Scientific Substantiation For _____

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The scientific information contained in this document is believed to be the most accurate representation of the scientific findings related to the ingredients of this product as of April 2016. The scientific sources used for this documentation were relevant publications that are listed within the PubMed database. Publications that are not listed in PubMed were not included due to the potentially low credibility of such journals, with little or undisclosed information about their peer-review process and, overall, missing procedural information about their publishing policies.

Therefore, this document might not include all the available data, but only the information deemed credible and relevant about the ingredients of this product.

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Contents

A) Ingredients for the "Day" formulation

1) Wild green oat extract

Possible functional claims for this ingredient include but are not limited to:
- Improved cognitive performance;
- Improved memory performance;
- Improved brain activity associated with wakefulness;
- Improved attention and concentration;
- Improved blood flow to the brain.

In a double-blind, placebo-controlled, within-subjects trial, with 42 adult subjects, it was shown that the administration of 800 mg extract increased, at 1, 2.5, 4, and 6 hours post-dose, the speed of performance across post-dose assessments on a global measure, including data from all of the timed tasks. It also improved the performance of a delayed word recall task in terms of errors, and an executive function task (Peg and Ball) as assessed by decreased thinking time and overall completion time (1). It was concluded that the administration of wild green oat extract induced acute cognitive effects, and suggesting that the optimal dose is at or below 800 mg.

In a double-blind, randomized study, the efficacy of the wild green oat extract on improving cognitive performance was tested in older subjects with below-average cognitive performance (n=36). Significantly fewer errors were made during the color-naming component of the Stroop test after consuming the 1600-mg dose than after the 0-mg or 2400-mg doses ($F(1,36) = 18.85$, $p < 0.001$). In 7 subjects with suspected cognitive impairment, Stroop interference score was improved by the 1600-mg dose compared to 0-mg and 2400-mg doses ($F(1, 34) = 2.40$, $p < 0.01$) (2). It was concluded that the oat herb extract may acutely improve attention, concentration, and the ability to maintain task focus in older adults with differing levels of cognitive status.

Using EEG assessment, *Dimpfel et al* measured the impact of 1250 or 2500 mg extract on the hyper activation of the left frontotemporal area, known to be involved in cognitive tasks (n=20 healthy adults). Using quantitative brain mapping technology (CATEEM), statistically significant differences were observed during resting (lowering of spectral δ power) and during performance of the d2-concentration test (enhancement of spectral θ power) ($p<0.01$ and $p<0.05$, respectively). Also, during performance of mental arithmetic, greater enhancement of θ power was observed but only at a lower error probability ($p=0.115$) (3). It was concluded that oat herb extract might be effective in healthy subjects, resulting in a positive impact on cognitive performance.

Vascular effects were also noted. In a randomized, double-blind, placebo-controlled study (n=37 participants), the administration of 1500 mg extract/day for 12 weeks was associated with increased cerebral vasodilator responsiveness (CVR) and flow-mediated dilatation (FMD) of the brachial artery, to a similar extent (42 and 41%, respectively, $p<0.01$ for both) (4). It was concluded that supplementation can improve vasodilator function in systemic and cerebral arteries, suggesting a potential role in the maintenance of cardiovascular health and brain function.

2) Periwinkle pant extract (Vinpocetine)

Possible functional claims for this ingredient include but are not limited to:
- Increased blood flow to the brain;
- Inhibition of proinflammatory factors in brain;
- Neuroprotection;
- Improves cognitive functions.

Vinpocetine is an alkaloid extracted from the periwinkle plant, and is a derivative of the alkaloid vincamine. It is used to enhance cerebral circulation and cognitive function for several years, and used in many countries as a dietary supplement to prevent cerebrovascular disorders and symptoms associated with aging (5,6).

Vinpocetine is an inhibitor of phosphodiesterase type 1 (PDE1), which can lead to increases in cAMP and cGMP, thus initiating plasticity-related gene expression (7). Vinpocetine has a high affinity for the 18-kDa translocator protein (TSPO a biomarker of activated microglia), and inhibits microglial proliferation through the NF-κB/activator protein-1 (AP-1) pathway. It also suppresses the release of inflammatory factors (8) by inhibiting the inhibitor of the IKK/NF-κB pathway after TNF-α stimulation (6). It and also inhibits oligodendroglial precursor cell differentiation thus having a direct negative effect on remyelination (9).

Various clinical trials have confirmed the multiple underlying mechanisms responsible for the beneficial neuroprotective effects produced by vinpocetine. Positron emission tomography (PET) measurements performed in chronic ischemic stroke patients after a single-dose injection showed significant changes in regional cerebral blood flow (rCBF) and metabolism (rCMRglu). The changes were positive in the peristroke regions and the healthy brain tissue, with peaks in the basal ganglia, thalamus and occipital cortex [68]. Furthermore, the neuroprotective activity of vinpocetine makes it useful for the treatment of early stage cerebrovascular diseases, such as the asymptomatic ischemic cerebrovascular disorders (AICVD) (10). In a pilot single-blinded randomized clinical trial, 30 patients with acute ischemic stroke were given either low-molecular weight dextran alone or in combination with vinpocetine. At the three-month follow-up, the relative risk (RR) reduction of a poor outcome was observed to be 30% (according to the modified Barthel Index) and 60% according to the modified Ranking score. In addition, no significant adverse effects were observed. Hence, this pilot study reported the efficacy and safety of vinpocetine (11). Another study conducted in 87 patients with chronic cerebral ischemia demonstrated that vinpocetine exerts an endothelium protective effect through the partial renewal of endothelium-dependent vasodilatation and inhibition of rejection of the von Willebrand factor during an arteriovenous occlusion test. However, the recovery of a neurological deficit depends on the extent of renewal of the endothelium-dependent vasodilatation (12).

The increase in the regional cerebral blood flow in response to vinpocetine administration is well established and strengthened by new diagnostic techniques (transcranial Doppler, near infrared spectroscopy, positron emission tomography). In vitro studies have revealed the effect of the compound on Ca(2+)/calmodulin dependent cyclic guanosine monophosphate-phosphodiesterase 1, voltage-operated Ca(2+) channels, glutamate receptors and voltage dependent Na(+)-channels; the latest being especially relevant to the neuroprotective action of vinpocetine (reviewed in (13)).

3) Guarana seed (seed extract containing caffeine)

Possible functional claims for this ingredient include but are not limited to:
- Improved alertness;
- Improved reaction time;
- Improved information processing;
- Improved mood and physical performance.

Because of the stimulant property of caffeine on the central nervous system, guarana has been widely used in the pharmaceutical market. It has also been included in the pharmacopoeias of Brazil, Mexico, the United States and several European countries (14). In addition to the stimulating action of caffeine on the central nervous system, other effects have been attributed to guarana, such as improved alertness, reaction time, speed of information processing, memory, mood and performance in physical exercises as well as thermogenic effects associated with weight loss and gastric acid secretion (15). Guarana has been shown to be a promising option for the treatment of mental and physical fatigue related to cancer because its use lacks significant side effects and it is low in cost compared with traditional drug therapy (16).

Several pharmacological studies demonstrated the mechanisms associated with the effects attributed to this plant, and the mechanisms of action of its components, especially the alkaloids and tannins (17-20). Most studies attributed bioactive effects to more than one substance. The stimulant property on the central nervous system is mainly attributed to guarana′s alkaloids because their mechanism of action is known, although catechins may also be involved, being present in high concentrations in guarana cotyledons (20-22). Regarding catechins, studies with guarana showed that they act as antioxidants by inhibiting lipid peroxidation, although antiviral, bactericidal and molluscicidal activities were also tested (23).

