


Review

Potential of Polyphenols for Improving Sleep: A Preliminary Results from Review of Human Clinical Trials and Mechanistic Insights

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Abstract: Global epidemiologic evidence supports an interrelationship between sleep disorders and fruits and vegetable ingestion. Polyphenols, a broad group of plant substances, are associated with several biologic processes, including oxidative stress and signaling pathways that regulate the expression of genes promoting an anti-inflammatory environment. Understanding whether and how polyphenol intake is related to sleep may provide avenues to improve sleep and contribute to delaying or preventing the development of chronic disease. This review aims to assess the public health implications of the association between polyphenol intake and sleep and to inform future research. The effects of polyphenol intake, including chlorogenic acid, resveratrol, rosmarinic acid, and catechins, on sleep quality and quantity are discussed to identify polyphenol molecules that may improve sleep. Although some animal studies have investigated the mechanisms underlying the effects of polyphenols on sleep, the paucity of trials, especially randomized controlled trials, does not allow for conducting a meta-analysis to reach clear conclusions about the relationships among these studies to support the sleep-improving effects of polyphenols.

Keywords: catechins; chlorogenic acids; circadian rhythm; phenylpropanoid; resveratrol



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1. Introduction

Sleep is essential for human body homeostasis, circadian rhythms, as well as metabolism, organ function, and other important physiologic functions, regulate the sleep-wake cycle [1]. The endogenous 24-h circadian rhythm is generated by the molecular clock, which is controlled by environmental factors. The circadian clock is the master regulator of physiologic functions, and disruption of the circadian rhythm severely affects health. The sleep-wake cycle is controlled by circadian rhythms that fluctuate on the basis of various factors, including diurnal variations in body temperature [2], blood pressure and pulse [3,4], and endocrine hormone secretion [5,6]. Sleep disturbances are well recognized to lead to psychological distress, physical dysfunction, and reduced quality of life [7]. Sleep quality and quantity are critical factors in achieving a healthy quality of life, and inadequate sleep is a potential risk factor for cerebrovascular disease, depression, and mortality [8,9]. Sleep disturbances are a major social issue in the United States, Europe, and Asia [10–12]. Disturbances in circadian rhythms caused by abnormal sleep patterns, irregular work shifts, and airplane travel across time zones are associated with an enhanced risk of developing various diseases [13,14]. Although diet appears to influence the circadian clock, few studies, especially intervention studies in humans, have demonstrated a clear relationship between the intake of specific food components and circadian clock activities [15,16].

Extensive evidence suggests that fruit and vegetable intake affects body weight and risk of chronic diseases, which may be associated with sleep disturbances [17–19]. Polyphenols found in many plant foods also exhibit diverse physiologic functions and have protective effects against certain diseases, such as coronary artery disease [20–22]. Notably, only a few studies have investigated the relationship between polyphenols and improved

sleep quality, duration, and onset time in obese and standard-weight individuals [23]. Godos et al. [24] performed an epidemiologic study to investigate the population demographic and dietary characteristics of 1936 adults inhabiting southern Italy, in order to determine the potential association of dietary polyphenol intake and sleep quality. Individuals with a high intake of flavonoids such as flavanones, flavones, phenolic acids (i.e., hydroxycinnamic acid), and lignans, had a significantly lower likelihood of inadequate sleep quality. These associations became even clearer when participants were stratified by weight; the effects were significant for normal-weight individuals but not for overweight/obese individuals. In addition, the UK Women's Cohort Study followed 13,958 women for approximately 4 years to assess the possible association between intake of fruit- and vegetable-derived dietary polyphenols and duration of sleep [25]. Their findings revealed a direct association between total intake of fruits and vegetables and the estimated total polyphenol content and duration of sleep, but no association between subgroups of polyphenols and sleep duration was detected [25]. Many factors contribute to sleep, but nutrients are considered to be among the most important factors affecting various sleep parameters. Strategies that ensure the proper timing of meals are thought to produce positive sleep outcomes [26]. In addition, high-protein diets containing essential amino acids, low glycemic index foods, and antioxidant-rich fruits are reported to contribute to better sleep quality [27–29].

St-Onge et al. [30] demonstrated that a plant-based diet may reduce the risk of developing cardiovascular disease by improving sleep. Recent clinical trials revealed that consumption of kiwifruit [31] or tart cherry juice [32] improved sleep (sleep efficiency, sleep quality, and insomnia) in healthy adults, as well as older adults. The relationship between sleep and the intake of polyphenols abundant in fruits and vegetables, however, remains unclear. From a clinical perspective, only a few published literature reviews have investigated the effects of polyphenol intake on sleep. Polyphenols have antioxidant and anti-obesity effects and improve vascular endothelial function. Numerous studies have reported beneficial effects of polyphenol intake on the autonomic nervous system activity and the intestinal microbiota [33,34]. Clarifying the effects and mechanisms of action of polyphenols on sleep will contribute to the body of knowledge on sleep-related health.

This review examines and discusses the effects of polyphenol intake on sleep, with particular emphasis on clinical and epidemiologic studies in humans and preclinical animal studies.

2. An Overview of Polyphenol Metabolism

Polyphenols are natural compounds with a structure containing at least two phenyl rings and at least one hydroxyl substituent. Polyphenols are found in plants, vegetables, grains, fruits, coffee, and tea. Polyphenols are secondary plant metabolites synthesized in plant tissues, and their structure provides protection against pathogens, ultraviolet irradiation, and oxidative injury [35,36]. Plant maturity at harvest, climatic conditions, infectious processes, and post-harvest processing and storage can affect both the polyphenol composition and content [37]. Polyphenols are bioactive phytochemicals comprising subclasses of flavonoids, phenolic acids, stilbenes, and lignans [38,39].

The flavonoid structure comprises a chroman ring attached to a second aromatic ring, and includes flavanols (e.g., quercetin in onions), flavanones (e.g., hesperidin in oranges), isoflavones (in soybeans), anthocyanins (in blueberries), and flavan-3-ols (e.g., epigallocatechin gallate in green tea) [40–42]. Moreover, several groups of simple phenols with diphenylpropane structures, such as lignans, stilbenoids, tannins, and phenylpropanoids, have been identified [43]. Flavonoids are glycoside and non-glycoside conjugates present in plants, and their bioavailability in humans depends on their moieties [38,44]. Dietary flavonoids are hydrolyzed enzymatically in the gastrointestinal tract, subsequently absorbed in the intestine, and then conjugated by phase II enzymes into the glucuronide/sulfate form in epithelial cells and the liver [45,46]. Although some flavonoids are absorbed in the small intestine, most are transported to the large intestine, where deconjugated metabo-

lites and aglycons are further broken down by the colonic microflora for easy absorption of molecules such as phenolic acids [45]. For example, quercetin-3-O-rutinoside from tomatoes is absorbed primarily in the large intestine, where multiple methylation and glucuronidation products are present, and metabolized by the intestinal bacterial flora [44]. Green tea flavan-3-ols are primarily metabolized in the small intestine and then enter the colon, where they are further broken down by the microflora to produce phenolic acids [47]. Intestinal bacteria as well as phenolic and polyphenolic compounds are considered critical for the absorption of numerous flavonoids and influence their bioavailability in the systemic circulation. Moreover, polyphenols remain in the colon longer than in the small intestine and thus have a high potential to influence the colonic microbiota and colon health [48].

Dietary-derived polyphenols have antioxidant, anti-inflammatory, and antiallergic effects in humans. They reduce and prevent aging-related diseases and may also be helpful against cardiovascular events, cancer, osteoporosis, diabetes, and neurodegenerative diseases in humans [49–51]. In vitro studies suggest that the direct antioxidant effects of polyphenols underlie their health benefits. These antioxidant effects may not be relevant in the human body, however, because the concentrations of scavenging free radicals reached after oral ingestion are not sufficient to exert significant effects in most tissues [39,52–54]. Nevertheless, many other biochemical and molecular mechanisms via multiple intra- and intercellular signaling pathways may underlie their effects, such as regulation of nuclear transcription factors, fat metabolism, and synthesis of inflammatory mediators (e.g., cytokines) [55,56]. Flavonoids are involved in glucoregulation through downstream signals such as increasing insulin secretion, decreasing apoptosis, promoting beta cell proliferation, and reducing insulin resistance, inflammation, and oxidative stress in muscle and other cells. Phlorizin, an apple dihydrochalcone, specifically and competitively inhibits sodium-dependent glucose transporter 1 (SGLT-1) in the gut and SGLT-2 in the kidney and may be useful for treating hyperglycemia [57]. Several systematic studies have demonstrated the antioxidant, anti-inflammatory, and other complex biologic roles of polyphenolic compounds, particularly their protective effects against metabolic disorders and chronic diseases [58]. Polyphenols may also act as bioactive substances that enhance the body's immune system and inhibit cellular inflammation and tumor angiogenesis [59,60]. While the potential of polyphenols to prevent disease may be due primarily to their antioxidant effects, they also induce targeted pharmacologic effects as well as epigenetic changes [33,61].

3. Sleep Assessment Methods

Sleep can be objectively assessed by polysomnography (PSG), electroencephalography (EEG), and actigraphy. PSG was first used in clinical settings in the 1970s and is widely regarded as the gold standard method for assessing sleep characteristics [62,63]. Typical PSG studies include central, frontal, and occipital EEG, recordings of eye and jaw movements, and other types of muscle activity (electromyography), an electrocardiogram, pulse oximetry, and monitoring of spontaneous breathing, nasal and oral airflow, and body position [64]. Various other sensors can also be integrated depending on the needs and circumstances of the individual study [65]. The data obtained by PSG are qualitatively and quantitatively accurate and can describe the sleep architecture, i.e., the sequence of the different sleep stages over the course of a night. The brain state during sleep consists of a cycle of two alternating phases: non-rapid eye movement sleep (slow wave sleep [SWS]) and rapid eye movement (REM) sleep. SWS is characterized by high-amplitude slow oscillations (<1 Hz) and sleep spindles (0.5–2-s bursts of 10–16 Hz), and REM sleep is characterized by low-amplitude, fast oscillating EEG activity (4–11 Hz) similar to that in the awake state [66–68]. Although PSG is the gold standard for sleep measurement, it is complicated, expensive, and time-consuming, and the equipment set-up and data output analysis require a high degree of expertise. Single-channel EEG signal meters were recently applied to research to reduce the effort required [69]. Koley et al. [70] utilized 39 time-domain, frequency-domain, and nonlinear features of EEG signals to develop a vector-based machine learning algorithm that automates sleep classification with an

accuracy of 85.7%. Further advances in these areas of research are expected to lead to more accurate assessments in this field.

Actigraphy is a method of continuously monitoring the amount of body movement and activity to objectively estimate sleep and wake behavior. Actigraphic devices typically include a 3-axis or 2-axis accelerometer that records movement as a function of time based on an algorithm; sleep/wake behavior is calculated and the activity/inactivity cycles are converted to reflect wake/sleep, respectively. Thus, sleep is indirectly measured as the average of an individual's movement activity. The wake/sleep data can be used to calculate several variables related to sleep duration and sleep quality, such as total sleep time, sleep onset latency, sleep efficiency (total sleep time/total time in bed), and wake after sleep onset.

