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REVIEW ARTICLE

Comprehensive effects of various nutrients on sleep

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Abstract
Sleep problems have become common among people today. Sleep disorders are closely associated with physiological and psychological diseases. Among the ways of improving objective or subjective sleep quality, controlling elements associated with food intake can be more efficient than other methods in terms of time and cost. Therefore, the purpose of this study was to understand the effects of nutrients and natural products on sleep. An extensive literature search was conducted, and related articles were identified through online databases, such as Elsevier, Google Scholar, PubMed, Springer, and Web of Science. Expert opinion, conference abstracts, unpublished studies, and studies published in languages other than English were excluded from this review. The effects of macronutrients and diet adjustment on sleep differed. Although not all nutrients independently affect sleep, they comprehensively affect it through tryptophan metabolism. Furthermore, natural foods related to GABA have an effect on sleep similar to that of sleeping pills. Taken together, our results suggest that humans can control both their objective and subjective sleep quality based on their lifestyle and food consumption. However, until now, direct studies on the relationship between human sleep and nutrition, such as clinical trials, have been insufficient. As both objective and subjective sleep quality are the factors determining the quality of life of individuals, further studies on those are needed to improve it.

Keywords Sleep · Nutrients · Tryptophan · GABA

Introduction

Humans spend one-third of their lives asleep. Sleep is regulated by the circadian rhythm and homeostasis. Many factors, including these two processes, determine the time of onset, duration, and quality of sleep [1]. Through sleep, humans gain several benefits, such as physical recovery from daily activities, energy conservation, storage of long-term memory, and proper maintenance of immune function [2]. Recently, millions of people worldwide suffer from sleep disorders for various reasons, such as work pressure, shift work, prolonged work hours, and stress [3]. Sleep disorders indicate that daily life is negatively affected by objectively and subjectively insufficient quality, timing, and amount of sleep. To date, studies have been conducted on the diagnosis of sleep disorders. According to the International Classification of Sleep Disorders (ICSD)-3, sleep disorders are classified into the following seven categories: insomnia, sleep-related breathing disorders such as sleep apnea, central disorders of hypersomnolence such as narcolepsy, circadian rhythm sleep-wake disorders such as irregular sleep-wake rhythm disorder, parasomnias such as enuresis, sleep-related movement disorders such as restless leg syndrome, and other sleep disorders [4]. Globally, the number of people with sleep disorders has been increasing. A nationally representative sample of 2,089 individuals revealed that many suffer from insufficient sleep (43.2%), insomnia (8.2%), and circadian rhythm sleep disorders (5.3%) [5]. Since sleep disorders have a negative influence on the life quality of individuals, early diagnosis using sleep tests, such as observational studies, polysomnography (PSG), neuroimaging, electromyography (EMG), and electroencephalogram (EEG) can be important for improving life qualities [6]. Recently these tests are used to measure objective sleep quality as well as subjective sleep quality measuring using

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a self-rated questionnaire [7]. Sleep disorders can lead to changes in biochemical and physical functions and are associated with certain diseases [8–10]. Therefore, it is necessary to understand the different ways of improving objective and subjective sleep quality to lead a healthy life. Sleep quality is associated with many factors, including circadian rhythms, physiological diseases (e.g., cardiovascular disease and type 2 diabetes mellitus), psychological disorders (e.g., depression and post-traumatic stress disorder), and nutritional factors. Nutrients and metabolites can directly and indirectly affect sleep regulation [11]. Therefore, it is important to understand the role of nutrients in sleep. During the last few decades, many studies have focused on the effects of dietary nutrients, such as carbohydrates, proteins, and fats on sleep. In addition, an increasing number of studies have reported that many types of natural extracts influence objective or subjective sleep quality. Therefore, this study reviewed the relationship between nutritional factors and objective and subjective sleep quality and sought to identify the potential underlying mechanisms.

Materials and methods

An extensive and systematic search was conducted using the Elsevier, Google Scholar, PubMed, Springer, and Web of Science databases. Our search strategy was based on previous scientific articles regarding the relationship between sleep and nutrition and natural extracts for sleep, and we included all appropriate search terms, such as nutrition and sleep, natural sleep aids. The search strategy was used to extract literature published before February, 2022 and was adapted to search each database for original research articles and books published in English. Expert opinion, conference abstracts, unpublished studies, and studies published in languages other than English were excluded from this review. The number of articles extracted from the databases was 1,980, including 508 articles read the title and abstracts, 195 articles read in full, and 82 articles referenced for this review. As this was a systematic review using only databases, approval from an ethics committee was not required.