In addition to the psychoactive effects, the use of guarana for metabolic disorders has been widely studied because it possesses functional properties similar to green tea, which is also rich in catechins. Studies have shown that guarana positively affects lipid metabolism, increases basal energy and weight loss and may be useful for obesity treatments (24-27).

4) Ginkgo biloba (leaf extract)

Possible functional claims for this ingredient include but are not limited to:
- Improved memory;
- Improved cognition;
- Consolidation of mental functions.

Because the leaf extract has been standardized, and used in USA and Europe as EGb 761 (sold also as Tanakan or Tebonin), the information below is based only on clinical trials and other studies using this standardized extract. The use of EGb 761 has not yet garnered FDA approval in the United States, but it is available by prescription in European countries. In US the extract is sold as a supplement, alone or as an ingredient in various dietary supplements.

The standardized formulation, EGb 761 was created to normalize the constituents to assure reliable and consistent drug performance and the absence of ginkgolic acid, a known allergen naturally found in Ginkgo (28). The standardized preparation of EGb 761 involves harvesting Ginkgo leaves while still green, and after morphological analysis, they are extracted in 60% (w/w) acetone and water, concentrated, and analyzed by high-performance liquid chromatography. The final product is adjusted to ~24% flavone glycosides (primarily quercetin, kaempferol, and isorhamnetin), 6% terpene lactones (consisting of 2.8%–3.4% ginkgolides A, B, and C, and 2.6%–3.2% bilobalide [BB]), and <5 ppm ginkgolic acid.

A large majority of clinical trials involving EGb 761 are directed at the improvement of cognition and memory, some of which target dementia (29) and more specifically Alzheimer's Disease (AD) (30). A recent study of the effect of EGb 761 on memory in healthy, middle-aged subjects indicated that, when administered daily, EGb 761 (240 mg daily) significantly improved the results in a memory recall test after a six-week regimen (31). Other studies in healthy individuals suggest that improvement of cognition, memory, or self-estimated mental health were attributed to EGb 761 (32-35).

Dementia is a category of brain diseases characterized by a gradual decline in cognition and memory that includes AD, vascular dementia, Lewy body dementia, and frontotemporal dementia (29). The abilities of EGb 761 to modulate excitotoxic glutamatergic neurotransmission (36), reduce amyloid-β aggregation and toxicity (37), and function as a radical scavenger (38) suggest its use in the various dementia pathologies. Clinical studies of 240 mg daily EGb 761 administration to patients with dementia indicate its efficacy in stabilizing or slowing the decline of mental function, particularly for patients with neuropsychiatric symptoms (30,39,40). The European studies included AD patients with Neuropsychiatric Inventory (NPI) composite scores >4 and reported significant improvements in NPI, as well as reductions in depression and anxiety. Additionally, a clinical investigation into the use of EGb 761 with a commonly prescribed cholinesterase inhibitor, donepezil, suggests that the combination of the two therapies is more effective than either one alone (41). It was shown that EGb 761 was not effective in preventing dementia (42); however, the clinical evidence for the use of EGb 761 to slow its progression is promising and warrants further clinical investigation.

5) Siberian Ginseng

Possible functional claims for this ingredient include but are not limited to:
- Increased alertness;
- Improved mental working capacity;
- Improved attention and concentration;
- Improved physical work capacity

The clinical studies using Siberian Ginseng extracts demonstrated that its bioactives act as plant adaptogens (reviewed in (43)), which are defined as compounds that increase the ability of an organism to adapt to environmental factors and to avoid damage from such factors (44).

The administration of Siberian ginseng extract proved to be beneficial, on either short or long term, for improvements in mental working capacity, and increased physical work capacity due to cardiovascular improvements, both in the context of optimization of the state of wakefulness (43).

In a study performed on sailors keeping watch (*Berdyshev VV, 1995*), a single dose administration of extract improved their state of wakefulness as measured 4 hours after the administration (n=357 healthy males, of which 49% had improved measurements) (cited by (43)). In radio operators, single dose administration decreased the number of errors in messages transmitted by tired operators (*Medvedev, 1963* cited by (43)). When a fixed, single dose, standardized combination of extracts of S. chinensis, E. senticosus and R. rosea [ADAPT-232; capsules containing 3 mg of salidroside, 4 mg of schizandrin and 3 mg eleutheroside B] was used on cosmonauts in prolonged isolation, the supplement significantly decreased the number of mistakes in complicated psychometric tests but had no significant effect in non-complicated tests (43,45). Similar results were obtained on computer operators on night duty under conditions that simulated long monotonous activity inducing fatigue (cited in (43)).

Several studies cited in (43) demonstrated improved physical working capacity due mainly to increased cardiovascular functions.

An expert opinion published in 2014 (46) stated that “The contraindication “arterial hypertension” is not evidence-based and should be carefully re-evaluated for not unnecessarily excluding a large patient group from the benefits of eleuthero.”, which referred to an older statement indicating that the administration of the extract is not indicated in hypertensive individuals.

6) Vitamin B12 (methylcobalamin form)

Possible functional claims for this ingredient include but are not limited to:
- Reduces average melatonin levels in a 24-hour period;
- Positive psychotropic alerting effect;
- Contributes to reducing sleep disturbances, towards sleep reduction.

This scientific substantiation refers only to the roles of methylcobalamin upon melatonin levels, and in the regulation of circadian rhythm.

When Vitamin B12 (methylcobalamin) was administered orally (3 mg/day) to 9 healthy subjects for 4 weeks, the 24-h melatonin rhythm was significantly phase-advanced (1.1 h) in the vitamin B12 trial as compared with that in the placebo trial. In addition, the 24-h mean of plasma melatonin level was much lower in the vitamin B12 trial than with the placebo. Furthermore, the nocturnal melatonin levels during bright light exposure were significantly lower in the vitamin B12 trial than with the placebo (47). As opposed to cyanocobalamin, only methylcobalamin was reported to have a positive psychotropic alerting effect with a distribution of the sleep-wake cycle toward sleep reduction (48).

The dosage required for enhancing the light-induced phase-shift in the human circadian rhythm varies from 0.5 mg to 3 mg (47,49).

When used in conjunction with other chronotherapy agents (such as bright light exposure), methylcobalamin proved useful in reducing circadian rhythm sleep disorders in affected adolescents (50).

Several case studies also reported that methylcobalamin treatment, used either alone or in conjunction with either melatonin receptor agonists, can be useful in reducing sleep disturbances in individuals with circadian rhythm abnormalities (51,52).

7) Niacin (Vitamin B3)

Possible functional claims for this ingredient include but are not limited to:
- Enhances cellular energy production;
- May contribute to attenuation of sleep disturbances.

A vast array of processes and enzymes involved in every aspect of peripheral and brain cell function are dependent on niacin derived nucleotides such as nicotinamide adenine dinucleotide (NAD) and NAD phosphate (NADP). Beyond energy production, these include oxidative reactions, antioxidant protection, DNA metabolism and repair, cellular signaling events (via intracellular calcium), and the conversion of folate to its tetrahydrofolate derivative (53).