Researchers may utilize sleep diaries and questionnaires to assess subjective estimates of sleep-related parameters. Sleep questionnaires are often used as a primary tool to screen for sleep disorders [71,72] on the basis of their characteristics. To assess overall sleep quality, standardized sleep diaries [71], the Pittsburgh Sleep Quality Index [73], the Athens Insomnia Scale [74], the Oguri-Shirakawa-Azumi sleep inventory MA version [75], the Berlin Questionnaire [76], and the Epworth Sleepiness Scale [77] are used. For example, the Pittsburgh Sleep Quality Index assesses 7 dimensions of sleep quality, latency, duration, habitual sleep efficiency, sleep disturbances, sleep medication, and daytime dysfunction over the previous month. Scores for each dimension are summed, providing a global sleep quality index, with higher scores indicating lower sleep quality [73]. When other sleep monitoring methods are difficult to use, a validated questionnaire can provide valuable information and fill gaps in existing evidence. Self-administered diaries are used to collect a variety of sleep-related data, such as bedtime/wake time, lights-out time, naps, daytime sleepiness, alertness, caffeine and alcohol intake, and exercise habits [71]. For a meaningful assessment, participants should monitor and record their sleep characteristics in the diary for at least a week, but this may diminish compliance.

4. Studies of the Effects of Polyphenols on Sleep

Caffeine is a xanthine alkaloid often included as a component of polyphenol-rich beverages such as coffee and tea. Clinical and pharmacologic evidence indicates that caffeine impairs sleep [78–80]. Therefore, the caffeine status should be noted in clinical sleep studies.

4.1. Chlorogenic Acids

Chlorogenic acids (CGAs) are phenolic compounds widely found in plant seeds and/or bodies, such as coffee beans, sweet potatoes, potatoes, apples, and burdock roots. CGAs are mainly known for their antioxidant properties [81] and vascular endothelial function-improving effects [82–84] and are reported to improve hypertension [85]. In addition, CGAs have a wide range of other beneficial effects, such as reducing body fat [86], improving cognitive function [87–89], and improving skin conditions [90]. Recent studies examined the possible effects of continuous consumption of CGA in the form of a coffee bean extract from which the caffeine was removed on human sleep and the autonomic nervous system. Table 1 summarizes the clinical trials that examined the effects of CGA on sleep. Ochiai et al. [91], who studied healthy adult males who consumed a beverage containing 300 mg of decaffeinated CGA derived from green coffee bean extract for 2 weeks, reported that the CGA group experienced less fatigue upon waking and significantly improved subjective sleep quality. Park et al. [92], in a study of nine healthy men and women who consumed a test beverage containing 600 mg of decaffeinated CGA or a placebo for 5 days, reported that CGA decreased sleep latency as measured by sleep EEG and increased parasympathetic activity as determined by measuring heart rate variability. In a recent randomized controlled trial (RCT) of healthy older adults, Saitou et al. [87] found that consumption of 300 mg of coffee bean extract for 16 weeks may improve cognitive function (motor speed, psychomotor speed, and executive function).

These findings are interesting, given the reported association between improved sleep and improved cognitive function.

Table 1. Summary of human clinical studies assessing the association between sleep and chlorogenic acid consumption.

Author (Year)	Study Design	Population	Primary Outcome	Sleep Assessment	Sample (n)	Duration	Intervention (Caffeine Content)	Control	Results on Sleep	Reference
Ochiai et al. (2018)	RCT, crossover	Healthy men aged 30–54 y	Fatigue and sleep	Activity meter, questionnaire (VAS)	16	2 weeks	300 mg/day of CGA < 3 mg caffeine/100 mL	Placebo	CGA significantly improved sleep quality assessed by VAS ($p < 0.05$) and sleep efficiency assessed by an activity meter compared with the control ($p = 0.046$)	[93]
Park et al. (2017)	RCT, crossover	Healthy young men and women	Energy metabolism and sleep	PSG	9	5 days	without caffeine	Placebo	CGA significantly shortened sleep latency compared with the control ($p = 0.043$)	[92]

Abbreviations: CGA, chlorogenic acid; PSG, polysomnography; RCT, randomized controlled trial; VAS, visual analogue scale.

Shinomiya et al. [94] studied how CGA and caffeic acid at doses of 500 and 200 mg/kg, respectively, affected the sleep-wake cycle in rats. They observed no significant effects of CGA and its metabolites on any sleep state and therefore could not investigate the mechanism of the effects of CGA on sleep architecture or sleep quality. While CGA is reported to have potential antidepressant effects, animal behavior studies with CGA revealed neuronal protective effects in the brain and promotion of serotonin release [95,96]. Studies of growing pigs showed that CGA supplementation increased the diversity of the gut microbiota and thus significantly augmented aspartic acid, threonine, alanine, and arginine in the serum, as well as serotonin (5-HT, 5-hydroxytryptamine) levels in the large intestine [97]. Low serotonin levels are associated with insomnia and sleep rhythm disorders, as well as depression [98].

Ferulic acid (4-hydroxy-3-methoxycinnamic acid), a typical bioactive metabolite of CGA, is a potential mediator of shortened sleep latency. Tu et al. [99] reported that ferulic acid significantly potentiated pentobarbital-induced (45 mg/kg, i.p.) sleep by prolonging the sleep time and shortening the sleep latency in mice, in a dose-dependent manner. One possible mechanism by which CGA intake improves sleep structure and quality may be its effects on autonomic nervous system activity. Werner et al. [100] demonstrated that higher resting high-frequency heart rate variability was associated with higher subjective (i.e., Pittsburgh Sleep Quality Index) and objective (i.e., PSG) sleep quality in 29 healthy young women during an extended neutral film clip. Park et al. [92] also demonstrated that CGA increases parasympathetic activation and reduces sleep latency. Furthermore, acute psychologic stress decreases sleep quality and reduces parasympathetic activity during sleep [101]. These findings suggest that CGA inhibits the effects of psychologic stress and other sleep quality-impairing factors via the autonomic nervous system, which promotes recovery from sleep-induced fatigue [91].

4.2. Resveratrol

Resveratrol, classified as a stilbenoid, is abundant in grape seed skins, mulberries, pea pod skins, wine, and tea. Resveratrol appears naturally as a *cis* and *trans* compound and has been identified as an activator of sirtuin 1 (SIRT1) [102]. SIRT1 is an NAD⁺-dependent histone deacetylase family member that regulates life span by its protective effects against metabolic stress, such as obesity caused by a high-fat diet [103]. Compounds such as resveratrol that activate SIRT1 are expected to prevent the onset of metabolic disorders and promote healthy aging. Animal studies showed that resveratrol enhances metabolic health by increasing insulin sensitivity and mitochondrial function in skeletal muscle [104].

Conflicting findings, however, are reported by human clinical trials. While some studies report significant improvements in metabolic health-related parameters [105–107], other studies report no effect [108–111]. A recent systematic review and meta-analysis of 17 RCTs involving 871 patients with type 2 diabetes mellitus revealed a superiority of resveratrol compared with placebo for improving fasting blood glucose and other parameters [112]. Resveratrol exhibits a variety of beneficial effects in neurodegenerative and neurocognitive disorders [113] and is also expected to have beneficial effects on sleep.

Only a few clinical trials have evaluated the effects of resveratrol on sleep, as shown in Table 2. In a study examining the effect of resveratrol intake for 6 months on insulin sensitivity, no differences in sleep and life qualities were detected between the resveratrol and placebo treatment groups, as assessed by a questionnaire that included a secondary endpoint [111]. In a questionnaire-based study by Pennisi et al. [114] to evaluate the effects of resveratrol on both sleep quality and sleep disturbances in hepatitis C patients receiving antiviral treatment with interferon, resveratrol supplementation improved sleep quality and quantity, and decreased sleep disturbances. Wightman et al. [115] reported that chronic supplementation with 500 mg/day of trans-resveratrol in healthy subjects improved cognitive function, but no significant treatment-related differences in sleep quality were detected by the Pittsburgh Sleep Quality Index and its subcomponents compared with placebo. Resveratrol supplementation did, however, reduce symptoms of associated anxiety, depression, and sleep disturbances, suggesting its potential anxiolytic effects.

Table 2. Summary of human clinical studies assessing the association between sleep and resveratrol consumption.

Author (Year)	Study Design	Population	Primary Outcome	Sleep Assessment	Sample (n)	Duration	Intervention	Control	Results on Sleep	Reference
Ligt et al. (2020)	RCT, parallel	Overweight men and women	Insulin sensitivity	Questionnaire (PSQI)	41	6 months	150 mg/d of trans-resveratrol	Placebo	No differences in sleep quality were detected	[111]
Pennisi et al. (2017)	RCT, parallel	Hepatitis C patients	Quality of sleep	Questionnaire (PSQI, ESS)	60	12 months	19.8 mg/d resveratrol	Placebo	Resveratrol significantly improved sleep quality	[114]
Wightman et al. (2015)	RCT, parallel	Healthy men and women	Cognitive performance	Questionnaire (PSQI)	60	4 weeks	500 mg/d of trans-resveratrol	Placebo	No differences in sleep quality were detected	[115]

Abbreviations: ESS, Epworth sleepiness scale; RCT, randomized controlled trial; PSQI, Pittsburgh Sleep Quality Index.

Pifferi et al. [116] investigated the effects of resveratrol administration on the EEG rhythm-based sleep-wake cycle in a non-human primate, the grey mouse lemur (*Microcebus murinus*). After three weeks of resveratrol administration, the percentage of active wake time was significantly increased, with the increase occurring mostly during the resting phase of the sleep-wake cycle. The increase in active wake time caused by resveratrol came at the expense of paradoxical sleep and SWS, which were significantly decreased. Dietary resveratrol may be involved in regulating the circadian clock in experimental animals [117]. Energy balance in several species is modulated by resveratrol activating several proteins that are part of the energy-regulating pathways, such as PGC1 α [118] and SIRT1 [119]. SIRT1 is involved in biologic clock processes [120,121], and regulation of this protein by resveratrol may cause changes in the biologic rhythm patterns of physiologic parameters. Recent studies in young animals showed that dietary supplementation with resveratrol can alter the structure of sleep-wake rhythms by reducing the amount of SWS and increasing activity [116]. How resveratrol affects sleep, especially in humans, remains unclear, and the mechanisms are mostly unknown.

4.3. Rosmarinic Acids

Rosmarinic acid is a natural polyphenol in spearmint (*Mentha spicata*), shiso (*Perilla frutescens*), rosemary (*Rosmarinus officinalis*), lemon balm (*Melissa officinalis*), and other plants [122,123]. Rosmarinic acid has antioxidant, antibacterial, antiviral, anti-inflammatory,

analgesic, neuroprotective, and cardioprotective effects against both gram-positive and gram-negative bacteria [124]. Rosmarinic acid may also support cognitive function in relation to a common polyphenolic component. This naturally occurring phenolic acid is the esterification product of caffeic acid and 3,4-dihydroxyphenyl lactic acid. In Table 3, a randomized, double-blind, placebo-controlled, parallel study was performed to assess cognitive function, sleep, mood, and quality of life by a validated questionnaire in healthy men and women ($n = 142$) taking 900 mg per day of a proprietary spearmint (*Mentha spicata*) extract ($\geq 14.5\%$ rosmarinic acid and 24% phenolic content) or placebo for 90 days [125]. The results showed that the aqueous extract improved cognitive function but did not significantly affect mood, sleep, or quality of life.

