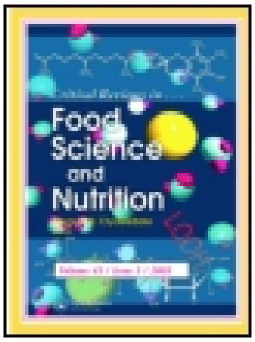

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REVIEW

Relationship between food consumption and improvements in circulating melatonin in humans: an integrative review

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ABSTRACT
Melatonin is an important hormone in the regulation of circadian rhythms and has great antioxidant power. Recent studies have demonstrated the benefits of its supplementation in the metabolic profile. Food sources have also been studied for complementary therapies. However, information on the bioavailability of food sources of melatonin is still scarce. Thus, the objective of this review is to gather in the literature studies that evaluate the relationship between food consumption and improvements in circulating melatonin in humans. In total, 178 studies were found, of which 11 were included in this review. The results show increases in the excretion of the melatonin metabolite (6- sulfatoxymelatonin) or circulating melatonin for foods such as cherries, grapes, bananas, pineapples, dark green vegetables, Japanese vegetables and beer. Significant increases in melatonin were observed even after ingesting cultivars with low concentrations of this hormone. It was possible to assume that other nutrients that precede their synthesis (serotonin and tryptophan) could also have led to this increase. Although consumption of the foods found is beneficial in increasing circulating melatonin, further confirmatory studies are needed.

KEYWORDS
Foods; melatonin; 6-sulfatoxymelatonin and bioavailability

Introduction

Melatonin is a hormone that plays an important role in synchronizing circadian rhythms, controlling onset and quality of sleep. Their endogenous levels vary according to the chronotype of each individual. In addition, they increase approximately 2 hours before the natural onset of sleep with a peak approximately 5 hours after (Xie et al. 2017). The stimulus for melatonin synthesis comes from photoperiodic signals that pass through the retina and are sent to the suprachiasmatic nuclei (SCN). The SCN, in turn, sends the signals for the pineal gland to produce this hormone. Melatonin is then released to the body distributing the signal for its production to several organs in addition to the pineal gland, it is mentioned, retina, skin, lymphocytes, bone marrow and gastrointestinal tract. (Souza Neto and Castro 2008; Salehi et al. 2019).

Regarding melatonin synthesis, the amino acid tryptophan is an important precursor. In this sense, it undergoes a decarboxylation by the enzymes *tryptophan hydroxylase* and *aromatic acid decarboxylase* and is converted into the neurotransmitter serotonin.Therefore, serotonin is converted to N-acetyl-serotonin by the enzyme *arylalkylamine N-acetyltransferase* and to melatonin by *hydroxyindole-O-methyltransferase* (Zhao et al. 2019; Salehi et al. 2019). Regarding its excretion, its main metabolite is 6-sulfatoxymelatonin (aMT6s) produced by the liver and excreted in the urine. Urinary levels of aMT6s are proportional to the plasma melatonin levels, being a good noninvasive indicator of this hormone (Amaral and Cipolla-Neto 2018).

Melatonin can be considered one of the most powerful natural antioxidants. It acts both in the chelation of reactive oxygen and nitrogen species and in the mobilization of the cellular antioxidant enzyme system (Amaral and Cipolla-Neto 2018). In humans, melatonin controls neuroendocrine processes through two membrane receptors called MT1 and MT2 which are coupled to protein G (Salehi et al. 2019; Aguiar and Pereira 2019; Amaral and Cipolla-Neto 2018). It should be noted that circulating melatonin levels can decrease significantly with age (Salehi et al. 2019). In addition, both changes in the expression of its receptors and in its endogenous production may be related to heart disease, depression, Alzheimer's and cancer (Pandi-Perumal et al. 2008).

Due to the great physiological importance of melatonin, its use in supplement form has been linked to improvements in the metabolic profile, antioxidant capacity and quality of sleep in adults (Koziróg et al. 2011; El-Sharkawy et al. 2019; Shabani et al. 2019). In addition, a recent review raised the hypothesis of using melatonin as an aid in the treatment of COVID 19. In this sense, due to its anti-inflammatory, antioxidant and immune-enhancing characteristics, melatonin can be considered an indirect antiviral (Zhang et al. 2020).

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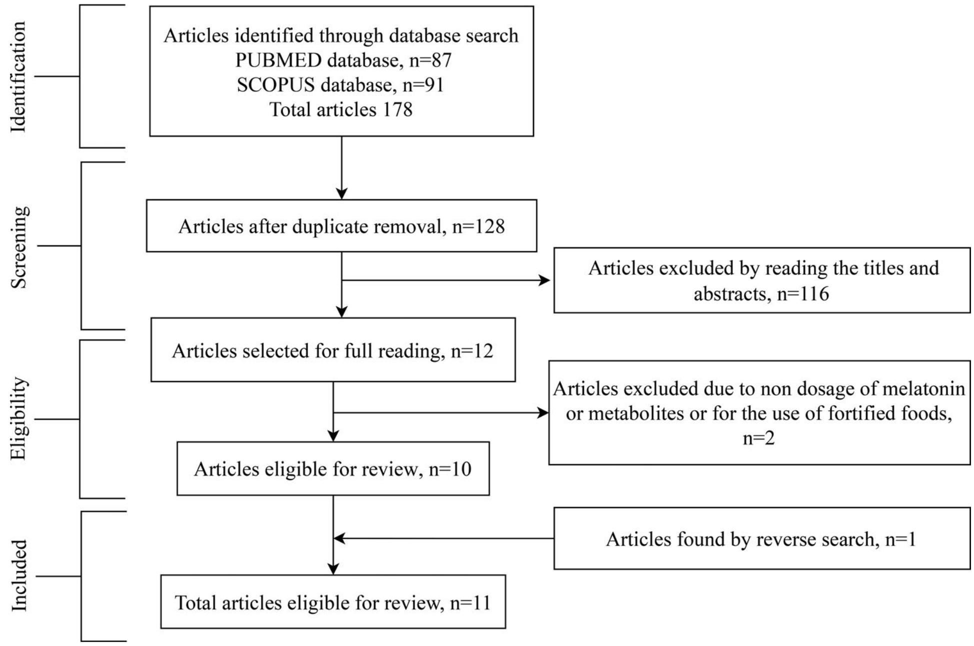

Figure 1. Stages of identification, inclusion and exclusion of articles in the integrative review.

