Nutraceuticals for Improving Sleep Quality

Subjects: Nutrition & Dietetics

Contributor: Amanda Bulman , Nathan M. D'Cunha , Wolfgang Marx , Andrew J. McKune , Rati Jani , Nenad Naumovski

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.

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][5][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][16][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][27][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][38][39]. These compounds are now being included in commercially available functional relaxation or sleep beverages.

2. Active Compounds

The summary of active compounds included here 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
	Markus et al. (2005) [40] Netherlands	Adults without sleep complaints (*n* = 14) Age (22 ± 3 years) Adults with mild sleep complaint (*n* = 14) Age (22 ± 2 years)	20 g L-TRP-enriched A-LAC protein (4.8 g L-TRP/100 g amino acids *w/w*) 1 night	Double-blind Placebo-controlled	Subjective Sleep Quality Measures: Stanford Sleepiness Scale	Improved morning alertness ($p = 0.013$) and increased attention ($p = 0.002$) in both groups. Improved performance in participants with sleep complaints only ($p = 0.05$).
L-Tryptophan	Ong et al. (2017) [41] Australia	Healthy males without sleep complaint (*n* = 10) Age (26.9 ± 5.3 years)	20 g L-TRP-enriched A-LAC protein (4.8 g L-TRP/100 g amino acids *w/w*) 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	Increased objective and subjective total sleep time by 12.8% ($p = 0.037$) and 10.8% ($p = 0.013$), respectively; increased objective

Compound	Reference/Country	Participants	Intervention/Duration	Study Design	Outcome Measures	Effects on Sleep
					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	sleep efficiency by 7.0% (*p* = 0.028).
	Cubero et al. (2007) [42] Spain	Pre-weaning infants (*n* = 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	Double-blind Randomized	Objective Sleep Quality Measures (Actigraphy): Time of nocturnal sleep Minutes of immobility Sleep latency Nocturnal awakenings Sleep efficiency (%)	Diet C improved objective total sleep time (*p* < 0.05) and subjective (parent) sleep improvement; Diet B and Diet C reduced objective sleep onset latency; Diet B improved

Compound	Reference/Country	Participants	Intervention/Duration	Study Design	Outcome Measures	Effects on Sleep
			protein) in the evening 1 week per formula		Sleep Diary: Sleep over 24 h Number of bottle feeds Observations or incidences that would influence the infants rest	objective sleep efficiency. (All *p's* < 0.05)
	Bravo et al. (2013) [43] Spain	Older adults with sleep difficulties (*n* = 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 ($p < 0.01$); increase in sleep efficiency ($p < 0.001$); increase in immobile time ($p < 0.01$); reduction in sleep latency ($p < 0.01$); wake bouts ($p < 0.05$); total activity

Compound	Reference/Country	Participants	Intervention/Duration	Study Design	Outcome Measures	Effects on Sleep
						($p < 0.01$); fragmentation index ($p < 0.001$).
5-HTP	Bruni et al. (2004) [44] Italy	Children with sleep terrors ($n = 45$) 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 ($p < 0.00001$). After 6 months: 51.6% were sleep-terror free ($p < 0.001$).
Melatonin	Scheer et al. (2012) [45] USA	Hypertensive adults on beta blockers ($n = 16$) 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	Increased total sleep time by 32 min ($p = 0.046$); increased sleep

Compound	Reference/Country	Participants	Intervention/Duration	Study Design	Outcome Measures	Effects on Sleep
					Time in bed Sleep efficiency (%) Objective Sleep Quality Measures (Actigraphy): Sleep onset latency Total sleep time Sleep efficiency (%)	efficiency by 7.6% (*p* = 0.046). Decreased sleep onset latency to stage 2 NREM sleep by 14 min (*p* = 0.001) and increased the duration of stage 2 NREM sleep by 42 min (*p* = 0.037).
	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	Improved subjective sleep quality (*p* < 0.0001) and objective sleep efficiency (*p* < 0.04).

