Dietary polyphenols and sleep modulation: Current evidence and perspectives

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Summary

Polyphenols are plant compounds with several biological activities. This review aims to summarize current knowledge on the potential role of polyphenols in modulating sleep. A total of 28 preclinical studies, 12 intervention studies and three observational studies exploring the role of polyphenol intake on sleep were identified. From animal studies, 26 out of the 28 studies found beneficial effects of polyphenols on sleep architecture. Three out of four human observational studies found a beneficial association between polyphenol intake and sleep parameters. And, among clinical intervention studies, eight from a total of 12 studies found some beneficial effect of polyphenol intake on various sleep parameters, although some discrepancies between studies were found. Overall, emerging evidence suggests a benefit of polyphenol intake on sleep. Several mechanisms of action have been suggested, ranging from effects on neurotransmitters to an action through the gut-brain axis. However, more research in this field is needed, emphasizing the use of nutritional doses in mechanistic studies and interventions targeting participants with sleep problems. This would allow to elucidate whether an additional biological effect of polyphenols is modulation of sleep, a behavior associated with adverse health outcomes.

Keywords: sleep, insomnia, polyphenols, food bioactive compounds, clinical trials

LIST OF ABBREVIATIONS

A1R: Adenosine receptor 1

~~BART: Balloon analogue risk task~~

BMI: Body mass index

FFQ: Food frequency questionnaire

GABA: Gamma-aminobutyric acid

$GABA_A$- BZD: Benzodiazepine site of $GABA_A$

~~GLP1: Glucagon-like peptide 1~~

NREMS: Non-rapid eye movement sleep

OR: Odds ratios

PSQI: Pittsburgh sleep quality index

REMS: Rapid eye movement sleep

~~SD: Sprague-Dawley~~

SEM: Standard error of mean

SOL: Sleep onset latency

SWS: Slow wave sleep

ZT: Zeitgeber time

1. Introduction

High quality, regular sleep of adequate duration is integral to health and well-being (1). Accumulating evidence suggest associations between insufficient or variable sleep and risk of obesity (2) , type 2 diabetes (3) and stroke (4). Indeed, sleep was recently included as one of the eight parameters suggested by the American Heart Association for assessing cardiometabolic health (5) based on its validation as a predictive parameter for cardiovascular outcomes in a prospective study (5). Similarly, circadian misalignment, i.e., a desynchrony between biological clock and meal/sleep timing leads to a disruption of numerous physiological processes, eventually increasing the risk of several non-communicable diseases (6).

Sleep characteristics are influenced by various factors (7) including diet (8). Plant-based diets (9), in particular the Mediterranean diet (10), may have beneficial effects on sleep due to their combination of nutrients implicated in sleep regulation and modulation of colonic microbiota, leading to a gut-brain axis effect [(7,9]) effect. Polyphenols, a wide family of secondary metabolites present in foods of vegetal plant origin, are a key constituent of these diets.

Recently, research on polyphenols has focused not only on cardiometabolic benefits (11, 12), but also on their potential neuromodulating effects. A neuromodulating effect of polyphenols can be derived from their antioxidant and anti-inflammatory activities, regulation of neuronal signaling cascades, and improvement of peripheral and cerebral blood flow (13). Several phenolic metabolites from microbiota have been reported to be able to cross the blood-brain barrier, e.g. 5-(hydroxyphenyl)-γ-valerolactone-sulfate (14). Since the colon is a key organ for polyphenol transformation, where a bidirectional polyphenol-microbiota interaction takes place (15), polyphenols could be an additional player in the postulated gut-brain axis (16, 17). Based on their metabolic fate, distribution and biological functions, polyphenols may modulate central nervous system processes.

Sleep is a centrally regulated process and, as such, studies have explored the role of dietary polyphenols in sleep modulation. The aim of this review is to provide an overview of current knowledge on the potential association between polyphenol intake and sleep modulation.

2. Current evidence for a role of polyphenols on sleep modulation

A bibliography search was performed in Scopus database with the terms “polyphenol* OR phenol* OR flavonoid* OR tannin* OR procyanidin* OR proanthocyanidin” and “sSleep*” appearing either in the title, the abstract or the keywords. Preclinical, clinical, and observational studies in which sleep parameters were measured as outcome after supplementation or exposure to polyphenols were collected.

2.1 Animal studies

A total of 28 animal studies were identified, mostly focused on testing the activity of effects of acute supplementation with various polyphenols, including phlorotannins (18-22), flavonoids (23-28), stilbenes (29), chalcones (30, 31), hydroxycinnamic acids (32-36), lignans (37-41) and polyphenol-rich extracts/foods (27, 42-45), on sleep architecture compared with well-known sedatives such as benzodiazepines (**Table 1**). This table also includes the most common food/plant sources for each one of the tested compounds (46, 47). Twenty-six of the 28 animal studies found that polyphenols increased sleep duration or decreased sleep onset latency -(SOL). Studies consistently observe that polyphenols increased non-rapid-eye movement sleep (NREMS)NREMS to a level similar to lower-dose benzodiazepines; this effect is physiologically relevant, since it is known that NREMS and REMS are associated towith distinctive functions (48). In contrast to benzoidiazepines, polyphenols did not decrease delta power, a specific parameter defining NRMEEMS;. iInterestingly, it was recently highlighted that both decreases and increases in delta power could indicate a higher sleep quality due to various factors (49). Finally, when tested, a dose-dependent effect was found ((17-19, 23, 26, 29, 32-37, 39, 41, 43)).