Results

Diet modulation and sleep

Sleep stage is divided into two stages based on EEG readings. It has been observed that, following the onset of sleep, the rapid movement of closed eyes, heart rate, and blood pressure increase to near-waking levels, with a desynchronized EEG associated with muscular atonia and the loss of the periodicity of the alpha, beta, and theta waves. This stage refers to the rapid eye movement (REM) [12, 13] stage. After REM sleep, a synchronous EEG associated with low muscle tone and minimal psychological activity, and characterized by K-complexes and delta waves, is observed. This state is referred to as non-rapid eye movement (NREM) sleep, which is also divided into three stages (N1–N3) according to the sleep level. The general pattern of sleep is a cycle that changes from REM to N3 periodically [2, 13]. REM sleep is associated with brain development, brain activation during sleep, memory formation, neuronal plasticity and excitability, and the processing of emotional information [12]. NREM sleep is related to growth hormone secretion, memory consolidation, and brain metabolite clearance [14]. Through alternation between REM and NREM stage, sleep might function to provide recovery following the undertaking of the waking activities.

The patterns of REM and NREM sleep are affected by macronutrients. Carbohydrates, fats, and proteins, which are representative macronutrients, are present in all organisms. Sleep architecture and subjective sleep quality can be influenced by adjusting the relative levels of various nutrients in our diet. Over the last few decades, an increasing number of studies have reported on the effects of diet modulation on sleep. A high-carbohydrate diet (HCD) is associated with decreased NREM sleep and sleep onset latency (SOL) [15–17], whereas a low-carbohydrate diet (LCD) is associated with decreased REM sleep and increased NREM sleep [18]. The LCD composition in most studies involved the use of minimal levels of carbohydrates and relatively high levels fat. Thus, the effect of LCD on sleep is similar to that of a high-fat diet (HFD). There has also been study comparing HCD and HFD. HCD decreased sleep duration compared with the observations in the HFD group. In addition, this study reported that the HFD group members were satisfied with their subjective sleep quality [19]. Unlike the results regarding the effects of carbohydrates and fats on sleep, reports regarding the effects of a protein-rich diet vary among the different studies. A study involving overweight and obese adults reported that a high-protein diet (HPD) increased subjective sleep quality to a greater extent than a control diet [20]. On the other hand, another study with exercise-trained females and males reported no significant differences between the HPD and control groups [21]. Another study in animals revealed that a HPD is a negative factor for initiating sleep [22].

Epidemiological studies have also reported the effects of nutrients on sleep. Intakes of carbohydrates, fats, proteins, and total nutrients were lower in those with insomnia than in healthy individuals [23]. A low-protein diet (LPD) is significantly associated with poor subjective sleep quality and marginally associated with difficulty in initiating sleep [24]. Furthermore, for the same dietary nutrient ratio, sleep quality depends on the source of foods. Those who consumed more rice had better subjective sleep quality than those who consumed more confectionaries and noodles [25]. Table 1 indicates details of the relationship between dietary nutrient composition changes and sleep.

Taken together, our analysis indicated that carbohydrates, fats, and proteins can affect the sleep architecture, SOL, sleep duration, and sleep quality. Therefore, it is necessary to understand the potential mechanisms through which each nutrient affects sleep quality.

Fats and sleep

Melatonin is an important hormone that regulates the circadian rhythm and promotes sleep. Melatonin formation and secretion in the pineal gland is high during the night when light exposure is less, whereas it is low during daytime [26]. In normal circadian rhythms, serotonin is converted to melatonin at night for sleeping. The pineal gland contains many n-6 (ω-6) and n-3 (ω-3) polyunsaturated fatty acids (PUFAs) [27]. A deficit in n-3 PUFAs reduces nocturnal melatonin secretion [28]. Since n-3 PUFA can alter the activity of arylylamine N-acetyltransferase (AANAT), which is involved in melatonin synthesis from the serotonin pathway [29], it is possible that n-3 PUFA has a positive effect on sleep.