The in vitro inhibition of gamma-aminobutyric acid (GABA) transaminase by rosmarinic acid suggests that the activation of GABA_A-ergic system is a potential treatment for insomnia [126]. In a pentylenetetrazole-induced kindling mouse model, 4 mg/kg of rosmarinic acid bound to diazepam shortened sleep latency in the diazepam-induced sleep time test [127]. In a recent study, the sleep-promoting effects of rosmarinic acid, which targets the adenosine receptor (a therapeutic target for insomnia), were evaluated by pentobarbital-induced sleep studies in mice, EEG and electromyography, and immunohistochemical techniques [128]. Simultaneously, the underlying mechanisms were evaluated by pharmacologic approaches using antagonists of the adenosine A1 receptor and the adenosine A2a receptor (8-cyclopentyl-1,3-dipropylxanthine and SCH5826, respectively). The results demonstrated that rosmarinic acid has direct binding activity and agonist activity against adenosine A1 receptors. Rosmarinic acid decreased sleep latency and increased total sleep time in a mouse pentobarbital (42 mg/kg, i.p.)-induced sleep model [129]. Rosmarinic acid also increased the effects of sub-hypnotic pentobarbital (28 mg/kg, i.p.) on sleep time and the number of mice that fell asleep [129]. EEG recordings in rats showed that rosmarinic acid (2.0 mg/kg) not only reduced the number of sleep/wake cycles and REM sleep but also enhanced total and non-REM sleep [129].

Table 3. Summary of human clinical studies assessing the association between sleep and RA consumption.

Author (Year)	Study Design	Population	Primary Outcome	Sleep Assessment	Sample (n)	Duration	Intervention (Caffeine)	Control	Results on Sleep	Reference
Tubbs et al. (2021)	RCT, parallel	Healthy men and women	Sleep, daytime functioning	Activity tracker, Sleep diary, ISI, PSQI	105	30 days	120 mg/d RA and EGCg < 4.85 mg caffeine	Placebo	RA and EGCg improved daily sleep quality ($p = 0.008$) and reduced insomnia severity ($p = 0.044$)	[130]
Falcone et al. (2019)	RCT, parallel	Healthy men and women	Cognitive performance, sleep	Questionnaire (LSEQ, PSQI)	142	90 days	130 mg/d RA	Placebo	No differences in the quality of sleep were detected	[125]
Herrlinger et al. (2018)	RCT, parallel	Healthy men and women	Cognitive performance	Questionnaire (LSEQ)	90	90 days	900 mg/d or 600 mg/d spearmint extract	Placebo	Spearmint extract improved the ability to fall asleep ($p = 0.0046$).	[131]

Abbreviations: EGCg, epigallocatechin gallate; ISI, insomnia severity index; LSEQ, Leeds sleep evaluation questionnaire, RA, rosmarinic acid; RCT, randomized controlled trial; PSQI, Pittsburgh Sleep Quality Index.

4.4. Catechins

Catechins (flavanols) are the predominant polyphenols in tea. Green tea is rich in catechins (e.g., epicatechin, epicatechin gallate, epigallocatechin, and epigallocatechin gallate [EGCg]) and their thermal isomers (e.g., catechin, catechin gallate, gallic catechin, and gallic catechin gallate) [132,133]. Many of the physiologic functions of catechins (e.g., antioxidant, antidiabetic, and antiatherosclerotic effects) have been established in vitro, in animal studies, and in human trials [134–138].

Unno et al. [139] examined the effects of a low-caffeine green tea (caffeine content was reduced to 20–25%) on the stress responses and sleep parameters in 20 middle-aged men and women; the results were compared with those of standard catechin and theanine-

containing teas (Table 4). Sleep parameters were measured with a single-channel EEG, the stress response was measured as salivary α -amylase activity, and subjective fatigue was assessed with a questionnaire. Compared with standard caffeine-containing tea, low-caffeine green tea consumption improved fatigue and tiredness but had no significant effect on sleep. Zhang et al. [140] conducted a crossover study of three groups of 12 non-obese men who consumed oolong tea (100 mg caffeine, 21.4 mg gallic acid, 97 mg catechins, and 125 mg polymerized polyphenols), caffeine (100 mg), or a placebo over a 14-day period. On day 14 of each session, energy metabolism by indirect calorimetry and sleep by PSG were measured. Caffeine and oolong tea consumption increased fat oxidation, and caffeine consumption increased parasympathetic nervous activity but had no effect on sleep parameters.

Table 4. Summary of human clinical studies assessing the association between sleep and catechin consumption.

Author (Year)	Study Design	Population	Primary Outcome	Sleep Assessment	Sample (n)	Duration	Intervention (Caffeine)	Control	Results on Sleep	Reference
Zhang (2020)	RCT, crossover	Healthy men aged 20–56 y	Energy metabolism	PSG, Questionnaire (PSQI)	12	2 weeks	48.5 mg/d catechins, 51.8 mg/d caffeine	Placebo, 51.8 mg caffeine	No differences in the sleep parameters were detected	[140]
Unno et al. (2017)	RCT, crossover	Healthy men and women	Stress responses, sleep parameters	Single-channel EEG	20	1 week	Standard green tea	Low-caffeine green tea	No significant difference in sleep parameters was detected	[139]

Abbreviations: EEG, electroencephalogram; ISI, insomnia severity index; LSEQ, Leeds sleep evaluation questionnaire, RCT, randomized controlled trial; PSQI, Pittsburgh Sleep Quality Index.

A recent review discussed the effects of tea components (L-theanine, caffeine, tea polyphenols [catechins], tea pigments, tea polysaccharides, and GABA) on sleep and brain function [141]. After ingestion of green tea, catechins and their main component EGCg can easily transit the blood-brain barrier and distribute in the brain, exerting neuroprotective effects; therefore, EGCg may regulate sleep [142,143]. EGCg binds to GABA_A receptors in vitro [144], and the relative levels of EGCg and epigallocatechin in low-caffeine green tea may modulate the effects of GABA through binding to GABA_A receptors [145]. Furthermore, catechins suppressed the expression of tumor necrosis factor α and reduced cognitive deficits in a mouse model of sleep deprivation [146], and EGCg, like the GABA_A receptor agonist muscimol, prolonged the duration of pentobarbital-induced sleep and reduced sleep latency in mice [147]. Vocalizations that normally occur during social isolation stress were suppressed when EGCg (50, 100, and 200 μ g) was administered intracerebroventricularly to chickens under acute stress conditions, and a dose-dependent reduction in wakefulness time and induction of sleep-like behavior were observed [148]. Although these basic studies in animals demonstrate the potential sleep-improving effects of catechins and EGCg without caffeine, further clinical investigation, especially in humans, is required.

5. Discussion

The present review examines the effects of polyphenol intake on sleep, with particular emphasis on human clinical and epidemiologic studies and preclinical animal studies. The relationship between polyphenol intake, which has many favorable health aspects, and sleep improvements has not been adequately investigated and remains unclear. Few reviews have examined the effects of polyphenols specifically and their intake on sleep, especially from a clinical perspective. Polyphenols exhibit many beneficial effects, including antioxidant and antiobesity effects, as well as effects on vascular endothelial function, and many studies have evaluated their effects on the autonomic nervous system and gut microbiota. Clarifying the effects of polyphenol intake on sleep would contribute to this body of research and guide future research. To our knowledge, this review is one of very few literature surveys to identify polyphenol molecules that may improve sleep quality. Due to the limited number of studies evaluating the effects of polyphenols on sleep, we

could not conduct a meta-analysis to draw definitive conclusions about the relationships among the studies. Further, a dose-response meta-analysis integrating the studies was also not available, and thus the dose responsiveness could not be considered.

This review examines the effects of the dietary polyphenol intake (i.e., CGA, resveratrol, rosmarinic acid, catechins, and lignans (phenylpropanoids)) on sleep. In addition, we discussed the absorption and metabolic properties of polyphenols and subjective, as well as objective, assessment methods of sleep. Sleep, especially when it is self-reported in questionnaires, cannot be completely excluded from biases (e.g., placebo effects). Therefore, studies in which sleep EEG is measured by appropriate methods and sleep state is determined are essential to determining the true effects of the intake of polyphenol components on sleep. A review of the literature revealed that only a few human studies have sufficiently investigated the pharmacologic mechanisms of polyphenols, and the types of polyphenols that can be concluded to be effective in improving sleep are limited. A small human study [92] demonstrated the potential efficacy of CGA for improving sleep on the basis of objective sleep measurements by EEG and discussed the mechanisms by which it may improve sleep, such as through ferulic acid, a CGA metabolite. No meta-analysis of CGA has been conducted, however, and further research, especially in human studies with large sample sizes, is warranted.

Several different neuronal systems regulate the sleep-wake cycle, including GABAergic, serotonergic, histaminergic, and adrenergic systems. The GABAergic system is a major sleep-promoting pathway with an important role in actions of many hypnotic drugs. Serotonergic activity is responsible for not only sleep, but also sleep inhibition and arousal. Serotonin has complex effects on the sleep-wake cycle, which may be due to its actions in different regions of the brain involved in sleep and wakefulness [149]. Ferulic acid, a phenolic acid categorized as a hydroxycinnamic acid, is a typical metabolite of CGA and may partially mediate sleep improvement. Ferulic acid binds to receptors in the GABAergic and serotonergic neurotransmitter systems and is suggested to affect sleep. Ferulic acid is found in many plants, including cabbage, wheat, rice bran, tomatoes, and onions, but its pharmacokinetic properties, such as low gastrointestinal stability, a short plasma half-life after oral administration, and low bioavailability limit its use in the treatment of sleep. More than 70% of ferulic acid is absorbed from the gastrointestinal tract within 30 min after oral administration and is rapidly excreted by the kidneys, resulting in a short residence time and low plasma concentrations. Furthermore, despite its ability to cross the blood-brain barrier, ferulic acid concentrations in the brain are very low, limiting its use in the treatment of sleep [150,151]. Therefore, ferulic acid as a metabolite of polyphenols such as CGA may beneficially affect sleep due to its improved bioavailability, stability in the gastrointestinal tract, and availability in the blood. Tu et al. [99] evaluated the hypnotic and sedative effects of ferulic acid and found that ferulic acid exerts sedative effects by suppressing motor activity; ferulic acid also significantly potentiates the hypnotic effects of pentobarbital, shortens sleep latency, prolongs sleep duration, and increases the rate of sleep onset. Rosmarinic acid inhibits GABA transaminases, suggesting an effect on sleep through activation of the GABAergic system [126]. Furthermore, rosmarinic acid enhances pentobarbital-induced sleep behavior via GABA_A neurotransmission, suggesting that the effects of rosmarinic acid on sleep are mediated through the GABA_A-ergic system [129]. Interestingly, CGA supplementation increases the diversity of the gut microbiota, and through these changes, significantly enhances serum aspartate, threonine, alanine, arginine, and colonic serotonin (5-HT) levels, which may lead to improvements in insomnia and sleep rhythm disorders [97]. Polyphenols are known to affect tryptophan metabolism through the gut microbiota [152]. Some effects seem inconsistent, however, which is attributed to changes in the bioavailability of polyphenols depending on the composition of the microbiota. The effects of polyphenols and their metabolites on sleep and sedative effects may be mediated by neural effects of the GABAergic or serotonergic neurotransmitter systems.