Niacin also binds agonistically at two G protein receptors, the high affinity Niacin receptor 1 (NIACR1), responsible for the skin flush associated with high intake of niacin, and the low affinity NIACR2. Niacin receptors are distributed both peripherally in immune cells and adipose tissue, and throughout the brain. Currently established roles include modulation of inflammatory cascades (54,55) and anti-atherogenic lipolysis in adipose tissue (56,57).

NIACR1 receptor populations have been shown to be down-regulated in the anterior cingulate cortex of schizophrenia sufferers (54) and upregulated in the substantia nigra of Parkinson's disease sufferers, (a group that have low niacin levels generally) with levels correlating with poorer sleep architecture in this group (58). A recent case study demonstrated that 250 mg niacin administration modulated peripheral immune cell NIACR1 expression and attenuated the disturbed sleep architecture associated with Parkinson's disease (59).

8) Pyridoxine (Vitamin B6)

Possible functional claims for this ingredient include but are not limited to:

- Contributes to intracellular glucose regulation in brain cells;
- Required for the synthesis of neurotransmitters in brain;
- Contributes to the regulation of sleep cycle.

Beyond its role as a necessary cofactor in the folate cycle, the role of vitamin B6 in amino acid metabolism makes it a rate limiting cofactor in the synthesis of neurotransmitters such as dopamine, serotonin, γ-aminobutyric acid (GABA), noradrenaline and the hormone melatonin. The synthesis of these neurotransmitters is differentially sensitive to vitamin B6 levels, with even mild deficiency resulting in preferential down-regulation of GABA and serotonin synthesis, leading to the removal of inhibition of neural activity by GABA and disordered sleep, behavior, and cardiovascular function and a loss of hypothalamus-pituitary control of hormone excretion (60).

Vitamin B6 also has a direct effect on immune function and gene transcription/expression and plays a role in brain glucose regulation (61). More broadly, levels of pyridoxal-5-phosphate are associated with increased functional indices and biomarkers of inflammation, and levels of pyridoxal-5-phosphate are down-regulated as a function of more severe inflammation (62,63), potentially as a consequence of pyridoxal-5'-phosphate's role either in the metabolism of tryptophan or in one-carbon metabolism (62). This role is particularly pertinent as inflammatory processes contribute to the etiology of numerous pathological states including dementia and cognitive decline (64).

B) Ingredients for the "Night" formulation

1) Reishi Mushroom (fruit extract)

Possible functional claims for this ingredient include but are not limited to:
- Contributes to increasing sleep time and reduced sleep latency;
- Mild hypnotic effect;
- Confers neuro-protection.

The role of the Reishi mushroom extract on inducing sleep was first revealed in animal studies, with significantly decreased sleep latency, increased sleeping time, non-REM sleep time and light sleep time in pentobarbital-treated rats. Suppression of locomotor activity in normal mice was also observed (65). Oral administration of Ganoderma extracts containing polysaccharides (100, 200 and 400 mg/kg) significantly reduced cerebral infarct area, attenuated neurological functional deficits, and reduced neuronal apoptosis in induced cortical ischemia, due to suppressed expression of active caspases-3, -8 and -9 and Bax, and inhibited the reduction of Bcl-2 expression (66). In freely moving rats, the extract has hypnotic effects, primarily related to the modulation of cytokines such as TNF-α (67).

G. lucidum is believed to have a neuro-protective effect and this notion is supported by work carried out by *Zhang et al* and *Zhao et al*, wherein a mixture of triterpenoid compounds in G. lucidum, including methyl GA-A, methyl GA-B, GA-S1, and GA-TQ, promoted neuronal survival and reduced fatigue (68,69).

In addition, the potential use of this fungus for the treatment of neurological diseases has also been examined. It was shown that long-term consumption of G. lucidum can decrease the progression of Alzheimer's disease (70,71). This observed neuroprotective effect is achieved by promotion of neuritogenesis and reduction of senescence of the neurons (72).

2) Valerian

Possible functional claims for this ingredient include but are not limited to:
- Increased sleep quality;
- Reduced anxiety;
- Induces somnolence.

Sleep

Although preliminary evidence had suggested moderate sedative activity for V officinalis , the most recent systematic review (18 RCTs including 2 large studies) found little objective evidence for the benefits of valerian in sleep problems, whereas it showed improved subjective sleep quality compared with placebo. Therefore, it was suggested that other more promising treatment strategies should be used before trying valerian for sleep (73).

Anxiety

A 4-week placebo-controlled RCT compared the effects of placebo (n = 12), V officinalis extract (mean dose 81.3 mg/d; n = 12), and diazepam (6.5 mg/d; n = 12) in patients with GAD. Compared with placebo, patients who received valerian or diazepam had significant improvement in HAM-A psychic factor (but not total anxiety scores), suggesting modest benefit in anxiety (74).

Obsessive-Compulsive Disorder

An 8-week double-blind RCT showed that V officinalis (765 mg/d) in patients with obsessive-compulsive disorder (OCD) significantly improved symptoms compared with placebo. The only frequent side effect in the valerian group was somnolence (75).

Adverse Effects and Toxicity

A systematic review of 37 studies (including 23 controlled trials) of valerian for insomnia found the herb to be safe (76). Valerian can potentiate sedative drugs, which can result in an increased risk of falls in the elderly. Valerian inhibited cytochrome P450 enzymes 3A4, 2D6, and 2C19 *in vitro*, and there are some reports that suggest hepatotoxicity in humans (77). Therefore, it is advisable to avoid valerian administration to patients with liver disease.

3) Passionflower (leaf extract)

Possible functional claims for this ingredient include but are not limited to:
- Anxiolytic;
- Improves sleep quality.

Several pre-clinical studies are available, indicating the anxiolytic and sedative effects of its extracts (reviewed in (78)).

Clinical studies in humans indicated that its sedative effects (single dose) can be objectivized by quantitative EEG measurements (n=12) (79). Improvements in subjective sleep quality assessment were reported in a double-blind, placebo-controlled intervention (n=41), using 2 g of dried plant administered as tea, over a period of 1 week (80).

In a placebo-controlled study (n=30/group), the pre-operative administration of a Passionflower extract (500 mg) reduced the anxiety score in patients without sedation (81). Suppression of anxiety was also reported in an independent study (n=30/group) in patients before spinal anesthesia (82).

Note. The clinical trials included in this review exhibit several weaknesses such as insufficient details regarding the drug extract ratio, limited patient samples, no description of blinding and randomization procedures, unclear placebo definition, and a lack of intention to treat analysis. Thus, some of the potential therapeutic effects of Passiflora incarnata need to be evaluated in new studies.

4) Hops (strobilus extract)

Possible functional claims for this ingredient include but are not limited to:
- Contributes to sleep inducement;
- Contributes to reducing sleep latency.

Receptor binding studies with a hops extract (Ze 119 as part of the fixed extract combination Ze 91019) revealed affinities to melatonin receptors (ML1 and ML2) as well as to serotonin receptor subtypes (5-HT4e, 5-HT6 and 5-HT7) (83). Xanthohumol, one of the hop constituents, was reported to bind to GABAA receptors at hippocampal neurons (84). A β-acid enriched fraction of hops reduced the GABA-induced IGABA in cerebellar granular cells in culture. This effect was dose dependent, reversed after wash-out, and could not be blocked by the benzodiazepine antagonist Ro 15–1788 (85).