2.1.1 Phlorotannins

Five studies of phlorotannins, the characteristic phenolic structure of seaweeds, have been published, all showing some benefit for sleep. Three (18-20) used a pentobarbital-induced sleep test and measured ~~sleep~~ onset ~~latency (~~SOL~~)~~ or sleep duration compared to a non-supplemented group (control). In all animal studies, ~~focused on~~ these parameters~~, they~~ were visually recorded by the researchers, with ~~sleep latency~~SOL corresponding to the period from pentobarbital injection to the time of sleep onset, and sleeping duration being~~s~~ defined as the difference in time between the loss and recovery of the righting reflex. In particular, *Ecklonia cava* Kjellman extract significantly increased sleep duration and decreased ~~sleep onset latency (~~SOL~~)~~ in Sprague-Dawley ~~(SD)~~ rats compared to a ~~control group~~ non-supplemented group (control) when tested at four doses (100, 250, 500, 1 000 mg/kg) (18). Doses ≥250 mg/kg generated an effect similar to diazepam (18). The major compounds identified in this extract were eckol, eckstolonol, dieckol and triphloethol A, which justified further studies with the isolated compounds. When tested individually, eckstolonol (19) (125, 250, 500 mg/kg) and triphlorethol A (20) (5, 10, 25 and 50 mg/kg) reduced SOL and increased sleep duration in mice compared to a ~~control group~~ non-supplemented group (control) (19, 20) or a vehicle-treated group. Also, polysomnography recordings during usual sleep consistently show increases in ~~non-rapid eye movement sleep (~~NREMS~~)~~ after supplementation with dieckol (50, 100 and 150 mg/kg) (22), without altering rapid-eye movement sleep (REMS). Although the effects of phlorotannins (20) on SOL and NREMS in mice were similar to those of zolpidem, phlorotannins did not reduce delta power during NREMS, as observed with zolpidem, demonstrating a better sleep profile resulting from phlorotannin supplementation. Lastly, in a ~~mice~~ caffeine-induced sleep disruption model in mice, a phlorotannin supplement (500 mg/kg) had a similar effect to zolpidem (10 mg/kg) in decreasing SOL and increasing NREMS, without altering REMS (21).

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2.1.2 Flavonoids

Studies find increases in sleep duration and decreases in SOL, in a dose-dependent manner, when ~~animals~~ mice or rats are supplemented with flavones spinosin (≥10 mg/kg) (24, 25), rats with linarin (7 and 14 mg/kg) (23), and mice with rhusflavone (25 and 50 mg/kg) (27). Spinosin decreases SOL at doses ≥5 mg/kg when pentobarbital was provided at a sub-hypnotic dose. Polysomnography data from studies with baicalin, another flavone, showed increases in both NREMS (specifically slow-wave sleep [SWS]) and REMS in Sprague-Dawley rats. The authors suggested a biphasic effect of baicalin (26) on sleep, causing a decrease in SWS during the light (inactive) period and an increase in SWS and REMS during the dark (active) period. Further research is needed to establish optimal timing of administration for somnogenic effects.

One study focused on the flavanol epigallocatechin~~en~~-3-*O*-gallate (5-20 mg/kg) (28), showing increased sleep duration and decreased SOL in a mice model of pentobarbital-induced sleep compared to ~~control~~ a non-supplemented group (control). Also, when pentobarbital was provided at a sub-hypnotic dose, epigallocatechin~~n~~-3-*O*-gallate increased sleep duration compared to ~~control~~a non-supplemented group (control).

2.1.3 Stilbenes

One study tested the main stilbene compound, resveratrol (29). This study supplemented a non-human primate gray mouse lemur (*Microcebus murinus*) with resveratrol (200 mg/kg) for 3 wk; recordings of sleep-wake rhythms were obtained by wireless telemetry. Resveratrol increased the proportion of active-wake time, an effect occurring mainly during the resting phase of the sleep-wake cycle. The increase in active-wake time with resveratrol supplementation was accompanied by a 95% reduction of paradoxical sleep and 38% reduction in SWS. The authors suggested a possible circadian rhythm-dependent difference in the extent of the effect of resveratrol on the 24-h sleep-wake rhythm, in line with the biphasic behavior observed with baicalin (26).