In a systematic review and meta-analysis of supplements that may improve sleep, Chan et al. [153] found that adding amino acids, melatonin, and vitamin D to the diet

improved subjective sleep quality, but, because of insufficient studies, especially RCTs, it is unclear whether or not the addition of zinc, resveratrol, magnesium, and nitrates to the diet also improves sleep quality. The authors considered that more RCTs should be conducted to examine the effects of resveratrol, a polyphenol, in various populations. In general mechanistic terms, metabolites of polyphenols can traverse the blood-brain barrier to varying degrees depending on the lipophilicity, while the less polar polyphenol metabolites can be taken up by the brain [154]. In the central nervous system, the major potential beneficial effects of dietary polyphenols include inhibiting neuronal apoptosis, modulating signaling pathways involved in neuronal survival, and stimulating neurogenesis [155,156]. With respect to specific mechanisms related to sleep characteristics, dietary polyphenols enhance recovery from sleep deprivation [157]. Furthermore, derivatives of hydroxycinnamic acid, such as ferulic acid, are GABA receptor agonists that act synergistically with 5-hydroxytryptophan, which has a sedative effect on motor activity, prolongs sleep duration, reduces sleep latency, and is involved in sleep quality [99,158]. The synergistic effects between polyphenols and other nutrients with distinct pharmacologic functions, such as phytosterols, should also be considered in future studies [159]. Lignans protect the blood-brain barrier from inflammatory cells by their antioxidant and anti-inflammatory properties in neurons, reducing oxidative stress, inflammation, and permeability [160–162]. Dietary polyphenols may improve endothelial dysfunction and help control blood pressure [163,164], and the improved endothelial function, along with decreased rates of REM sleep and increased REM sleep latency, may be associated with improved sleep quality [165,166]. The gut microbiota also influences the brain and behavior associated with anxiety and depression symptoms in response to modulation through dietary polyphenol intake [167]. Recent studies suggested that dietary polyphenols play a role in modulating the metabolism of the gut microbiota and that fluctuations in the gut microbiota can affect activity through polyphenol metabolites [168]. The current evidence, however, is based primarily on cellular and animal studies, and human studies are needed to identify specific metabolic types associated with activity in the brain.

This literature review was performed to identify polyphenol molecules with the potential to improve sleep quality and to reveal the potential role of individual polyphenols on sleep. The findings presented in this review should be considered in light of several limitations. First, this study was not a comprehensive review of the literature, which may lead to potential oversights (in particular, studies in which the effects on sleep are not the primary endpoints). It is also possible that some relevant studies published in non-English languages were missed. Despite the fact that herbs are very popular in Asia, no Chinese or Japanese language studies were included. Improving the quality of clinical studies published in those local languages could be improved, which would allow them to be included in future meta-analyses. Second, the discussion of mechanisms was drawn only from the studies and reports cited in the current review. Third, sleep quality and quantity were not considered, even though they may be related to some mental health issues.

6. Conclusions

A literature review was conducted to identify polyphenol molecules that may improve sleep quality. Several animal studies have examined the mechanistic effects of CGA, resveratrol, rosmarinic acid, and catechins on sleep, but the limited number of studies, especially RCTs, evaluating the effects of polyphenols on sleep did not allow for a meta-analysis to reach clear conclusions about the relationships among these studies. The dose responsiveness could not be considered because of the lack of a dose-response meta-analysis merging the studies.

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References

1. Siegel, J.M. Sleep viewed as a state of adaptive inactivity. *Nat. Rev. Neurosci.* **2009**, *10*, 747–753. [\[CrossRef\]](#)
2. Landolt, H.P.; Moser, S.; Wieser, H.G.; Borbely, A.A.; Dijk, D.J. Intracranial temperature across 24-hour sleep-wake cycles in humans. *Neuroreport* **1995**, *6*, 913–917. [\[CrossRef\]](#) [\[PubMed\]](#)
3. Nilsson, P.M.; Nilsson, J.A.; Hedblad, B.; Berglund, G. Sleep disturbance in association with elevated pulse rate for prediction of mortality—consequences of mental strain? *J. Intern. Med.* **2001**, *250*, 521–529. [\[CrossRef\]](#)
4. Schwimmer, H.; Stauss, H.M.; Abboud, F.; Nishino, S.; Mignot, E.; Zeitzer, J.M. Effects of sleep on the cardiovascular and thermoregulatory systems: A possible role for hypocretins. *J. Appl. Physiol.* **1985**, *109*, 1053–1063. [\[CrossRef\]](#) [\[PubMed\]](#)
5. Morris, C.J.; Aeschbach, D.; Scheer, F.A. Circadian system, sleep and endocrinology. *Mol. Cell Endocrinol.* **2012**, *349*, 91–104. [\[CrossRef\]](#) [\[PubMed\]](#)
6. Barion, A.; Zee, P.C. A clinical approach to circadian rhythm sleep disorders. *Sleep Med.* **2007**, *8*, 566–577. [\[CrossRef\]](#) [\[PubMed\]](#)
7. Medic, G.; Wille, M.; Hemels, M.E. Short- and long-term health consequences of sleep disruption. *Nat. Sci. Sleep* **2017**, *9*, 151–161. [\[CrossRef\]](#)
8. Tamakoshi, A.; Ohno, Y.; Group, J.S. Self-reported sleep duration as a predictor of all-cause mortality: Results from the JACC study, Japan. *Sleep* **2004**, *27*, 51–54.
9. Gallicchio, L.; Kalesan, B. Sleep duration and mortality: A systematic review and meta-analysis. *J. Sleep Res.* **2009**, *18*, 148–158. [\[CrossRef\]](#)
10. Caraballo, C.; Mahajan, S.; Valero-Elizondo, J.; Massey, D.; Lu, Y.; Roy, B.; Riley, C.; Annapureddy, A.R.; Murugiah, K.; Elumn, J.; et al. Evaluation of Temporal Trends in Racial and Ethnic Disparities in Sleep Duration Among US Adults, 2004–2018. *JAMA Netw. Open* **2022**, *5*, e226385. [\[CrossRef\]](#)
11. Chen, R.; Slopen, N.; Lee, S. Perceived stress, recent stressors, and distress in relation to sleep disturbance and duration among middle-aged and older Asian immigrants. *Sleep Health*, 2022; *in press*. [\[CrossRef\]](#)
12. Benjafield, A.V.; Ayas, N.T.; Eastwood, P.R.; Heinzer, R.; Ip, M.S.M.; Morrell, M.J.; Nunez, C.M.; Patel, S.R.; Penzel, T.; Pepin, J.L.; et al. Estimation of the global prevalence and burden of obstructive sleep apnoea: A literature-based analysis. *Lancet Respir. Med.* **2019**, *7*, 687–698. [\[CrossRef\]](#)
13. Lane, J.M.; Qian, J.; Mignot, E.; Redline, S.; Scheer, F.; Saxena, R. Genetics of circadian rhythms and sleep in human health and disease. *Nat. Rev. Genet.* **2023**, *24*, 4–20. [\[CrossRef\]](#) [\[PubMed\]](#)
14. Zhang, L.; Jain, M.K. Circadian regulation of cardiac metabolism. *J. Clin. Investig.* **2021**, *131*, e148276. [\[CrossRef\]](#) [\[PubMed\]](#)
15. Boege, H.L.; Bhatti, M.Z.; St-Onge, M.P. Circadian rhythms and meal timing: Impact on energy balance and body weight. *Curr. Opin. Biotechnol.* **2021**, *70*, 1–6. [\[CrossRef\]](#) [\[PubMed\]](#)
16. Mohd Azmi, N.A.S.; Juliana, N.; Mohd Fahmi Teng, N.I.; Azmani, S.; Das, S.; Effendy, N. Consequences of Circadian Disruption in Shift Workers on Chrononutrition and their Psychosocial Well-Being. *Int. J. Environ. Res. Public Health* **2020**, *17*, 2043. [\[CrossRef\]](#) [\[PubMed\]](#)
17. Aune, D.; Giovannucci, E.; Boffetta, P.; Fadnes, L.T.; Keum, N.; Norat, T.; Greenwood, D.C.; Riboli, E.; Vatten, L.J.; Tonstad, S. Fruit and vegetable intake and the risk of cardiovascular disease, total cancer and all-cause mortality—a systematic review and dose-response meta-analysis of prospective studies. *Int. J. Epidemiol.* **2017**, *46*, 1029–1056. [\[CrossRef\]](#) [\[PubMed\]](#)
18. Peuhkuri, K.; Sihvola, N.; Korpela, R. Diet promotes sleep duration and quality. *Nutr. Res.* **2012**, *32*, 309–319. [\[CrossRef\]](#) [\[PubMed\]](#)
19. Frank, S.; Gonzalez, K.; Lee-Ang, L.; Young, M.C.; Tamez, M.; Mattei, J. Diet and Sleep Physiology: Public Health and Clinical Implications. *Front. Neurol.* **2017**, *8*, 393. [\[CrossRef\]](#)
20. Fraga, C.G.; Galleano, M.; Verstraeten, S.V.; Oteiza, P.I. Basic biochemical mechanisms behind the health benefits of polyphenols. *Mol. Asp. Med.* **2010**, *31*, 435–445. [\[CrossRef\]](#)
21. Storniolo, C.E.; Sacanella, I.; Mitjavila, M.T.; Lamuela-Raventos, R.M.; Moreno, J.J. Bioactive Compounds of Cooked Tomato Sauce Modulate Oxidative Stress and Arachidonic Acid Cascade Induced by Oxidized LDL in Macrophage Cultures. *Nutrients* **2019**, *11*, 1880. [\[CrossRef\]](#)
22. Mitjavila, M.T.; Moreno, J.J. The effects of polyphenols on oxidative stress and the arachidonic acid cascade. Implications for the prevention/treatment of high prevalence diseases. *Biochem. Pharmacol.* **2012**, *84*, 1113–1122. [\[CrossRef\]](#) [\[PubMed\]](#)
23. Lian, Y.; Yuan, Q.; Wang, G.; Tang, F. Association between sleep quality and metabolic syndrome: A systematic review and meta-analysis. *Psychiatry Res.* **2019**, *274*, 66–74. [\[CrossRef\]](#) [\[PubMed\]](#)
24. Godos, J.; Ferri, R.; Castellano, S.; Angelino, D.; Mena, P.; Del Rio, D.; Caraci, F.; Galvano, F.; Grosso, G. Specific Dietary (Poly)phenols Are Associated with Sleep Quality in a Cohort of Italian Adults. *Nutrients* **2020**, *12*, 1226. [\[CrossRef\]](#) [\[PubMed\]](#)
25. Noorwali, E.; Hardie, L.; Cade, J. Fruit and Vegetable Consumption and Their Polyphenol Content Are Inversely Associated with Sleep Duration: Prospective Associations from the UK Women’s Cohort Study. *Nutrients* **2018**, *10*, 1803. [\[CrossRef\]](#) [\[PubMed\]](#)