Clinical evidence indicates that hops extracts can influence sleep only in combination with valerian extracts. Of special interest is the use of a standardized extract (containing both hops and valerian), Ze 91019, as sleep-inducing aid. In 30 patients suffering from non-organic insomnia, the combination (containing 120 mg hops extract/dose) revealed declines in the sleep latency and the wake time. As a consequence the sleep efficiency increased. Sleep stage 1 (S1) was reduced and the slow wave sleep increased. In addition, the patients judged their being refreshed in the morning by assigning a rating of 1 to 6. They reported an improvement after 2 weeks of treatment. No adverse events were observed (86). In a different study, the administration of Ze 91019 reduced the sleep latency whilst the single valerian extract failed to be superior to the placebo, suggesting that both components are synergistic, and have to be administered in combination (87).

5) 5-HTP

Possible functional claims for this ingredient include but are not limited to:
- Increases sleep quality.

5-Hydroxytryptophan (5-HTP) is an aromatic amino acid naturally produced by the body from the essential amino acid L-tryptophan (LT). 5-HTP has been used clinically for over 30 years. The clinical efficacy of 5-HTP is due to its ability to increase production of serotonin in the brain (reviewed in (88)).

5-HTP has been shown to be beneficial in treating insomnia, especially in improving sleep quality by increasing REM sleep (89-91). In these initial studies eight normal subjects were monitored to determine the effect of 5-HTP on rapid eye movement (REM) sleep. A total of 600 mg 5-HTP was administered to the subjects in the following manner: 200 mg at 9:15 pm, followed by 400 mg at 11:15 pm. A significant increase in the amount of REM sleep was observed while the subjects were taking 5-HTP (118 ± 14 mins vs. 98 ± 11 mins, $p<0.005$). A smaller study using a 200 mg dose also showed increases in REM sleep, but to a lesser degree (91).

In 2004, *Bruni et al* indicated, for the first time, that 5-HTP administered in children is able to modulate the arousal level in children and to induce a long-term improvement of sleep quality (92).

6) Melatonin

Possible functional claims for this ingredient include but are not limited to:
- Resets the circadian clock to night time
- Soporific effect.

Melatonin (N-Acetyl-5-methoxytryptamine) is a hormone secreted by the pineal gland. In both nocturnal and diurnal (day-active) animals it is secreted during the nighttime and as such can be thought of as a marker for the biological night. As first shown by *Redman et al*, exogenous melatonin administration is capable of resetting the circadian pacemaker to both an earlier and later time (phase advance and phase delay, respectively) (93). Subsequent studies have shown this to be true in humans as well (94,95). There are 2 melatonin receptor subtypes, MT1 and MT2, and there is evidence demonstrating that both help to mediate the circadian resetting effects of melatonin (96,97).

A variety of exogenous melatonin doses have been examined for circadian resetting (94,95,98,99). There is evidence of a dose-response relationship at lower doses of 0.02 and 0.30 mg (99). By contrast, when 0.5 mg and 3.0 mg were compared across a range of administration times, maximum phase advances and phase delays were similar (95).

Higher doses of exogenous melatonin (≥10 mg) may result in a smaller resetting effect (98,100). This finding is likely because increasing the dose of exogenous melatonin simultaneously increases the concentration of melatonin in the circulation and the duration of administration or exposure. Initially, increases in dose simply cause increased resetting effects (99), but as higher doses are used, exogenous melatonin levels remain elevated in the circulation for longer periods of time. As a result, additional parts of the melatonin PRC may be stimulated, resulting in less net circadian resetting (i.e. a less discrete time signal is provided). Such “spill over” (100) of melatonin onto the “wrong” portion of the melatonin PRC is possible, despite a half-life of just about an hour, because even 0.5-mg to 1.0-mg doses of melatonin can produce supra-physiological levels over several hours or more (94,101).

Melatonin also has well-demonstrated soporific effects (101-103). At doses between 0.3-mg and 5.0-mg, this effect was confined to circadian times when endogenous melatonin levels were low (i.e. the biological day) (104).

7) L-Theanine

Possible functional claims for this ingredient include but are not limited to:
- Increase sleep efficiency and quality.

L-theanine (γ glutamylethylamide), a non-protein amino acid, was used to investigate a treatment of ADHD-related sleep disorders in one double-blind, placebo-controlled, parallel-group study (105). The study consisted of 93 ADHD-diagnosed males, between 8 and 12 years of age, 46 of whom received oral L-theanine at a dose of 400 mg daily (200 mg in the morning, and 200 mg in the afternoon), and 47 of whom were given placebo. It was observed through actigraphy that L-theanine produced no significant difference in sleep latency or total sleep time from baseline levels; however, a significant increase in sleep efficiency was seen, as well as a reduction in nocturnal activity.

Sleep efficiency in men, and sleep quality in women, were improved by the administration of L-theanine (200 mg taken 1 hour before going to bed) (106). L-Theanine was found to improve relaxation, modulate neurotransmitters, and inhibit excitatory neurons by improving the quality of sleep in men, women, and children. Actigraphic and OSA inventory sleep assessments have shown an improved quality of sleep with the administration of 200 mg of l-theanine by reducing intermittent awakening (WASO) and thereby improving the sleep percentage and sleep efficiency. The improvement in the quality of sleep was further reflected in the recovery from exhaustion and refreshed awakening. On the other hand, the modulation of the automatic nervous system, namely, the sympathetic and parasympathetic nervous system, during sleep determines the quality of sleep. The administration of Ll-theanine simulated increased parasympathetic nerve system responses and decreased sympathetic nerve system responses (reviewed in (106)).

8) Magnesium

Possible functional claims for this ingredient include but are not limited to:

- May reduce the risk of nocturnal leg cramps occurrence.

Magnesium plays an important role in hundreds of metabolic reactions and in muscle function (107). Elderly people are particularly at risk for magnesium deficiency, because of the combination of chronic diseases, poor nutrition, decreased absorption of magnesium and increased renal exertion (107). As magnesium deficiency leads to neuronal excitability and enhances neuromuscular transmission (108), and since its substitution has been shown to be effective in eclampsia-related seizures (107), some authors have suggested a beneficial role of magnesium in the prevention of nocturnal leg cramps (NLC).

Only two studies, both involving pregnant women, showed a statistically significant effect of magnesium therapy with a larger reduction in the number and severity of NLC in the intervention group compared to the placebo group (109,110).

Two studies reported patient self-evaluation of the effectiveness of treatment as an outcome. In both studies, the proportion of patients reporting that the treatment was effective was significantly higher in the group receiving magnesium (109,111).