2.1.4 Chalcones

Two studies tested isoliquiritigenin (30, 31). In a ~~mice~~ pentobarbital-induced sleep model in mice, this chalcone increased sleep duration and decreased SOL (25 and 50 mg/kg) (30). Polysomnography recordings after supplementation with the highest dose showed that isoliquiritigenin increased NREMS by 61% during the first 3 h after administration, an effect equivalent to that of 2 mg/kg diazepam. However, diazepam also caused a decrease in delta activity during NREMS which was not observed during supplementation with isoliquiritigenin (31), similar to findings with spinosin (20).

2.1.5 Hydroxycinnamic acids

Ferulic acid supplementation in mice, before pentobarbital-induced sleep (33), caused a dose-dependent decrease in SOL and increase in sleep duration starting at doses ≥15 mg/kg with a dose of 30 mg/kg having similar effects as 2 mg/kg diazepam. Similarly, rosmarinic acid supplementation (0.5-30 mg/kg) increased sleep duration and decreased SOL in mice compared to a ~~control~~ non-supplemented group (control) (35, 36).

Despite these positive results with ferulic and rosmarinic acids, there are also two studies with other hydroxycinnamic acids in which no effects on sleep were observed ~~were performed with polyphenols belonging to the class of hydroxycinnamic acids~~ (32, 34). Thus, v~~V~~erbascoside supplementation at considerably high doses (399 and 798 mg/kg) did not modify sleep duration or NREMS in Sprague-Dawley rats during regular sleep (32). Also, chlorogenic acid (500 mg/kg) and caffeic acid (200 mg/kg) supplementation increased SOL in Sprague-Dawley rats (34)~~.~~ these doses were ~~. The authors~~However, ~~when compared to doses these doses with the ones needed by caffeic acid?ine to increase SOL, and they these doses were~~ 50-fold and 20-fold higher, respectively, than the one needed by caffeine to increase SOL.

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2.1.6 Lignans

The lignan honokiol has been explored in three studies (37-39). In a ~~mice~~ pentobarbital-induced sleep model in mice, honokiol increased sleep duration at doses of 0.1 and 0.2 mg/kg (37) compared to ~~control~~ a non-supplemented group (control). Another study using a usual sleep model found that honokiol decreased SOL (20 mg/kg) and increased NREMS (10 and 20 mg/kg) similar to diazepam (6 mg/kg). Since a limitation for the use of honokiol is its low oral bioavailability, a study tested whether ~~high-bioavailability~~high bioavailability honokiol microparticles would have sleep benefits. This study showed a 6.5-fold increase in maximal blood concentration of honokiol in the microparticle formulation compared to free honokiol. NREMS in Sprague-Dawley rats was correspondingly increased, along with a decrease in the number of wake episodes (39) compared to vehicle. Compared to diazepam treatment, honokiol microparticle administration led to longer deep NREMS.

Magnolol, another lignan, also increased sleep duration in a mice pentobarbital-induced sleep model (40) and decreased SOL and increased total amount and number of REMS/NREMS episodes in a model of mice usual sleep compared to ~~control~~a non-supplemented group (control) (41).

2.1.7 Complex extracts or whole foods

Some studies tested extract combinations or foods. Three studies used pentobarbital-induced sleep animal models to show that supplementation to mice with a *Glycyrhiza glabra* extract (containing phenolic acids and flavones) (42), with *Rhus parviflora* (providing mainly phenolic acids) (27) or with instant jujube powder (rich in flavonoids form different subclasses) (45) significantly increased sleep duration and decreased SOL compared to ~~control~~a non-supplemented group (control). One study showed that supplementation with peanut stem and leaf for one week significantly increased total sleep, SWS and REMS compared to ~~control~~a non-supplemented group (control) in a mice usual sleep model (44).

Finally, one study (43) induced psychophysiological stress in ~~animals~~ mice in which disrupted circadian rhythms was induced for 30 days to generate chronic sleep disorders. Supplementation with pure cocoa during this period restored the amplitude reduction of day-night activity rhythms as measured by polygraphic recordings, compared to ~~control~~a non-supplemented group (control).

~~***2.1.8 Main findings from animal studies***~~

~~Animal studies (Table 1) have mostly focused on the effects of acute polyphenol supplementation before sleep induction. Twenty-six of the 28 animal studies found that polyphenols increased sleep duration or decreased SOL. Studies consistently observe that polyphenols increased NREMS to a level similar to lower-dose benzodiazepines but with greater delta power. When tested, a dose-dependent effect was found [17-19, 23, 26, 29, 32-37, 39, 41, 43].~~