Health benefits have also been shown with food sources of melatonin, such as improvements in antioxidant capacity and sleep time (Garrido et al. 2013; Garrido et al., 2010; Howatson et al. 2012; Sae-Teaw et al. 2013). Thus, due to the great importance of non-drug therapies in improving parameters such as sleep, immunity and oxidative stress, together with the benefits of melatonin, (Salehi et al. 2019; Bjørklund and Chirumbolo 2017; Z Tal et al. 2015) several authors have identified food sources of this indolamine in their studies. Standing out food groups such as fruits, milk, cereals, among others (González-Gómez et al. 2009; Sae-Teaw et al. 2013; Schaper, Braun, and Koethe 2015; Badria 2002).

Although there are increasing studies identifying melatonin in foods, knowing about its bioavailability in food sources is essential for more reliable nutritional prescriptions. This information will help to identify which food groups, dietary patterns and specific foods have an impact on melatonin concentrations. Thus, we elaborate the following question: Does the consumption of melatonin sources have an impact on circulating melatonin in humans? In this sense, the present review aims to gather in the literature studies that show the relationship between food consumption and improvements in circulating melatonin in humans.

Methodology

For this integrative review the PubMed (National Library of Medicine, Bethesda, MD) and Scopus databases were consulted. The following combinations of descriptors were used to perform the searches in above-mentioned databases: "Melatonin and Food sources" or "Melatonin and food and 6-sulfatoxymelatonin" . The search was conducted by independent researchers in January 2020 and there was no limit to the date of publication. In order to locate possible studies not found in the initial search, the authors performed a reverse search using the reference lists of selected articles.

As exclusion criteria were considered: bibliographic reviews, letters to the author, book chapters, articles that used supplements, drugs or fortified foods, articles that did not analyze the increase of plasma melatonin or its metabolite 6- sulfatoxymelatonin, articles with animals and duplicates. The inclusion criteria were original articles, that related the consumption of food or a specific food with the plasma increase of melatonin or urinary excretion of its metabolite 6-sulfatoxymelatonin. A total of 178 articles were found, these 50 were repeated. Of the 128 remaining articles, the titles were read and when necessary, the abstracts were also read. After applying the exclusion criteria, 12 articles remained for full reading. Of these, 2 were excluded, as one used fortified food and the other did not measure serum melatonin or its metabolite. Finally, 10 articles met the eligibility criteria. After reverse search, 1 article was added. Thus, 11 articles were selected for this review (Figure 1).

Results and discussion

Studies characteristics

Among the 11 studies included in this review, we highlight that the majority are intervention (nine studies). Regarding the interventions, six studied only the consumption of one type of food in the increasing the circulating melatonin levels or excretion aMT6s (González-Flores et al. 2011, 2012; Garrido et al. 2010; Garrido et al. 2013; Howatson et al. 2012; Maldonado, Moreno, and Calvo 2009). One study related the consumption of different vegetables with urinary aMT6s (Oba et al. 2008) and two analyzed the consumption of fruit or fruit juice with circulating melatonin levels or excretion aMT6s (Johns et al. 2013; Sae-Teaw et al. 2013). In turn, cross-sectional studies used the Food Frequency

Questionnaire (FFQ) to relate food consumption with excretion of aMT6s (Nagata et al. 2005; Schernhammer et al. 2009).

Regarding the sample size, intervention studies ranged from 7 to 94 individuals (Garrido et al. 2010; Oba et al. 2008) and in the cross-sections varied from 289 to 998 individuals (Nagata et al. 2005; Schernhammer et al. 2009). Regarding the place where the studies were carried out, four were carried out in the Badajoz province, Extremadura, Spain (González-Flores et al. 2012, 2011; Garrido et al. 2013; Garrido et al. 2010), one study in Seville, Spain (Maldonado, Moreno, and Calvo 2009) two were conducted in Gifu City, Japan (Nagata et al. 2005; Oba et al. 2008), one in Boston city, England (Schernhammer et al. 2009), one in Newcastle upon Tyne, England (Howatson et al. 2012) and two in Mueang Khon Kaen district, Thailand (Johns et al. 2013; Sae-Teaw et al. 2013), no studies with Brazilian population were found. The detailed description of selected studies are presented in Tables 1 and 2.

Among experimental studies that evaluated only one food species, three evaluated the consumption of cherries (Garrido et al. 2013; Garrido et al. 2010; Howatson et al. 2012); one analyzed the consumption of grape juice (González-Flores et al. 2012) one of Japanese plums (González-Flores et al. 2011) and a study analyzed beer consumption (Maldonado, Moreno, and Calvo 2009). Among those who evaluated more than one food, the consumption of orange, pineapple or blueberry juices and the consumption of bananas or mangoes *in natura* were presented (Johns et al. 2013; Sae-Teaw et al. 2013). Finally, the consumption of seven specific vegetables of the Japanese diet, Sweet Corn, Bitter Gourd, Japanese Radish Sprouts, Garland Chrysanthemum (shungiku), Shimeji Mushroom and Shiitake Mushroom (Oba et al. 2008).