REFERENCES

1. Kennedy, D. O., Jackson, P. A., Forster, J., Khan, J., Grothe, T., Perrinjaquet-Moccetti, T., and Haskell-Ramsay, C. F. (2015) Acute effects of a wild green-oat (Avena sativa) extract on cognitive function in middle-aged adults: A double-blind, placebo-controlled, within-subjects trial. *Nutr Neurosci*
2. Berry, N. M., Robinson, M. J., Bryan, J., Buckley, J. D., Murphy, K. J., and Howe, P. R. (2011) Acute effects of an Avena sativa herb extract on responses to the Stroop Color-Word test. *Journal of alternative and complementary medicine* **17**, 635-637
3. Dimpfel, W., Storni, C., and Verbruggen, M. (2011) Ingested oat herb extract (Avena sativa) changes EEG spectral frequencies in healthy subjects. *Journal of alternative and complementary medicine* **17**, 427-434
4. Wong, R. H., Howe, P. R., Coates, A. M., Buckley, J. D., and Berry, N. M. (2013) Chronic consumption of a wild green oat extract (Neuravena) improves brachial flow-mediated dilatation and cerebrovascular responsiveness in older adults. *Journal of hypertension* **31**, 192-200
5. (2002) Vinpocetine. Monograph. *Alternative medicine review : a journal of clinical therapeutic* **7**, 240-243
6. Jeon, K. I., Xu, X., Aizawa, T., Lim, J. H., Jono, H., Kwon, D. S., Abe, J., Berk, B. C., Li, J. D., and Yan, C. (2010) Vinpocetine inhibits NF-kappaB-dependent inflammation via an IKK-dependent but PDE-independent mechanism. *Proc Natl Acad Sci U S A* **107**, 9795-9800
7. Beavo, J. A. (1995) Cyclic nucleotide phosphodiesterases: functional implications of multiple isoforms. *Physiological reviews* **75**, 725-748
8. Zhao, Y. Y., Yu, J. Z., Li, Q. Y., Ma, C. G., Lu, C. Z., and Xiao, B. G. (2011) TSPO-specific ligand vinpocetine exerts a neuroprotective effect by suppressing microglial inflammation. *Neuron glia biology* **7**, 187-197
9. Torres, K. J., Gottle, P., Kremer, D., Rivera, J. F., Aguirre-Cruz, L., Corona, T., Hartung, H. P., and Kury, P. (2012) Vinpocetine inhibits oligodendroglial precursor cell differentiation. *Cellular physiology and biochemistry : international journal of experimental cellular physiology, biochemistry, and pharmacology* **30**, 711-722
10. Hadjiev, D. (2003) Asymptomatic ischemic cerebrovascular disorders and neuroprotection with vinpocetine. *Ideggyogyaszati szemle* **56**, 166-172
11. Feigin, V. L., Doronin, B. M., Popova, T. F., Gribatcheva, E. V., and Tchervov, D. V. (2001) Vinpocetine treatment in acute ischaemic stroke: a pilot single-blind randomized clinical trial. *Eur J Neurol* **8**, 81-85
12. Vaizova, O. E., Vengerovskii, A. I., and Alifirova, V. M. (2006) [An effect of vinpocetine (cavinton) on endothelium function in patients with chronic cerebral ischemia]. *Zhurnal nevrologii i psikhiatrii imeni S.S. Korsakova / Ministerstvo zdravookhraneniia i meditsinskoi promyshlennosti Rossiiskoi Federatsii, Vserossiiskoe obshchestvo nevrologov [i] Vserossiiskoe obshchestvo psikhiat* **Suppl 16**, 46-50
13. Bonoczk, P., Gulyas, B., Adam-Vizi, V., Nemes, A., Karpati, E., Kiss, B., Kapas, M., Szantay, C., Koncz, I., Zelles, T., and Vas, A. (2000) Role of sodium channel inhibition in neuroprotection: effect of vinpocetine. *Brain research bulletin* **53**, 245-254
14. Schimpl, F. C., da Silva, J. F., Gonçalves, J. F. d. C., and Mazzafera, P. (2013) Guarana: Revisiting a highly caffeinated plant from the Amazon. *Journal of Ethnopharmacology* **150**, 14-31
15. Sigma-Aldrich. (2010) Plant Profiler: Guarana (Paullinia cupana).

16. de Oliveira Campos, M. P., Riechelmann, R., Martins, L. C., Hassan, B. J., Casa, F. B., and Del Giglio, A. (2011) Guarana (Paullinia cupana) improves fatigue in breast cancer patients undergoing systemic chemotherapy. *Journal of alternative and complementary medicine* **17**, 505-512
17. Bempong, D. K., and Houghton, P. J. (1992) Dissolution and absorption of caffeine from guarana. *The Journal of pharmacy and pharmacology* **44**, 769-771
18. Espinola, E. B., Dias, R. F., Mattei, R., and Carlini, E. A. (1997) Pharmacological activity of Guarana (Paullinia cupana Mart.) in laboratory animals. *Journal of ethnopharmacology* **55**, 223-229
19. Basile, A., Ferrara, L., Pezzo, M. D., Mele, G., Sorbo, S., Bassi, P., and Montesano, D. (2005) Antibacterial and antioxidant activities of ethanol extract from Paullinia cupana Mart. *Journal of ethnopharmacology* **102**, 32-36
20. Heard, C. M., Johnson, S., Moss, G., and Thomas, C. P. (2006) In vitro transdermal delivery of caffeine, theobromine, theophylline and catechin from extract of Guarana, Paullinia Cupana. *International journal of pharmaceutics* **317**, 26-31
21. Henman, A. R. (1982) Guarana (Paullinia cupana var. sorbilis): ecological and social perspectives on an economic plant of the central Amazon basin. *Journal of ethnopharmacology* **6**, 311-338
22. Dalonso, N., and Petkowicz, C. L. (2012) Guarana powder polysaccharides: characterisation and evaluation of the antioxidant activity of a pectic fraction. *Food chemistry* **134**, 1804-1812
23. Yamaguti-Sasaki, E., Ito, L. A., Canteli, V. C., Ushirobira, T. M., Ueda-Nakamura, T., Dias Filho, B. P., Nakamura, C. V., and de Mello, J. C. (2007) Antioxidant capacity and in vitro prevention of dental plaque formation by extracts and condensed tannins of Paullinia cupana. *Molecules* **12**, 1950-1963
24. Boozer, C. N., Nasser, J. A., Heymsfield, S. B., Wang, V., Chen, G., and Solomon, J. L. (2001) An herbal supplement containing Ma Huang-Guarana for weight loss: a randomized, double-blind trial. *International journal of obesity and related metabolic disorders : journal of the International Association for the Study of Obesity* **25**, 316-324
25. Lima, W. P., Carnevali, L. C., Jr., Eder, R., Costa Rosa, L. F., Bacchi, E. M., and Seelaender, M. C. (2005) Lipid metabolism in trained rats: effect of guarana (Paullinia cupana Mart.) supplementation. *Clinical nutrition* **24**, 1019-1028
26. Opala, T., Rzymski, P., Pischel, I., Wilczak, M., and Wozniak, J. (2006) Efficacy of 12 weeks supplementation of a botanical extract-based weight loss formula on body weight, body composition and blood chemistry in healthy, overweight subjects--a randomised double-blind placebo-controlled clinical trial. *European journal of medical research* **11**, 343-350
27. Krewer Cda, C., Ribeiro, E. E., Ribeiro, E. A., Moresco, R. N., da Rocha, M. I., Montagner, G. F., Machado, M. M., Viegas, K., Brito, E., and da Cruz, I. B. (2011) Habitual intake of guarana and metabolic morbidities: an epidemiological study of an elderly Amazonian population. *Phytotherapy research : PTR* **25**, 1367-1374
28. Jacobs, B. P., and Browner, W. S. (2000) Ginkgo biloba: a living fossil. *The American journal of medicine* **108**, 341-342
29. Gauthier, S., and Schlaefke, S. (2014) Efficacy and tolerability of Ginkgo biloba extract EGb 761(R) in dementia: a systematic review and meta-analysis of randomized placebo-controlled trials. *Clinical interventions in aging* **9**, 2065-2077
30. Ihl, R., Tribanek, M., Bachinskaya, N., and Group, G. S. (2012) Efficacy and tolerability of a once daily formulation of Ginkgo biloba extract EGb 761(R) in Alzheimer's disease and vascular dementia: results from a randomised controlled trial. *Pharmacopsychiatry* **45**, 41-46

