







Review

Nutraceuticals as Potential Targets for the Development of a Functional Beverage for Improving Sleep Quality

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Abstract: Functional beverages can be a valuable component of the human diet with the ability to not only provide essential hydration but to deliver important bioactive compounds that can contribute to chronic disease treatment and prevention. One area of the functional beverage market that has seen an increase in demand in recent years are beverages that promote relaxation and sleep. Sleep is an essential biological process, with optimal sleep being defined as one of adequate duration, quality and timing. It is regulated by a number of neurotransmitters which are, in turn, regulated by dietary intake of essential bioactive compounds. This narrative review aimed to evaluate the latest evidence of the sleep promoting properties of a selection of bioactive compounds (such as L-theanine and L-tryptophan) for the development of a functional beverage to improve sleep quality; and the effectiveness of traditional sleep promoting beverages (such as milk and chamomile). Overall, the bioactive compounds identified in this review, play essential roles in the synthesis and regulation of important neurotransmitters involved in the sleep-wake cycle. There is also significant potential for their inclusion in a number of functional beverages as the main ingredient on their own or in combination. Future studies should consider dosage; interactions with the beverage matrix, medications and other nutraceuticals; bioavailability during storage and following ingestion; as well as the sensory profile of the developed beverages, among others, when determining their effectiveness in a functional beverage to improve sleep quality.

Keywords: sleep; nutraceuticals; theanine; chamomile extract; tryptophan; cysteine; functional beverages

1. Introduction

Beverages play an important role in human health and nutrition, not only from the perspective of hydration, but also as mediators of social and cultural connectedness. They can also serve as a source of essential nutrients, particularly for people who may not consume a balanced diet [1]. Beverages are also becoming increasingly popular carriers for the development of functional food products. The last few decades have seen increasing awareness and emphasis on the importance of nutrition for overall health [2]. In addition, busy lifestyles, an aging population and rising healthcare costs in most developed

countries have fueled demand for functional food products, particularly beverages [3,4]. These products may contain naturally derived bioactive compounds that can be used to potentially treat and prevent a range of chronic illnesses in addition to optimizing general health [4–6].

A substantial body of evidence exists on the health-protective benefits of specific dietary patterns rich in antioxidants and polyphenols, most notably the Mediterranean diet [7,8]. In addition, traditional medicine is now widely accepted in modern medicine as consumers seek more ‘natural remedies’ to treat and prevent illness [9]. In Indian Ayurvedic medicine, for example, Ashwagandha root, is used to treat a range of brain disorders including, anxiety, depression, Alzheimer’s disease, Parkinson’s disease, Schizophrenia and bipolar disorder [10]; Malkangani oil or Jyothishmati oil, obtained from *Celastrus paniculatus*, provides neuromodulatory, anti-oxidant, anti-inflammatory and sedative properties, among others [11]; *Nardostachys jatamansi* provides numerous beneficial properties by acting as an anticonvulsant, neuro-protective, hepatoprotective, neuroprotective and hypotensive [12]; and *Terminalia arjuna* which is used for angina, hypertension, congestive heart failure and dyslipidemia [13].

These dietary patterns and the integration of traditional medicine have led to the research and development of bioactive compounds originating from plant, fungi and animal sources, representing an innovative and fast-emerging area of the food industry [14,15]. Advancement in extraction technologies and refinement of isolation and purification techniques has given rise to specifically formulated products with relatively high purity of selective ingredients of near pharmaceutical standards, providing the amalgamation of nutritional and pharmaceutical products jointly identified as nutraceuticals [15–17]. Whilst consumption of a number of supplements in the form of tablets, powders and extracts to improve health is widely accepted, the benefit of a functional beverage is the ability to deliver one or several nutraceutical compounds in one product [18]. Additional benefits include their convenience, storage capabilities, size and flavor variabilities, acceptability and relatively low cost [19]. Some successful commercial examples of the functional beverage concept include sports drinks, ready to drink teas, energy drinks and vitamin-enriched water [20]. These beverages are often designed to improve hydration, concentration and endurance; and delivery of essential vitamins, minerals and polyphenols [4,18]. One area of the commercial health and wellness market which has seen an increase in demand are functional beverages to improve sleep quality [21].

Sleep is essential for wide ranging physiological processes including growth, cognition, immune function, metabolism and cardiovascular health [22,23]. Optimal sleep comprises adequate duration, quality and timing that is regulated by several neurotransmitters including glutamate, acetylcholine, dopamine, serotonin, norepinephrine, histamine, orexin, gamma-aminobutyric acid (GABA), adenosine, melatonin and melanin-concentrating hormone, among others [24]. Some of these compounds are also important in mood, cognition, appetite, behavior and stress [25]. A bidirectional relationship exists between sleep disruption and physiological state, that is influenced by a number of different modalities (Figure 1), and an alteration in neurotransmitter levels can result in sleep disruption, fatigue, impaired performance and impaired memory [26–28]. Furthermore, chronic sleep disruption is associated with an increased risk of cognitive decline and memory impairment [27,29], metabolic syndrome (MetS) [30], anxiety and depression [31], type 2 diabetes mellitus (T2DM) [32], cardiovascular disease (CVD) [33], inflammation and infection [34].



Figure 1. Factors Affecting Sleep Quality.

In support of the bidirectional relationship between diet and sleep, macronutrients have also been found to influence sleep quality. A review by St. Onge et al. (2016) reported that a high carbohydrate diet can negatively affect sleep quality by reducing slow-wave sleep and increasing rapid eye movement sleep (REM) [35]. Whereas, a high protein diet can positively effect sleep quality by reducing sleep onset latency and the number of wake episodes during the night [35]. Analysis of data from the National Health and Nutrition Survey (NHANES) conducted in the USA ($n = 26,211$) has also found that micronutrient deficiencies are inversely associated with sleep duration [36]. Furthermore, adherence to diets that are rich in fish, fruits, vegetables and nuts, such as the Mediterranean diet, have been found to be associated with better sleep quality, including better sleep efficiency and reduced sleep disturbances [37,38]. These diets are rich sources of important compounds involved in the sleep-wake cycle such as L-tryptophan, melatonin, magnesium and vitamin B6, among others, which have been the subject of numerous intervention studies to improve sleep quality [37–39]. These compounds are now being included in commercially available functional relaxation or sleep beverages.

Therefore, the aim of this narrative review is to evaluate the latest evidence of the sleep promoting properties of the aforementioned compounds and a number of candidate compounds that demonstrate promise as ingredients in the development of functional beverages. Additionally, we will also assess the latest available evidence for beverages traditionally used to promote sleep and the active compounds potentially responsible for their sleep promoting properties.

2. Active Compounds

The summary of active compounds included in this review is presented in Table 1. The range of compounds is comprised of amino acid, hormone, vitamin and mineral compounds that influence the neurological pathways involved in sleep with potential for development into a functional beverage.

Table 1. Selected nutraceuticals used in the promotion and improvement of quality of sleep and their outcomes in different population groups.

Compound	Reference/Country	Participants	Intervention/Duration	Study Design	Outcome Measures	Effects on Sleep
L-Tryptophan	Markus et al. (2005) [40] Netherlands	Adults without sleep complaints (<i>n</i> = 14) Age (22 ± 3 years) Adults with mild sleep complaint (<i>n</i> = 14) Age (22 ± 2 years)	20 g L-TRP-enriched A-LAC protein (4.8 g L-TRP/100 g amino acids <i>w/w</i>) 1 night	Double-blind Placebo-controlled	Subjective Sleep Quality Measures: Stanford Sleepiness Scale	Improved morning alertness (<i>p</i> = 0.013) and increased attention (<i>p</i> = 0.002) in both groups. Improved performance in participants with sleep complaints only (<i>p</i> = 0.05).
	Ong et al. (2017) [41] Australia	Healthy males without sleep complaint (<i>n</i> = 10) Age (26.9 ± 5.3 years)	20 g L-TRP-enriched A-LAC protein (4.8 g L-TRP/100 g amino acids <i>w/w</i>) of A-LAC protein 2 nights	Double-blind Placebo-controlled Randomized Crossover	Objective Sleep Quality Measures (Actigraphy): Total sleep time Sleep onset latency Sleep efficiency (%) Wake time after sleep onset Subjective Sleep Measures (Sleep Log): Bedtime Time taken to fall asleep Frequency of awakenings Time taken to return to sleep Waking time Rising time Total sleep time	Increased objective and subjective total sleep time by 12.8% (<i>p</i> = 0.037) and 10.8% (<i>p</i> = 0.013), respectively; increased objective sleep efficiency by 7.0% (<i>p</i> = 0.028).
	Cubero et al. (2007) [42] Spain	Pre-weaning infants (<i>n</i> = 30) Age (4–20 weeks)	Diet A: Standard formula Diet B: Standard formula during the day and night formula (3.4 g L-TRP/100 g protein) Diet C: Day formula during the day (1.5 g L-TRP/100 g protein) + night formula (3.4 g L-TRP/100 g protein) in the evening 1 week per formula	Double-blind Randomized	Objective Sleep Quality Measures (Actigraphy): Time of nocturnal sleep Minutes of immobility Sleep latency Nocturnal awakenings Sleep efficiency (%) Sleep Diary: Sleep over 24 h Number of bottle feeds Observations or incidences that would influence the infants rest	Diet C improved objective total sleep time (<i>p</i> < 0.05) and subjective (parent) sleep improvement; Diet B and Diet C reduced objective sleep onset latency; Diet B improved objective sleep efficiency. (All <i>p</i> 's < 0.05)

Table 1. Cont.