Some studies have reported that PUFAs are associated with sleep quality. A study involving healthy children found that children taking n-3 supplements slept 1 h longer and more quietly than their peers. In addition, this study suggested that the concentration of docosahexaenoic acid (DHA) in the blood, a biomarker of n-3 fatty acids found in the brain, was significantly associated with superior sleep performance, including less bedtime resistance and fewer instances of parasomnias and total sleep disturbance [30]. Another study reported that the continued consumption of fatty fish had a positive effect on daily functioning, including sleep performance. Fatty fish constitutes the main dietary source of marine n-3 fatty acids, such as eicosatetraenoic acid (EPA) and DHA. The fatty fish consumption group exhibited significantly better vitamin D status and higher levels of EPA + DHA than the control group. This study showed that the positive effect of fatty fish consumption on sleep results from the positive correlation between sleep efficiency and vitamin D status [31]. This result is consistent with that of another study that reported that oily fish consumption is related to better subjective sleep quality [32]. Furthermore, saturated fatty acids are also capable of affecting sleep. In fruit flies, the feeding of hexanoic acid promoted sleep by increasing the number of sleep episodes [82].

Protein and sleep

Previous studies have reported that protein consumption differently affects sleep, depending on the amino acid composition. Among the many amino acids that make up proteins, tryptophan (Trp) is closely related to a positive effect on sleep, being a serotonin precursor. Nocturnal administration of Trp increases the levels of serotonin and melatonin in the brain and plasma [33]. Since melatonin formation is elevated at night, nocturnal administration of Trp is beneficial for initiating sleep. Interestingly, another study reported a significant negative correlation between plasma Trp levels and SOL after Trp administration [34]. A study involving insomniacs also demo nstrated that the consumption of Trp significantly increased both subjective and objective measures of sleep [35]. Because Trp cannot be synthesized in the body, it must be obtained from dietary proteins. However, there is an apparent contradiction in that a protein meal for Trp supply decreases the levels of brain Trp, while simultaneously increasing plasma Trp levels [22]. Plasma concentrations of Trp and large neutral amino acids (LNAAs; tyrosine, phenylalanine, leucine, isoleucine, valine, and methionine) increase with protein intake. To synthesize melatonin in the brain, plasma Trp, but not plasma LNAAs, are required [36]. However, since Trp and LNAAs use identical active transporter sites at the blood–brain barrier (BBB), LNAAs can cause a competitive inhibition of Trp [36]. Therefore, for Trp to be easily supplied to the brain, plasma Trp concentrations must be high and plasma LNAA concentrations must be low. In other words, the ratio of the concentration of Trp to that of LNAAs (Trp/LNAA ratio) in the plasma should be high. A previous study observed that when the Trp/LNAA ratio was 200 and 300% from baseline, there was an increase in the nocturnal sleepiness effect of Trp [37].

Silber and Schmitt [36] suggested that α-lactalbumin consumption is a suitable way to increase the ratio of Trp/LNAAs. α-Lactalbumin is a whey-derived protein with the highest Trp content and Trp/LNAA ratio among all food protein sources. α-Lactalbumin has been shown to increase the plasma Trp/LNAA ratio by up to 130% [36]. Another means to increase the ratio of Trp/LNAAs is a carbohydrate-rich/protein-poor diet. Markus et al. reported that a carbohydrate-rich/protein-poor diet increased the plasma Trp/LNAA ratio by 20–25% [38, 39]. The effect of this diet is likely related to an increase in insulin levels according to the carbohydrate intake.

Carbohydrates and sleep

Carbohydrates influence sleep via insulin. Insulin can alter not only glucose levels, but also amino acid composition in the blood. Insulin decreases plasma amino acid levels by inducing muscle tissues to uptake amino acids, except Trp, since Trp is largely protein-bound [35]. This action increases the ratio of Trp/LNAAs in the plasma. As mentioned above, increasing the Trp/LNAA ratio is important