2.2 Human studies

2.2.1 Observational studies

Four observational studies examined associations between polyphenol intake and sleep with contradicting findings~~, as summarized in~~ (~~-~~**Table 2**). Polyphenol intake was assessed using food frequency questionnaires (FFQ) and Phenol-Explorer database; sleep measures differed. One cross-sectional study of randomly selected adults assessed sleep using the Pittsburgh Sleep Quality Index (PSQI)(50). ~~Inverse~~ Significant ($p < 0.05$) associations between polyphenol intake and sleep quality as assessed by PSQI were found for the class of hydroxycinnamic acids (~~O~~odds ratios, OR, 0.67 Q4 *vs* Q1, 95% CI: 0.46, 0.98) and for some individual polyphenols (naringenin: ~~with~~ OR for Q4 0.66, 95% CI: 0.46, 0.95; ~~,~~ apigenin: ~~with~~ O~~F~~R for Q4 0.65, 95% CI: 0.44, 0.90; ~~,~~ matairesinol: ~~with~~ OR for Q4 0.66, 95% CI 0.46, 0.96). When participants were categorized by weight status, associations were also observed for other individual lignans (~~with~~ OR for Q4 0.54, 95% CI 0.31, 0.94) and for total polyphenols (~~with~~ OR for Q4 0.70, 95% CI 0.39, 1.25) in adults with normal weight. No associations were observed in participants with overweight/obesity.

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However, the study included many tests of association with no adjustments for multiple comparisons, raising concerns about the robustness of the findings.

Among 92 young Saudi females with and without obesity and mostly poor sleep quality (82% of sample), total polyphenol intake higher than the median (>236 mg polyphenols/1,000 kcal/day) was ~~associated~~significantly associated (OR 0.24, 95% CI: 0.07, 083) with better sleep quality, using PSQI, after adjusting for age and BMI (51). And, in a study in 278 Iranian women with overweight/obesity, a trend towards an ~~inverse marginally significant (p = 0.074)~~ association (p = 0.074) was found between polyphenol intake and sleep quality as assessed by PSQI (52).

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The other observational study was a prospective study of 13,958 UK females followed for four years (53). Sleep duration during weekdays or weekends was self-reported. Fruit and vegetable consumption and total polyphenol intake were ~~inversely associated~~significantly and inversely associated with sleep duration: one additional gram of total polyphenols from fruits and vegetables was ~~associated~~~~significantly~~ associated with 18 min shorter sleep. The authors highlighted that effect sizes were small and the results may not be clinically relevant. These results conflict with other observational studies showing an association between the Mediterranean diet, known to have a high fruit and vegetable content, and longer sleep duration (54, 55). Also, since daily polyphenol intake in several populations has been estimated to be ≤1 g when non-extractable polyphenols are not included (56, 57), the relevance of a model based on the incorporation of one additional gram of polyphenols is questionable. It is also important to note that adverse effects have been reported when polyphenol intakes are above nutritional doses (58). This could also be the case for sleep modulation. Overall, this shows the need for additional studies.

2.2.2 Intervention studies

Eight of 12 identified intervention studies found a significant effect of polyphenol supplementation compared to placebo/control groups (unless otherwise specified) in at least one sleep-related

outcome (**Table ~~2~~3**). The studies reporting beneficial effects on sleep outcomes used doses 20-600 mg/d ~~and they found~~with improvements in at least one sleep parameter: better self-reported sleep quality [57-59, 61-63, 65], decrease in SOL [56], decrease in wakefulness after sleep onset [61], increased sleep efficiency [57], and reduced nocturnal awakening [57]. ~~While the s~~Studies reporting no ~~-~~effect on sleep tested doses 50-900 mg/d, and sleep was measured ~~either~~ by objective me~~asure~~thods (59, 60)~~(59)~~ ~~[66]~~ or self-reported questionnaire (PSQI) (61, 62) ~~[60].~~

Chlorogenic acid (5-caffeoylquinic acid), a hydroxycinnamic acid characteristic of coffee was given in a daily dose of 600 mg to nine healthy participants (four males and five females, mean age 25.7 y) for five days, in a double-blind placebo-controlled cross-over design (63). All participants had good quality sleep based on PSQI. Chlorogenic acid significantly shortened SOL, measured with polysomnography (from 15.6 ± (SEM) 4.5 min to 8.7 ~~SEM~~± 2.7 min), ~~by seven minutes~~ with no impact on sleep stages or wake after sleep onset. Chlorogenic acid intake led to higher parasympathetic activity, measured from heart-rate variability,~~–~~ a parameter associated with sleep architecture~~-~~, during sleep, compared to placebo (999 SD 77vs 919 SD 54, respectively) (64).~~Chlorogenic acid enhanced parasympathetic activity measured from heart-rate variability during sleep± ± (60).~~ In another double-blind placebo-controlled parallel study with healthy males, participants received either placebo or a mixture of caffeoylquinic acids (300 mg/d) for two weeks (65). At the end of the study, supplemented participants reported significantly lower fatigue and higher sleep quality, as measured by visual analogue scales. The participants also exhibited ~~and had~~significantly increased actigraphy-measured sleep efficiency ~~(p = 0.046)~~ and reduced nocturnal awakenings ~~(p= 0.039)~~.