Compound	Reference/Country	Participants	Intervention/Duration	Study Design	Outcome Measures	Effects on Sleep
	Bravo et al. (2013) [43] Spain	Older adults with sleep difficulties (<i>n</i> = 35) Age (55–75 years)	L-TRP (60 mg) enriched cereal for breakfast and dinner 1 week	Blind assay	Objective Sleep Quality Measures (Actigraphy): Time in bed Assumed sleep Actual sleep time Sleep onset latency Sleep efficiency (%) Number of awakenings Immobile time Total activity Fragmentation index (indicator of quality of rest)	Improvements in objective sleep measures including increase in actual sleep time (<i>p</i> < 0.01); increase in sleep efficiency (<i>p</i> < 0.001); increase in immobile time (<i>p</i> < 0.01); reduction in sleep latency (<i>p</i> < 0.01); wake bouts (<i>p</i> < 0.05); total activity (<i>p</i> < 0.01); fragmentation index (<i>p</i> < 0.001).
5-HTP	Bruni et al. (2004) [44] Italy	Children with sleep terrors (<i>n</i> = 45) Age (3.2–10.6 years)	2 mg/kg (Daily) 20 days	Randomized, controlled	Frequency of sleep terrors	After 1-month: Sleep terrors reduced > 50% from baseline in 93.5% of children treated with 5-HTP (<i>p</i> < 0.00001). After 6 months: 51.6% were sleep-terror free (<i>p</i> < 0.001).
Melatonin	Scheer et al. (2012) [45] USA	Hypertensive adults on beta blockers (<i>n</i> = 16) Age (45–64 years)	2.5 mg (nightly, 1 h before bedtime) 3 weeks	Randomized, Double-blind Placebo-controlled Parallel-group design	Objective Sleep Quality Measures (Polysomnography): Sleep stages Total sleep time Time in bed Sleep efficiency (%) Objective Sleep Quality Measures (Actigraphy): Sleep onset latency Total sleep time Sleep efficiency (%)	Increased total sleep time by 32 min (<i>p</i> = 0.046); increased sleep efficiency by 7.6% (<i>p</i> = 0.046). Decreased sleep onset latency to stage 2 NREM sleep by 14 min (<i>p</i> = 0.001) and increased the duration of stage 2 NREM sleep by 42 min (<i>p</i> = 0.037).

Table 1. Cont.

Compound	Reference/Country	Participants	Intervention/Duration	Study Design	Outcome Measures	Effects on Sleep
	Grima et al. (2018) [46] Australia	Adults with sleep disturbance post onset of traumatic brain injury ($n = 33$) Age (37 ± 11 years)	2 mg (nightly 2 h before bedtime) 4 weeks	Randomized, Double-blind Placebo-controlled Two-period Two-treatment Crossover study	Objective Sleep Quality Measures (Actigraphy) Sleep onset latency Total sleep time Sleep duration Sleep efficiency (%) Sleep Diary: Sleep onset/offset Sleep duration Subjective Sleep Quality Measures: PSQI ESS FSS	Improved subjective sleep quality ($p < 0.0001$) and objective sleep efficiency ($p < 0.04$).
	Xu et al. (2020) [47] China	Adults with primary insomnia ($n = 97$) Age (45–60 years)	3 mg (nightly 1 h before bedtime) 4 weeks	Randomized, Double-blind Placebo-controlled Parallel study	Objective Sleep Quality Measures (Polysomnography): Sleep stages Total sleep time Sleep onset latency Wake after sleep onset Sleep efficiency (%) Subjective Sleep Quality Measures: PSQI ESS ISI	Decreased objective sleep measures including early morning wake ($p = 0.001$) and decreased percentage of Stage 2 NREM sleep ($p = 0.031$).
L-Cysteine	Sadasivam et al. (2011) [48] India	Adults with obstructive sleep apnea ($n = 20$) Age (53.1 ± 2.3 years)	600 mg (Mucinac, Cipla), three times per day 30 days	Randomized, Placebo-controlled	Objective Sleep Quality Measures (Polysomnography): Sleep stages Total sleep time Sleep onset latency Wake after sleep onset Sleep efficiency (%) Sleep apnea Snoring Subjective Sleep Quality Measures: ESS	Improvements in objective slow wave sleep as sleep percent time ($p < 0.001$) and sleep efficiency. ($p < 0.05$). Reduction in subjective Epworth Sleepiness Score ($p < 0.001$).

Table 1. Cont.

Compound	Reference/Country	Participants	Intervention/Duration	Study Design	Outcome Measures	Effects on Sleep
L-Theanine	Rao et al. (2019) [49] Japan	Healthy adult males (<i>n</i> = 22) Age (27.5 ± 0.9 years)	4 × 50 mg (nightly, 1 h before bedtime) 6 days	Randomized, Double-blind Placebo-controlled Crossover trial	Objective Sleep Quality Measures (Actigraphy): Time in bed Wake after sleep onset Sleep onset latency Sleep length Sleep efficiency (%) Subjective Sleep Quality Measures: Obstructive Sleep Apnea Inventory questionnaire	Improvements in objective sleep measures including an increase in objective sleep efficiency (<i>p</i> < 0.047) and reduction in intermittent awakening (<i>p</i> < 0.044). Improvements in subjective sleep measures including feeling of recovery from exhaustion or fatigue scores (<i>p</i> < 0.042) and improvement in refreshed upon awakening scores (<i>p</i> < 0.014).
	Lyon et al. (2011) [50] Canada	Boys with ADHD (<i>n</i> = 98) Age (8–12 years)	2 × 100 mg (twice per day, morning and evening) 6 weeks	Randomized, Double-blind Placebo-controlled Parallel trial	Objective Sleep Quality Measures (Actigraphy): Wake after sleep onset Sleep onset latency Sleep length Nocturnal activity Sleep efficiency (%) Subjective Sleep Quality Measures: Pediatric Sleep Questionnaire	Improved objective measures including sleep efficiency (<i>p</i> < 0.05), and reduced nocturnal activity (<i>p</i> < 0.05).
	Sarris et al. (2019) [51] Australia	Adults with GAD (<i>n</i> = 46) Age (40.7 ± 15 years in TG; 32.2 ± 9.29 years in PG)	225 mg (twice daily); increased to 450 mg (twice daily) if anxiety score did not reduce by ≥35% after 4 weeks 8 weeks	Randomized, Double-blind Placebo-controlled Multi-center pilot study	Subjective Sleep Quality Measures: ISI	Improved subjective sleep satisfaction (<i>p</i> < 0.015); improvements in ISI scores for “difficulty in falling asleep” (<i>p</i> < 0.049); “Problems waking up too early” (<i>p</i> < 0.017); and “interference with daily functioning” (<i>p</i> = 0.030) in control.

Table 1. Cont.

Compound	Reference/Country	Participants	Intervention/Duration	Study Design	Outcome Measures	Effects on Sleep
Vitamin B12	Hidese et al. (2019) [52] Japan	Healthy Adults (<i>n</i> = 30) Age (48.3 ± 11.9 years)	200 mg tablet daily before sleep 4 weeks	Randomized, Double-blind Placebo-controlled Crossover trial	Subjective Sleep Quality Measures: PSQI	Improved subjective sleep quality (<i>p</i> < 0.013), reduced sleep onset latency, sleep disturbance and use of sleep medication (All <i>p</i> 's < 0.05).
	Mayer et al. (1996) [53]	Healthy Adults (<i>n</i> = 20) Age (CB12 = 36.6 ± 5.2 years. MB12 = 36.2 ± 5.2 years)	3 mg (cyano-(CB12) or methylcobalamin (MB12)) 14 days	Randomized Single-blind Between subject's design	Objective Sleep Quality Measures (Actigraphy): Wake after sleep onset Sleep onset latency Sleep length Nocturnal activity Sleep efficiency (%) Subjective Sleep Quality Measures: Morning and Evening VAS	Reduction in objective sleep time (<i>p</i> = 0.036) in MB12 group improvements in sleep quality and daytime alertness (All <i>p</i> 's < 0.05).
Vitamin B6	Luboshitzky et al. (2002) [54] Israel	Healthy Adult Males (<i>n</i> = 12) Age (22–26 years)	100 mg (5.00 PM) Once	Randomized Placebo-controlled Parallel trial	Objective Sleep Quality Measures (EEG): Sleep stages (%) Total recording time Sleep latency Actual sleep time Sleep efficiency (%) REM latency	No effect.
	Ebben et al. (2002) [55] USA	Healthy Adults (<i>n</i> = 12) Age (18–28 years)	100 mg 250 mg Placebo (All nightly before bed) 5 days per treatment 120 mg (pyridoxine hydrochloride)	Placebo-controlled Double-blind Crossover trial	Subjective Sleep Quality Measures: Sleep questionnaire Dream Salience Scale	Increase in dream salient scores in 250 mg B6 treatment compared to placebo (<i>p</i> = 0.05).
	Aspy et al. (2018) [56] Australia	Healthy Adults (<i>n</i> = 100) Age (mean = 27.5)	Vitamin B Complex (120 mg pyridoxine hydrochloride + other B vitamins) Placebo (All nightly before bed) 5 days	Randomized Double-blind Placebo-controlled trial	Subjective Sleep Quality Measures: Sleep log	Increased the amount of dream content recalled (<i>p</i> = 0.032) and decrease in sleep quality (<i>p</i> = 0.014) in B complex group.