26. Pattnaik, H.; Mir, M.; Boike, S.; Kashyap, R.; Khan, S.A.; Surani, S. Nutritional Elements in Sleep. *Cureus* **2022**, *14*, e32803. [[CrossRef](#)] [[PubMed](#)]
27. Rostami, H.; Khayyatadeh, S.S.; Tavakoli, H.; Bagherniya, M.; Mirmousavi, S.J.; Farahmand, S.K.; Tayefi, M.; Ferns, G.A.; Ghayour-Mobarhan, M. The relationship between adherence to a Dietary Approach to Stop Hypertension (DASH) dietary pattern and insomnia. *BMC Psychiatry* **2019**, *19*, 234. [[CrossRef](#)] [[PubMed](#)]
28. Afaghi, A.; O'Connor, H.; Chow, C.M. High-glycemic-index carbohydrate meals shorten sleep onset. *Am. J. Clin. Nutr.* **2007**, *85*, 426–430. [[CrossRef](#)]
29. Yaghtin, Z.; Beigrezaei, S.; Yuzbashian, E.; Ghayour-Mobarhan, M.; Khayyatadeh, S.S. A greater modified Mediterranean diet score is associated with lower insomnia score among adolescent girls: A cross-sectional study. *BMC Nutr.* **2022**, *8*, 60. [[CrossRef](#)]
30. St-Onge, M.P.; Crawford, A.; Aggarwal, B. Plant-based diets: Reducing cardiovascular risk by improving sleep quality? *Curr. Sleep Med. Rep.* **2018**, *4*, 74–78. [[CrossRef](#)]
31. Lin, H.H.; Tsai, P.S.; Fang, S.C.; Liu, J.F. Effect of kiwifruit consumption on sleep quality in adults with sleep problems. *Asia Pac. J. Clin. Nutr.* **2011**, *20*, 169–174.
32. Pigeon, W.R.; Carr, M.; Gorman, C.; Perlis, M.L. Effects of a tart cherry juice beverage on the sleep of older adults with insomnia: A pilot study. *J. Med. Food* **2010**, *13*, 579–583. [[CrossRef](#)] [[PubMed](#)]
33. Tresserra-Rimbau, A.; Lamuela-Raventos, R.M.; Moreno, J.J. Polyphenols, food and pharma. Current knowledge and directions for future research. *Biochem. Pharmacol.* **2018**, *156*, 186–195. [[CrossRef](#)] [[PubMed](#)]
34. Wan, M.L.Y.; Co, V.A.; El-Nezami, H. Dietary polyphenol impact on gut health and microbiota. *Crit. Rev. Food Sci. Nutr.* **2021**, *61*, 690–711. [[CrossRef](#)] [[PubMed](#)]
35. Olszowy, M. What is responsible for antioxidant properties of polyphenolic compounds from plants? *Plant. Physiol. Biochem.* **2019**, *144*, 135–143. [[CrossRef](#)]
36. Melini, V.; Melini, F.; Luziatelli, F.; Ruzzi, M. Functional ingredients from agri-food waste: Effect of inclusion thereof on phenolic compound content and bioaccessibility in bakery products. *Antioxidants* **2020**, *9*, 1216. [[CrossRef](#)]
37. Pino, C.; Sepulveda, B.; Tapia, F.; Saavedra, J.; Garcia-Gonzalez, D.L.; Romero, N. The impact of mild frost occurring at different harvesting times on the volatile and phenolic composition of virgin olive oil. *Antioxidants* **2022**, *11*, 852. [[CrossRef](#)]
38. Manach, C.; Williamson, G.; Morand, C.; Scalbert, A.; Remesy, C. Bioavailability and bioefficacy of polyphenols in humans. I. Review of 97 bioavailability studies. *Am. J. Clin. Nutr.* **2005**, *81*, 230S–242S. [[CrossRef](#)]
39. Fraga, C.G.; Croft, K.D.; Kennedy, D.O.; Tomas-Barberan, F.A. The effects of polyphenols and other bioactives on human health. *Food Funct.* **2019**, *10*, 514–528. [[CrossRef](#)]
40. Singla, R.K.; Dubey, A.K.; Garg, A.; Sharma, R.K.; Fiorino, M.; Ameen, S.M.; Haddad, M.A.; Al-Hiary, M. Natural Polyphenols: Chemical Classification, Definition of Classes, Subcategories, and Structures. *J. AOAC Int.* **2019**, *102*, 1397–1400. [[CrossRef](#)]
41. Corcoran, M.P.; McKay, D.L.; Blumberg, J.B. Flavonoid basics: Chemistry, sources, mechanisms of action, and safety. *J. Nutr. Gerontol. Geriatr.* **2012**, *31*, 176–189. [[CrossRef](#)]
42. Bohn, S.K.; Ward, N.C.; Hodgson, J.M.; Croft, K.D. Effects of tea and coffee on cardiovascular disease risk. *Food Funct.* **2012**, *3*, 575–591. [[CrossRef](#)]
43. Del Rio, D.; Rodriguez-Mateos, A.; Spencer, J.P.; Tognolini, M.; Borges, G.; Crozier, A. Dietary (poly)phenolics in human health: Structures, bioavailability, and evidence of protective effects against chronic diseases. *Antioxid. Redox Signal.* **2013**, *18*, 1818–1892. [[CrossRef](#)] [[PubMed](#)]
44. Crozier, A.; Del Rio, D.; Clifford, M.N. Bioavailability of dietary flavonoids and phenolic compounds. *Mol. Asp. Med.* **2010**, *31*, 446–467. [[CrossRef](#)] [[PubMed](#)]
45. Selma, M.V.; Espin, J.C.; Tomas-Barberan, F.A. Interaction between phenolics and gut microbiota: Role in human health. *J. Agric. Food Chem.* **2009**, *57*, 6485–6501. [[CrossRef](#)] [[PubMed](#)]
46. Murota, K.; Nakamura, Y.; Uehara, M. Flavonoid metabolism: The interaction of metabolites and gut microbiota. *BioSci. Biotechnol. Biochem.* **2018**, *82*, 600–610. [[CrossRef](#)] [[PubMed](#)]
47. Neilson, A.P.; Ferruzzi, M.G. Influence of formulation and processing on absorption and metabolism of flavan-3-ols from tea and cocoa. *Annu. Rev. Food Sci. Technol.* **2011**, *2*, 125–151. [[CrossRef](#)]
48. Storniolo, C.E.; Sacanella, I.; Lamuela-Raventos, R.M.; Moreno, J.J. Bioactive Compounds of Mediterranean Cooked Tomato Sauce (Sofrito) Modulate Intestinal Epithelial Cancer Cell Growth through Oxidative Stress/Arachidonic Acid Cascade Regulation. *ACS Omega* **2020**, *5*, 17071–17077. [[CrossRef](#)]
49. Pandey, K.B.; Rizvi, S.I. Plant polyphenols as dietary antioxidants in human health and disease. *Oxid. Med. Cell Longev.* **2009**, *2*, 270–278. [[CrossRef](#)]
50. Graf, B.A.; Milbury, P.E.; Blumberg, J.B. Flavonols, flavones, flavanones, and human health: Epidemiological evidence. *J. Med. Food* **2005**, *8*, 281–290. [[CrossRef](#)]
51. Arts, I.C.; Hollman, P.C. Polyphenols and disease risk in epidemiologic studies. *Am. J. Clin. Nutr.* **2005**, *81*, 317S–325S. [[CrossRef](#)]
52. Fraga, C.G. Plant polyphenols: How to translate their in vitro antioxidant actions to in vivo conditions. *IUBMB Life* **2007**, *59*, 308–315. [[CrossRef](#)] [[PubMed](#)]
53. Fraga, C.G.; Oteiza, P.I. Dietary flavonoids: Role of (-)-epicatechin and related procyanidins in cell signaling. *Free Radic. Biol. Med.* **2011**, *51*, 813–823. [[CrossRef](#)] [[PubMed](#)]

54. Galleano, M.; Verstraeten, S.V.; Oteiza, P.I.; Fraga, C.G. Antioxidant actions of flavonoids: Thermodynamic and kinetic analysis. *Arch. Biochem. Biophys.* **2010**, *501*, 23–30. [[CrossRef](#)] [[PubMed](#)]
55. Kim, H.S.; Quon, M.J.; Kim, J.A. New insights into the mechanisms of polyphenols beyond antioxidant properties; lessons from the green tea polyphenol, epigallocatechin 3-gallate. *Redox Biol.* **2014**, *2*, 187–195. [[CrossRef](#)]
56. Fraga, C.G.; Oteiza, P.I.; Galleano, M. Plant bioactives and redox signaling: (-)-Epicatechin as a paradigm. *Mol Aspects Med.* **2018**, *61*, 31–40. [[CrossRef](#)]
57. Ehrenkranz, J.R.; Lewis, N.G.; Kahn, C.R.; Roth, J. Phlorizin: A review. *Diabetes Metab. Res. Rev.* **2005**, *21*, 31–38. [[CrossRef](#)]
58. Ganesan, K.; Xu, B. A critical review on polyphenols and health benefits of black soybeans. *Nutrients* **2017**, *9*, 455. [[CrossRef](#)]
59. Ding, S.; Xu, S.; Fang, J.; Jiang, H. The protective effect of polyphenols for colorectal cancer. *Front. Immunol.* **2020**, *11*, 1407. [[CrossRef](#)]
60. Compaore, M.; Bakasso, S.; Meda, R.N.T.; Nacoulma, O.G. Antioxidant and anti-inflammatory activities of fractions from *Bidens engleri* O.E. Schulz (Asteraceae) and *Boerhavia erecta* L. (Nyctaginaceae). *Medicines* **2018**, *5*, 53. [[CrossRef](#)]
61. Tarragon, E.; Moreno, J.J. Polyphenols and taste 2 receptors. Physiological, pathophysiological and pharmacological implications. *Biochem. Pharmacol.* **2020**, *178*, 114086. [[CrossRef](#)]
62. Penzel, T.; Conrad, R. Computer based sleep recording and analysis. *Sleep Med. Rev.* **2000**, *4*, 131–148. [[CrossRef](#)] [[PubMed](#)]
63. Rundo, J.V.; Downey, R., 3rd. Polysomnography. *Handb. Clin. Neurol.* **2019**, *160*, 381–392. [[CrossRef](#)]
64. Holland, J.; Dement, W.; Raynal, D. Polysomnography: A Response to a Need for Improved Communication. In Proceedings of the 14th Annual Meeting of the Association for the Psychophysiological Study of Sleep, Jackson Hole, MY, USA, 6–9 June 1974; p. 121.
65. Berry, R.B.; Gamaldo, C.E.; Harding, S.M.; Brooks, R.; Lloyd, R.M.; Vaughn, B.V.; Marcus, C.L. AASM Scoring Manual Version 2.2 Updates: New Chapters for Scoring Infant Sleep Staging and Home Sleep Apnea Testing. *J. Clin. Sleep Med.* **2015**, *11*, 1253–1254. [[CrossRef](#)] [[PubMed](#)]
66. Aserinsky, E.; Kleitman, N. Regularly occurring periods of eye motility, and concomitant phenomena, during sleep. *Science* **1953**, *118*, 273–274. [[CrossRef](#)] [[PubMed](#)]
67. Sun, L.; Zhou, H.; Cichon, J.; Yang, G. Experience and sleep-dependent synaptic plasticity: From structure to activity. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* **2020**, *375*, 20190234. [[CrossRef](#)] [[PubMed](#)]
68. Hori, T.; Sugita, Y.; Koga, E.; Shirakawa, S.; Inoue, K.; Uchida, S.; Kuwahara, H.; Kousaka, M.; Kobayashi, T.; Tsuji, Y.; et al. Proposed supplements and amendments to ‘A Manual of Standardized Terminology, Techniques and Scoring System for Sleep Stages of Human Subjects’, the Rechtschaffen & Kales (1968) standard. *Psychiatry Clin. Neurosci.* **2001**, *55*, 305–310. [[CrossRef](#)] [[PubMed](#)]
69. Zhao, S.; Long, F.; Wei, X.; Ni, X.; Wang, H.; Wei, B. Evaluation of a single-channel EEG-based sleep staging algorithm. *Int. J. Environ. Res. Public Health* **2022**, *19*, 2845. [[CrossRef](#)]
70. Koley, B.; Dey, D. An ensemble system for automatic sleep stage classification using single channel EEG signal. *Comput. Biol. Med.* **2012**, *42*, 1186–1195. [[CrossRef](#)]
71. Carney, C.E.; Buysse, D.J.; Ancoli-Israel, S.; Edinger, J.D.; Krystal, A.D.; Lichstein, K.L.; Morin, C.M. The consensus sleep diary: Standardizing prospective sleep self-monitoring. *Sleep* **2012**, *35*, 287–302. [[CrossRef](#)]
72. Ibanez, V.; Silva, J.; Cauli, O. A survey on sleep questionnaires and diaries. *Sleep Med.* **2018**, *42*, 90–96. [[CrossRef](#)]
73. Buysse, D.J.; Reynolds, C.F., 3rd; Monk, T.H.; Berman, S.R.; Kupfer, D.J. The Pittsburgh Sleep Quality Index: A new instrument for psychiatric practice and research. *Psychiatry Res.* **1989**, *28*, 193–213. [[CrossRef](#)]
74. Soldatos, C.R.; Dikeos, D.G.; Paparrigopoulos, T.J. Athens Insomnia Scale: Validation of an instrument based on ICD-10 criteria. *J. Psychosom. Res.* **2000**, *48*, 555–560. [[CrossRef](#)]
75. Yamamoto, Y. Standardization of revised version of OSA sleep inventory for middle age and aged. *Brain Sci. Ment. Disord.* **1999**, *10*, 401–409.
76. Netzer, N.C.; Stoohs, R.A.; Netzer, C.M.; Clark, K.; Strohl, K.P. Using the Berlin Questionnaire to identify patients at risk for the sleep apnea syndrome. *Ann. Intern. Med.* **1999**, *131*, 485–491. [[CrossRef](#)] [[PubMed](#)]
77. Johns, M.W. A new method for measuring daytime sleepiness: The Epworth sleepiness scale. *Sleep* **1991**, *14*, 540–545. [[CrossRef](#)] [[PubMed](#)]
78. Smith, A. Effects of caffeine on human behavior. *Food Chem Toxicol* **2002**, *40*, 1243–1255. [[CrossRef](#)] [[PubMed](#)]
79. Sawyer, D.A.; Julia, H.L.; Turin, A.C. Caffeine and human behavior: Arousal, anxiety, and performance effects. *J. Behav. Med.* **1982**, *5*, 415–439. [[CrossRef](#)]
80. Rosenthal, L.; Roehrs, T.; Zwyghuizen-Doorenbos, A.; Plath, D.; Roth, T. Alerting effects of caffeine after normal and restricted sleep. *Neuropsychopharmacology* **1991**, *4*, 103–108.
81. Natella, F.; Nardini, M.; Giannetti, I.; Dattilo, C.; Scaccini, C. Coffee drinking influences plasma antioxidant capacity in humans. *J. Agric. Food Chem.* **2002**, *50*, 6211–6216. [[CrossRef](#)]
82. Watanabe, T.; Arai, Y.; Mitsui, Y.; Kusaura, T.; Okawa, W.; Kajihara, Y.; Saito, I. The blood pressure-lowering effect and safety of chlorogenic acid from green coffee bean extract in essential hypertension. *Clin. Exp. Hypertens.* **2006**, *28*, 439–449. [[CrossRef](#)]
83. Suzuki, A.; Nomura, T.; Jokura, H.; Kitamura, N.; Saiki, A.; Fujii, A. Chlorogenic acid-enriched green coffee bean extract affects arterial stiffness assessed by the cardio-ankle vascular index in healthy men: A pilot study. *Int. J. Food Sci. Nutr.* **2019**, *70*, 901–908. [[CrossRef](#)] [[PubMed](#)]