Table 1 Relationship between nutrient composition changes in diet and sleep

Number	Subjects	Duration	Diet composition	Results	References
1	44 healthy young adults	4 days	HCD (56% carbohydrate, 22% fat, 22% protein) Control (50% carbohydrate, 35% fat, 15% protein)	SOL ↓ (HCD vs control)	[13]
2	10 healthy men	3 days	HCD (80% carbohydrate, 10% fat, 10% protein) HFD (12% carbohydrate, 78% fat, 12% protein)	NREM ↓ (HCD vs HFD)	[14]
3	8 healthy men	4 days	HCD (84.7% carbohydrate, 4.7% fat, 10.6% protein) LCD (23.2% carbohydrate, 59.3% fat, 17.5% protein) Control (62% carbohydrate, 24.8% fat, 13.2% protein)	NREM ↓ (HCD vs LCD, control)	[15]
4	14 healthy men	5 days	LCD (< 1% carbohydrate, 61% fat, 38% protein) HCD (72% carbohydrate, 12.5% fat, 15.5% protein)	REM ↓, NREM ↑ (LCD vs HCD)	[16]
5	36 young adults	4 days	HCD (80% carbohydrate, 10% fat, 10% protein) HFD (25% carbohydrate, 65% fat, 10% protein) Control (50% carbohydrate, 35% fat, 15% protein)	Waking minutes (after sleep onset) ↓ (HCD vs HFD, control) PSQI score ↓ (HFD vs HCD, control)	[17]
6	14 overweight and obese adults	6 weeks	A (65% carbohydrate, 25% fat, 10% protein) B (55% carbohydrate, 25% fat, 20% protein) C (45% carbohydrate, 25% fat, 30% protein)	Gss ↓ (B vs A, C)	[18]
7	18 exercise-trained adults	2 weeks	HPD (> 2.2 g/kg/day) Control (< 2.2 g/kg/day)	No effect (HPD vs control)	[19]
8	87 males and females (34 healthy adults + 53 insomnia patients)	3 days	Not available	Quantities of nutrients ↓ Intakes of carbohydrate, fat, and protein ↓ (insomnia patients vs healthy adults)	[22]
9	4,435 non-shift workers	Not available		SOL ↑ and subjective sleep quality ↓ in LPD Sleep maintenance ↓ in LCD	[23]
10	3,129 female workers	April 2011 ~ May 2012	Not available	Low intake of vegetables and fish → subjectively poor sleep quality High intake of confectionary and noodles → subjectively poor sleep quality Consumption of energy drinks and sugar-sweetened beverages → subjectively poor sleep quality High carbohydrate intake → subjectively poor sleep quality	[24]

1–7: experimental studies; 8–10: epidemiological studies; Duration: experiment or study period; (A vs B): result of A group compared to B group

HCD high carbohydrate diet, *LCD* low carbohydrate diet, *HFD* high fat diet, *HPD* high protein diet, *LPD* low protein diet, *SOL* sleep onset latency, *REM* rapid eye movement, *NREM* non-rapid eye movement, *PSQI* Pittsburgh sleep quality index, *Gss* global sleep score for commencing sleep. Thus, insulin is one of the factors that stimulate sleep by reducing plasma LNAAs and increasing the ratio of Trp/LNAAs. A carbohydrates diet affects sleep differently depending on the glycemic index (GI), which represents the relative rise in blood glucose levels after consuming food. Consumption of food with high GI values results in a more rapid increase in blood glucose levels and the extent of blood glucose peak levels, and in an increased formation and release of insulin compared with the consumption of food with low GI values.

A study involving healthy men reported that a diet with a high GI induces a decrease in SOL compared with a low GI diet [40]. Another study with men who exercised at least three times a week for the previous 2 years also reported that a diet with high GI decreased SOL and increased total sleep time and sleep efficiency after exercise compared with a diet with low GI [41]. In addition, the difference in GI according to starch source also affects sleep quality. A previous study reported that high rice consumption was associated with good sleep, whereas high bread consumption was associated with poor sleep. Because the GI of rice is higher than that of bread, it is possible that a high GI diet is associated with better sleep [42].

In addition to the differences involving the GI, the timing of carbohydrate intake also affects sleep. The intake of an HCD with a high GI 4 h before sleep lowered SOL compared to intake 1 h before sleep [40]. Drinks containing carbohydrates have also been reported to affect sleep quality. Consumption of a drink with a high GI 1 h before sleep increased arousal during sleep compared with the consumption of drinks with a low GI [43]. Thus, for better sleep, carbohydrate intake prior to bedtime is not recommended.