Table 1. Cont.

Compound	Reference/Country	Participants	Intervention/Duration	Study Design	Outcome Measures	Effects on Sleep
Vitamin D	Ghaderi et al. (2017) [57] Iran	Adults undergoing Methadone Treatment. (<i>n</i> = 68) Age (25–70 years)	50,000 IU (once per fortnight) 12 weeks	Randomized Double-blind Placebo-controlled trial	Subjective Sleep Quality Measures: PSQI	Improvement in subjective sleep score (<i>p</i> = 0.02).
	Mason et al. (2016) [58] USA	Overweight menopausal females with low VitD (<i>n</i> = 218) Age (50–75 years)	2000 IU vitamin D3 (daily) 12 months	Randomized Double-blind Placebo-controlled trial	Subjective Sleep Quality Measures: PSQI	Increase in PSQI score (<i>p</i> = 0.01) and increase in need to take sleep medication (<i>p</i> < 0.01).
Vitamin C	Dadashpour et al. (2018) [59] Iran	Adults on hemodialysis with sleep disorder (<i>n</i> = 90) Age (18–70 years)	500 mg /5 cc intravenously–3 times per week 8 weeks	Randomized Double-blind Trial	Subjective Sleep Quality Measures: PSQI VAS	Reductions in subjective sleep quality, sleep latency, daytime dysfunction (All <i>p</i> 's = 0.001).
	Yeom et al. (2007) [60] Korea	Adults with Stage IV cancer (<i>n</i> = 39) Age (53.5 ± 10.5 years)	10 g vitamin C intravenously twice with 3-day interval, then 4 g oral supplement daily 1 week	Prospective study	Subjective Sleep Quality Measures: European Organization for Research and Treatment of Cancer Core Quality-of-Life questionnaire (EORTC QLQ-C30)-Korean Version	Lower subjective scores for sleep disturbance and fatigue (<i>p</i> < 0.005).
Magnesium	Murck et al. (2000) [61] Germany	Older adults without sleep disturbances (<i>n</i> = 12) Age (60–80 years)	10 mmol for 3 days, then 20 mmol for 3 days, then 30 mmol daily for 14 days	Randomized Placebo-controlled Crossover design	Objective Sleep Quality Measures (EEG): Sleep stages (%) Total recording time Sleep latency Actual sleep time Sleep efficiency (%) REM latency	Increase in slow wave sleep (<i>p</i> < 0.05), delta and sigma waves (<i>p</i> < 0.05 for both).
	Abbasi et al. (2012) [62] Iran	Older adults (<i>n</i> = 43) Age (65 ± 4.6 years)	414 mg magnesium oxide (250 mg Mg) Twice per day 8 weeks	Double-blind Placebo-controlled trial	Subjective Sleep Quality Measures: ISI Sleep Log	Increase in subjective sleep time (<i>p</i> = 0.002) and subjective sleep efficiency (<i>p</i> = 0.03); decrease in subjective sleep onset latency (<i>p</i> = 0.04), and insomnia severity index (<i>p</i> = 0.006).

Table 1. Cont.

Compound	Reference/Country	Participants	Intervention/Duration	Study Design	Outcome Measures	Effects on Sleep
	Hornyak et al. (2004) [63] Germany	Alcohol dependent adults in subacute withdrawal with sleep disturbance ($n = 11$)	30 mmol Magnesium L-aspartate hydrochloride (10 mmol morning and 20 mmol evening) daily 4 weeks	Open Pilot Study	Objective Sleep Quality Measures (Polysomnography): Sleep stages Total sleep time Sleep onset latency Wake after sleep onset Sleep efficiency (%) Periodic leg movements in sleep (PLMS) Subjective Sleep Quality Measures: PSQI	Decrease in objective sleep latency ($p = 0.03$), improvement in subjective sleep quality ($p = 0.05$).
Zinc	Saito et al. (2017) [64] Japan	Healthy Adults ($n = 94$) Age (20–84 years)	Group A: Placebo Group B: 15 mg Group C: 15 mg + Astx Group D: Placebo + 16 mg + Astx 12 weeks	Randomized Double-blind Placebo-controlled Parallel group trial	Objective Sleep Quality Measures (Actigraphy): Wake after sleep onset Sleep onset latency Sleep length Frequency Nocturnal activity Sleep efficiency (%) Subjective Sleep Quality Measures: PSQI	Improvements in objective sleep efficiency in group B ($p = 0.025$); objective sleep onset latency in Group B and D ($p < 0.032$) and ($p = 0.004$), respectively.
	Gholipour et al. (2018) [65] Iran	ICU nurses ($n = 54$) Age (31.2 ± 5.42 years)	1 × 220 mg (every 72 h) 1 month	Multi-center Randomized Two parallel group Placebo-controlled trial	Subjective Sleep Quality Measures: PSQI	Improvements in subjective total sleep quality ($p < 0.002$); sleep onset latency ($p < 0.003$), sleep duration ($p < 0.02$) and total sleep quality score ($p < 0.008$).

Note: L-TRP-L-Tryptophan; A-LAC–alpha-lactalbumin; EEG–Electroencephalography; 5-HTP–5-hydroxytryptophan; SWS–Slow Wave Sleep; REM–Rapid Eye Movement; NREM–Non-Rapid Eye Movement; ADHD–Attention Deficit Hyperactivity Disorder; GAD–Generalized Anxiety Disorder; TG–Treatment Group; PG–Placebo Group; PSQI–Pittsburgh Sleep Quality Index; ICU–Intensive Care Unit; ESS–Epworth Sleepiness Scale; FSS–Fatigue Severity Scale; ISI–Insomnia Severity Index; VAS–Visual Analogue Scale; Astx–Astaxanthin.

2.1. L-Tryptophan

L-Tryptophan (L-TRP) is an essential amino acid required for protein synthesis and plays an important substrate role for several bioactive compounds including serotonin, tryptamine, melatonin and niacin, among others [66,67]. It is obtained by consuming L-TRP rich foods such as dairy products (milk, cheese), meat, poultry, fish, pumpkin, walnuts, green leafy vegetables, some fruits (bananas, plums, kiwi fruit, tomatoes) and eggs [68–70]. Only approximately 1%–2% of ingested L-TRP is transported into the brain for synthesis of central serotonin and melatonin, both essential compounds in the ‘sleep-wake cycle’ [71,72].

The majority of L-TRP is degraded via the kynurenine pathway, an important pathway for the synthesis of nicotinamide adenine dinucleotide (NAD⁺), essential for many cellular processes including energy production [73,74]. The kynurenine pathway also produces neuroprotective and neurotoxic metabolites (kynurenic acid and quinolinic acid). [75,76]. These compounds are involved in modulating the glutamatergic and cholinergic pathways (part of the waking mechanism of the sleep-wake cycle) via the N-methyl-D-aspartate (NMDA) receptor [74,77–84].

For several decades, L-TRP loading has been studied as a potential therapeutic for improving sleep quality, given its essential role in serotonin and melatonin synthesis. A systematic review, meta-analysis and meta-regression by Sutanto et al. (2021) reported 18 studies on the effectiveness of varying L-TRP supplements (0.25–15 g) on sleep and sleep quality. A meta-analysis on 4 studies found that L-TRP supplementation reduced wake after sleep onset (WASO) ($p = 0.017$), and improved sleep efficiency with doses > 1 g ($p = 0.001$) in participants with mild to moderate insomnia [85].

The milk whey protein isolate, α -lactalbumin, containing one of the richest sources of L-TRP, became an alternative source to synthetic L-TRP following an outbreak of eosinophilia-myalgia syndrome (EMS), which saw the synthetic supplement banned for a 10 year period in the 1990s [86]. In a double-blind, placebo-controlled trial, Markus et al. (2005) studied the effects of evening consumption of a milkshake containing 20 g tryptophan-enriched (4.8 g/100 g *w/w*) α -lactalbumin protein in participants with ($n = 14$) and without ($n = 14$) mild sleep complaints [40]. They found that the tryptophan-enriched milkshake improved morning alertness in both groups ($p = 0.013$) and vigilance performance in those with a mild sleep complaint ($p = 0.002$). This was attributed to a 130% increase in plasma TRP:LNAA ($p = 0.0001$) resulting in a large increase in available L-TRP for uptake into the brain, thereby increasing serotonin and melatonin synthesis and promoting sleep [40].

In a similar study, Ong et al. (2017) found that evening consumption with a tryptophan-enriched milkshake (L-TRP (20 g) in α -lactalbumin (4.8 g/100 g)) improved objective (actigraphy) and subjective (sleep log) total sleep time and objective sleep efficiency in healthy males without sleep complaints ($n = 10$) ($p = 0.037$, $p = 0.013$, and $p = 0.028$, respectively) [41].