Compound	Reference/Country	Participants	Intervention/Duration	Study Design	Outcome Measures	Effects on Sleep
					Subjective Sleep Quality Measures: PSQI ESS FSS	
	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]	Adults with obstructive sleep apnea	600 mg (Mucinac,	Randomized,	Objective Sleep Quality Measures	Improvements in objective slow wave

Compound	Reference/Country	Participants	Intervention/Duration	Study Design	Outcome Measures	Effects on Sleep
	India	(*n* = 20) Age (53.1 ± 2.3 years)	Cipla), three times per day 30 days	Placebo-controlled	(Polysomnography): Sleep stages Total sleep time Sleep onset latency Wake after sleep onset Sleep efficiency (%) Sleep apnea Snoring Subjective Sleep Quality Measures: ESS	sleep as sleep percent time ($p < 0.001$) and sleep efficiency. ($p < 0.05$). Reduction in subjective Epworth Sleepiness Score ($p < 0.001$).
	Rao et al. (2019) [49] Japan	Healthy adult males (*n* = 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 (%)	Improvements in objective sleep measures including an increase in objective sleep efficiency ($p < 0.047$) and reduction in intermittent wakening ($p < 0.044$).

Compound	Reference/Country	Participants	Intervention/Duration	Study Design	Outcome Measures	Effects on Sleep
					Subjective Sleep Quality Measures: Obstructive Sleep Apnea Inventory questionnaire	Improvements in subjective sleep measures including feeling of recovery from exhaustion or fatigue scores ($p < 0.042$) and improvement in refreshed upon awakening scores ($p < 0.014$).
L-Theanine	Lyon et al. (2011) [50] Canada	Boys with ADHD ($n = 98$) 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 (%)	Improved objective measures including sleep efficiency ($p < 0.05$), and reduced nocturnal activity ($p < 0.05$).

Compound	Reference/Country	Participants	Intervention/Duration	Study Design	Outcome Measures	Effects on Sleep
					Subjective Sleep Quality Measures: Pediatric Sleep Questionnaire	
	Sarris et al. (2019) [51] Australia	Adults with GAD (n = 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 ($p < 0.015$); improvements in ISI scores for "difficulty in falling asleep" ($p < 0.049$); "Problems waking up too early" ($p < 0.017$); and "interference with daily functioning" ($p = 0.030$) in control.
	Hidese et al. (2019) [52] Japan	Healthy Adults (n = 30)	200 mg tablet daily before sleep 4 weeks	Randomized, Double-blind	Subjective Sleep Quality Measures: PSQI	Improved subjective sleep quality ($p < 0.013$), reduced sleep

Compound	Reference/Country	Participants	Intervention/Duration	Study Design	Outcome Measures	Effects on Sleep
		Age (48.3 ± 11.9 years)		Placebo-controlled Crossover trial		onset latency, sleep disturbance and use of sleep medication (All p's < 0.05).
Vitamin B12	Mayer et al. (1996) [53]	Healthy Adults (*n* = 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 (p = 0.036) in MB12 group improvements in sleep quality and daytime alertness (All p's < 0.05).
	Luboshitzky et al. (2002) [54] Israel	Healthy Adult Males (*n* = 12)	100 mg (5.00 PM) Once	Randomized Placebo-controlled Parallel trial	Objective Sleep Quality Measures (EEG): Sleep stages (%)	No effect.

Compound	Reference/Country	Participants	Intervention/Duration	Study Design	Outcome Measures	Effects on Sleep
		Age (22–26 years)			Total recording time Sleep latency Actual sleep time Sleep efficiency (%) REM latency	
Vitamin B6	Ebben et al. (2002) [55] USA	Healthy Adults (*n* = 12) Age (18–28 years)	100 mg 250 mg Placebo (All nightly before bed) 5 days per treatment	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 (p = 0.05).
	Aspy et al. (2018) [56] Australia	Healthy Adults (*n* = 100) Age (mean = 27.5)	120 mg (pyridoxine hydrochloride) Vitamin B Complex (120 mg pyridoxine hydrochloride + other B vitamins) Placebo	Randomized Double-blind Placebo-controlled trial	Subjective Sleep Quality Measures: Sleep log	Increased the amount of dream content recalled (p = 0.032) and decrease in sleep quality (p = 0.014) in B complex group.