Comprehensive relationship between macronutrients and sleep

The results of previous studies suggest that Trp may play an important role in regulating SOL and maintaining sleep. Trp must be supplied to the brain to produce melatonin. Since LNAAs inhibit the supply of Trp, the ratio of Trp/LNAAs in plasma is important. Although a protein-rich diet increases Trp, it also increases more LNAAs, thereby decreasing the ratio of Trp/LNAAs. In contrast, as insulin secreted for regulating glucose levels causes muscles to absorb LNAAs, a carbohydrate-rich diet with a high GI increases the ratio of Trp/LNAAs. The Trp supplied to the brain is converted to melatonin through a series of chemical reactions.

In addition, a fat-rich diet can affect sleep not only through PUFA, but also through cholecystokinin (CCK). CCK, a mediator of fat-induced satiety, is a hormone released in response to the intake of fats and proteins [44]. Previous studies have reported that CCK is related to insulin levels and sleep [45, 46]. Rats injected with CCK have a high plasma insulin concentration and increased NREM time during the first sleep cycle compared with the control group [46]. Therefore, carbohydrates, fats, and proteins comprehensively affect sleep (Fig. 1).

Natural products for sleep

To improve sleep onset and quality, various types of sleeping pills have been developed. Barbiturates represent first-generation sleeping pills but were soon replaced by benzodiazepines (BZDs) and non-benzodiazepines (non-BZDs) due to various adverse effects, including addiction. However, non-BZDs are more commonly used to treat sleep disorders due to the side effects of BZDs, such as alterations to sleep architecture, carry-over effects, synergism with alcohol, and alteration of cognitive functions and performance [47]. These agents potentiate the activity of γ-aminobutyric acid (GABA), an inhibitory neurotransmitter, by binding to the $GABA_A$ receptor [47, 48]. The $GABA_A$ receptor, which acts as a chloride ion channel-linked receptor, has binding sites for these drugs. Reinforcement of GABA leads to the hyperpolarization of neurons and inhibition of nerve excitatory reflexes. However, both BZDs and non-BZDs can induce various adverse effects, especially after long-term use, as all of these agents affect the central nervous system (CNS) and have the potential for abuse and addiction [47, 49]. As a replacement for sleeping pills, some natural foods have been spotlighted. Although they do not guarantee their safety, quality, and effectiveness for sleep and have a shortcoming, such as a higher recommended intake amount for effectiveness and more discomfort in eating than sleeping pills, they have shown a positive effect on sleep with fewer side effects than it. Furthermore, a comparative study on natural products and drugs reported that in terms of side effects and toxicity, natural products, herbal medicines, and synthetic drugs are safe in the order named [50]. For example, casein, the primary protein component of cow's milk, had less sleep-promoting effects, but with minimal side effects, such as sedation compared to diazepam, one of the BZDs, in mice. [51]. Therefore, recently, supplementary natural foods have been researched for the treatment of mild forms of sleep disorders.

Tart cherry (*Prunus cerasus*)

Several studies have reported the effects of tart cherries on sleep. Tart cherry, also known as the Montmorency cherry, is a variety of sour cherry grown in Europe, Canada, and America. As tart cherries contain abundant phytochemicals, they provide numerous benefits, such as oxidative stress reduction, improved recovery after damaging exercise, and analgesic effects after long-distance running [52–54].