84. Kajikawa, M.; Maruhashi, T.; Hidaka, T.; Nakano, Y.; Kurisu, S.; Matsumoto, T.; Iwamoto, Y.; Kishimoto, S.; Matsui, S.; Aibara, Y.; et al. Coffee with a high content of chlorogenic acids and low content of hydroxyhydroquinone improves postprandial endothelial dysfunction in patients with borderline and stage 1 hypertension. *Eur. J. Nutr.* **2019**, *58*, 989–996. [\[CrossRef\]](#) [\[PubMed\]](#)
85. Qadir, O.K.; Seal, C.J.; Ashor, A.W.; Tassotti, M.; Mena, P.; Del Rio, D.; Siervo, M.; Brandt, K. Double-blind controlled dietary cross-over intervention with differentially fertilised intact lettuce leaves shows acute reduction in blood pressure in young adults, associated with faster uptake of nitrate than of phenolics. *Eur. J. Nutr.* **2022**, *61*, 4191–4203. [\[CrossRef\]](#) [\[PubMed\]](#)
86. Watanabe, T.; Kobayashi, S.; Yamaguchi, T.; Hibi, M.; Fukuhara, I.; Osaki, N. Coffee abundant in chlorogenic acids reduces abdominal fat in overweight adults: A randomized, double-blind, controlled trial. *Nutrients* **2019**, *11*, 1617. [\[CrossRef\]](#) [\[PubMed\]](#)
87. Saitou, K.; Ochiai, R.; Kozuma, K.; Sato, H.; Koikeda, T.; Osaki, N.; Katsuragi, Y. Effect of chlorogenic acids on cognitive function: A randomized, double-blind, placebo-controlled trial. *Nutrients* **2018**, *10*, 1337. [\[CrossRef\]](#)
88. Jackson, P.A.; Haskell-Ramsay, C.; Forster, J.; Khan, J.; Veasey, R.; Kennedy, D.O.; Wilson, A.R.; Saunders, C.; Wightman, E.L. Acute cognitive performance and mood effects of coffee berry and apple extracts: A randomised, double blind, placebo controlled crossover study in healthy humans. *Nutr. Neurosci.* **2022**, *25*, 2335–2343. [\[CrossRef\]](#)
89. Ochiai, R.; Saitou, K.; Suzukamo, C.; Osaki, N.; Asada, T. Effect of chlorogenic acids on cognitive function in mild cognitive impairment: A randomized controlled crossover trial. *J. Alzheimers Dis.* **2019**, *72*, 1209–1216. [\[CrossRef\]](#)
90. Shoji, T.; Masumoto, S.; Moriichi, N.; Ohtake, Y.; Kanda, T. Administration of apple polyphenol supplements for skin conditions in healthy women: A randomized, double-blind, placebo-controlled clinical trial. *Nutrients* **2020**, *12*, 1071. [\[CrossRef\]](#)
91. Ochiai, R.; Tomonobu, K.; Ikushima, I. Effect of chlorogenic acids on fatigue and sleep in healthy males: A randomized, double-blind, placebo-controlled, crossover study. *Food Sci. Nutr.* **2018**, *6*, 2530–2536. [\[CrossRef\]](#)
92. Park, I.; Ochiai, R.; Ogata, H.; Kayaba, M.; Hari, S.; Hibi, M.; Katsuragi, Y.; Satoh, M.; Tokuyama, K. Effects of subacute ingestion of chlorogenic acids on sleep architecture and energy metabolism through activity of the autonomic nervous system: A randomised, placebo-controlled, double-blinded cross-over trial. *Br. J. Nutr.* **2017**, *117*, 979–984. [\[CrossRef\]](#)
93. Ostfeld, I.; Ben-Moshe, Y.; Hoffman, M.W.; Shalev, H.; Hoffman, J.R. Effect of Spearmint Extract Containing Rosmarinic Acid on Physical and Executive Functioning After a Tactical Operation. *J. Spec. Oper. Med.* **2018**, *18*, 92–96. [\[CrossRef\]](#) [\[PubMed\]](#)
94. Shinomiya, K.; Omichi, J.; Ohnishi, R.; Ito, H.; Yoshida, T.; Kamei, C. Effects of chlorogenic acid and its metabolites on the sleep-wakefulness cycle in rats. *Eur. J. Pharmacol.* **2004**, *504*, 185–189. [\[CrossRef\]](#) [\[PubMed\]](#)
95. Wu, J.; Chen, H.; Li, H.; Tang, Y.; Yang, L.; Cao, S.; Qin, D. Antidepressant Potential of Chlorogenic Acid-Enriched Extract from *Eucommia ulmoides* Oliver Bark with Neuron Protection and Promotion of Serotonin Release through Enhancing Synapsin I Expression. *Molecules* **2016**, *21*, 260. [\[CrossRef\]](#) [\[PubMed\]](#)
96. Park, S.-H.; Sim, Y.-B.; Han, P.-L.; Lee, J.-K.; Suh, H.-W. Antidepressant-like effect of chlorogenic acid isolated from *Artemisia capillaris* Thunb. *Anim. Cells Syst.* **2010**, *14*, 253–259. [\[CrossRef\]](#)
97. Wu, Y.; Liu, W.; Li, Q.; Li, Y.; Yan, Y.; Huang, F.; Wu, X.; Zhou, Q.; Shu, X.; Ruan, Z. Dietary chlorogenic acid regulates gut microbiota, serum-free amino acids and colonic serotonin levels in growing pigs. *Int. J. Food Sci. Nutr.* **2018**, *69*, 566–573. [\[CrossRef\]](#)
98. Jouvet, M. Sleep and serotonin: An unfinished story. *Neuropsychopharmacology* **1999**, *21*, 24S–27S. [\[CrossRef\]](#)
99. Tu, Y.; Cheng, S.X.; Sun, H.T.; Ma, T.Z.; Zhang, S. Ferulic acid potentiates pentobarbital-induced sleep via the serotonergic system. *Neurosci. Lett* **2012**, *525*, 95–99. [\[CrossRef\]](#)
100. Werner, G.G.; Ford, B.Q.; Mauss, I.B.; Schabus, M.; Blechert, J.; Wilhelm, F.H. High cardiac vagal control is related to better subjective and objective sleep quality. *Biol. Psychol.* **2015**, *106*, 79–85. [\[CrossRef\]](#)
101. Hall, M.; Vasko, R.; Buysse, D.; Ombao, H.; Chen, Q.; Cashmere, J.D.; Kupfer, D.; Thayer, J.F. Acute stress affects heart rate variability during sleep. *Psychosom. Med.* **2004**, *66*, 56–62. [\[CrossRef\]](#)
102. Howitz, K.T.; Bitterman, K.J.; Cohen, H.Y.; Lamming, D.W.; Lavu, S.; Wood, J.G.; Zipkin, R.E.; Chung, P.; Kisilewski, A.; Zhang, L.L.; et al. Small molecule activators of sirtuins extend *Saccharomyces cerevisiae* lifespan. *Nature* **2003**, *425*, 191–196. [\[CrossRef\]](#)
103. Yu, J.; Auwerx, J. The role of sirtuins in the control of metabolic homeostasis. *Ann. N. Y. Acad. Sci.* **2009**, *1173* (Suppl. S1), E10–E19. [\[CrossRef\]](#) [\[PubMed\]](#)
104. de Ligt, M.; Timmers, S.; Schrauwen, P. Resveratrol and obesity: Can resveratrol relieve metabolic disturbances? *Biochim. Biophys. Acta* **2015**, *1852*, 1137–1144. [\[CrossRef\]](#) [\[PubMed\]](#)
105. Timmers, S.; Konings, E.; Bilet, L.; Houtkooper, R.H.; van de Weijer, T.; Goossens, G.H.; Hoeks, J.; van der Krieken, S.; Ryu, D.; Kersten, S.; et al. Calorie restriction-like effects of 30 days of resveratrol supplementation on energy metabolism and metabolic profile in obese humans. *Cell Metab.* **2011**, *14*, 612–622. [\[CrossRef\]](#) [\[PubMed\]](#)
106. Bhatt, J.K.; Thomas, S.; Nanjan, M.J. Resveratrol supplementation improves glycemic control in type 2 diabetes mellitus. *Nutr. Res.* **2012**, *32*, 537–541. [\[CrossRef\]](#) [\[PubMed\]](#)
107. Brasnyo, P.; Molnar, G.A.; Mohas, M.; Marko, L.; Laczy, B.; Cseh, J.; Mikolas, E.; Szijarto, I.A.; Merei, A.; Halmai, R.; et al. Resveratrol improves insulin sensitivity, reduces oxidative stress and activates the Akt pathway in type 2 diabetic patients. *Br. J. Nutr.* **2011**, *106*, 383–389. [\[CrossRef\]](#) [\[PubMed\]](#)
108. Thazhath, S.S.; Wu, T.; Bound, M.J.; Checklin, H.L.; Standfield, S.; Jones, K.L.; Horowitz, M.; Rayner, C.K. Administration of resveratrol for 5 wk has no effect on glucagon-like peptide 1 secretion, gastric emptying, or glycemic control in type 2 diabetes: A randomized controlled trial. *Am. J. Clin. Nutr.* **2016**, *103*, 66–70. [\[CrossRef\]](#)