Compound	Reference/Country	Participants	Intervention/Duration	Study Design	Outcome Measures	Effects on Sleep
			(All nightly before bed) 5 days			
Vitamin D	Ghaderi et al. (2017) [57] Iran	Adults undergoing Methadone Treatment. (*n* = 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 ($p = 0.02$).
	Mason et al. (2016) [58] USA	Overweight menopausal females with low VitD (*n* = 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 ($p = 0.01$) and increase in need to take sleep medication ($p < 0.01$).
Vitamin C	Dadashpour et al. (2018) [59] Iran	Adults on hemodialysis with sleep disorder (*n* = 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 *p*'s = 0.001).

oups: A … ing and … ges: … -1206. … nto, J. … rients … tive. … tary … gra, D. … . Pr.

9. Pan, S.-Y.; Litscher, G.; Gao, S.-H.; Zhou, S.-F.; Yu, Z.-L.; Chen, H.-Q.; Zhang, S.-F.; Tang, M.-K.; Sun, J.-N.; Ko, K.-M. Historical Perspective of Traditional Indigenous Medical Practices: The Current Renaissance and Conservation of Herbal Resources. Evid. Based Complement. Altern. Med. 2014, 2014, 1–20.

Compound	Reference/Country	Participants	Intervention/Duration	Study Design	Outcome Measures	Effects on Sleep
	Yeom et al. (2007) [60] Korea	Adults with Stage IV cancer (*n* = 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 ($p < 0.005$).
	Murck et al. (2000) [61] Germany	Older adults without sleep disturbances (*n* = 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 ($p < 0.05$), delta and sigma waves ($p < 0.05$ for both).
Magnesium	Abbasi et al. (2012) [62] Iran	Older adults (*n* = 43)	414 mg magnesium oxide (250 mg Mg) Twice per day	Double-blind Placebo-controlled trial	Subjective Sleep Quality Measures: ISI	Increase in subjective sleep time

1 andha 6.
1 astrus
1 s of 6.
1 Tradit.
1 ealth.
1 s to be Saf.
1 n, and
1 ls: 2017,
1 ffects s.
1 nd
2 nd
21. Businesswire. Global Relaxation Drinks Market (2019 to 2027)—CAGR of 14.06% Expected During the Forecast Period—ResearchAndMarkets.com. 2020. Available online: https://www.businesswire.com/news/home/20200317005330/en/Global-Relaxation-Drinks-Market-2019-to-2027---CAGR-of-14.06-Expected-During-the-Forecast-Period---ResearchAndMarkets.com (accessed on 17 March 2021).

Compound	Reference/Country	Participants	Intervention/Duration	Study Design	Outcome Measures	Effects on Sleep
		Age (65 ± 4.6 years)	8 weeks		Sleep Log	($p = 0.002$) and subjective sleep efficiency ($p = 0.03$); decrease in subjective sleep onset latency ($p = 0.04$), and insomnia severity index ($p = 0.006$).
	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:	Decrease in objective sleep latency ($p = 0.03$), improvement in subjective sleep quality ($p = 0.05$).

34. Ibarra-Coronado, E.G.; Pantaleón-Martínez, A.M.; Velazquéz-Moctezuma, J.; Prospéro-García, O.; Méndez-Díaz, M.; Pérez-Tapia, M.; Pavón, L.; Morales-Montor, J. The Bidirectional Relationship between Sleep and Immunity against Infections. J. Immunol. Res. 2015, 2015, 1–14.

35. St-Onge, M.-P.; Mikic, A.; Pietrolungo, C.E. Effects of Diet on Sleep Quality. Adv. Nutr. 2016, 7, 938–949.

Compound	Reference/Country	Participants	Intervention/Duration	Study Design	Outcome Measures	Effects on Sleep
					PSQI	
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

47. Xu, H.; Zhang, C.; Qian, Y.; Zou, J.; Li, X.; Liu, Y.; Zhu, H.; Meng, L.; Liu, S.; Zhang, W.; et al. Efficacy of melatonin for sleep disturbance in middle-aged primary insomnia: A double-blind, randomised clinical trial. Sleep Med. 2020, 76, 113–119.