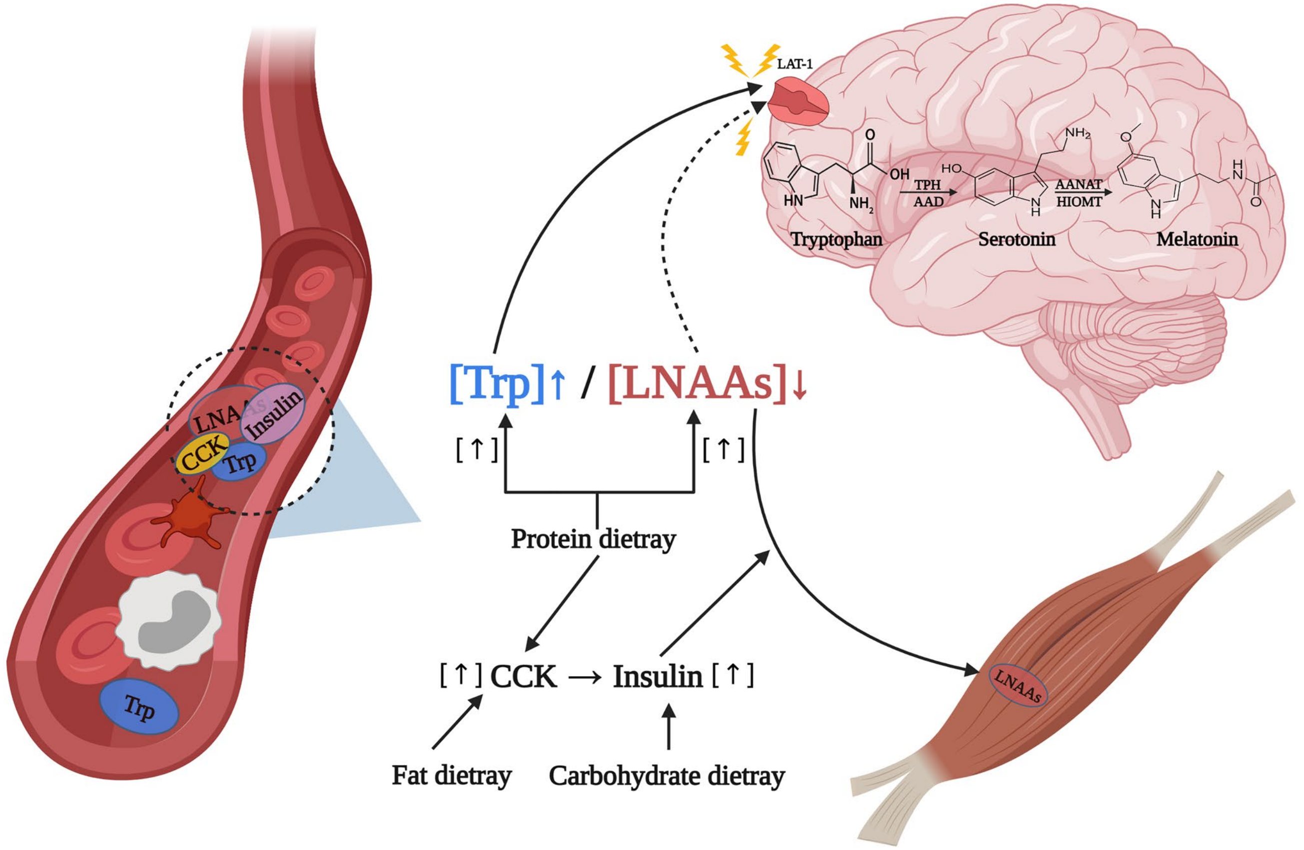

Fig. 1 Potential relationship between nutrients and melatonin affecting sleep. Nutrients affect sleep through the melatonin pathway. Dietary proteins increase plasma Trp, LNAAs, and CCK concentrations. In addition, plasma CCK concentration is increased by a fatty diet. Increased CCK levels lead to elevated insulin concentration, which is increased by a carbohydrate diet. Among plasma amino acids, the relative amounts of Trp and LNAAs are factors that determine melatonin synthesis in the brain. In the BBB, LNAAs and Trp are co-transported to LAT-1. That is, since LNAAs cause competitive inhibition of Trp, Trp can be supplied to the brain only when the relative amount of Trp in plasma is greater than that of LNAAs. Insulin may be involved in reducing the plasma concentration of LNAAs. Insulin increases the relative amount of Trp by allowing plasma LNAAs to be absorbed by muscle tissue. Therefore, an increased Trp/LNAAs ratio elevates melatonin synthesis in the brain by increasing the amount of Trp supplied to the brain. *Trp* tryptophan, *LNAAs* large neutral amino acids, *CCK* cholecystokinin, *BBB* blood-brain barrier, *LAT-1* large amino acid transporter 1, *TPH* tryptophan hydroxylase, *AAD* amino acid decarboxylase, *AANAT* arylalkylamine *N*-acetyltransferase, *HIOMT* hydroxyindole-*O*-methyltransferase