Ellagic acid, a phenolic acid belonging to the hydroxybenzoic acid family, was tested in a randomized double-blind cross-over trial in 44 patients, aged 24-55 y, with type 2 diabetes and good sleep quality (66). Participants were given 180 mg of ellagic acid or placebo for eight weeks. Based on self-report~~ing~~, ~~E~~ellagic acid significantly improved sleep quality as assessed by PSQI

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(score from 8.86 +SD± 2.07 to 5.39 +±SD 1.11), increased sleep duration (from 5.69 +±SD 1.2 h to 7.47 +±SD 2.1 h), and efficiency (from 8.8 +±SD 16.1% to 88.0 +±SD 19.0%), andand reduced disturbances (score from 2.1 +±SD 0.9 to 0.9 +±SD 0.1), SOL (from 52.1 +±SD 14.2 min to 29.2 +±SD 9.1 min), use of sleep medication (from 2.3 +±SD 0.7 times/week to 0.9 +±SD 0.1 times/week), and daytime dysfunction (from score 2.0 +±SD 0.3 to 0.7 +±SD 0.1).

Two studies tested resveratrol. One was performed in patients with hepatitis C supplemented at with a dose of 19.8 mg/d, or placebo, for 12 months, with a randomized parallel arm design. Significant iImprovements in sleep quality assessed by PSQI and sleepiness ratings, measured by Epworth Sleepiness Scale, were observed at six and 12 months; for instance, at 12 months PSQI score was 16.1 +±SD 3.2 atin the control group *vs* 10.2 +±SD 2.4 atin the supplemented group ; (67). On the contrary, in a parallel-arm, double-blind clinical trial with 41 adults with overweight (24 males aged 40-70 years and 17 postmenopausal females aged 50-70 years) (61), sleep quality as assessed by PSQI was not improved from supplementation with 150 mg/d resveratrol for six months, supplemented at 150 mg/d for six months, compared to placebo. However, this study was not designed to evaluate effects of resveratrol on sleep *a priori*.

The other seven studies tested polyphenol mixtures or foods. Regarding extracts, a phlorotannin-rich supplement was provided to 24 participants (13 males, 11 females), aged 21-44 years (68), with self-reported sleep disturbances (routine difficulty falling sleep, frequent waking during the night or awakening in the morning feeling tired) but no history of sleep disorders or severe insomnia. In this randomized double-blind parallel trial, participants consumed 500 mg/d of either the supplement or the placebo for one week. Sleep quality was assessed by questionnaires and polysomnography. Phlorotannin extract supplementation significantly increased sleep duration and sleep maintenance based on PSQI, at the same timewhile itand decreased wakefulness after sleep onset as measured by polysomenography but did not improve self-reported sleep quality.

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Another tested extract was HolisFiit®, a commercial product containing a mixture of phenolic compounds (90 mg of (-)-epigallocatechin 3-*O*-gallate, 80 mg of naringin and 1.5 mg of anthocyanins, among others). This supplement was tested in a randomized double-blind parallel trial on 32 overweight males and females aged 30-50 years (69). Participants received a daily dose of 250 mg of HolisFiit® or placebo. Polyphenol supplementation significantly improved five of the eight items on the Athens Insomnia Scale, including 38% reduction in awakening during the night and 43% improvement in sleep quality. The third study evaluated a polyphenol botanical blend, containing 120 mg of polyphenols with at least 65 mg of the combination of rosmarinic acid and ~~epigallocatechin gallate,~~ (-)-epigallocatechin 3-*O*-gallate in 89 healthy males and females aged 22-50 years (70). Participants received one daily dose or placebo for 30 days in a randomized crossover design. ~~T~~The polyphenol blend significantly improved sleep quality (score from 6.37 ~~±~~±SD 1.05 to 7.33 ~~±~~±SD 1.09), measured using a diary where higher scores signify better quality sleep ~~(score~~on a scale of ~~from~~, 0 to 10~~)~~. It also ~~it~~ reduced ~~insomnia symptoms~~morning sleepiness (from score of 5.57 ~~±~~±SD 1.84 to 4.56 ~~±~~±SD 1.68). At the same time, it significantly increased sleep duration as measured by polysomnography (from 395.6 ~~±~~SD 67.~~384~~ min to 425.5 ~~±~~SD 40.9)~~,~~ and significantly improved some elements of neurocognitive functioning, such as N-Back Accuracy or Balloon Analogues Risk Task ~~(BART)~~ optimal pumps difference. Finally, supplementation to healthy subjects with a spearmint extract (900 mg/d with at least a 14% of rosmarinic acid and at least a 24% of total polyphenols) for 90 days did not improve sleep quality (62).