109. Timmers, S.; de Ligt, M.; Phielix, E.; van de Weijer, T.; Hansen, J.; Moonen-Kornips, E.; Schaart, G.; Kunz, I.; Hesselink, M.K.; Schrauwen-Hinderling, V.B.; et al. Resveratrol as Add-on Therapy in Subjects With Well-Controlled Type 2 Diabetes: A Randomized Controlled Trial. *Diabetes Care* **2016**, *39*, 2211–2217. [\[CrossRef\]](#)
110. Yoshino, J.; Conte, C.; Fontana, L.; Mittendorfer, B.; Imai, S.; Schechtman, K.B.; Gu, C.; Kunz, I.; Rossi Fanelli, F.; Patterson, B.W.; et al. Resveratrol supplementation does not improve metabolic function in nonobese women with normal glucose tolerance. *Cell Metab.* **2012**, *16*, 658–664. [\[CrossRef\]](#)
111. De Ligt, M.; Bergman, M.; Fuentes, R.M.; Essers, H.; Moonen-Kornips, E.; Havekes, B.; Schrauwen-Hinderling, V.B.; Schrauwen, P. No effect of resveratrol supplementation after 6 months on insulin sensitivity in overweight adults: A randomized trial. *Am. J. Clin. Nutr.* **2020**, *112*, 1029–1038. [\[CrossRef\]](#)
112. Abdelhaleem, I.A.; Brakat, A.M.; Adayel, H.M.; Asla, M.M.; Rizk, M.A.; Aboalfetoh, A.Y. The effects of resveratrol on glycemic control and cardiometabolic parameters in patients with T2DM: A systematic review and meta-analysis. *Med. Clin.* **2022**, *158*, 576–585. [\[CrossRef\]](#)
113. Park, S.J.; Ahmad, F.; Philp, A.; Baar, K.; Williams, T.; Luo, H.; Ke, H.; Rehmann, H.; Taussig, R.; Brown, A.L.; et al. Resveratrol ameliorates aging-related metabolic phenotypes by inhibiting cAMP phosphodiesterases. *Cell* **2012**, *148*, 421–433. [\[CrossRef\]](#)
114. Pennisi, M.; Bertino, G.; Gagliano, C.; Malaguarnera, M.; Bella, R.; Borzi, A.M.; Madeddu, R.; Drago, F.; Malaguarnera, G. Resveratrol in hepatitis C patients treated with pegylated-interferon-alpha-2b and ribavirin reduces sleep disturbance. *Nutrients* **2017**, *9*, 897. [\[CrossRef\]](#)
115. Wightman, E.L.; Haskell-Ramsay, C.F.; Reay, J.L.; Williamson, G.; Dew, T.; Zhang, W.; Kennedy, D.O. The effects of chronic trans-resveratrol supplementation on aspects of cognitive function, mood, sleep, health and cerebral blood flow in healthy, young humans. *Br. J. Nutr.* **2015**, *114*, 1427–1437. [\[CrossRef\]](#) [\[PubMed\]](#)
116. Pifferi, F.; Rahman, A.; Languille, S.; Auffret, A.; Babiloni, C.; Blin, O.; Lamberty, Y.; Richardson, J.C.; Aujard, F. Effects of dietary resveratrol on the sleep-wake cycle in the non-human primate gray mouse lemur (*Microcebus murinus*). *Chronobiol. Int.* **2012**, *29*, 261–270. [\[CrossRef\]](#) [\[PubMed\]](#)
117. Pifferi, F.; Dal-Pan, A.; Languille, S.; Aujard, F. Effects of resveratrol on daily rhythms of locomotor activity and body temperature in young and aged grey mouse lemurs. *Oxid. Med. Cell Longev.* **2013**, *2013*, 187301. [\[CrossRef\]](#) [\[PubMed\]](#)
118. Yu, L.; Yang, S.J. AMP-activated protein kinase mediates activity-dependent regulation of peroxisome proliferator-activated receptor gamma coactivator-1alpha and nuclear respiratory factor 1 expression in rat visual cortical neurons. *Neuroscience* **2010**, *169*, 23–38. [\[CrossRef\]](#)
119. Baur, J.A. Resveratrol, sirtuins, and the promise of a DR mimetic. *Mech. Ageing Dev.* **2010**, *131*, 261–269. [\[CrossRef\]](#) [\[PubMed\]](#)
120. Asher, G.; Gatfield, D.; Stratmann, M.; Reinke, H.; Dibner, C.; Kreppel, F.; Mostoslavsky, R.; Alt, F.W.; Schibler, U. SIRT1 regulates circadian clock gene expression through PER2 deacetylation. *Cell* **2008**, *134*, 317–328. [\[CrossRef\]](#)
121. Nakahata, Y.; Kaluzova, M.; Grimaldi, B.; Sahar, S.; Hirayama, J.; Chen, D.; Guarente, L.P.; Sassone-Corsi, P. The NAD⁺-dependent deacetylase SIRT1 modulates CLOCK-mediated chromatin remodeling and circadian control. *Cell* **2008**, *134*, 329–340. [\[CrossRef\]](#)
122. Shakeri, A.; Sahebkar, A.; Javadi, B. *Melissa officinalis* L.—A review of its traditional uses, phytochemistry and pharmacology. *J. Ethnopharmacol.* **2016**, *188*, 204–228. [\[CrossRef\]](#)
123. Ghazizadeh, J.; Hamedeyazdan, S.; Torbati, M.; Farajdokht, F.; Fakhari, A.; Mahmoudi, J.; Araj-Khodaei, M.; Sadigh-Eteghad, S. *Melissa officinalis* L. hydro-alcoholic extract inhibits anxiety and depression through prevention of central oxidative stress and apoptosis. *Exp. Physiol.* **2020**, *105*, 707–720. [\[CrossRef\]](#)
124. Hitl, M.; Kladar, N.; Gavaric, N.; Bozin, B. Rosmarinic Acid-Human Pharmacokinetics and Health Benefits. *Planta Med.* **2021**, *87*, 273–282. [\[CrossRef\]](#)
125. Falcone, P.H.; Nieman, K.M.; Tribby, A.C.; Vogel, R.M.; Joy, J.M.; Moon, J.R.; Slayton, C.A.; Henigman, M.M.; Lasrado, J.A.; Lewis, B.J.; et al. The attention-enhancing effects of spearmint extract supplementation in healthy men and women: A randomized, double-blind, placebo-controlled, parallel trial. *Nutr. Res.* **2019**, *64*, 24–38. [\[CrossRef\]](#)
126. Awad, R.; Muhammad, A.; Durst, T.; Trudeau, V.L.; Arnason, J.T. Bioassay-guided fractionation of lemon balm (*Melissa officinalis* L.) using an in vitro measure of GABA transaminase activity. *Phytother. Res.* **2009**, *23*, 1075–1081. [\[CrossRef\]](#)
127. Coelho, V.R.; Vieira, C.G.; de Souza, L.P.; da Silva, L.L.; Pfluger, P.; Regner, G.G.; Papke, D.K.; Picada, J.N.; Pereira, P. Behavioral and genotoxic evaluation of rosmarinic and caffeic acid in acute seizure models induced by pentylenetetrazole and pilocarpine in mice. *Naunyn. Schmiedeberg's Arch. Pharmacol.* **2016**, *389*, 1195–1203. [\[CrossRef\]](#) [\[PubMed\]](#)
128. Kim, T.H.; Bormate, K.J.; Custodio, R.J.P.; Cheong, J.H.; Lee, B.K.; Kim, H.J.; Jung, Y.S. Involvement of the adenosine A(1) receptor in the hypnotic effect of rosmarinic acid. *BioMed. Pharmacother.* **2022**, *146*, 112483. [\[CrossRef\]](#) [\[PubMed\]](#)
129. Kwon, Y.O.; Hong, J.T.; Oh, K.W. Rosmarinic Acid Potentiates Pentobarbital-Induced Sleep Behaviors and Non-Rapid Eye Movement (NREM) Sleep through the Activation of GABA(A)-ergic Systems. *Biomol. Ther.* **2017**, *25*, 105–111. [\[CrossRef\]](#) [\[PubMed\]](#)
130. Tubbs, A.S.; Kennedy, K.E.R.; Alfonso-Miller, P.; Wills, C.C.A.; Grandner, M.A. A Randomized, Double-Blind, Placebo-Controlled Trial of a Polyphenol Botanical Blend on Sleep and Daytime Functioning. *Int. J. Environ. Res. Public Health* **2021**, *18*, 3044. [\[CrossRef\]](#) [\[PubMed\]](#)
131. Saper, C.B.; Scammell, T.E.; Lu, J. Hypothalamic regulation of sleep and circadian rhythms. *Nature* **2005**, *437*, 1257–1263. [\[CrossRef\]](#)
132. Del Rio, D.; Stewart, A.J.; Mullen, W.; Burns, J.; Lean, M.E.; Brighenti, F.; Crozier, A. HPLC-MSn analysis of phenolic compounds and purine alkaloids in green and black tea. *J. Agric. Food Chem.* **2004**, *52*, 2807–2815. [\[CrossRef\]](#)