Experimental studies

Cherries consumption

Two randomized clinical trials analyzed the relationship of the daily consumption of cherries in natura or in the form of beverages with the excretion of aMT6s urinary and in sleep quality (Garrido et al. 2010; Garrido et al. 2013). The first study analyzed the daily consumption of about 400 grams of seven different cherry cultivars (Bourlat, Navalinda, Van, Ambrunés, Pico Limón, Pico Negro, and Pico Colorado), a three-day washout period was performed to change cultivars. Improvements in sleep time, increased urinary aMT6s and total urinary antioxidant activity were observed for all cultivars. In terms of night activity, sleep latency, immobility and number of awakenings, improvements were observed only for some cultivars (Garrido et al. 2010). In the second study, the consumption of 18.85 grams of freeze-dried cherries, equivalent to 141 grams of fresh cherries, was analyzed. Each drink contained equal parts of four cherry cultivars (Bourlat, Navalinda, Pico Negro, and Pico Colorado) and was offered twice a day. Improvement in sleep efficiency was observed, especially in the elderly, in addition, there was an increase in urinary aMT6s and improvement in pro-sonogenic cytokine concentrations (Garrido et al. 2013).

In a previous study, with the cherry cultivars analyzed in the above studies, Bourlat type cherries had the highest melatonin concentrations (22.4 ± 1.2 ng/100g fresh fruit). The Ambrunes type cherry had the highest concentrations of serotonin (37.6 ± 1.4 ng/100 g fresh fruit), however melatonin was not detected (González-Gómez et al. 2009). Inverse correlations between serotonin and melatonin levels were observed in some cherries, which can be explained by the biosynthesis pathway of melatonin (González-Gómez et al. 2009; Zhao et al. 2019). Thus, it is observed in the studies even cherries that did not present melatonin (such as the Ambrunes type) were related to the increase in urinary aMT6s. Thus, it was possible to infer that both melatonin and serotonin present in cherries may have contributed to improvements in sleep parameters and aMT6s excretion (Garrido et al. 2013; Garrido et al. 2010).

Another study analyzed the consumption of beverage containing 30 mL of Montmoreney Cherry juice concentrate. The drink was consumed twice a day and offered approximately 42 µg of melatonin. Volunteers received juices or placebo for seven days, there was a washout period of 14 days, then they received juice or placebo again for another seven days (Howatson et al. 2012). Increased urinary excretion of aMT6s, improvements in sleep efficiency, sleep and bed time, and reduction in the number of naps was observed, after the supplementation period, in the test group. A differential of this study is that all 48-hour urinary emptyings at baseline and in the last 48 hours of intervention were used for comparisons, a fact that can provide more real data on melatonin metabolism (Howatson et al. 2012).

Regarding sleep improvements, only studies with cherries present this parameter (Garrido et al. 2010; Garrido et al. 2013; Howatson et al. 2012). Reinforcing these findings studies show that melatonin supplementation has a positive effect on sleep quality (Grima et al. 2018; Sletten et al. 2018). However, we must consider that the increase in antioxidant capacity may also have contributed to sleep improvement. In this sense, antioxidant dietary interventions can lead to significant changes in circadian rhythm (Oseguera-Castro et al. 2019; Garrido et al. 2010)

Plums consumption

The Japanese plum was also investigated, 390 grams of this fruit per day was offered to young, adult and elderly individuals. An increase in aMT6s excression and total urine antioxidant capacity was observed. Although melatonin has been identified in these cultivars, it has not been quantified. In turn, serotonin, a precursor of melatonin in the tryptophan pathway, was identified and quantified at a concentration of 213 ± 7.7 ng/kg. In this sense, from the identification of these indolamines the authors infer the presence of the precursor tryptophan and the increase of aMT6-s urinary as a consequence of the consumption of melatonin contained in plums (González-Flores et al. 2011). It is also noted that the presence of tryptophan could stimulate the melatonin secretion from the gastrointestinal tract (Konturek et al.

Table 1. Intervention studies that link food consumption with 6-sulfatoxymelatonin (aMT6s) excretion or serum melatonin.

Author/Year/ Location	Study Design	Objective	Sample	Methodology	MainResults
(González-Flores et al. 2012)/Badajoz province, Extremadura, Spain	Clinical Trial	To evaluate the effect of grape juice consumption on the total antioxidant capacity and aMT6s excretion in young, adult and elderly individuals.	6 young individuals (20 ± 10 years), 6 adults (45 ± 10 years) and 6 elderly (75 ± 10 years)	**Food:** Grape juice **Administration:** 200mL after lunch and 200mL after dinner **Duration:** 5 days **Biological material:** Urine	↑ urinary aMT6s; ↑ total antioxidant capacity
(González-Flores et al. 2011)/Badajoz province, Extremadura, Spain	Clinical Trial	To evaluate the antioxidant effect of Japanese Plums consumption in young, adult and elderly individuals.	6 young individuals (20 ± 10 years), 6 adults (45 ± 10 years) and 6 elderly (75 ± 10 years)	**Food:** Seedless Japanese Plum **Administration:** 195g after lunch and 195g after dinner **Duration:** 5 days **Biological material:** Urine	↑ urinary aMT6s; ↑ total antioxidant capacity
(M. Garrido et al. 2013)/ Badajoz province, Extremadura, Spain	Randomized, placebo-controlled, double-blind, crossover clinical trial	To observe the effect of ingesting a product based on 4 cherry cultivars on sleep quality, urinary aMT6s and il-1β, TnF-α and il-8 cytokines.	10 young (20-30 years) 10 adults (35-55 years) and 10 elderly (65-85 years)	**Food:** Drink containing 18.85 g of freeze-dried cherries per serving (141g fresh cherries/ dose) or placebo **Administration:** 1 serving after lunch and dinner **Duration:** 5 days **Washout period for change of intervention:** 1 week **Biological material:** Serum and Urine **Sleep quality:** Altimeter	**Intervention with respect to basal** ↑ total sleep time and immobility ↑ sleep efficiency only in the elderly ↓ number of awakenings and night activity ↑ urinary aMT6s ↑ serum concentrations of il-1β, TnF-α and il-8 **Placebo with respect to basal** No changes
(María Garrido et al. 2010)/Badajoz province, Extremadura, Spain	Randomized Clinical Trial	To evaluate the effect of eating seven cherry cultivars on the sleep-wake cycle and urinary excretion of aMT6	6 adults (35-55 years old) and 6 elderly (65-85 years old)	**Food:** 7 different cherry cultivars **Administration:** 200 g after lunch and dinner **Duration:** 3 days **Washout period for cultivar change:** 1 week **Biological material:** Urine **Sleep quality:** Altimeter	↑ urinary aMT6s for all cultivars ↑ sleep time in adults for 6 cultivars ↑ sleep time in elderly for all cultivars ↑ total antioxidant capacity for all cultivars
(Howatson et al. 2012)/ Newcastle upon Tyne, England	Randomized, double-blind, placebo-controlled clinical trial	To investigate the effects of concentrated sour cherry juice (Montmorency) on urinary aMT6s and sleep quality	10 healthy men (18-40 years) and 10 healthy women (18-40 years)	**Food:** Drink containing 30 mL of concentrated cherry juice per serving (90-100g fresh cherries/dose) or placebo **Intervention:** Juice twice a day (after waking up and before the last meal) or placebo **Duration:** 7 days **Washout period for change of intervention :** 14 days **Biological material:** Urine **Sleep quality:** Altimeterand subjective sleep questionnaires	**Intervention with respect to basal** ↑ urinary aMT6s ↓ naps ↑ sleep efficiency ↑ bedtime ↑ total sleep time **Placebo with respect to basal** No changes
(Oba et al. 2008)/ Gifu, Japan	Randomized Clinical Trial	To evaluate the effect of vegetable consumption on urinary concentrations of aMT6s.	94 women (24-55years)	**Food:** Seven vegetables of the Japanese diet, Sweet Corn, Bitter Gourd, Japanese Radish Sprout, Garland Chrysanthemum (shungiku), Shimeji Mushroom and Shiitake Mushroom **Intervention:** Consumption of 350g of vegetables a day or avoid consumption of the same **Duration:** 65 days **Intervention:** 46 women **Control:** 48 women **Biological material:** Urine	**Control group with respect to baseline** ↓ urinary aMT6s **Intervention group with respect to baseline** ↔ urinary aMT6s **Intervention group with respect to control** major net changes in urinary aMT6s

