. After two weeks, a full-night polysomnography was performed and blood samples were collected. The polysomnography showed an average increase of 84 min in total sleep time ($P = 0.082$), and the habitual sleep efficiency (measured by the Pittsburgh Sleep Quality Index) was significantly increased in the group that received the cherry juice (0.0331). There was no statistically significant difference in the Insomnia Severity Index, the Epworth Scale, or in the Beck Depression Inventory. The authors concluded that the consumption of the tart cherry juice was effective for the treatment of insomnia, with no adverse effects (Losso et al., 2017).

The findings showed that sour cherry is an important source of melatonin, and confirm that daily consumption of this fruit may increase the endogenous production of melatonin, thus improving sleep quality.

Conclusion

Although melatonin is found in a variety of foods, to date, there have been very few randomized placebo-controlled studies on the effects of consuming foods containing melatonin on sleep quality. Although the number of available studies are limited and they do not allow to conclude about treatment dosage and duration, their examination did indicate that the consumption of milk and sour cherries, sources of melatonin, may improve sleep quality in humans. These observations point out to the potential suitability of food sources of melatonin as adjuvants in the prevention and treatment of sleep disorders. Due to cited limitations, however, further studies are necessary to better ascertain the aspects relevant to their use.

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Transparency Declaration

The lead author affirms that this manuscript is an honest, accurate, and transparent account of the review being reported. The reporting of this work is compliant with PRISMA guideline. The lead author affirms that no important aspects of the study have been omitted and that any discrepancies from the study as planned have been explained.

Author's Contributions

Nádia Pereira: Made substantial contributions to the conception and design of this review. She also contributed substantially in drafting the work. The author gave final approval of the version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy of any part of the work were appropriately investigated and resolved.

Maria Fernanda Naufel: Made substantial contributions to the conception and design of this review. She also contributed in drafting and revising the work. The author gave final approval of the version to be published.

Eliane Beraldi Ribeiro: Made substantial contributions to the conception of this review. She also contributed in revising it critically. The author gave final approval of the version to be published.

Sérgio Tufik: Made substantial contributions to the conception of this review. He also contributed in revising it critically. The author gave final approval of the version to be published.

Helena Hachul: Made substantial contributions to the conception and design of this review. She also contributed substantially in revising it critically. The author gave final approval of the version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy of any part of the work were appropriately investigated and resolved.

Conflict of Interest

The authors declare no conflict of interest.

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