Furthermore, tart cherries are known to be an ideal source of melatonin. Therefore, the use of tart cherries as a natural sleep supplement is not extraordinary. A study on chronic insomnia in the elderly found that tart cherry juice consumption had beneficial effects on sleep. The consumption of this beverage was related to significant improvements in subjective SOL, sleep duration, total sleep time, and sleep efficiency compared with the observations made prior to treatment. Among the sleep variables, sleep duration was significantly improved in the beverage group compared with the placebo group [55]. However, this study did not offer objective measures of sleep, such as those obtained by undertaking actigraphy. Another study surrounding the same topic in healthy adults provided both objective and subjective results. This study found that the consumption of tart juice increased total sleep time and sleep efficiency, and decreased SOL. In addition, this study reported that levels of urinary 6-sulphatoxymelatonin (aMT6s), a melatonin metabolite, were increased in the beverage group compared to the pre-treatment and placebo group. The effects of tart cherries on sleep are associated with increased exogenous melatonin consumption [56].

Kiwifruit (Actinidiaceae)

A number of studies have demonstrated the effects of kiwifruit on sleep. Worldwide, kiwifruit is one of the most popular fruits grown in New Zealand, Italy, Japan, Greece, and France. Recently, many studies have shown that kiwifruits have a positive effect on antioxidant [57], impart cardiovascular protection [58], and exhibit anti-allergic effects [59]. Since it also, contains abundant amounts of natural antioxidants, vitamins C and E, flavonoids, anthocyanins, and carotenoids, it is considered a medically useful natural product [60].

In addition, as kiwifruit contains melatonin and serotonin, its effects on sleep is understandable [61, 62]. A study on sleep disturbances in adults reported that kiwifruit consumption had a positive effect on both subjective and objective sleep quality. Subjects with kiwifruit intake had significantly improved total sleep time and sleep efficiency compared to subjects in the pre-treatment group [7]. Another study concerning chronic insomnia in young adults showed that kiwifruit consumption significantly increased sleep efficiency, subjective sleep quality and sleep duration, and decreased SOL among the sleep diary parameters [63]. Furthermore, the peels of both green and gold kiwifruit can act as natural sleep aids. A study involving mice demonstrated that oral treatment with the ethanol extracts of green and gold kiwifruit peel decreased SOL and increased sleep duration. It is considered that the effect of kiwifruit peel on sleep is associated with the mechanism involving GABA, as these effects are weakened by treatment with flumazenil, an antagonist of the BZD-binding site of the $GABA_A$ receptor, and are potentiated by the effect of pentobarbital, a $GABA_A$ receptor agonist [64].

Passionflower (*Passiflora incarnata*)

Passiflora incarnata, commonly known as passionfruit, is widespread in warm and tropical regions. Since passionflowers contain several compounds, such as alkaloids, phenols, glycosyl flavonoids, and cyanogenic compounds, they have attracted public attention as a potential medicinal plant for the treatment of diseases, such as anxiety, opiate withdrawal, insomnia, attention deficit hyperactivity disorder, and cancer [65]. Moreover, passionflower has been reported to exert hypnotic effects. Pretreatment with flumazenil, a $GABA_A$ antagonist, attenuates this hypnotic effect *in vivo*; thus, indicating that the underlying mechanism of the effect of passionflower on sleep is associated with GABA [66]. A study in rats identified that passionflower extracts significantly increased total sleep time. The authors explained that this effect was caused by increased NREM time and decreased wakefulness [67]. Another study involving healthy adults showed that passionflower has a positive effect on sleep. Those who consumed passionflower tea at night had significantly improved subjective sleep quality compared to a placebo group [68].

Valerian (*Valeriana officinalis*)

Valeriana officinalis is a perennial herb that is grown in Europe, Asia, and North America. Valerian root extracts are widely used in patients with sleep disorders or insomnia. Some researchers have reviewed the effects of valerian as a sleep aid and found that valerian extracts improve subjective sleep quality and induce sleep with few side effects [69, 70]. The sedative effect of valerian is associated with GABA reinforcement activity. As the binding site of valerian extract compounds is the $GABA_A$ receptor, which is the same as the binding site for sleeping pill drugs, valerian may potentiate the sedative effects of sleeping pills [71]. In recent years, valerian extracts have been available in various forms, such as capsules, powders, and teas. The recommended dose of valerian for the treatment of insomnia ranges from 300─600 mg (dried herbal valerian root, 2–3 g). It is required to be ingested 30 min to 2 h before bedtime [70].