(*continued*)

Table 1. Continued.

Author/Year/ Location	Study Design	Objective	Sample	Methodology	MainResults
(Johns et al. 2013)/ Mueang Khon Kaen district, Thailand	Clinical Trial	To investigate the effect of consumption of six tropical fruits on urinary excretion of aMT6s	15 men (18 to 25 years) and 15 women (18 to 25 years)	**Food:** juice of 1 kg of fruit (orange, pineapple, Thai mirtillo or papaya) or 190 g of banana pulp or 500 g of mango pulp. **Intervention:** Each participant should consume the portion of juice or fruit in the evening after a standard meal. **Washout period to change fruit:** 1 week **Biological material:** Urine	↑ aMT6s urine for orange, pineapple and banana ↔ aMT6s urine for mirtillo, papaya and mango
(Sae-Teaw et al. 2013)/ Mueang Khon Kaen district, Thailand	Clinical Trial	To evaluate the relationship between consumption of tropical fruits in serum melatonin concentrations and plasma antioxidant capacity	12 men (18-25 years)	**Food:** Fruit juice (1 kg of orange or pineapple) or 2 peeled bananas 190 g **Intervention:** Consumption of juice or fruit after a standard breakfast. **Washout period to change fruit:** 1 week **Biological material:** Plasma	↑ serum melatonin in 120 me in relation to the fasting collection ↑ plasma antioxidant capacity by FRAP and ORAC after fruit consumption Positive correlation between serum melatonin and plasma antioxidant capacity
(Maldonado, Moreno, and Calvo 2009) /Seville, Spain	Clinical Trial	Analyze the melatonin content in beers and whether moderate consumption of beer with the highest melatonin content would influence the total antioxidant status of human serum.	4 healthy men (20-30 years) and 3 healthy women (20-30 years)	**Food:** The beer with the highest melatonin content, among 18 types of beers consumed in Spain **Intervenção:** Consumption of 330 ml for women and 660 ml for men, after one night fasting. **Biological material:** Plasma	↑ serum melatonin ↑ plasma antioxidant capacity

Legend: ↓=significant decrease, ↑= significant increase, ↔= no significant changes, aMT6s= 6-sulfatoxymelatonin, me = minutes; Kg = Kilograms; g = gram

Table 2. Observational studies that link food consumption with 6-sulfatoxymelatonin (aMT6s) excretion.

Author/Year/ Location	Study Design	Objective	Sample	Methodology	Main Results
(Nagata et al. 2005)/ Gifu, Japan	Cross-sectional	To associate the consumption of vegetables with the excretion of urinary aMT6s.	289 women (48.1 ± 8.7 years)	**Food consumption assessment:** semi-quantitative QFF **Biological material:** Urine **Adjustment variables:** Total energy consumption, BMI, alcohol intake, menopause and day length	Positive associations with urinary aMT6s: total vegetables and dark green vegetables No association for the groups: other vegetables and fruits
(Schernhammer et al. 2009)/ Boston, England	Cross-sectional	Associate food and nutrient consumption with urinary aMT6s	998 women (34-80 years)	**A Food consumption assessment:** QFF **Biological material:** Urine **Adjustment variables:** Total energy consumption, age, number of children, BMI, smoking, time of urine collection (first urine in the morning or not)	Positive association with urinary aMT6s: orange juice Negative associations with urinary aMT6s: cream, tomato, total meat and red meat No associations for nutrients and for total vegetables and total fruits

Legend: Food Frequency Questionnaire = QFF; Body Mass Index = BMI; aMT6s= 6- sulfatoxymelatonin

2007; González-Flores et al. 2011). In relation to the increase in urinary antioxidant capacity, the authors attributed to compounds such as phenolic and carotenoids present in plums, however they did not rule out the hypothesis of melatonin participation (González-Flores et al. 2011).