It has also been reported that carbohydrates (found in cereals) can increase the TRP:LNAA ratio through activation of insulin [86]. Insulin mediates the selective uptake of LNAAs into muscle, thereby reducing their levels in the plasma [87]. This effect was utilized by Cubero et al. (2007) in a prospective study conducted on formula-fed infants ($n = 30$) with disrupted sleep/wake cycles [42]. In this study, the researchers attempted to emulate the varying levels of L-TRP in human milk that occurs through the day and night by dissociating a commercial infant formula to a daytime milk containing low L-TRP (1.2 g/100 g protein), low carbohydrates and higher protein levels; and a L-TRP enriched nighttime milk (3.4 g/100 g protein), higher carbohydrates and lower protein. The infants were fed three different formula combinations consisting of the standard formula (that had not been modified), and the daytime formula, and nighttime formula. Objective sleep data (actigraphy) showed that the daytime/nighttime modified formula and the standard/nighttime formula combination reduced sleep onset latency; the daytime/nighttime modified formula also significantly increased total sleep time ($p < 0.05$ for all) [42]. Although not specifically studying the effect of carbohydrates on L-TRP uptake,

Bravo et al. (2013) reported improvements in actual sleep time ($p < 0.01$), sleep efficiency ($p < 0.001$), and immobile time ($p < 0.01$) following morning and evening consumption of an L-TRP rich cereal in a simple blind assay in older people ($n = 35$). Reductions in the onset of sleep ($p < 0.01$), number of wake bouts during the night ($p < 0.05$), and total activity ($p < 0.01$) were also reported. [43]. This was attributed to the increase in L-TRP alone; however, the cereal may have contributed to the effect through the action of insulin [35]. In addition, Afaghi et al. (2007) found that a carbohydrate-rich meal with a high glycemic index, consumed four hours before bedtime, reduced the onset of sleep ($p = 0.009$) [88], indicating the importance of glycemic index in developing a potentially effective sleep promoting beverage.

It is important to consider that L-TRP supplementation may not only influence serotonin levels in the brain, but also serotonin levels in areas such as the gut and blood [89]. This could potentially lead to increases in blood pressure or gastrointestinal issues such as nausea and diarrhea; despite this, only mild cases of nausea have been reported [89].

2.2. 5-Hydroxytryptophan

5-Hydroxytryptophan (5-HTP) is the intermediary amino acid produced naturally in the body from hydroxylation of L-TRP during serotonin synthesis [90]. It is also extracted from the seeds of the *Griffonia simplicifolia* and used as a therapeutic agent for treating various conditions, including insomnia, binge eating associated with obesity, chronic headaches and fibromyalgia [90]. Exogenous 5-HTP is readily absorbed in the gut and can cross the BBB without using a transport system, unlike L-TRP [91]. Much of the evidence for the use of 5-HTP for improving sleep in humans was conducted more than five decades ago with reported increases in REM sleep and eye movements [92]. However, in a more recent study by Bruni et al. (2004), the effects of 5-HTP supplementation on children with sleep terrors was investigated [44]. Sleep terrors are a type of parasomnia and are thought to result from dysfunction in the serotonergic system characterized by waking suddenly from deep sleep with fear, terror, screaming, sweating, confusion and increased heart rate [44]. In this randomized controlled trial (RCT), the treatment group ($n = 31$) was supplemented with 2 mg/kg (w/w) of 5-HTP per day for 20 days, and sleep parameters were measured by electroencephalography. It was found that of children supplemented with 5-HTP, over 50% were sleep terror free after one month, and the remaining 50% showed a reduction in the number of episodes ($p < 0.001$). After six months, children treated with 5-HTP, 77% of children were sleep terror-free ($p < 0.001$). The authors proposed that 5-HTP supplementation reduces intermittent awakening and the intensity of non-rapid eye movement (NREM) sleep without affecting sleep duration [44]. The role of serotonin in the sleep mechanism is complex and it has been hypothesized to have both sleep promoting and wake promoting properties depending on when the serotonergic system is activated [93]. This study demonstrates that 5-HTP may improve aspects of sleep; however, a more rigorous study examining the specific effects of 5-HTP on the sleep architecture in other populations would be beneficial.

Adverse events associated with 5-HTP supplementation are predominantly associated with the gastrointestinal system and range from mild to moderate. Its use has not been associated with serotonin syndrome [94].

2.3. Melatonin

Melatonin is a neurosecretory hormone synthesized in the pineal gland (and to a lesser extent in the retina and gut) from L-TRP and serotonin [39]. Its primary function is regulation of the sleep-wake cycle, transmitting night information to cells and organs following secretion into the circulation as well as modulating the cardiovascular system, metabolism, inflammation and immunity [95].

Melatonin supplementation and its effects on sleep quality has been studied extensively and shown to be effective in a range of clinical groups [96]. Scheer et al. (2012) conducted a double-blind, placebo-controlled RCT in participants taking beta-blockers

($n = 16$) which have been associated with night-time sleep disturbances and daytime fatigue due to melatonin suppression [45]. The treatment group were provided with 2.5 mg melatonin nightly for three weeks and sleep quality was measured by polysomnography. The study found that repeated melatonin supplementation improved total sleep time ($p = 0.046$), sleep efficiency ($p = 0.046$) and decreased sleep onset latency to stage 2 of non-rapid eye movement sleep ($p = 0.001$). Melatonin also significantly increased the duration of stage 2 non-rapid eye movement sleep compared to placebo ($p = 0.037$); however, no significant changes to the duration of the other stages of non-rapid eye movement sleep were observed [45].

Grima et al. (2018) studied the effects of melatonin supplementation in people with traumatic brain injury, of which sleep disturbances are common [46]. In this double-blind, placebo-controlled two-period, two-treatment crossover trial, participants ($n = 33$) were treated with 2 mg Circadin[®] melatonin formula nightly for four weeks. Melatonin treatment improved overall subjective sleep quality (PSQI) ($p < 0.0001$) and objective (actigraphy) sleep efficiency ($p = 0.04$), however no significant effect on sleep onset latency was reported. Additional secondary outcomes showed melatonin to significantly reduce daily anxiety and fatigue on the fatigue severity scale ($p = 0.006$, and $p = 0.03$, respectively) [46].

Xu et al. (2020) studied the effects of melatonin supplementation in middle-aged people with primary insomnia ($n = 97$) [47]. In this randomized, double-blind, parallel study, the treatment group ($n = 51$) received 3 mg fast-release melatonin one hour before bedtime for four weeks and were compared to a placebo group ($n = 46$). Overnight polysomnography data showed melatonin improved sleep quality by decreasing early morning wake ($p < 0.001$) and percentage of stage 2 of non-rapid eye movement sleep (moving into slow-wave or deep sleep more quickly) ($p = 0.031$). No changes to the other objective sleep parameters were reported. There were no significant changes reported in the subjective sleep measures PSQI, Insomnia Severity Index and Epworth Sleepiness Scale in the treatment group compared to the placebo [47].

No adverse events were observed in these studies with melatonin supplementation considered as safe. Headaches, drowsiness and fatigue are commonly associated with melatonin supplementation, but are usually reported as being mild [97].

2.4. L-Theanine

L-Theanine (L-THE) is a water-soluble, unique, non-proteinogenic amino acid known for its anxiolytic and relaxation effects. It is considered a leading candidate for potentially improving sleep quality for its role in modulating neurotransmitters that play key roles in the sleep mechanism [49,98]. L-THE is found in the leaves of the *Camellia sinensis* plant that is commonly used to produce black, green and fermented tea varieties [99] and, to a lesser extent, in the basidiomycete mushroom (*Xerocomus badius*) [98].

L-THE contains a glutamine backbone existing as an ethylamine derivative of glutamate also known as N-ethyl-L-glutamine [98]. Following consumption, L-THE is readily absorbed through the intestine into the bloodstream, reaching maximum concentration after approximately 30 minutes to two hours [100].

In the brain, L-THE influences the release of dopamine, serotonin, glycine and gamma-aminobutyric acid (GABA) [101]. As it is a natural analog of glutamate and glutamine, it has been shown to have a strong affinity for the glutamine transporter inhibiting glutamine uptake, thereby inhibiting excitatory neurotransmission release [102]. Electroencephalography data following intake of 50–250 mg of L-THE shows an increase in alpha waves in the brain, which indicates a state of relaxation [103,104]. Additionally, L-THE has been shown to be effective in reducing blood pressure increases following a mental task or from the effects of caffeine consumption [105,106].

The direct effects of L-THE supplementation on sleep quality have been the subject of several studies. Rao et al. (2019) found that supplementation with pure L-THE tablets (Suntheanine[®]) (200 mg) for six days, one hour before bed improved sleep quality in healthy male subjects ($n = 22$) [49]. In this randomized, double-blind, placebo-controlled, crossover

trial, objective sleep data (actigraphy) showed a significant increase in sleep efficiency ($p < 0.047$) and a significant reduction in intermittent waking ($p < 0.044$). The subjective sleep data (Obstructive Sleep Apnea sleep inventory questionnaire) also showed significant improvements in the “feeling of recovery from exhaustion or fatigue” ($p < 0.042$) and “a refreshed feeling upon awakening” ($p < 0.014$) parameters in the treatment group compared to the placebo group. However, no effect on sleep onset latency was observed [49].