48. Sadasivam, K.; Patial, K.; Vijayan, V.K.; Ravi, K. Anti-oxidant treatment in obstructive sleep apnoea syndrome. Indian J. chest Dis. Allied Sci. 2011, 53, 153–162.

Compound	Reference/Country	Participants	Intervention/Duration	Study Design	Outcome Measures	Effects on 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 Dissorder; 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.

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

The researchers 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 research 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 [66]. 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, the researchers 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 here, 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 [67][68]. Melatonin, for example, has a bioavailability of approximately 15% following consumption of 2 mg and 4 mg [69].

4... 2015,

5... ve ... uble-

51. Sarris, J.; Byrne, G.J.; Cribb, L.; Oliver, G.; Murphy, J.; Macdonald, P.; Nazareth, S.; Karamacoska, D.; Galea, S.; Short, A.; et al. L-theanine in the adjunctive treatment of generalized anxiety disorder: A double-blind, randomised, placebo-controlled trial. J. Psychiatr. Res. 2019, 110, 31–37.

52. Hidese, S.; Ogawa, S.; Ota, M.; Ishida, I.; Yasukawa, Z.; Ozeki, M.; Kunugi, H. Effects of L-Theanine Administration on Stress-Related Symptoms and Cognitive Functions in Healthy Adults: A Randomized Controlled Trial. Nutrients 2019, 11, 2362.

53. Mayer, G.; Kröger, M.; Meier-Ewert, K. Effects of Vitamin B12 on Performance and Circadian Rhythm in Normal Subjects. Neuropsychopharmacology 1996, 15, 456–464.

54. Luboshitzky, R.; Ophir, U.; Nave, R.; Epstein, R.; Shen-Orr, Z.; Herer, P. The effect of pyridoxine administration on melatonin secretion in normal men. Neuro Endocrinol. Lett. 2002, 23, 213–217.

55. Ebben, M.; Lequerica, A.; Spielman, A. Effects of Pyridoxine on Dreaming: A Preliminary Study. Percept. Mot. Skills 2002, 94, 135–140.

56. Aspy, D.J.; Madden, N.A.; Delfabbro, P. Effects of Vitamin B6 (Pyridoxine) and a B Complex Preparation on Dreaming and Sleep. Percept. Mot. Ski. 2018, 125, 451–462.

57. Ghaderi, A.; Banafshe, H.R.; Motmaen, M.; Rasouli-Azad, M.; Bahmani, F.; Asemi, Z. Clinical trial of the effects of vitamin D supplementation on psychological symptoms and metabolic profiles in maintenance methadone treatment patients. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 2017, 79, 84–89.

58. Mason, C.; Tapsoba, J.D.D.; Duggan, C.; Wang, C.-Y.; Korde, L.; McTiernan, A. Repletion of vitamin D associated with deterioration of sleep quality among postmenopausal women. Prev. Med. 2016, 93, 166–170.

59. Dadashpour, S.; Hajmiri, M.S.; Roshani, D. Effect of intravenous vitamin C supplementation on the quality of sleep, itching and restless leg syndrome in patients undergoing hemodialysis; A double-blind randomized clinical trial. J. Nephropharmacol. 2018, 7, 131–136.

60. Yeom, C.H.; Jung, G.C.; Song, K.J. Changes of Terminal Cancer Patients' Health-related Quality of Life after High Dose Vitamin C Administration. J. Korean Med. Sci. 2007, 22, 7–11.

61. Murck, H.; Held, K.; Antonijevic, I.; Künzel, H.; Golly, I.; Steiger, A. Oral Mg^{2+}-supplementation reverses age related sleep-endocrine changes in humans. Eur. Neuropsychopharmacol. 2000,

Whereas L-THE is reported to have a bioavailability of approximately 45%–54% following digestion [70]. 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 [68]. These compounds may need microencapsulation, whereby a compound is encapsulated in a food-grade, biodegradable shell to protect its bioavailability and shelf life [71]. Vitamin C is susceptible to degradation during food preservation [72], whereas L-THE is stable in acidic environments, can withstand high temperatures and has been found to have a long shelf-life [73]. 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 [74]. 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.