31. Kaschel, R. (2011) Specific memory effects of Ginkgo biloba extract EGb 761 in middle-aged healthy volunteers. *Phytomedicine : international journal of phytotherapy and phytopharmacology* **18**, 1202-1207
32. Cieza, A., Maier, P., and Poppel, E. (2003) Effects of Ginkgo biloba on mental functioning in healthy volunteers. *Archives of medical research* **34**, 373-381
33. Mix, J. A., and Crews, W. D., Jr. (2002) A double-blind, placebo-controlled, randomized trial of Ginkgo biloba extract EGb 761 in a sample of cognitively intact older adults: neuropsychological findings. *Human psychopharmacology* **17**, 267-277
34. Stough, C., Clarke, J., Lloyd, J., and Nathan, P. J. (2001) Neuropsychological changes after 30-day Ginkgo biloba administration in healthy participants. *The international journal of neuropsychopharmacology / official scientific journal of the Collegium Internationale Neuropsychopharmacologicum* **4**, 131-134
35. Mix, J. A., and Crews, W. D., Jr. (2000) An examination of the efficacy of Ginkgo biloba extract EGb761 on the neuropsychologic functioning of cognitively intact older adults. *Journal of alternative and complementary medicine* **6**, 219-229
36. Williams, B., Watanabe, C. M., Schultz, P. G., Rimbach, G., and Krucker, T. (2004) Age-related effects of Ginkgo biloba extract on synaptic plasticity and excitability. *Neurobiol Aging* **25**, 955-962
37. Wu, Y., Wu, Z., Butko, P., Christen, Y., Lambert, M. P., Klein, W. L., Link, C. D., and Luo, Y. (2006) Amyloid-beta-induced pathological behaviors are suppressed by Ginkgo biloba extract EGb 761 and ginkgolides in transgenic Caenorhabditis elegans. *J Neurosci* **26**, 13102-13113
38. Kampkotter, A., Pielarski, T., Rohrig, R., Timpel, C., Chovolou, Y., Watjen, W., and Kahl, R. (2007) The Ginkgo biloba extract EGb761 reduces stress sensitivity, ROS accumulation and expression of catalase and glutathione S-transferase 4 in Caenorhabditis elegans. *Pharmacological research* **55**, 139-147
39. Gavrilova, S. I., Preuss, U. W., Wong, J. W., Hoerr, R., Kaschel, R., Bachinskaya, N., and Group, G. I. S. (2014) Efficacy and safety of Ginkgo biloba extract EGb 761 in mild cognitive impairment with neuropsychiatric symptoms: a randomized, placebo-controlled, double-blind, multi-center trial. *International journal of geriatric psychiatry* **29**, 1087-1095
40. Tan, M. S., Yu, J. T., Tan, C. C., Wang, H. F., Meng, X. F., Wang, C., Jiang, T., Zhu, X. C., and Tan, L. (2015) Efficacy and adverse effects of ginkgo biloba for cognitive impairment and dementia: a systematic review and meta-analysis. *J Alzheimers Dis* **43**, 589-603
41. Yancheva, S., Ihl, R., Nikolova, G., Panayotov, P., Schlaefke, S., Hoerr, R., and Group, G. S. (2009) Ginkgo biloba extract EGb 761(R), donepezil or both combined in the treatment of Alzheimer's disease with neuropsychiatric features: a randomised, double-blind, exploratory trial. *Aging & mental health* **13**, 183-190
42. Vellas, B., Coley, N., Ousset, P. J., Berrut, G., Dartigues, J. F., Dubois, B., Grandjean, H., Pasquier, F., Piette, F., Robert, P., Touchon, J., Garnier, P., Mathiex-Fortunet, H., Andrieu, S., and GuidAge Study, G. (2012) Long-term use of standardised Ginkgo biloba extract for the prevention of Alzheimer's disease (GuidAge): a randomised placebo-controlled trial. *The Lancet. Neurology* **11**, 851-859
43. Panossian, A., and Wagner, H. (2005) Stimulating effect of adaptogens: an overview with particular reference to their efficacy following single dose administration. *Phytotherapy research : PTR* **19**, 819-838
44. Panossian, A., Gabrielian, E., and Wagner, H. (1999) On the mechanism of action of plant adaptogens with particular reference to cucurbitacin R diglucoside. *Phytomedicine : international journal of phytotherapy and phytopharmacology* **6**, 147-155

45. Bogatova, R. I., Shlykova, L. V., Sal'nitskii, V. P., and Vikman, G. (1997) [Evaluation of the effect of a single dose of phytoadaptogen on human's working ability during long-term isolation]. *Aviakosmicheskaia i ekologicheskaia meditsina = Aerospace and environmental medicine* **31**, 51-54
46. Schmidt, M., Thomsen, M., Kelber, O., and Kraft, K. (2014) Myths and facts in herbal medicines: Eleutherococcus senticosus (Siberian ginseng) and its contraindication in hypertensive patients. *Botanics: Targets and Therapy* **4**, 27-32
47. Honma, K., Kohsaka, M., Fukuda, N., Morita, N., and Honma, S. (1992) Effects of vitamin B12 on plasma melatonin rhythm in humans: increased light sensitivity phase-advances the circadian clock? *Experientia* **48**, 716-720
48. Mayer, G., Kroger, M., and Meier-Ewert, K. (1996) Effects of vitamin B12 on performance and circadian rhythm in normal subjects. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology* **15**, 456-464
49. Hashimoto, S., Kohsaka, M., Morita, N., Fukuda, N., Honma, S., and Honma, K. (1996) Vitamin B12 enhances the phase-response of circadian melatonin rhythm to a single bright light exposure in humans. *Neurosci Lett* **220**, 129-132
50. Okawa, M., Uchiyama, M., Ozaki, S., Shibui, K., and Ichikawa, H. (1998) Circadian rhythm sleep disorders in adolescents: clinical trials of combined treatments based on chronobiology. *Psychiatry and clinical neurosciences* **52**, 483-490
51. Tomoda, A., Miike, T., and Matsukura, M. (1995) Circadian rhythm abnormalities in adrenoleukodystrophy and methyl B12 treatment. *Brain & development* **17**, 428-431
52. Yanagihara, M., Nakamura, M., Usui, A., Nishida, S., Ito, E., Okawa, M., and Inoue, Y. (2014) The melatonin receptor agonist is effective for free-running type circadian rhythm sleep disorder: case report on two sighted patients. *The Tohoku journal of experimental medicine* **234**, 123-128
53. Bailey, L. B. (2007) Folic acid. in *Handbook of Vitamins* (Zempleni, J., Rucker, R. B., McCormick, D. B., and Suttie, J. W. eds.), 4th ed Ed., CRC Press, Boca Raton, FL, USA. pp
54. Miller, C. L., and Dulay, J. R. (2008) The high-affinity niacin receptor HM74A is decreased in the anterior cingulate cortex of individuals with schizophrenia. *Brain research bulletin* **77**, 33-41
55. Digby, J. E., McNeill, E., Dyar, O. J., Lam, V., Greaves, D. R., and Choudhury, R. P. (2010) Anti-inflammatory effects of nicotinic acid in adipocytes demonstrated by suppression of fractalkine, RANTES, and MCP-1 and upregulation of adiponectin. *Atherosclerosis* **209**, 89-95
56. Zhang, Y., Schmidt, R. J., Foxworthy, P., Emkey, R., Oler, J. K., Large, T. H., Wang, H., Su, E. W., Mosior, M. K., Eacho, P. I., and Cao, G. (2005) Niacin mediates lipolysis in adipose tissue through its G-protein coupled receptor HM74A. *Biochemical and Biophysical Research Communications* **334**, 729-732
57. Linke, A., Sonnabend, M., Fasshauer, M., Hollriegel, R., Schuler, G., Niebauer, J., Stumvoll, M., and Bluher, M. (2009) Effects of extended-release niacin on lipid profile and adipocyte biology in patients with impaired glucose tolerance. *Atherosclerosis* **205**, 207-213
58. Wakade, C., Chong, R., Bradley, E., Thomas, B., and Morgan, J. (2014) Upregulation of GPR109A in Parkinson's disease. *PLoS One* **9**, e109818
59. Wakade, C., Chong, R., Bradley, E., and Morgan, J. C. (2015) Low-dose niacin supplementation modulates GPR109A, niacin index and ameliorates Parkinson's disease symptoms without side effects. *Clinical Case Reports* **3**, 635-637
60. Kennedy, D. O. (2016) B Vitamins and the Brain: Mechanisms, Dose and Efficacy—A Review. *Nutrients* **8**, 68