Lyon et al. (2011) investigated the effects of pure L-THE (Suntheanine[®]) on the sleep quality of boys aged 8–12 years with Attention Deficit Hyperactivity Disorder (ADHD) ($n = 98$) [50]. In this randomized, placebo-controlled study, the treatment group consumed 200 mg pure L-THE supplement in the form of chewable tablets (Suntheanine[®]) twice per day for six weeks. Sleep quality was measured objectively (actigraphy) and subjectively (Pediatric Sleep Questionnaire), with parents completing the latter on behalf of the boys. The actigraphy data showed an improvement in sleep efficiency and a reduction in sleep activity in the treatment group compared to the placebo group ($p < 0.05$ for both) compared to the placebo group. A reduction in the number of minutes spent awake after sleep onset was also reported in the treatment group but was not statistically significant. There was no significant difference reported in sleep onset or sleep duration between the two groups. Furthermore, there was no significant correlation between the sleep questionnaire data and the actigraphy data, however, this was attributed to parents being unable to accurately report their child’s sleep behavior at baseline [50].

Sarris et al. (2019) examined the effects of L-THE supplementation in individuals diagnosed with generalized anxiety disorder in a randomized, double-blind, placebo-controlled study [51]. Participants in the treatment group were supplemented with 225 mg L-THE twice per day (total 450 mg) for eight weeks in addition to their anti-depressant medication. If, after four weeks, the anxiety score did not reduce by $\geq 35\%$, the dosage of L-THE was adjusted to 450 mg twice per day (total 900 mg). L-THE supplementation was reported to improve the sleep satisfaction item of the Insomnia Severity Index (ISI) only ($p < 0.015$). Participants in the treatment group that did not meet the clinical insomnia criteria also reported reductions in difficulty in falling asleep ($p = 0.049$) and early waking ($p = 0.017$), and improvements in daily functioning ($p = 0.030$) [51].

Hidese et al. (2019) examined the effects of L-THE supplementation on stress-related symptoms: depression, anxiety, sleep quality and cognitive function. In this randomized controlled trial, individuals were supplemented with 200 mg L-THE per day for four weeks. They found improvements in subjective scores relating to sleep quality (using PSQI) ($p = 0.013$), in particular, improvements in sleep onset latency ($p = 0.036$) and daytime dysfunction ($p = 0.022$) following L-THE supplementation compared to placebo. Improvements in depression (Self-Rating Depression Scale) ($p = 0.019$) and anxiety (State-Trait Anxiety inventory) ($p = 0.006$) scores were also reported. Additionally, cognitive function also improved in the Brief Assessment of Cognition in Schizophrenia (BACS) instrument for verbal fluency ($p = 0.001$) and executive function ($p = 0.031$) following L-THE supplementation compared to placebo [52].

No significant adverse events were reported in the above-mentioned studies. However, Sarris et al. (2019) did report symptoms such as sleep disturbance, drowsiness, weakness, fatigue, irritability, trouble concentrating and gastrointestinal discomfort. Even though these events were reported in both the treatment and placebo groups [51]. L-THE is generally well tolerated, with animal toxicity studies revealing no significant adverse events [98]. Additionally, the U.S. Food and Drug Administration regards the commercially available L-THE product, Suntheanine[®] as safe, with an upper limit of 1284 mg/day [100].

2.5. L-Cysteine

L-Cysteine (L-CYS) is a semi-essential amino acid that can be sourced through dietary intake, synthesized from the degradation of the essential amino acid methionine via the trans-sulfuration pathway, and the breakdown of endogenous proteins [107]. L-CYS is vital for maintaining cellular homeostasis by playing an essential role in the production

of glutathione (GSH), hydrogen sulfide (H₂S) and taurine, important compounds with antioxidant, cytoprotective and neuroprotective functions [108]. GSH is the tripeptide and primary antioxidant responsible for the removal of free radicals, reactive oxygen species (ROS), reactive nitrogen species (RNS) and electrophiles [109].

Sleep disruption is associated with reduced GSH and its precursor L-CYS, resulting in an imbalance of ROS, giving way to oxidative stress and damage to cells, proteins and DNA [109–111].

N-acetyl cysteine (NAC) is a precursor to L-CYS and is a safe and effective medication that has been used for decades for the treatment of a variety of medical conditions [112]. It is an effective antioxidant that stimulates glutathione synthesis and scavenges free radicals supporting defense against stress, infection, toxicity and inflammation [113,114]. An additional advantage of NAC over L-CYS is that it can cross the BBB more easily than GSH supplements [115].

To the best of our knowledge, there is only one study by Sadasavim et al. (2011) that observed the effects of NAC on improving sleep. This randomized, placebo-controlled trial focused on people with Obstructive Sleep Apnea ($n = 20$), a breathing disorder in sleep, whereby people experience intermittent hypoxia as a result of airway obstruction resulting in the generation of ROS/RNS and oxidative stress [48,116]. Participants were supplemented with either 600 mg NAC (Mucinac, Cipla) or placebo three times per day for 30 days. Polysomnography data showed significant improvements in the amount of time spent in slow-wave sleep ($p < 0.001$), and an increase in sleep efficiency ($p < 0.05$) in the treatment group compared to placebo. Additionally, the treatment group reported a reduction in the subjective ESS score, which measures daytime sleepiness ($p < 0.001$). Furthermore, improvements in biochemical markers of oxidative stress were observed, including a reduction in lipid peroxidation levels ($p < 0.001$) and an increase in total reduced GSH ($p < 0.001$) [48].

Despite limited clinical evidence, this suggests that L-CYS may provide a novel mechanism for improving sleep quality in addition to other physiological benefits.

As mentioned previously, NAC is regarded as safe without any significant side effects being reported [113].

2.6. Micronutrients

As mentioned previously, adherence to diets rich in micronutrients, such as the Mediterranean Diet, is associated with better sleep quality [37]. In addition, data from the NHANES survey from 2005–2016 reports an association between short sleep duration and inadequate intake of several vitamins and minerals including the B group vitamins, vitamin C, D, magnesium and zinc [36]. This section will evaluate the effects of vitamin and mineral supplementation on sleep quality.

B group vitamins are comprised of eight water soluble compounds that are essential for cellular functioning and play important roles in the synthesis of melatonin [117,118]. Pyridoxine (vitamin B6) and folate (vitamin B9) act as coenzymes in the synthesis of serotonin, and thereby melatonin, from L-TRP, whereas vitamin B12 is thought to suppress melatonin by increasing the light sensitivity of the circadian pacemaker [118,119]. Furthermore, niacin (vitamin B3) is a coenzyme in the production of NAD⁺ and its phosphorylated form Nicotinamide Adenosine Dinucleotide Phosphate (NADP). It can be synthesized from tryptophan endogenously via the kynurenine pathway which can deplete tryptophan availability for serotonin and melatonin synthesis [82,120]. An increase in niacin through dietary supplementation reduces the need for L-TRP for this process, consequently increasing L-TRP bioavailability [39]. Evidence to support B vitamin supplementation as an effective therapy for improving sleep quality is promising, but still relatively limited.

Pyridoxine supplementation has been reported to increase REM sleep and dream recall, however, the information on whether sleep quality is improved is limited. A randomized, double-blind, placebo-controlled study in healthy men ($n = 12$) by Luboshitzky et al. (2002) reported no effect on polysomnographic sleep recordings or melatonin secretion following

evening treatment with 100 mg oral pyridoxine [54]. Participants supplemented with pyridoxine spent 33% more time in REM sleep than the placebo group, although this was reported as not statistically significant. A placebo, double-blind study conducted by Ebben et al. (2002) investigated the effects of vitamin B6 supplementation on dream recall in healthy adults ($n = 12$). An increase in the vividness of dreams following 250 mg vitamin B6 supplementation for five days ($p = 0.005$) compared to placebo was reported [55]. Aspy et al. (2018) replicated this study in a randomized, placebo-controlled, double-blind trial. Participants ($n = 100$) were treated with either 240 mg of vitamin B6 (pyridoxine hydrochloride), a B complex supplement or a placebo. The authors reported a greater amount of dream content recalled following the B6 only supplement compared to the placebo ($p = 0.032$). Sleep questionnaires were also completed by the participants with no significant difference in sleep quality reported in the vitamin B6 only group compared with the placebo group. However, the B complex group did show lower sleep quality and increased tiredness upon waking ($p = 0.014$ and $p = 0.037$, respectively) when compared to the vitamin B6 only group [56].

The evidence of vitamin B12 supplementation on sleep quality is also limited. A preliminary study conducted by Mayer et al. (1996) compared the effects of supplementation of 3 mg cyanocobalamin (synthetic version of the vitamin B12) or its activated form methylcobalamin in healthy adults ($n = 20$) for fourteen days. Sleep was measured by actigraphy and visual analogue scales in addition to the urinary melatonin metabolite 6-sulfatoxymelatonin and urinary potassium levels. They found a significant decrease in urinary 6-sulfatoxymelatonin ($p < 0.007$) between 7 and 11 AM, but there was no increase in potassium levels, indicating suppression of melatonin by vitamin B12. The actigraphy data showed a significant reduction in sleep time in the methylcobalamin group compared to the cyanocobalamin group ($p = 0.036$). In addition, the subjective data from the visual analogue scale showed significant improvements in sleep, increased freshness and daytime concentration ($p < 0.05$). In this study, vitamin B12 was able to suppress melatonin secretion, improve sleep quality and daytime alertness, however, the study is limited by its sample size and no control [53].

Supplementation with B group vitamins above recommended daily intake is considered safe [117]. However, long term (greater than 6 months) intake of vitamin B6 above 50 mg/day is not recommended due to the increased risk of peripheral neuropathy [121].

Vitamin D is a hormone, but is also classified as a fat-soluble vitamin that is predominantly synthesized from 7-dehydrocholesterol in the skin through exposure to ultraviolet B radiation (sunlight) [122]. It can also be obtained through supplements, fortified foods and beverages and, to a lesser extent, naturally containing foods such as fatty fish, dairy, eggs and mushrooms [123].