Grape consumption

The consumption of grape juice (*VitisVinifera genus, Tempranillo cultivar*) was also studied. Researchers observed that the intake of 400 mL of grape juice per day (200 mL after lunch and dinner) contributed to the increase in urinary excretion of aMT6-s. There was an increase in the urinary antioxidant capacity that the authors attributed to melatonin together with the other antioxidants present in grapes (González-Flores et al. 2012). The study exposed here did not show quantification of melatonin from Tempranillo cultivars grape (González-Flores et al. 2012). However, a previous study identified the melatonin content in eight different cultivars of the genus *VitisVinifera*. A large variety of this indolamine has been shown among the cultivars, ranging from 0.965 ng/g to 0.005 ng/g (Iriti, Rossoni, and Faoro 2006).

A randomized clinical trial analyzed the consumption of seven plants consumed in Japan with known melatonin content: Sweet Corn, Bitter Gourd, Japanese Radish Sprout, Garland Chrysanthemum (shungiku), Shimeji Mushroom and Shiitake Mushroom. Before the study, baseline volunteers completed QFF, which showed that the control group (n = 48) and the intervention group (n = 46) consumed equal amounts of the seven vegetables studied. The intervention group was encouraged to consume 350 g of the vegetables daily and the control group was encouraged not to consume them. In addition, both groups were advised to maintain their usual diet. After the study, no significant differences in aMT6s urinary levels were observed in the intervention group. There was a significant decrease in aMT6s in the control group. Therefore, greater net changes in aMT6s urinary concentrations were observed in the intervention group with respect to control (Oba et al. 2008). Interestingly, at baseline, the participants of the control group had a higher excression of MT6s compared to the intervention group, and similarly, they had a higher consumption of total vegetables (Oba et al. 2008). However, the authors did not present correlations between vegetable consumption and melatonin metabolite excretion at baseline.

Tropical fruits consumption

Johns and collaborators' study analyzed the effect of consumption of six tropical fruits, grown in Thailand, on aMT6-s urinary levels. For this, 30 healthy volunteers were invited to consume the evening, after a standard meal, juice of 1 kg of fruit (orange, pineapple, Thai mirtillo or papaya) or 190 g of banana pulp or 500 g of mango pulp. Urine samples were collected prior to fruit consumption (07:00pm) and in the morning after consumption (07:00 am). Each volunteer went through a one-week washout period for the next fruit consumption. It was observed significant improvements in the aMT6s exception only to orange, pineapple and banana. With the exception of bananas (8.86 ± 0.6 pg/g) and myrtle (melatonin below detection limits), orange (150 ± 6 pg/g) , pineapple (302 ± 47 pg/g) and mango (699 ± 75 pg/g) showed considerable melatonin concentrations (Johns et al. 2013).The authors emphasized that the lack of results of some fruits may be due to components present in them. Such components could have interfered in the analysis of melatonin from fruits, as well as in the absorption of this indolamine. They also pointed out that the consumption of fruit *in nature* could be more effective than the juice (Johns et al. 2013). However, the mango fruit was consumed *in nature* and had no impact on the aMT6s excretion, a fact the authors did not comment on.

Based on the previous study, a clinical trial analyzed the effect of fruit juice (orange or pineapple) or banana consumption on plasma melatonin concentrations. Each participant was encouraged to sleep before midnight and at dawn to eat a standard breakfast (two breads of cream). Half an hour after breakfast, juice extracted from one kilogram of orange or pineapple or two peeled bananas (190 grams) was offered. For each intervention (fruit or juice) there was a whashout period of one week. Blood was collected 5 minutes before breakfast and 60, 120, 180 and 270 minutes after the intervention. After 120 minutes of consumption of all fruits, in relation to the measurement of fasting, a significant increase in serum melatonin was observed. A significant increase in plasma antioxidant capacity was also observed after the interventions, as well as a positive correlation between serum melatonin concentration and plasma antioxidant capacity (Sae-Teaw et al. 2013). Interestingly, among the participants there was a wide variation in the serum concentrations of melatonin for the same fruit (pineapple 13.9 to 151 pg/mL, orange 0 to 239 pg/mL and banana 0 to 174 pg/mL) (Sae-Teaw et al. 2013).

Beer consumption

Considering beer consumption, a study analyzed the content of melatonin in 18 different brands of this drink consumed in Spain. They observed that all beers had melatonin and that there was a positive correlation between melatonin content and alcohol content in beers. With a sample of seven volunteers, they analyzed the consumption of beer with the highest melatonin content among those analyzed (169.7 ± 8.7 pg/mL). After a night of fasting, women received 330 mL of beer and men 660 mL. For all volunteers, a significant increase in melatonin and Total Antioxidant Capacity of the serum was observed. (Maldonado, Moreno, and Calvo 2009). An interesting point in this study was that the authors argued that neither hops nor malt would be sufficient to explain the identified melatonin values. However, the fermentation process could be decisive in melatonin production. (Sprenger et al. 1999; Maldonado, Moreno, and Calvo 2009).

Another interesting point is the relationship between alcohol content and melatonin (Maldonado, Moreno, and Calvo 2009). Therefore, care should be taken when adding beer as a nutritional strategy to increase melatonin consumption. Mainly as a strategy for greater control of the circadian cycle since the individual will also be consuming alcohol. Thus, it is important to point out that low or moderate doses of alcohol can promote sleep, however its chronic use can disturb its physiology. (Stein and Friedmann 2005). In addition, the beer offered had an alcohol content of 7.2%, which generated an alcohol consumption, per portion consumed, higher than that recommended by the World Health Organization (10-15 gr for women and 20 to 30 gr for men).

Considerations about intervention studies

For most of the foods studied here it was possible to observe improvements in the urinary aMT6s excretion or serum melatonin. Thus we can assume that most of the foods studied have good bioavailability and could be used in diets as good sources of melatonin. However, it is important to note that the melatonin concentrations presented between foods varied significantly. It can then be considered that in addition to melatonin other nutrients preceding its synthesis (serotonin and tryptophan) could have led to increased urinary aMT6s. A good example is the cherry type Ambrunes where melatonin was not identified in a previous study. However, after its consumption there was an increase in the excretion of aMT6s, this fact could be explained by the high concentration of serotonin of this type of cherry (González-Gómez et al. 2009; Garrido et al. 2010).