10, 373.

62. Abbasi, B.; Kimiagar, M.; Sadeghniiat, K.; Shirazi, M.M.; Hedayati, M.; Rashidkhani, B. The effect of magnesium supplementation on primary insomnia in elderly: A double-blind placebo-controlled clinical trial. J. Res. Med. Sci. 2012, 17, 1161–1169.

63. Hornyak, M.; Haas, P.; Veit, J.; Gann, H.; Riemann, D. Magnesium Treatment of Primary Alcohol-Dependent Patients During Subacute Withdrawal: An Open Pilot Study with Polysomnography. Alcohol. Clin. Exp. Res. 2004, 28, 1702–1709.

64. Saito, H.; Cherasse, Y.; Suzuki, R.; Mitarai, M.; Ueda, F.; Urade, Y. Zinc-rich oysters as well as zinc-yeast- and astaxanthin-enriched food improved sleep efficiency and sleep onset in a randomized controlled trial of healthy individuals. Mol. Nutr. Food Res. 2017, 61, 1600882.

65. Baradari, A.G.; Alipour, A.; Mahdavi, A.; Sharifi, H.; Nouraei, S.M.; Zeydi, A.E. The Effect of Zinc Supplementation on Sleep Quality of ICU Nurses: A Double Blinded Randomized Controlled Trial. Work Health Saf. 2018, 66, 191–200.

66. Liguori, I.; Russo, G.; Curcio, F.; Bulli, G.; Aran, L.; DELLA-Morte, D.; Gargiulo, G.; Testa, G.; Cacciatore, F.; Bonaduce, D.; et al. Oxidative stress, aging, and diseases. Clin. Interv. Aging 2018, ume 13, 757–772.

67. Granato, D.; Nunes, D.S.; Barba, F.J. An integrated strategy between food chemistry, biology, nutrition, pharmacology, and statistics in the development of functional foods: A proposal. Trends Food Sci. Technol. 2017, 62, 13–22.

68. Santana-Gálvez, J.; Cisneros-Zevallos, L.; Jacobo-Velázquez, D.A. A practical guide for designing effective nutraceutical combinations in the form of foods, beverages, and dietary supplements against chronic degenerative diseases. Trends Food Sci. Technol. 2019, 88, 179–193.

69. DeMuro, R.L.; Nafziger, A.N.; Blask, D.E.; Menhinick, A.M.; Bertino, J.S., Jr. The Absolute Bioavailability of Oral Melatonin. J. Clin. Pharmacol. 2000, 40, 781–784.

70. Scheid, L.; Ellinger, S.; Alteheld, B.; Herholz, H.; Ellinger, J.; Henn, T.; Helfrich, H.-P.; Stehle, P. Kinetics of L-Theanine Uptake and Metabolism in Healthy Participants Are Comparable after Ingestion of L-Theanine via Capsules and Green Tea. J. Nutr. 2012, 142, 2091–2096.

71. Ye, Q.; Georges, N.; Selomulya, C. Microencapsulation of active ingredients in functional foods: From research stage to commercial food products. Trends Food Sci. Technol. 2018, 78, 167–179.

72. Dhakal, S.P.; He, J. Microencapsulation of vitamins in food applications to prevent losses in processing and storage: A review. Food Res. Int. 2020, 137, 109326.

73. Williams, J.; Kellett, J.; Roach, P.D.; McKune, A.; Mellor, D.; Thomas, J.; Naumovski, N. l-Theanine as a Functional Food Additive: Its Role in Disease Prevention and Health Promotion. Beverages 2016, 2, 13.

74. Greene, S.C.; Noonan, P.K.; Sanabria, C.; Peacock, W.F. Effervescent N-Acetylcysteine Tablets versus Oral Solution N-Acetylcysteine in Fasting Healthy Adults: An Open-Label, Randomized, Single-Dose, Crossover, Relative Bioavailability Study. Curr. Ther. Res. 2016, 83, 1–7.