There has been a growing interest in the role of vitamin D in the regulation of sleep, with epidemiological studies showing an association between low vitamin D levels and sleep disruption, short sleep and poor sleep quality [124–126]. Whilst the mechanism has not yet been fully elucidated, Patrick and Ames (2014) showed that vitamin D plays a regulatory role in the synthesis of serotonin by regulating the expression of tryptophan hydroxylase 2, the rate-limiting enzyme that converts L-TRP to serotonin [127].

Several studies have investigated the effects of vitamin D supplementation on sleep quality. In a randomized, double-blinded, placebo-controlled study by Majid et al. (2017), adults with sleep disorders ($n = 89$) were supplemented with 50,000 IU per fortnight for eight weeks. Subjective sleep quality data measured using the PSQI showed significant improvements in sleep score ($p < 0.001$), sleep latency ($p = 0.001$), sleep efficiency ($p = 0.001$), subjective sleep quality ($p = 0.019$), sleep disturbances ($p = 0.024$) and sleep duration ($p < 0.001$) for the treatment group compared to the placebo groups [128]. Another study by Ghaderi et al. (2017) investigated the effects of vitamin D supplementation on sleep quality, depression, anxiety and metabolic profiles in maintenance methadone treatment (MMT) patients. In this randomized, double-blinded, placebo-controlled, the treatment group ($n = 34$) were supplemented with 50,000 IU of vitamin D every two weeks for 12 weeks and

compared to a placebo group ($n = 34$). Significant improvements were reported in the PSQI ($p = 0.02$) and Beck Depression Inventory scores ($p = 0.04$). Vitamin D supplementation also significantly improved glutathione and total antioxidant capacity ($p < 0.001$ for both), and significantly reduced levels of the inflammatory marker high sensitivity C-Reactive Protein ($p < 0.001$) [57]. Conversely, a randomized, double-blinded, placebo-controlled study was conducted by Mason et al. (2016) in overweight postmenopausal women ($n = 218$) with low vitamin D levels on a 12-month lifestyle-based weight loss program [58]. The program combined a calorie reduced diet with 225 min of moderate to vigorous aerobic exercise per week. In contrast to the previous studies, they found overall subjective sleep quality measures worsened in participants whose vitamin D levels had the biggest change from baseline following supplementation with 2000 IU vitamin D per day, although the reasons for why this may affect sleep quality remain unclear [58].

No adverse events have been reported in studies where high doses of vitamin D supplementation (>4000 IU) have been used, however, excessive vitamin D usage has the potential to cause hypercalciuria which may affect kidney function [129]. Whilst two of the above studies used 50,000 IU as an intervention, this dose was given once every two weeks.

Vitamin C or ascorbic acid is a water-soluble antioxidant that cannot be synthesized in humans and must be obtained from dietary intake of fruits and vegetables, particularly citrus fruits (grapefruit, orange) [130]. In addition to its antioxidant role as a free radical scavenger, vitamin C is a cofactor in the synthesis of a number of compounds including serotonin, dopamine and noradrenaline, important neurotransmitters in the sleep mechanism [131,132].

Vitamin C supplementation has been shown to be effective in improving sleep quality in clinical groups. In a randomized, double-blind, placebo-controlled trial, Dadashpour et al. (2018) studied the effects of vitamin C supplementation in hemodialysis patients with sleep disorders ($n = 90$), which is common in these patients. They found that by supplementing 500 mg vitamin C intravenously three times per week for eight weeks subjective sleep measures, such as sleep quality, sleep latency and daily dysfunction improved significantly ($p = 0.0001$ for all) compared to the placebo group [59]. A decrease in itching ($p = 0.0001$) and restless leg syndrome ($p = 0.001$) was also reported in the treatment group. A study conducted by Yeom et al. (2007) in stage IV cancer patients ($n = 39$) supplemented all participants with a high dose of vitamin C (10 g twice, intravenously, with a three day interval, and oral intake of 4 g vitamin C daily for one week) [60]. Improvements in fatigue and sleep disturbances ($p < 0.005$) (as part of a quality of life questionnaire) were reported [60].

Vitamin C supplementation is mostly regarded as safe even at high doses with side effects mostly associated with gastrointestinal issues [133]. More serious side effects that are less common include calcium oxalate stones in people with renal issues, and the risk of developing hemolysis in people with glucose-6-dehydrogenase deficiency [60,134].

Magnesium is a mineral found in milk, cocoa and nut beverages and is essential for many enzymatic reactions in the body; in particular, it has an important role in the synthesis of melatonin by stimulating serotonin *n*-acetyl enzymatic activity [118,135]. It also acts as an antagonist of the NMDA receptor and agonist of the GABA receptor [118]. Several studies have shown improvements in sleep quality following magnesium supplementation. In an early randomized placebo-controlled cross over study conducted by Murck et al. (2000), older participants ($n = 12$) without sleep disturbances were supplemented with magnesium in the form of effervescent tablets at a concentration of 10 mmol for the first three days, 20 mmol for another three days and 30 mmol for the remaining fourteen days [61]. An increase in slow-wave sleep ($p < 0.05$) was reported following magnesium treatment as measured by electroencephalography (EEG). Increases in delta, and sigma power (indicators of NREM sleep [136]) were also reported ($p < 0.05$ for both) [61]. More recently, Abbasi et al. (2012) studied the effects of magnesium supplementation on older participants ($n = 46$) with primary insomnia. In this double-blind, randomized, placebo-controlled study, participants were supplemented with 250 mg magnesium tablet or placebo twice per day for

eight weeks and completed the Insomnia Severity Index (ISI), physical activity and sleep log questionnaires [62]. Significant increases in sleep time ($p = 0.002$) and sleep efficiency ($p = 0.03$) were reported, alongside a significant decrease in sleep onset latency ($p = 0.02$) and the Insomnia Severity Index score ($p = 0.006$). Several biochemical markers that are indicative of insomnia were also analyzed and the results showed an increase in renin and melatonin levels, and a decrease in cortisol following magnesium supplementation ($p < 0.001$, $p = 0.007$ and $p = 0.008$, respectively) [62]. A pilot study by Hornyak et al. (2004) in alcohol-dependent participants ($n = 11$) during subacute withdrawal, supplemented participants with 30 mmol magnesium daily for four weeks. Polysomnography recordings measured sleep quality for two nights at two weeks and at the end of the treatment in addition to the PSQI questionnaire. The polysomnography data showed a significant decrease in sleep onset latency ($p = 0.03$), no other sleep parameters reached significance. Total sleep time and slow wave sleep increased but were not statistically significant. In addition, an improvement in subjective sleep quality ($p = 0.05$) was also reported [63].

Adverse events associated with magnesium supplementation are mostly gastrointestinal issues including nausea and diarrhea, however it can affect the absorption of some drugs such as calcium channel blockers [137].

Zinc is an essential trace mineral and, similarly to magnesium, it is a cofactor in many cellular processes, including the modulation of several receptors in the brain that are involved in the sleep mechanism such as the NMDA receptor, and receptors for the neurotransmitters serotonin, dopamine and adenosine, among others [138]. The effect of zinc supplementation on sleep quality has also been the subject of several studies. In a randomized, double-blinded, placebo-controlled parallel-group trial, Saito et al. (2017) investigated the effects of zinc rich foods on healthy participants ($n = 94$). They found that participants who consumed zinc-rich oysters (containing 15 mg zinc) showed a significant improvement in sleep efficiency ($p = 0.025$) and a decrease in sleep onset latency ($p = 0.032$) as reported from the actigraphy data. In addition, participants who consumed the zinc-enriched placebo containing astaxanthin (an antioxidant to improve zinc absorption) also reported a decrease in sleep onset latency [64]. Gholipour et al. (2018) investigated the effects of zinc supplementation in Intensive Care Unit (ICU) nurses ($n = 54$) for which sleep deprivation and poor sleep quality are prevalent [65]. In this double-blind, randomized, placebo-controlled trial, participants were supplemented with 220 mg zinc capsule or placebo once every 72 hours before bed for one month. It was found that zinc supplementation significantly improved subjective (PSQI) sleep quality ($p = 0.002$), sleep duration ($p = 0.02$), sleep onset latency ($p = 0.003$) and total sleep quality score ($p = 0.001$). Serum zinc concentration also significantly improved in this group ($p < 0.001$) [65].

No adverse events were reported in these studies, and zinc supplementation is generally regarded as safe and well tolerated when consumed within recommended daily intakes [139].