One study tested the impact of grape juice (rich in flavanols, flavonols, hydroxybenzoic acids, hydroxycinnamic acids and stilbenes) on sleep in females with breast cancer (71). The intervention group had a reduction in sleep disorder scale score after five weeks, although there were no differences between groups for overall PSQI score. It was not possible to get a full English version of this study, so no detailed information on the participant characteristics or on the

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polyphenol dose was available. One other study found no beneficial effects of polyphenol intake, from oolong tea containing 48.5 mg of catechins, on sleep ~~parameters~~ architecture assessed by polysomnography in healthy males, aged 20-56 years, as compared to a placebo (59). No differences in sleep architecture were observed between oolong tea and placebo, assessed by polysomnography. Importantly, oolong tea contains caffeine and theophylline, which might counteract polyphenol effect (72). And another study compared daily consumption of green tea or low caffeine green tea (≥ 300 mL/d) by healthy adults for seven days (60). Supplementation with low caffeine green tea did not lead to differences in sleep parameters compared to regular green tea. However, it should be noted that no polyphenol-free supplement was evaluated in this study and baseline values were not reported. Thus, it is unknown whether the supplements either did not influence sleep or equally influenced sleep. Future studies should report baseline values for outcomes and strive to include a polyphenol-free control.~~Supplementation with low caffeine green tea did not modify any of the sleep parameters measured with polysomnography. However, it should be highlighted that no polyphenol-free supplement was evaluated in this study.~~

~~In summary, from the 13 clinical intervention studies, four found no effect on sleep, with doses 50-900 mg/d, either by objective measures [66] or self-reported questionnaire (PSQI) [60]. The other eight studies, with doses 20-600 mg/d, found improvements in at least one sleep parameter: self-reported sleep quality [57-59, 61-63, 65], decrease in SOL [56], decrease in wakefulness after sleep onset [61], increased sleep efficiency [57], and reduced nocturnal awakening [57].~~

3. Potential mechanisms of actions of polyphenols on sleep regulation

3.1 Specific sleep-related mechanisms

Many animal studies described in section two attempted to elucidate the molecular mechanisms supporting the sleep promoting activities of the tested polyphenols. The most plausible appears to be related to gamma-aminobutyric acid (GABA), the main neurotransmitter involved in

decreasing brain excitability. Polyphenols can exert a positive allosteric modulation of the benzodiazepine site of $GABA_A$ ($GABA_A$-BZD) receptor. This was shown, for instance, in *in vitro* studies where the lignans honokiol and magnalol (20 and 50 μM) increased chloride influx in primary culture of cerebellar granule cells, leading to a selective increase of the GABA receptor α-subunit expression, while no effect was observed on the abundance of β or γ-subunits (37, 40). This agrees with findings that polyphenols exert similar effects to those of diazepam (18, 20, 42) or zolpidem (22) in rodent models. Indeed, binding affinity studies have shown that certain polyphenols, such as the chalcone isoliquiritigenin, have a higher affinity for $GABA_A$-BZD receptor (30). Finally, cell culture studies showed that some polyphenols, such as apigenin and epigallocatechin gallate, were able to enhance GABA responses caused by diazepam, exhibiting a second order modulatory action. And, it was recently shown that rosmarinic acid was able to bind adenosine receptor 1 (A1R), which did not take place in the presence of A1R antagonists; this mechanism should be further explored (36).

Dopaminergic and serotonergic pathways have been explored as potential systems involved in the role of polyphenols on sleep modulation. The dopaminergic system was dismissed as a viable explanation since spinosin did not alter the sleep decrease observed after three days of treatment with L-DOPA (3,4-dihydroxyphenylalanine) (24). In contrast, two animal studies observed that spinosin and ferulic acid showed synergic effects with 5-hydroxytryptophan (5-HTP) (24, 33), the serotonin precursor in melatonin synthesis. Moreover, both compounds inhibited para-chlorophenylalanine-induced suppression of the hypnotic effects of pentobarbital, which occurs via tryptophan hydroxylase blockade, the rate-limiting enzyme in serotonin biosynthesis. Although further studies are needed, mechanistic approaches have evidenced that this polyphenol action would be related to postsynaptic 5-HT1a receptor (25).

Another mechanism of action could be related to improvements in endothelial dysfunction, in particular flow mediated dilation and augmentation index. This role of polyphenols has been

widely shown in intervention studies (73) resulting in an approved health claim for increased flow-mediated dilation for cocoa flavanols in Europe (74). Flow-mediated dilatation is associated with better perceived sleep quality and greater REMS (75). Also, it has been suggested that nitric oxide-mediated vasodilation in the brain facilitates REMS (76). Thus, regulation of vasodilation by polyphenols, perhaps particularly flavanols, could also improve sleep quality.