61. Anitha, M., Abraham, P. M., and Paulose, C. S. (2012) Striatal dopamine receptors modulate the expression of insulin receptor, IGF-1 and GLUT-3 in diabetic rats: effect of pyridoxine treatment. *European journal of pharmacology* **696**, 54-61
62. Sakakeeny, L., Roubenoff, R., Obin, M., Fontes, J. D., Benjamin, E. J., Bujanover, Y., Jacques, P. F., and Selhub, J. (2012) Plasma Pyridoxal-5-Phosphate Is Inversely Associated with Systemic Markers of Inflammation in a Population of U.S. Adults. *The Journal of Nutrition* **142**, 1280-1285
63. Morris, M. S., Sakakeeny, L., Jacques, P. F., Picciano, M. F., and Selhub, J. (2010) Vitamin B-6 Intake Is Inversely Related to, and the Requirement Is Affected by, Inflammation Status. *The Journal of Nutrition* **140**, 103-110
64. Tracy, R. P. (2003) Emerging relationships of inflammation, cardiovascular disease and chronic diseases of aging. *International journal of obesity and related metabolic disorders : journal of the International Association for the Study of Obesity* **27 Suppl 3**, S29-34
65. Chu, Q. P., Wang, L. E., Cui, X. Y., Fu, H. Z., Lin, Z. B., Lin, S. Q., and Zhang, Y. H. (2007) Extract of Ganoderma lucidum potentiates pentobarbital-induced sleep via a GABAergic mechanism. *Pharmacology, biochemistry, and behavior* **86**, 693-698
66. Zhou, Z. Y., Tang, Y. P., Xiang, J., Wua, P., Jin, H. M., Wang, Z., Mori, M., and Cai, D. F. (2010) Neuroprotective effects of water-soluble Ganoderma lucidum polysaccharides on cerebral ischemic injury in rats. *Journal of ethnopharmacology* **131**, 154-164
67. Cui, X. Y., Cui, S. Y., Zhang, J., Wang, Z. J., Yu, B., Sheng, Z. F., Zhang, X. Q., and Zhang, Y. H. (2012) Extract of Ganoderma lucidum prolongs sleep time in rats. *J Ethnopharmacol* **139**, 796-800
68. Zhang, X. Q., Ip, F. C., Zhang, D. M., Chen, L. X., Zhang, W., Li, Y. L., Ip, N. Y., and Ye, W. C. (2011) Triterpenoids with neurotrophic activity from Ganoderma lucidum. *Natural product research* **25**, 1607-1613
69. Zhao, H., Zhang, Q., Zhao, L., Huang, X., Wang, J., and Kang, X. (2012) Spore Powder of Ganoderma lucidum Improves Cancer-Related Fatigue in Breast Cancer Patients Undergoing Endocrine Therapy: A Pilot Clinical Trial. *Evidence-based complementary and alternative medicine : eCAM* **2012**, 809614
70. Lai, C. S., Yu, M. S., Yuen, W. H., So, K. F., Zee, S. Y., and Chang, R. C. (2008) Antagonizing beta-amyloid peptide neurotoxicity of the anti-aging fungus Ganoderma lucidum. *Brain Res* **1190**, 215-224
71. Zhou, Y., Qu, Z. Q., Zeng, Y. S., Lin, Y. K., Li, Y., Chung, P., Wong, R., and Hagg, U. (2012) Neuroprotective effect of preadministration with Ganoderma lucidum spore on rat hippocampus. *Experimental and toxicologic pathology : official journal of the Gesellschaft fur Toxikologische Pathologie* **64**, 673-680
72. Ling-Sing Seow, S., Naidu, M., David, P., Wong, K. H., and Sabaratnam, V. (2013) Potentiation of neuritogenic activity of medicinal mushrooms in rat pheochromocytoma cells. *BMC complementary and alternative medicine* **13**, 157
73. Fernandez-San-Martin, M. I., Masa-Font, R., Palacios-Soler, L., Sancho-Gomez, P., Calbo-Caldentey, C., and Flores-Mateo, G. (2010) Effectiveness of Valerian on insomnia: a meta-analysis of randomized placebo-controlled trials. *Sleep medicine* **11**, 505-511
74. Andreatini, R., Sartori, V. A., Seabra, M. L., and Leite, J. R. (2002) Effect of valepotriates (valerian extract) in generalized anxiety disorder: a randomized placebo-controlled pilot study. *Phytotherapy research : PTR* **16**, 650-654
75. Pakseresht, S., Boostani, H., and Sayyah, M. (2011) Extract of valerian root (Valeriana officinalis L.) vs. placebo in treatment of obsessive-compulsive disorder: a randomized double-blind study. *Journal of complementary & integrative medicine* **8**