2.7. Nutraceutical Combinations

The effects of combining nutraceutical compounds for improving sleep quality has also been explored. As many compounds are required for the synthesis of a neurotransmitter or hormone, a supplement comprising a combination of compounds has the potential to produce a greater effect on the primary outcome of improving sleep quality. Rondanelli et al. (2011) investigated the effects of a supplement containing melatonin, magnesium and zinc on sleep quality in the residents of a long-term care facility [140]. As magnesium and zinc are cofactors in the synthesis of melatonin, it was proposed that this combination would create a synergistic effect and improve sleep quality. In a parallel, double-blind, placebo-controlled trial in participants ($n = 43$), the treatment group ($n = 22$) were provided with a food supplement comprising of 5 mg melatonin, 225 mg magnesium and 11.25 mg zinc mixed in pear pulp and consumed one hour before bedtime for eight weeks. A series of questionnaires were completed including the PSQI, Epworth Sleepiness Scale (ESS), Leeds Sleep Evaluation Questionnaire (LSEQ), Short Insomnia Questionnaire (SDQ) and

the SF-36 physical score. In addition, participants wore the SenseWear Pro 2 armband to measure total sleep time, total steps taken and time in bed. Significant improvements in the intervention group were reported for PSQI ($p < 0.001$) and the LESQ for ease of getting to sleep ($p < 0.001$), quality of sleep ($p < 0.001$), hangover on awakening from sleep ($p = 0.005$) and alertness and behavioral integrity the following morning ($p = 0.001$). An improvement in the SDQ score and the SenseWear data for total sleep time ($p < 0.001$ for both) was also reported [140]. No adverse events were reported in the participants, thus a melatonin, magnesium, zinc supplement was able to effectively improve sleep quality in these participants.

B vitamins also act as cofactors in the synthesis of melatonin, alongside magnesium. A study by Djokic et al. (2019) examined the effects of a melatonin, magnesium and B vitamin complex combination on insomnia severity. In this randomized, placebo-controlled study, participants ($n = 60$) with insomnia were given either a supplement comprising of 175 mg liposomal magnesium oxide, 10 mg Vitamin B6, 16 µg vitamin B12, 1 mg melatonin and 600 mg Extrafolate-S[®] or a placebo. Participants were required to take the capsule one hour before bedtime daily for three months. The severity of insomnia was measured using the Athens Insomnia Scale, with a significant improvement in scores in the treatment group compared to the placebo ($p < 0.001$) [141].

The limitation of these studies was that there were no parallel studies of the compounds separately to determine if the improvements were due to a single compound or the combination working together. In addition, sleep assessment was conducted subjectively, future studies would benefit from the collection of objective data.

2.8. Traditional Sleep Promoting Beverages

In many cultures, herbal products and beverages have been traditionally used to promote sleep. In Western culture, milk has been traditionally used as a bedtime beverage, particularly for children [118]. It contains the essential amino acid L-TRP and to a lesser extent melatonin, as well as the aforementioned vitamins and minerals [142–144]. The effects of milk consumption on sleep have been the subject of many studies for over 80 years, however, conflicting effects on sleep measures have been reported [39,145]. An increase in sleep duration and reduction in waking after sleep onset following consumption of a malted milk drink were first reported in the early 1970s where the beverage was comprised of milk fortified with malted wheat barley [146,147]. However, one of the major limitations in these studies is that there were no findings from milk consumption alone. The results of a third study that included both malted milk and pure milk did not show any change to sleep measures in milk alone [148]. This is likely due to the relatively low levels of tryptophan found in milk, whereas malted milk contains many additional nutrients that may positively affect sleep [149]. Additional factors such as dietary intake of macronutrients, can also be used to improve the bioavailability of the nutraceutical once ingested. As mentioned previously, ingestion of carbohydrates has been shown to enhance L-TRP uptake into the brain by increasing the TRP:LNAA ratio. A randomized controlled trial conducted by Fakhri-Movahedi et al. (2018) looked at the effects of a milk and honey combination to improve sleep quality in coronary care patients ($n = 68$). These patients can suffer from poor sleep quality due to their medical interventions for the treatment of their condition. Patients in the treatment group were given 150 mL warm milk with 30 g honey in the morning and the evening for three days. Sleep quality scores in the intervention group significantly improved on day three ($p < 0.001$) [88,150]. In addition, honey is also reported to have a number of beneficial health benefits, including antioxidant and anti-inflammatory properties, which may provide synergistic effects via reducing oxidative stress [88,150].

Cow's milk is not suitable for people who suffer from lactose intolerance or a cow's milk allergy, however, to the best of our knowledge, there is only anecdotal evidence of milk alternatives such as almond milk with sleep promoting properties [151].

Chamomile, a traditional herb from Europe, is one of the most popular herbal teas made from the dried flower heads of the *Matricaria recutita* L. plant and is renowned as a

sleep-promoting beverage [152–155]. Chamomile contains over 120 bioactive constituents, however, the flavonoid, apigenin, is proposed as the chief compound responsible for potential sleep-inducing effects [152,153]. Apigenin is a low water-soluble, highly permeable compound with in vitro and in vivo studies showing it to have a wide-ranging role in cell cycle arrest, apoptosis, anti-inflammatory and antioxidant properties [156]. It can cross the BBB where it has an affinity for the GABA_A receptor, although its actions here have not been fully identified yet. Apigenin has also been shown to enhance the expression of antioxidants such as glutathione-synthase, catalase and superoxide dismutase to neutralize oxidative and electrophilic stress [157].

Several studies have looked at the effects of chamomile consumption on sleep quality. A single-blind randomized controlled trial conducted by Adib-Hajbaghery et al. (2017) in older adults ($n = 60$) demonstrated improved sleep quality in those that consumed a capsule containing 200 mg chamomile extract compared to those that consumed a placebo ($p < 0.05$) [158]. A randomized controlled trial conducted by Chang and Chen (2016), investigated the effects of drinking one cup of chamomile tea per day for two weeks in a group of post-partum women (six weeks post-childbirth). Following two weeks of treatment with chamomile tea (2 g dried flowers steeped in 300 mL hot water for 10–15 min), significantly lower scores were reported for the Postpartum Sleep Quality Scale subscale “Physical-symptoms-related sleep inefficiency” ($p = 0.015$). However, there was no difference in the overall sleep quality score between the two groups. The treatment group also reported lower scores in the Edinburgh Postnatal Depression Scale score ($p = 0.020$). At four weeks post-treatment follow up, there was no difference in subjective measures between the two groups, indicating the effects were not long-lasting [154]. The limitations of these studies are that only subjective sleep quality measures were attained and no objective measures such as polysomnography or actigraphy for comparison. A study by Zick et al. (2011) reported no significant changes to sleep parameters in people with chronic insomnia following treatment with a standardized chamomile extract [159]. In this randomized, double-blind, placebo-controlled study, participants with primary insomnia ($n = 34$) were treated with 270 mg chamomile extract twice per day for 28 days. Sleep quality was measured using a sleep diary. No effect was observed on sleep efficiency or total sleep time. Slight improvements were seen in sleep onset latency and nighttime awakenings, although these did not reach significance [159]. A repeat of this study is warranted with objective sleep measures such as actigraphy or polysomnography to validate the results.

The studies conducted by Adib-Hajbaghery et al. (2017) and Chang and Chen (2016) reported no adverse reactions to the chamomile extract or tea, respectively. The study conducted by Zick et al. (2011) reported side effects such as headaches, dizziness and gastrointestinal symptoms, however, these were reported in both the treatment and placebo groups [159]. Other reported adverse events include fatigue, indigestion and diarrhea associated with chamomile extract [153].

Ashwagandha (*Withania somnifera*), is found in Northwestern and central India. It is used in various traditional medicine systems, such as Ayurveda and Chinese, to benefit health, particularly for neurological disorders [10]. In Ayurvedic medicine, it is administered as a beverage by boiling the roots in milk or grounding the roots into a powder and then mixing with water, milk or honey [10]. Ashwagandha modulates oxidative stress markers in the brain, including superoxide dismutase, catalase, glutathione peroxidase, lipid peroxidation and GSH [160]. The major bioactive constituents of Ashwagandha are the steroidal lactones, withanolides and it is believed that these compounds produce the physiological benefits of this herb [161].

The effects of Ashwagandha have been studied using the extract in a capsule form. A randomized, double-blind, placebo-controlled study by Langade et al. (2019) in adults with insomnia ($n = 60$) were supplemented with either a twice daily dose of 300 mg ashwagandha extract or placebo for 10 weeks. The actigraphy data showed improvements in sleep onset latency ($p = 0.019$), and sleep efficiency ($p < 0.001$) following 10 weeks of treatment compared to placebo. PSQI scores were also improved in the treatment group compared

to placebo ($p < 0.0001$) as well as self-reported sleep quality ($p = 0.002$) [162]. The same group conducted another study of similar design but in both healthy subjects ($n = 40$) and insomnia patients ($n = 40$) for eight weeks. Both groups showed significant improvements in sleep onset latency ($p < 0.0001$), sleep efficiency ($p < 0.0001$), wake after sleep onset ($p < 0.040$) and total sleep time ($p < 0.002$). Improvements were also seen in anxiety score ($p < 0.05$), mental alertness on rising ($p = 0.01$) and sleep quality ($p < 0.05$) [163].

No adverse events were reported with these studies and ashwagandha root extract is currently regarded as safe [10].

Valerian root is another traditional herb commonly used in Europe known for its sedative effects which were initially thought to be due to valepotriates, however, research to date has shown no clear evidence to support this mechanism of action [164]. Several other compounds including the ligand, Linarin, flavonol 6-methylapigenin and 2S (-)Hesperidin, have since been identified as potential candidates. The 6-methylapigenin is a flavone derivative that is a ligand for the benzodiazepine binding site of the GABA_A receptor was shown to have a high affinity for the benzodiazepine receptor and is able to produce anxiolytic effects. Marder et al. (2003) also produced synergistic effects on sleep-inducing effects when 2 S (-) Hesperidin was combined with 6-methylapigenin [164]. Valerenic acid is a sesquiterpenoid that is believed to modulate the GABA_A receptor through potentiation of other components [165]. Linarin is a flavonoid glycoside that also has sedative and sleep-enhancing properties, the mechanism of which is still unclear. Fernandez et al. (2004) were able to show that the sleep-enhancing properties of Linarin was potentiated by valerenic acid in mice [166]. The authors proposed that 6-methylapigenin, 2 S(-) Hesperidin, Linarin and Valerenic acid work synergistically to produce the sleep-inducing effects of Valerian root [166].