It is also important to ask about the extrapolation of the results to make dietary recommendations. Some studies have analyzed the consumption of large portions of food such as 400 cherries (Garrido et al. 2010) or 1 kg of pineapple juice (Johns et al. 2013). Thus, we must note that large portions are not in compliance with the World Health Organization's consumption recommendation (6 to 8 servings of fruits and vegetables days; 400 to 600 grams). Furthermore, it is important in a healthy diet that the types of fruits and vegetables are varied (Rodriguez-Casado 2016). Another fact is that the pattern of consumption of fruits and vegetables varies according to the socioeconomic factors of each country (Baars et al. 2019; Olinto et al. 2011). In this sense, it is important that new studies trace a consumption profile of the population studied to build recommendations.

Another important point is that to measure the absolute increase in melatonin it would be necessary to measure the increase in its levels after fasting (Johns et al. 2013; Sae-Teaw et al. 2013). Thus, in some studies presented here, it is not possible to state for certain whether the components of the diet, in addition to the foods analyzed, may have interfered in the aMT6-s excretion. (González-Flores et al. 2012, 2011; Garrido et al. 2013; Garrido et al. 2010; Howatson et al. 2012; Oba et al. 2008; Johns et al. 2013). In some studies strategies for dietary intake control were used. Among them, maintaining the usual diet and controlling the intake of food sources of melatonin (Oba et al. 2008), control of daily consumption of fruit and vegetables (Johns et al. 2013)and recommendation to maintain the usual diet and food recall (Howatson et al. 2012). Other studies, however, reported no food control during the intervention period (González-Flores et al. 2012, 2011; Garrido et al. 2013; Garrido et al. 2010). This shows the need for further studies with greater accuracy of food intake in order to reaffirm the results presented here.

Cross-sectional studies

Regarding cross-sectional studies, the first evaluated the relationship between vegetable intake and increased aMT6s excretion in 289 healthy women. In this study there was an increase in aMT6-s urinary excretion in women who were in the highest quartile of consumption of "Total Plants" and "Green and Yellow Plants". No significant association was observed for the "Other Plants" group. For the "Fruits" group the associations lost significance after adjusting for confounding factors (Nagata et al. 2005). Despite the associations, the authors highlighted a variety of melatonin in certain vegetables and the lack of information on the concentration of this indolamine in others. Thus, it is possible that the consumption of some food groups was not enough to affect an increase in the excretion of aMT6s. In this sense, the authors pointed out that the correlations may have been only due to reverse causality, that is, due to other factors (Nagata et al. 2005).

In the second cross-sectional study FFQ and morning urine samples were also used. In this study, 998 women members of the Nurses Health Study participated. No association was observed for the consumption of food groups such as vegetables, fruits, seeds, as well as macro and micro nutrients with the concentrations of urinary aMT6s. Curiously they found inverse and unexpected associations between the consumption of milk cream, meats and tomatoes with aMT6s. In contrast, orange juice consumption showed a positive association with urinary aMT6s. Due to the unexpected inverse associations and the transversal nature of the study, the authors stated the need for further studies to prove their findings (Schernhammer et al. 2009).

Considerations about cross-sectional studies

An important point to be questioned, especially in cross-sectional studies, are the factors that interfere in the melatonin biodisponibility in food. In this sense, it is possible to observe, after consuming the same type of food, a variety of responses in the aMT6s excretion among healthy individuals (Sae-Teaw et al. 2013). Already with oral supplementation of melatonin the average bioavailability is close to 15% and can be affected by factors such as age and individual absorption capacity (Harpsøe et al. 2015).Thus, the physiological conditions of each individual, or individual groups, can affect the response to food. With respect to food, it is important to consider that melatonin concentrations can also vary considerably according to the type of soil, climate, time of year and region in which they were grown. In addition, higher concentrations of melatonin in plants can be found in their reproductive organs, especially in seeds (Salehi et al. 2019). Changes can also occur through culinary processes such as baking, cooking and fermenting food (Gomes Domingos, Hermsdorff, and Bressan 2019). However, culinary processes were not considered in the cross-sectional analyzed here (Nagata et al. 2005; Schernhammer et al. 2009).

Conclusion

Further confirmatory studies are needed and it is not possible to affirm that the changes in aMT6s excretion are due only to the consumption of the analyzed foods. However, it is possible to infer that a varied diet in melatonin sources such as cherries, grapes, bananas, pineapples, dark green vegetables, Japanese vegetables and beer, can contribute to improvements in melatonin levels and thus contribute to maintaining health.

Footnotes

The authors declare that they have no conflict of interest.

Author contributions

Study conception and design, critical revisions of manuscript, data collection and analysis – Aguiar, A.S. Pereira G.A. Domingos, A.L.G.

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References

Aguiar, A. S., and G. A. Pereira. 2019. Benefits of melatonin in health through the regulation of biological rhythms : An update on its therapeutic use. *Journal of Endocrinology and Thyroid Research* 5: 10–2. doi: 10.19080/JETR.2019.05.555651.

Amaral, F. G., and J. Cipolla-Neto. 2018. A brief review about melatonin, a pineal hormone. *Archives of Endocrinology and Metabolism* 62 (4):472–9. doi: 10.20945/2359-3997000000066.

Baars, A. E., J. R. Rubio-Valverde, Y. Hu, M. Bopp, H. Brønnum-Hansen, R. Kalediene, M. Leinsalu, P. Martikainen, E. Regidor, C. White, et al. 2019. Fruit and vegetable consumption and its contribution to inequalities in life expectancy and disability-free life expectancy in ten European countries. *International Journal of Public Health* 64 (6):861–72. doi: 10.1007/s00038-019-01253-w.