76. Taibi, D. M., Landis, C. A., Petry, H., and Vitiello, M. V. (2007) A systematic review of valerian as a sleep aid: safe but not effective. *Sleep medicine reviews* **11**, 209-230
77. Vassiliadis, T., Anagnostis, P., Patsiaoura, K., Giouleme, O., Katsinelos, P., Mpoumponaris, A., and Eugenidis, N. (2009) Valeriana hepatotoxicity. *Sleep medicine* **10**, 935
78. Miroddi, M., Calapai, G., Navarra, M., Minciullo, P. L., and Gangemi, S. (2013) Passiflora incarnata L.: ethnopharmacology, clinical application, safety and evaluation of clinical trials. *J Ethnopharmacol* **150**, 791-804
79. Schulz, H., Jobert, M., and Hubner, W. D. (1998) The quantitative EEG as a screening instrument to identify sedative effects of single doses of plant extracts in comparison with diazepam. *Phytomedicine : international journal of phytotherapy and phytopharmacology* **5**, 449-458
80. Ngan, A., and Conduit, R. (2011) A double-blind, placebo-controlled investigation of the effects of Passiflora incarnata (passionflower) herbal tea on subjective sleep quality. *Phytotherapy research : PTR* **25**, 1153-1159
81. Movafegh, A., Alizadeh, R., Hajimohamadi, F., Esfehani, F., and Nejatfar, M. (2008) Preoperative oral Passiflora incarnata reduces anxiety in ambulatory surgery patients: a double-blind, placebo-controlled study. *Anesthesia and analgesia* **106**, 1728-1732
82. Aslanargun, P., Cuvas, O., Dikmen, B., Aslan, E., and Yuksel, M. U. (2012) Passiflora incarnata Linneaus as an anxiolytic before spinal anesthesia. *Journal of anesthesia* **26**, 39-44
83. Abourashed, E. A., Koetter, U., and Brattstrom, A. (2004) In vitro binding experiments with a Valerian, hops and their fixed combination extract (Ze91019) to selected central nervous system receptors. *Phytomedicine : international journal of phytotherapy and phytopharmacology* **11**, 633-638
84. Meissner, O., and Haberlein, H. (2006) Influence of xanthohumol on the binding behavior of GABAA receptors and their lateral mobility at hippocampal neurons. *Planta medica* **72**, 656-658
85. Zanoli, P., Zavatti, M., Rivasi, M., Brusiani, F., Losi, G., Puia, G., Avallone, R., and Baraldi, M. (2007) Evidence that the beta-acids fraction of hops reduces central GABAergic neurotransmission. *Journal of ethnopharmacology* **109**, 87-92
86. Fussel, A., Wolf, A., and Brattstrom, A. (2000) Effect of a fixed valerian-Hop extract combination (Ze 91019) on sleep polygraphy in patients with non-organic insomnia: a pilot study. *European journal of medical research* **5**, 385-390
87. Koetter, U., Schrader, E., Kaufeler, R., and Brattstrom, A. (2007) A randomized, double blind, placebo-controlled, prospective clinical study to demonstrate clinical efficacy of a fixed valerian hops extract combination (Ze 91019) in patients suffering from non-organic sleep disorder. *Phytotherapy research : PTR* **21**, 847-851
88. Birdsall, T. C. (1998) 5-Hydroxytryptophan: a clinically-effective serotonin precursor. *Alternative medicine review : a journal of clinical therapeutic* **3**, 271-280
89. Soulairac, A., and Lambinet, H. (1977) [Effect of 5-hydroxytryptophan, a serotonin precursor, on sleep disorders]. *Annales medico-psychologiques* **1**, 792-798
90. Guilleminault, C., Cathala, J. P., and Castaigne, P. (1973) Effects of 5-hydroxytryptophan on sleep of a patient with a brain-stem lesion. *Electroencephalography and clinical neurophysiology* **34**, 177-184
91. Wyatt, R. J., Zarcone, V., Engelman, K., Dement, W. C., Snyder, F., and Sjoerdsma, A. (1971) Effects of 5-hydroxytryptophan on the sleep of normal human subjects. *Electroencephalography and clinical neurophysiology* **30**, 505-509
92. Bruni, O., Ferri, R., Miano, S., and Verrillo, E. (2004) L -5-Hydroxytryptophan treatment of sleep terrors in children. *European journal of pediatrics* **163**, 402-407

93. Redman, J., Armstrong, S., and Ng, K. T. (1983) Free-running activity rhythms in the rat: entrainment by melatonin. *Science* **219**, 1089-1091
94. Lewy, A. J., Bauer, V. K., Ahmed, S., Thomas, K. H., Cutler, N. L., Singer, C. M., Moffit, M. T., and Sack, R. L. (1998) The human phase response curve (PRC) to melatonin is about 12 hours out of phase with the PRC to light. *Chronobiology international* **15**, 71-83
95. Burgess, H. J., Revell, V. L., Molina, T. A., and Eastman, C. I. (2010) Human phase response curves to three days of daily melatonin: 0.5 mg versus 3.0 mg. *J Clin Endocrinol Metab* **95**, 3325-3331
96. Reppert, S. M., Weaver, D. R., and Godson, C. (1996) Melatonin receptors step into the light: cloning and classification of subtypes. *Trends in pharmacological sciences* **17**, 100-102
97. Dubocovich, M. L. (2007) Melatonin receptors: role on sleep and circadian rhythm regulation. *Sleep medicine* **8 Suppl 3**, 34-42
98. Sack, R. L., Brandes, R. W., Kendall, A. R., and Lewy, A. J. (2000) Entrainment of free-running circadian rhythms by melatonin in blind people. *N Engl J Med* **343**, 1070-1077
99. Lewy, A. J., Emens, J. S., Lefler, B. J., Yuhas, K., and Jackman, A. R. (2005) Melatonin entrains free-running blind people according to a physiological dose-response curve. *Chronobiology international* **22**, 1093-1106
100. Lewy, A. J., Emens, J. S., Sack, R. L., Hasler, B. P., and Bernert, R. A. (2002) Low, but not high, doses of melatonin entrained a free-running blind person with a long circadian period. *Chronobiology international* **19**, 649-658
101. Dollins, A. B., Zhdanova, I. V., Wurtman, R. J., Lynch, H. J., and Deng, M. H. (1994) Effect of inducing nocturnal serum melatonin concentrations in daytime on sleep, mood, body temperature, and performance. *Proc Natl Acad Sci U S A* **91**, 1824-1828
102. James, S. P., Mendelson, W. B., Sack, D. A., Rosenthal, N. E., and Wehr, T. A. (1987) The effect of melatonin on normal sleep. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology* **1**, 41-44
103. Rajaratnam, S. M., Middleton, B., Stone, B. M., Arendt, J., and Dijk, D. J. (2004) Melatonin advances the circadian timing of EEG sleep and directly facilitates sleep without altering its duration in extended sleep opportunities in humans. *The Journal of physiology* **561**, 339-351
104. Wyatt, J. K., Dijk, D. J., Ritz-de Cecco, A., Ronda, J. M., and Czeisler, C. A. (2006) Sleep-facilitating effect of exogenous melatonin in healthy young men and women is circadian-phase dependent. *Sleep* **29**, 609-618
105. Lyon, M. R., Kapoor, M. P., and Juneja, L. R. (2011) The effects of L-theanine (Suntheanine(R)) on objective sleep quality in boys with attention deficit hyperactivity disorder (ADHD): a randomized, double-blind, placebo-controlled clinical trial. *Alternative medicine review : a journal of clinical therapeutic* **16**, 348-354
106. Rao, T. P., Ozeki, M., and Juneja, L. R. (2015) In Search of a Safe Natural Sleep Aid. *Journal of the American College of Nutrition* **34**, 436-447
107. Guerrera, M. P., Volpe, S. L., and Mao, J. J. (2009) Therapeutic uses of magnesium. *American family physician* **80**, 157-162
108. Monderer, R. S., Wu, W. P., and Thorpy, M. J. (2010) Nocturnal leg cramps. *Current neurology and neuroscience reports* **10**, 53-59
109. Dahle, L. O., Berg, G., Hammar, M., Hurtig, M., and Larsson, L. (1995) The effect of oral magnesium substitution on pregnancy-induced leg cramps. *American journal of obstetrics and gynecology* **173**, 175-180
110. Supakatisant, C., and Phupong, V. (2015) Oral magnesium for relief in pregnancy-induced leg cramps: a randomised controlled trial. *Matern Child Nutr* **11**, 139-145

111. Roffe, C., Sills, S., Crome, P., and Jones, P. (2002) Randomised, cross-over, placebo controlled trial of magnesium citrate in the treatment of chronic persistent leg cramps. *Medical science monitor : international medical journal of experimental and clinical research* **8**, CR326-330