Its effects on sleep have been widely studied, although the results are conflicting. Taibi et al. (2009) conducted a randomized, double-blind, placebo-controlled crossover study in older women with insomnia ($n = 16$) [167]. Participants were supplemented with 300 mg valerian extract or placebo 30 minutes before bedtime for two weeks. Sleep was measured by polysomnography, actigraphy and a sleep log. No significant improvements were reported in any of the measures between valerian and placebo [167]. Ziegler et al. (2002) treated participants ($n = 202$) with either 600 mg valerian extract or 10 mg oxazepam each night for six weeks. Participants were required to answer questions regarding their sleep duration and quality, with both groups reporting a marked increase in sleep quality ($p < 0.01$) [168]. Ekbatanin et al. (2013) investigated the effects of valerian supplementation on healthy menopausal women with insomnia ($n = 100$) [169]. In this randomized, triple-blind controlled study, participants were supplemented with either 530 mg valerian or placebo twice daily. Sleep quality was measured using the PSQI. A decrease in PSQI score was reported following valerian supplementation compared to placebo ($p = 0.0000$) [169]. Diaper and Hindmarsh (2004) conducted a placebo-controlled three-way crossover in adults with a mild sleep complaint [170]. In this study participants were supplemented with either 300 mg or 600 mg of valerian (Sedonium[®]) or placebo. No significant differences in either EEG or subjective questionnaires were identified [170].

In a systematic review and meta-analysis on the effectiveness of valerian conducted by Shinjyo et al. (2020) suggest the inconsistencies in these outcomes may be a result of variable quality in the herbal extracts due to unstable bioactive constituents [171]. Valerian is also regarded as being safe and well tolerated, with only mild adverse events being reported in clinical population groups such as patients with Restless Leg Syndrome, arthritis and insomnia. Symptoms included gastrointestinal, sleepiness, fatigue and vivid dreams [171].

Green tea, produced from the tea plant *Camellia sinensis*, is a popular beverage in many Asian countries, particularly Japan and China [172]. It is renowned for its anti-stress effects and other health benefits attributed to the numerous bioactive compounds, including catechins, caffeine and amino acids, particularly L-THE [172,173]. As mentioned previously in this review, L-THE has sleep-promoting properties, however, these properties are counteracted by caffeine [174]. Unno et al. (2017) conducted two studies looking at

the effects of reduced caffeine green tea on stress and sleep in both older and middle-aged adults. The first study was a single-arm, non-randomized design, in which older adults ($n = 10$) consumed a low caffeine green tea for two weeks at all mealtimes, following one week's consumption of standard green tea. Sleep quality and stress were measured using a portable EEG and salivary α -amylase (sAA) levels, respectively. A significant reduction in sAA was reported in eight of the participants when they consumed the low caffeine green tea ($p = 0.008$), and this correlated with a significant reduction in B2 wake after sleep onset (WASO) ($p = 0.0026$). B2 WASO refers to the total awakening time in the two hours before the final awakening. Despite no significant difference in the other sleep parameters between the low caffeine green tea and standard green tea, a negative correlation was observed between sAA and total sleep time and sleep efficiency [174].

The second study was a randomized, double-blind, crossover design in healthy middle-aged adults ($n = 40$). Participants consumed standard green tea (SGT) or low caffeine green tea (LCGT) for 7 days. Sleep EEG, sAA (before and after work) and subjective stress data were collected. sAA after work was significantly reduced when participants consumed LCGT ($p = 0.046$). Like the previous study, a reduction in B2 WASO only was observed following consumption of LCGT compared to SGT, although this did not reach significance. Additionally, sAA level before work was significantly correlated with total period of sleep and total sleep time following consumption of SGT ($p = 0.046$ and $p = 0.036$, respectively). Whereas a positive correlation was observed between the volume of LCGT consumed and slow wave sleep ($p = 0.045$). No significant differences were reported in the other sleep parameters between standard green tea and low caffeine green tea [175].

Both studies, despite having small sample sizes, show promising results with improving sleep quality by reducing the caffeine content. Green tea is regarded as safe, however, excessive intake may lead to mild adverse events such as gastrointestinal issues [176].

3. Discussion

This review aimed to present the evidence for the effectiveness of active compounds currently used as functional ingredients in commercial sleep and relaxation beverages, and some of the promising new candidate compounds. We also reviewed the evidence of the effectiveness of traditionally used sleep promoting beverages and the active compounds responsible for their sleep promoting properties.

We have indicated that L-TRP and melatonin may effectively improve sleep quality, as expected, due to their central roles in the sleep-wake cycle and the extensive studies conducted on these compounds. While the evidence is still relatively limited, micronutrients and 5-HTP may also be effective as functional ingredients due to their important roles in modulating the neurotransmitters of the sleep-wake cycle, particularly serotonin and melatonin. Another finding of this review is the association between inflammation and oxidative stress on sleep quality. Oxidative stress leads to overexcitation of glutamate, decreasing L-CYS uptake. This also activates the kynurenine pathway, redirecting L-TRP and reducing sleep quality [177]. The use of compounds with antioxidant properties, such as L-THE, NAC and vitamins C and D may also be effective in improving sleep quality by reducing oxidative stress. In addition, we have presented the supporting evidence on the effectiveness of traditional sleep promoting beverages, however these findings require further investigation in well-designed clinical trials. In many cases, particularly for the herbal varieties, an extract in the form of a capsule was used to evaluate its effectiveness, and thus the same effect may not be achieved through usual daily consumption of the beverage.

Given the common physiological pathways of the compounds presented in this review, preliminary data suggests nutraceutical combinations could be effective in improving sleep quality through either a synergistic or enhancing effect. This was evident from the studies looking at the effect of a melatonin/magnesium/B vitamin complex combination, and a melatonin/magnesium/zinc combination.

The future directions for development of functional beverages to improve sleep quality must consider several factors to ensure its claims of functionality are substantiated. The

bioavailability and functionality of the nutraceutical compound within the beverage may be affected by dose, solubility, pH, possible interactions with the beverage matrix and other nutraceutical compounds, digestion and gut microbiota following consumption [178,179]. Melatonin, for example, has a bioavailability of approximately 15% following consumption of 2 mg and 4 mg [180]. Whereas L-THE is reported to have a bioavailability of approximately 45%–54% following digestion [181]. The mechanism of action of the nutraceutical and its interaction with other drugs is also important to consider as it may interfere with the action of the drug. For example, magnesium supplementation and the absorption of calcium channel blockers. It may enhance the effect of a drug resulting in an adverse reaction, such as L-TRP supplementation potentially increasing peripheral serotonin in conjunction with SSRI's. Furthermore, herbal extracts, which can contain over 100 bioactive constituents, may reduce the effectiveness of other nutraceuticals due to chemical interactions. Processing and preserving the beverage and the stability of the nutraceutical compounds within the beverage during storage may also affect their bioavailability [179]. These compounds may need microencapsulation, whereby a compound is encapsulated in a food-grade, biodegradable shell to protect its bioavailability and shelf life [182]. Vitamin C is susceptible to degradation during food preservation [183], whereas L-THE is stable in acidic environments, can withstand high temperatures and has been found to have a long shelf-life [98]. Additionally, a sensory profile of the beverage is essential to ensure its likeability. NAC is reported to have a pungent taste and smell due to its sulfur groups and would therefore require additional flavors and delivery to make it more palatable [184]. The volume of the beverage must also be considered as an increased propensity to urinate after consuming the drink may disrupt normal sleep. Furthermore, when assessing the effectiveness of the beverage, the use of objective sleep assessments such as actigraphy, used in combination with subjective sleep diaries and questionnaires, and a food diary will offer a more comprehensive assessment of efficacy.

4. Limitations

In this narrative literature review we have attempted to capture the latest research on some of the lead bioactive compounds and traditionally consumed beverages and their effectiveness for improving sleep quality. The outcomes of this literature review are also subjected to some limitations. Firstly, it is difficult to draw a general conclusion about their effectiveness in improving sleep quality due to the variations in study design and small number of studies. Secondly, as we focused on human studies, we could only provide a brief overview of the mechanism of action for the bioactive compounds. Thirdly the quality of sleep analysis in most of the studies were retrospectively reported using sleep diaries with variation in sleeping patterns also being influenced by daily activities, stressors and even climatic changes. Nevertheless, this narrative review, despite some limitations, has summarized some of the most common traditional beverages and lead bioactive compounds that can be used in future studies for the development of functional beverages orientated towards the improvements in the quality of sleep.

5. Conclusions

Beverages provide an ideal matrix for the delivery of nutraceuticals evidence that supports their effectiveness for improving sleep quality. Several compounds may potentially improve sleep quality based on their mechanism of action and preliminary studies. However, standardization in study design comprising of both objective and subjective sleep measures are needed in future studies. Furthermore, the concentration of the compound is an important consideration, particularly its bioavailability after ingestion, and other dietary factors such as the composition of the overall long-term diet.

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