Finally, an aspect to be further explored is the potential role of polyphenols in the regulation of sleep-related genes. One of the animal studyies assessed in this review showed that cocoa supplementation increased hypothalamic mRNA expression of *Hspa1*, a gene that encodes HSP70 and is associatedassociated with sleep regulation (43). Indeed, this agrees with some other animal studies not focused on sleep outcomes and thus excluded from this review, but whichthat observed that polyphenol supplementation was significantly with a significant increased expression of certain sleep-related genes with polyphenol supplementation. In particular, a higher expression of clock genes (such as *Clock*, *Sir1*, *Per1*, *Per2*, *Per3*, *Cry 1* or *Rora*) either in the liver or the hypothalamus after polyphenol supplementation has been observed in murine models of circadian rhythm disorders (77, 78). Also, resveratrol supplementation in a high-fat diet rat model restored the alterations in the expression of *Rev-Erbα* to those ones present in the liver of rats fed with standard diet (79). Interestingly, the increase of liver *Per1* expression observed in mice supplemented with cocoa procyanidins at zeitgeber time (ZT) 3 took place through the glucagon-like peptide 1 (GLP1) signaling pathway, a process known to be regulated by polyphenols (80). Finally, grape seed procyanidin supplementation to rats at ZT0 reduced the hypothalamus expression level of *Nampt* as compared to a non-supplemented group, which was concomitant towith an increase in circulating melatonin levels; these effects were not observed whe supplementation took place at ZT12 (81).

3.2 Contribution of other polyphenol biological actions

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Other well-known biological actions of polyphenols may also indirectly affect sleep. Polyphenols have bidirectional interactions with colonic bacteria. Polyphenols stimulate the growth of beneficial bacteria, showing a prebiotic effect; and microbiota yield new metabolites from original phenolic structures. These phenolic-derived metabolites are absorbable and exhibit biological activities, called postbiotics. At the same time, there is an increasing understanding of the multiple direct and indirect mechanisms by which the microbiota-gut-brain axis may affect sleep architecture and sleep disorders (82). Postbiotics derived from polyphenols, known to be absorbed and exert biological actions, can interact with $GABA_A$-BZD receptors to impact sleep. Also, polyphenols can stimulate the generation of serotonin from microbiota effects (83). Polyphenols have been shown in animal models to ameliorate the imbalanced intestinal microbial environment induced circadian rhythm disorder and, indeed, this modulation of microbiota was concomitant with an adjustment of the expression of core clock genes *Csnk1d*, *Clock*, *Per3*, *Cry2*, and *Bhlhe41,* altered by circadian disruption (84). Studies should be designed to establish how the polyphenol-microbiota bidirectional interaction may influence sleep regulation through gut brain-axis.

3.3 Beneficial aspects of polyphenols in adverse health effects of poor sleep

Other studies have tested the effects of polyphenol supplementation on the alterations caused by sleep deprivation (85-94) (**Supplementary Table S1**). Ten animal studies found that supplementation with polyphenols belonging to flavanols, flavonols, anthocyanins, flavanones and ellagitannins, and complex extracts from tea or grape seed, induced local antioxidant (85-89) and anti-inflammatory (88-90) actions in the brain. In all studies, supplementation with polyphenols restored at least some of the disturbances in health outcomes caused by sleep disorders. Similarly, an intervention study where participants consumed a flavanol-rich chocolate (520 mg) or a common chocolate (88 mg) after one night of total sleep deprivation found that consumption of the flavanol-rich chocolate decreased subjective sleepiness, counteracted vascular impairment, and restored working memory performance induced by total sleep

deprivation (95). These restorative effects, in the context of sleep alterations, are physiologically relevant. In pathologies that involve sleep disorders, such as Alzheimer's disease, the regulatory local effect of polyphenols in ameliorating oxidative stress and inflammation deserves further attention. Similarly, improvements in negative outcomes of sleep deprivation or poor-quality sleep, such as restoration in cognitive or behavioral aspects, and markers of inflammation or oxidation, are of importance given the prevalence of insufficient sleep in the population. Finally, since apnea involves a higher oxidation status, it has been suggested that polyphenols, due to their antioxidant action, might have a beneficial health effect (96, 97).

4. Perspectives

This review highlights emerging evidence of a potential beneficial role of polyphenol intake on sleep. The integrated analysis of animals and human studies shows as promising phenolic compounds some widespread constituents, such as caffeoylquinic acids, ferulic acid, ellagic acid or naringenin. Other tested phenolic compounds are present in more specific foods, such as rosmarinic acid (in rosemary), punicalagin (in pomegranate), epigallocatechin 3-*O*-gallate (-)-epigallocatechin 3-*O*-gallate (in green tea) or phlorotannins (in seaweeds), but it is feasible to include them in a common diet. Lastly, there were some phenolic compounds isolated from specific plants or seaweeds, i.e., honokiol, linarin or spinosin which are not commonly ingested. This variety of phenolic structures showing effects on sleep outcomes indicates that a plant-based varied diet, may provide enough polyphenols with sleep-regulating properties, especially since some of the suggested mechanisms of actions for polyphenols on sleep seem to be shared by the different polyphenol families. However, the detailed analysis of the existing literature reveals various flaws that deserve attention in upcoming research.