Gamtae (*Ecklonia cava*)

Ecklonia cava is a marine brown algal species found in the coastal areas surrounding Jeju Island, Korea. It contains important bioactive compounds, such as phlorotannins, fucoidans, fucoxanthins, and carotenoids [72]. *Ecklonia cava* extract exhibits various biological characteristics, such as antioxidative [73], immune-enhancing [74], anti-allergic [75], anti-cancer [76], and anti-inflammatory properties [72]. Moreover, *E. cava* ethanol extracts improve sleep quality. A previous study found that *E. cava* ethanol extracts have an effect on sleep through the induction of NREM sleep [77]. Subsequently, an animal study reported that dieckol, an *E. cava* ethanol extract component, exerts sleep-enhancing effects by decreasing SOL and increasing NREM sleep duration. The effects of gamtae on sleep are blocked by flumazenil; these effects occur via its binding to the BZD site of the $GABA_A$ receptor and its allosteric regulation [78].

Discussion

Sleep problems influence the life quality of the people in various ways. Sleep problems are one of the factors involved in the development of various physiological diseases. For example, stress responses to sleep deprivation activate the sympathetic-adrenal-medullary (SAM) axis. Increased sympathetic modulation by the SAM axis increases levels of catecholamines, such as norepinephrine and epinephrine, and has a direct effect on inflammatory cytokines [79]. These changes can induce inflammation and influence metabolic pathways related to Trp. As mentioned above, for sleep onset, Trp represents a source of serotonin; however, an inordinately activated sympathetic system and inflammation caused by sleep deprivation allow Trp to be a resource for kynurenine, not serotonin, since indoleamine-2,3-dioxygenase and tryptophan 2,3-dioxygenase, enzymes related to the kynurenine pathway, are activated by inflammatory cytokines and stress responses. Inordinate concentrations of kynurenine metabolites produced by the stimulated kynurenine pathway are associated with cognitive dysfunction and various neurodegenerative diseases, such as Alzheimer's disease, Parkinson's disease, and Huntington's disease [8]. In addition, since an activated sympathetic system and inflammation can lead to cardiovascular disease [80] and type 2 diabetes mellitus [10], sleep disorders are associated with certain physiological diseases.

Moreover, disturbed sleep is correlated with psychosis as well as physical diseases. Major depressive disorder (MDD) is more strongly associated with sleep problems than other psychiatric disorders. In patients with MDD, 90% experience insomnia or hypersomnia. Conversely, those with insomnia or hypersomnia are approximately ten times as likely to have MDD compared to a control group without sleep disorders. As with MDD, changes in sleep are among the core features of generalized anxiety disorder (GAD). Roughly over half of the patients with GAD experience difficulty falling or staying asleep. Those with insomnia are approximately twice as likely to have GAD than control group individuals with out insomnia. In addition, there are correlations between sleep deprivation and other psychiatric disorders, such as bipolar disorder, post-traumatic stress disorder, and schizophrenia [81].

In conclusion, since sleep problems can lead to decreased life quality, it is important to endeavor to increase sleep induction and objective and subjective quality. There are several ways to improve these. However, many experts usually recommend fundamentally altering the lifestyle or life patterns of patients with sleep disorders, because the currently available therapeutic drugs have severe side effects, especially during long-term use. Among the means of improving objective and subjective sleep quality related to daily habits, controlling food intake can be more efficient than other methods in terms of time and cost. Although the intake of carbohydrates, fats, and proteins in methods involving diet modulation exerts different effects on sleep, such as changes in sleep onset latency, total sleep time, and sleep duration, these macronutrients, not independently, affect sleep through Trp metabolism. In addition, natural products improve sleep quality through serotonin or melatonin supply, or via GABA-related mechanisms, such as those of the currently available sleeping pills and induce fewer side effects. Thus, humans can control their sleep quality by controlling their lifestyle and dietary habits. Although the weaker sleeping functions of nutrients and natural products than the currently available sleeping pills, further studies related to natural products will suggest novel therapeutic targets that can compensate for several side effects of the sleeping pills, such as the potential for abuse and addiction.

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Declarations

Conflict of interest The authors confirm that they have no conflicts of interest.

Ethical committee permission Not applicable.

Research involving human participants and/or animals Not applicable.

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