133. Seto, R.; Nakamura, H.; Nanjo, F.; Hara, Y. Preparation of epimers of tea catechins by heat treatment. *Biosci. Biotechnol. Biochem.* **1997**, *61*, 1434–1439. [[CrossRef](#)]
134. Rice-Evans, C.A.; Miller, N.J.; Bolwell, P.G.; Bramley, P.M.; Pridham, J.B. The relative antioxidant activities of plant-derived polyphenolic flavonoids. *Free Radic. Res.* **1995**, *22*, 375–383. [[CrossRef](#)]
135. Sabu, M.C.; Smitha, K.; Kuttan, R. Anti-diabetic activity of green tea polyphenols and their role in reducing oxidative stress in experimental diabetes. *J. Ethnopharmacol.* **2002**, *83*, 109–116. [[CrossRef](#)] [[PubMed](#)]
136. Miura, Y.; Chiba, T.; Tomita, I.; Koizumi, H.; Miura, S.; Umegaki, K.; Hara, Y.; Ikeda, M.; Tomita, T. Tea catechins prevent the development of atherosclerosis in apoprotein E-deficient mice. *J. Nutr.* **2001**, *131*, 27–32. [[CrossRef](#)] [[PubMed](#)]
137. Legeay, S.; Rodier, M.; Fillon, L.; Faure, S.; Clere, N. Epigallocatechin Gallate: A Review of Its Beneficial Properties to Prevent Metabolic Syndrome. *Nutrients* **2015**, *7*, 5443–5468. [[CrossRef](#)] [[PubMed](#)]
138. Hibi, M.; Takase, H.; Iwasaki, M.; Osaki, N.; Katsuragi, Y. Efficacy of tea catechin-rich beverages to reduce abdominal adiposity and metabolic syndrome risks in obese and overweight subjects: A pooled analysis of 6 human trials. *Nutr. Res.* **2018**, *55*, 1–10. [[CrossRef](#)] [[PubMed](#)]
139. Unno, K.; Noda, S.; Kawasaki, Y.; Yamada, H.; Morita, A.; Iguchi, K.; Nakamura, Y. Reduced stress and improved sleep quality caused by green tea are associated with a reduced caffeine content. *Nutrients* **2017**, *9*, 777. [[CrossRef](#)]
140. Zhang, S.; Takano, J.; Murayama, N.; Tominaga, M.; Abe, T.; Park, I.; Seol, J.; Ishihara, A.; Tanaka, Y.; Yajima, K.; et al. Subacute ingestion of caffeine and oolong tea increases fat oxidation without affecting energy expenditure and sleep architecture: A randomized, placebo-controlled, double-blinded cross-over trial. *Nutrients* **2020**, *12*, 3671. [[CrossRef](#)]
141. Wei, Y.; Xu, J.; Miao, S.; Wei, K.; Peng, L.; Wang, Y.; Wei, X. Recent advances in the utilization of tea active ingredients to regulate sleep through neuroendocrine pathway, immune system and intestinal microbiota. *Crit. Rev. Food Sci. Nutr.* **2022**, 1–29. [[CrossRef](#)]
142. Suganuma, M.; Okabe, S.; Oniyama, M.; Tada, Y.; Ito, H.; Fujiki, H. Wide distribution of [³H](−)-epigallocatechin gallate, a cancer preventive tea polyphenol, in mouse tissue. *Carcinogenesis* **1998**, *19*, 1771–1776. [[CrossRef](#)]
143. Grabska-Kobylecka, I.; Kaczmarek-Bak, J.; Figlus, M.; Prymont-Przyminska, A.; Zwolinska, A.; Sarniak, A.; Wlodarczyk, A.; Glabinski, A.; Nowak, D. The Presence of Caffeic Acid in Cerebrospinal Fluid: Evidence That Dietary Polyphenols Can Cross the Blood-Brain Barrier in Humans. *Nutrients* **2020**, *12*, 1531. [[CrossRef](#)]
144. Campbell, E.L.; Chebib, M.; Johnston, G.A. The dietary flavonoids apigenin and (−)-epigallocatechin gallate enhance the positive modulation by diazepam of the activation by GABA of recombinant GABA(A) receptors. *Biochem. Pharmacol.* **2004**, *68*, 1631–1638. [[CrossRef](#)] [[PubMed](#)]
145. Huang, Y.W.; Xu, H.H.; Wang, S.M.; Zhao, Y.; Huang, Y.M.; Li, R.B.; Wang, X.J.; Hao, S.M.; Sheng, J. Absorption of caffeine in fermented Pu-er tea is inhibited in mice. *Food Funct.* **2014**, *5*, 1520–1528. [[CrossRef](#)]
146. Yang, C.S.; Maliakal, P.; Meng, X. Inhibition of carcinogenesis by tea. *Annu. Rev. Pharmacol. Toxicol.* **2002**, *42*, 25–54. [[CrossRef](#)] [[PubMed](#)]
147. Park, K.S.; Han, J.Y.; Moon, D.C.; Hong, J.T.; Oh, K.W. (−)-epigallocatechin-3-O-gallate augments pentobarbital-induced sleeping behaviors through Cl[−] channel activation. *J. Med. Food* **2011**, *14*, 1456–1462. [[CrossRef](#)]
148. Adachi, N.; Tomonaga, S.; Tachibana, T.; Denbow, D.M.; Furuse, M. (−)-Epigallocatechin gallate attenuates acute stress responses through GABAergic system in the brain. *Eur. J. Pharmacol.* **2006**, *531*, 171–175. [[CrossRef](#)] [[PubMed](#)]
149. Dugovic, C. Role of serotonin in sleep mechanisms. *Rev. Neurol.* **2001**, *157*, S16–S19. [[PubMed](#)]
150. Adam, A.; Crespy, V.; Levrat-Verny, M.A.; Leenhardt, F.; Leuillet, M.; Demigne, C.; Remesy, C. The bioavailability of ferulic acid is governed primarily by the food matrix rather than its metabolism in intestine and liver in rats. *J. Nutr.* **2002**, *132*, 1962–1968. [[CrossRef](#)] [[PubMed](#)]
151. Zhao, Z.; Egashira, Y.; Sanada, H. Ferulic acid sugar esters are recovered in rat plasma and urine mainly as the sulfoglucuronide of ferulic acid. *J. Nutr.* **2003**, *133*, 1355–1361. [[CrossRef](#)] [[PubMed](#)]
152. Westfall, S.; Pasinetti, G.M. The Gut Microbiota Links Dietary Polyphenols With Management of Psychiatric Mood Disorders. *Front. Neurosci.* **2019**, *13*, 1196. [[CrossRef](#)]
153. Chan, V.; Lo, K. Efficacy of dietary supplements on improving sleep quality: A systematic review and meta-analysis. *Postgrad. Med. J.* **2022**, *98*, 285–293. [[CrossRef](#)] [[PubMed](#)]
154. Youdim, K.A.; Qaiser, M.Z.; Begley, D.J.; Rice-Evans, C.A.; Abbott, N.J. Flavonoid permeability across an in situ model of the blood-brain barrier. *Free Radic. Biol. Med.* **2004**, *36*, 592–604. [[CrossRef](#)] [[PubMed](#)]
155. Moghadam, F.H.; Mesbah-Ardakani, M.; Nasr-Esfahani, M.H. Ferulic Acid exerts concentration-dependent anti-apoptotic and neuronal differentiation-inducing effects in PC12 and mouse neural stem cells. *Eur. J. Pharmacol.* **2018**, *841*, 104–112. [[CrossRef](#)]
156. Kurauchi, Y.; Hisatsune, A.; Isohama, Y.; Mishima, S.; Katsuki, H. Caffeic acid phenethyl ester protects nigral dopaminergic neurons via dual mechanisms involving haem oxygenase-1 and brain-derived neurotrophic factor. *Br. J. Pharmacol.* **2012**, *166*, 1151–1168. [[CrossRef](#)] [[PubMed](#)]
157. Zhao, W.; Wang, J.; Bi, W.; Ferruzzi, M.; Yemul, S.; Freire, D.; Mazzola, P.; Ho, L.; Dubner, L.; Pasinetti, G.M. Novel application of brain-targeting polyphenol compounds in sleep deprivation-induced cognitive dysfunction. *Neurochem. Int.* **2015**, *89*, 191–197. [[CrossRef](#)] [[PubMed](#)]
158. Garrido, J.; Gaspar, A.; Garrido, E.M.; Miri, R.; Tavakkoli, M.; Pourali, S.; Saso, L.; Borges, F.; Firuzi, O. Alkyl esters of hydroxycinnamic acids with improved antioxidant activity and lipophilicity protect PC12 cells against oxidative stress. *Biochimie* **2012**, *94*, 961–967. [[CrossRef](#)]

159. Vivancos, M.; Moreno, J.J. Effect of resveratrol, tyrosol and beta-sitosterol on oxidised low-density lipoprotein-stimulated oxidative stress, arachidonic acid release and prostaglandin E2 synthesis by RAW 264.7 macrophages. *Br. J. Nutr.* **2008**, *99*, 1199–1207. [[CrossRef](#)]
160. Jung, H.W.; Mahesh, R.; Lee, J.G.; Lee, S.H.; Kim, Y.S.; Park, Y.K. Pinorexinol from the fruits of *Forsythia koreana* inhibits inflammatory responses in LPS-activated microglia. *Neurosci. Lett.* **2010**, *480*, 215–220. [[CrossRef](#)]
161. Lee, K.Y.; Kim, S.H.; Jeong, E.J.; Park, J.H.; Kim, S.H.; Kim, Y.C.; Sung, S.H. New secoisolaricresinol derivatives from *Lindera obtusiloba* stems and their neuroprotective activities. *Planta Med.* **2010**, *76*, 294–297. [[CrossRef](#)]
162. Rom, S.; Zuluaga-Ramirez, V.; Reichenbach, N.L.; Erickson, M.A.; Winfield, M.; Gajghate, S.; Christofidou-Solomidou, M.; Jordan-Sciutto, K.L.; Persidsky, Y. Secoisolaricresinol diglucoside is a blood-brain barrier protective and anti-inflammatory agent: Implications for neuroinflammation. *J. Neuroinflamm.* **2018**, *15*, 25. [[CrossRef](#)]
163. Yamagata, K. Do coffee polyphenols have a preventive action on metabolic syndrome associated endothelial dysfunctions? An assessment of the current evidence. *Antioxidants* **2018**, *7*, 26. [[CrossRef](#)] [[PubMed](#)]
164. Godos, J.; Vitale, M.; Micek, A.; Ray, S.; Martini, D.; Del Rio, D.; Riccardi, G.; Galvano, F.; Grosso, G. Dietary Polyphenol Intake, Blood Pressure, and Hypertension: A Systematic Review and Meta-Analysis of Observational Studies. *Antioxidants* **2019**, *8*, 152. [[CrossRef](#)] [[PubMed](#)]
165. Behl, M.; Bliwise, D.; Veledar, E.; Cunningham, L.; Vazquez, J.; Brigham, K.; Quyyumi, A. Vascular endothelial function and self-reported sleep. *Am. J. Med. Sci.* **2014**, *347*, 425–428. [[CrossRef](#)] [[PubMed](#)]
166. Cooper, D.C.; Ziegler, M.G.; Milic, M.S.; Ancoli-Israel, S.; Mills, P.J.; Lored, J.S.; Von Kanel, R.; Dimsdale, J.E. Endothelial function and sleep: Associations of flow-mediated dilation with perceived sleep quality and rapid eye movement (REM) sleep. *J. Sleep Res.* **2014**, *23*, 84–93. [[CrossRef](#)] [[PubMed](#)]
167. Ceppa, F.; Mancini, A.; Tuohy, K. Current evidence linking diet to gut microbiota and brain development and function. *Int. J. Food Sci. Nutr.* **2019**, *70*, 1–19. [[CrossRef](#)]
168. Tomas-Barberan, F.A.; Selma, M.V.; Espin, J.C. Interactions of gut microbiota with dietary polyphenols and consequences to human health. *Curr. Opin Clin. Nutr. Metab. Care* **2016**, *19*, 471–476. [[CrossRef](#)] [[PubMed](#)]

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