In animal studies, doses ranged from $5x10^{-6}$ to 800 mg/kg in rat models (32, 93), and from 0.05 to 780 mg/kg in mice models (37, 85). Applying corresponding conversion values (98), these doses would be equivalent to $6x10^{-5}$-8,000 and 1-15,000 mg/d, respectively, for a human adult

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with a body weight of 60 kg. Since intakes for individual polyphenols have been reported in humans to range from 0.01 to 200 mg/d (57), this means that some of the studies have been performed outside of the nutritional range. These aspects should be considered when extrapolating the results to humans and estimating the potential influence on sleep parameters of the phenolic compound studied, as consumed within the usual diet or as dietary supplements.

In human studies, a clear definition of inclusion/exclusion criteria related to sleep characteristics is necessary. As such, it is important to have a proper baseline sleep evaluation and to consider aspects such as chronotype, shift work, use of sleep aids, existence of pathologies, and medication use that may affect sleep. In one study, participants were allowed to use sleep aids as needed during the development of the study, and their weekly use was recorded as a study outcome (66). Specifically, since only one of the intervention studies was focused on participants with sleep problems, more efforts should be directed towards studies in this population. Variations in definition of sleep quality were also noted with some studies fixing a minimum PSQI score of three (70) or five as inclusion cut points. Second, studies should use validated techniques for measuring polyphenol intake and sleep outcomes. Individual polyphenol intake assessment is preferred to total polyphenol intake, since it may provide useful information on specific structure-effect aspects. Third, objective measures of sleep should be included alongside self-reported outcomes. Only five of the intervention studies included objective sleep measurements, such as polysomnography, actigraphy, thermometry or autonomic nervous system activity evaluation based on electrocardiograms (59, 60, 63, 65, 68). Fourth, future studies should establish sleep parameters as primary outcomes with appropriate sample size determinations. Among intervention studies, four (59, 65, 69, 95), did not provide a sample size calculation, eight (59, 62, 63, 66, 67, 69, 70, 95) did not mention the primary outcome, sleep parameters were a secondary outcome (61) in one and, in some, sample size was based on non-sleep related parameters, such as malondialdehyde variation (66) or salivary α-amylase (60). Fifth, to emulate a nutritional and

not a pharmacological approach, studies should assess the effects of polyphenol-rich foods or diets rather than extracts or supplements. Sixth, specific instructions should be provided to the volunteers regarding polyphenol intake from other sources during the study, keeping in mind that advice for a polyphenol-free diet during a long period generates an unconventional situation that may affect the validity of the results. Other sleep-affecting food constituents, such as caffeine, should also be restricted or monitored. Among the studies reviewed herein, one prescribed a resveratrol-free diet (61), while others had recommendations about caffeine (59, 63, 70) and cocoa (95) consumption. Finally, since meal timing (99, 100) may also influence sleep, it would be relevant to monitor and set timing of polyphenol intake in supplementation studies. For example, resveratrol has opposing effects on oxidative status depending on time of day (101). In most studies participants were asked to consume the product some time before going to bed, although others suggested consumption with meals (66), most often breakfast and lunch (59). This is related to the mechanism of action to be explored; while some of the mechanisms described above, such as the relationship with GABA, would be more immediate, aspects related to microbiota would have a long-term effect and would not be effective if consumed right before sleeping. Two of the animal studies (26, 29) suggested circadian rhythm-dependent differences for the effects of baicalin and resveratrol, since they did not exert the same effects regarding parameters related to sleepiness/wake state, depending on time of day (101) and, in particular, baicalin exerted somnogenic effects 8 h after administration. Despite these limitations, it is important to note that all intervention studies were double-blind trials, reducing the risk of bias.

Research on polyphenol health effects has come a long way during the last decades. Since their first characterization as dietary antioxidants, other mechanisms of action were identified and, today, their role in the modulation of cardiometabolic alterations is well established (102, 103). Ongoing research is also showing that brain may be another target organ of dietary polyphenol and, while most studies up to this moment have been focused on other aspects such as cognitive

function, this review shows that polyphenols may also have a beneficial effect on sleep. Upcoming research, combining properly designed intervention and observational studies, with mechanistic studies in animal models considering nutritional doses, are needed to elucidate whether polyphenols are implicated in sleep health.

Practice Points

Current evidence on polyphenol intake and sleep parameters show:

1. Significant improvements, as compared to a ~~control~~non-supplemented group (control), in SOL, sleep duration, REMS and NREMS, in preclinical studies.

2. Beneficial effects on sleep quality, although they were mostly based on self-reported sleep in placebo-controlled randomized clinical trials.

3. Several mechanisms of action, notably a role on $GABA_R$ receptors.

Research Agenda

The following aspects are relevant for future studies on polyphenols and sleep:

1. Animal studies should focus on nutritional doses.

2. Observational and intervention studies include both objective and self-reported sleep assessment whenever possible.

3. Intervention studies should be designed considering a sleep parameter as primary outcome.

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Conflict of interest statement

The authors have no conflict of interest to declare.

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