Badria, F. A. 2002. Melatonin, serotonin, and tryptamine in some Egyptian food and medicinal plants. *Journal of Medicinal Food* 5 (3):153–7. doi: 10.1089/10966200260398189.

Bjørklund, G., and S. Chirumbolo. 2017. Role of oxidative stress and antioxidants in daily nutrition and human health. *Nutrition (Burbank, Los Angeles County, Calif.)* 33:311–21. doi: 10.1016/j.nut.2016.07.018.

El-Sharkawy, H., S. Elmeadawy, U. Elshinnawi, and M. Anees. 2019. Is dietary melatonin supplementation a viable adjunctive therapy for chronic periodontitis?—A randomized controlled clinical trial. *Journal of Periodontal Research* 54 (2):190–7. doi: 10.1111/jre.12619.

Garrido, M., D. González-Gómez, M. Lozano, C. Barriga, S. D. Paredes, and A. B. Rodríguez. 2013. A jerte valley cherry product provides beneficial effects on sleep quality. Influence on aging. *The Journal of Nutrition, Health & Aging* 17 (6):553–60. doi: 10.1007/s12603-013-0029-4.

Garrido, M., S. D. Paredes, J. Cubero, M. Lozano, A. F. Toribio-Delgado, J. L. Muñoz, R. J. Reiter, C. Barriga, and A. B. Rodríguez. 2010. Jerte valley cherry-enriched diets improve nocturnal rest and increase 6-sulfatoxymelatonin and total antioxidant capacity in the urine of middle-aged and elderly humans. *The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences* 65 (9):909–14. doi: 10.1093/gerona/glq099.

Gomes Domingos, A. L., H. H. M. Hermsdorff, and J. Bressan. 2019. Melatonin intake and potential chronobiological effects on human health. *Critical Reviews in Food Science and Nutrition* 59 (1):133–40. doi: 10.1080/10408398.2017.1360837.

González-Flores, D., E. Gamero, M. Garrido, R. Ramírez, D. Moreno, J. Delgado, E. Valdés, C. Barriga, A. B. Rodríguez, and S. D. Paredes. 2012. Urinary 6-sulfatoxymelatonin and total antioxidant capacity increase after the intake of a grape juice cv. Tempranillo stabilized with HHP. *Food & Function* 3 (1):34–9. doi: 10.1039/c1fo10146c.

González-Flores, D., B. Velardo, M. Garrido, D. González-Gómez, M. Lozano, A. M. Concepción, C. Barriga, S. D. Paredes, and A. B. Rodríguez. 2011. Ingestion of Japanese plums (Prunus Salicina Lindl. Cv. Crimsonglobe) increases the urinary 6-sulfatoxymelatonin and total antioxidant capacity levels in young, middle-aged and elderly humans: Nutritional and functional characterization of their content. *Journal of Food and Nutrition Research* 50 (4):229–36.

González-Gómez, D., M. Lozano, M. F. Fernández-León, M. C. Ayuso, M. J. Bernalte, and A. B. Rodríguez. 2009. Detection and quantification of melatonin and serotonin in eight sweet cherry cultivars (Prunus Avium L.). *European Food Research and Technology* 229 (2):223–9. doi: 10.1007/s00217-009-1042-z.

Grima, N. A., S. M. W. Rajaratnam, D. Mansfield, T. L. Sletten, G. Spitz, and J. L. Ponsford. 2018. Efficacy of melatonin for sleep disturbance following traumatic brain injury: A randomised controlled trial. *BMC Medicine* 16 (1):8. doi: 10.1186/s12916-017-0995-1.

Harpsøe, N. G., L. P. H. Andersen, G. Ismail, and J. Rosenberg. 2015. Clinical pharmacokinetics of melatonin: A systematic review. *European Journal of Clinical Pharmacology* 71 (8):901–9. doi: 10.1007/s00228-015-1873-4.

Howatson, G., P. G. Bell, J. Tallent, B. Middleton, M. P. McHugh, and J. Ellis. 2012. Effect of tart cherry juice (Prunus Cerasus) on melatonin levels and enhanced sleep quality. *European Journal of Nutrition* 51 (8):909–16. doi: 10.1007/s00394-011-0263-7.

Iriti, M., M. Rossoni, and F. Faoro. 2006. Melatonin content in grape: Myth or panacea? *Journal of the Science of Food and Agriculture* 86 (10):1432–8. doi: 10.1002/jsfa.2537.

Johns, N. P., J. Johns, S. Porasuphatana, P. Plaimee, and M. Sae-Teaw. 2013. Dietary intake of melatonin from tropical fruit altered urinary excretion of 6-sulfatoxymelatonin in healthy volunteers. *Journal of Agricultural and Food Chemistry* 61 (4):913–9. doi: 10.1021/jf300359a.

Konturek, S. J., P. C. Konturek, T. Brzozowski, and G. A. Bubenik. 2007. Role of melatonin in upper gastrointestinal tract. *Journal of Physiology and Pharmacology* 58:23–52. http://www.ncbi.nlm.nih.gov/pubmed/18212399.

Koziróg, M., A. R. Poliwczak, P. Duchnowicz, M. Koter-Michalak, J. Sikora, and M. Broncel. 2011. Melatonin treatment improves blood pressure, lipid profile, and parameters of oxidative stress in patients with metabolic syndrome. *Journal of Pineal Research* 50 (3):261–6. doi: 10.1111/j.1600-079X.2010.00835.x.

Maldonado, M. D., H. Moreno, and R. J. Calvo. 2009. Melatonin present in beer contributes to increase the levels of melatonin and antioxidant capacity of the human serum. *Clinical Nutrition (Edinburgh, Scotland)* 28 (2):188–91. doi: 10.1016/j.clnu.2009.02.001.

Nagata, C., Y. Nagao, C. Shibuya, Y. Kashiki, and H. Shimizu. 2005. Association of vegetable intake with urinary 6-sulfatoxymelatonin level. *Cancer Epidemiology and Prevention Biomarkers* 14 (5):1333–5. doi: 10.1158/1055-9965.EPI-04-0915.

Oba, S., N. Nakamura, Y. Sahashi, A. Hattori, and C. Nagata. 2008. Consumption of vegetables alters morning urinary 6-sulfatoxymelatonin concentration. *Journal of Pineal Research* 45 (1):17–23. doi: 10.1111/j.1600-079X.2007.00549.x.

Olinto, M. T A., W. C. Willett, D. P. Gigante, and C. G. Victora. 2011. Sociodemographic and lifestyle characteristics in relation to dietary patterns among young Brazilian adults. *Public Health Nutrition* 14 (1):150–9. doi: 10.1017/S136898001000162X.

Oseguera-Castro, K. Y., J. A. Madrid, M. J. Martínez Madrid, O. P. García, M. D. del Castillo, and R. Campos-Vega. 2019. Antioxidant dietary fiber isolated from spent coffee (Coffea Arabica L.) grounds improves chronotype and circadian locomotor activity in young adults. *Food & Function* 10 (8):4546–56. doi: 10.1039/C9FO01021A.

Pandi-Perumal, S. R., I. Trakht, V. Srinivasan, D. W. Spence, G. J. M. Maestroni, N. Zisapel, and D. P. Cardinali. 2008. Physiological effects of melatonin: Role of melatonin receptors and signal transduction pathways. *Progress in Neurobiology* 85 (3):335–53. doi: 10.1016/j.pneurobio.2008.04.001.

Rodriguez-Casado, A. 2016. The health potential of fruits and vegetables phytochemicals: Notable examples. *Critical Reviews in Food Science and Nutrition* 56 (7):1097–107. doi: 10.1080/10408398.2012.755149.

Sae-Teaw, M., J. Johns, N. P. Johns, and S. Subongkot. 2013. Serum melatonin levels and antioxidant capacities after consumption of pineapple, orange, or banana by healthy male volunteers. *Journal of Pineal Research* 55 (1):58–64. doi: 10.1111/jpi.12025.

Salehi, B., F. Sharopov, P. Fokou, A. Kobylinska, L. Jonge, K. Tadio, J. Sharifi-Rad, M. Posmyk, M. Martorell, N. Martins, et al. 2019. Melatonin in medicinal and food plants: Occurrence, bioavailability, and health potential for humans. *Cells* 8 (7):681. doi: 10.3390/cells8070681.

Schaper, C., P. Braun, and M. Koethe. 2015. Comparison of melatonin concentrations in raw and processed cow's milk. *Journal of Food Safety and Food Quality-Archiv Fur Lebensmittelhygiene* 66 (5): 149–53. https://doi.org/. doi: 10.2376/0003-925X-66-149.

Schernhammer, E. S., D. Feskanich, C. Niu, R. Dopfel, M. D. Holmes, and S. E. Hankinson. 2009. Dietary correlates of urinary 6-sulfatoxymelatonin concentrations in the nurses' health study cohorts. *The American Journal of Clinical Nutrition* 90 (4):975–85. doi: 10.3945/ajcn.2009.27826.

Shabani, A., F. Foroozanfard, E. Kavossian, E. Aghadavod, V. Ostadmohammadi, R. J. Reiter, T. Eftekhar, and Z. Asemi. 2019. Effects of melatonin administration on mental health parameters, metabolic and genetic profiles in women with polycystic ovary syndrome: A randomized, double-blind, placebo-controlled trial. *Journal of Affective Disorders* 250:51–6. doi: 10.1016/j.jad.2019.02.066.

Sletten, T. L., M. Magee, J. M. Murray, C. J. Gordon, N. Lovato, D. J. Kennaway, S. M. Gwini, D. J. Bartlett, S. W. Lockley, L. C. Lack, et al. 2018. Efficacy of melatonin with behavioural sleep-wake scheduling for delayed sleep-wake phase disorder: A double-blind, randomised clinical trial. *PLOS Medicine* 15 (6):e1002587. doi: 10.1371/journal.pmed.1002587.

Souza Neto, J. A., and B. F. Castro. 2008. Melatonin, biological rhythms and sleep-a review o the literature. *Revista Brasileira de Neurologia* 44 (1):5–11.

Sprenger, J., R. Hardeland, B. Fuhrberg, and Z. Han. 1999. Melatonin and other 5-methoxylated indoles in yeast: Presence in high concentrations and dependence on tryptophan availability. *Cytologia* 64 (2):209–13. doi: 10.1508/cytologia.64.209.

Stein, M. D., and P. D. Friedmann. 2005. Disturbed sleep and its relationship to alcohol use. *Substance Abuse* 26 (1):1–13. doi: 10.1300/j465v26n01_01.

Xie, Z., F. Chen, W. A. Li, X. Geng, C. Li, X. Meng, Y. Feng, W. Liu, and F. Yu. 2017. A review of sleep disorders and melatonin. *Neurological Research* 39 (6):559–65. doi: 10.1080/01616412.2017.1315864.

Z Tal, J., S. A. Suh, C. L. Dowdle, and S. Nowakowski. 2015. Treatment of insomnia, insomnia symptoms, and obstructive sleep apnea during and after menopause: Therapeutic approaches. *Current Psychiatry Reviews* 11 (1):63–83. doi: 10.2174/1573400510666140929194848.

Zhang, R., X. Wang, L. Ni, X. Di, B. Ma, S. Niu, C. Liu, and R. J. Reiter. 2020. COVID-19: Melatonin as a potential adjuvant treatment. *Life Sciences* 250:117583. doi: 10.1016/j.lfs.2020.117583.

Zhao, D., Y. Yu, Y. Shen, Q. Liu, Z. Zhao, R. Sharma, and R. J. Reiter. 2019. Melatonin synthesis and function: Evolutionary history in animals and plants. *Frontiers in Endocrinology* 10:249–65. doi: 10.3389/fendo.2019.00249.