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## L-Theanine

### Evidence Summary

L-theanine appears to be safe and have positive short-term effects on cognitive function, blood pressure, and sleep, but no studies have tested whether it can prevent dementia or age-related diseases.

**Neuroprotective Benefit:** While some positive short-term effects on memory, attention, and relaxation have been observed in healthy adults, long-term effects on brain health are unknown.

**Aging and related health concerns:** L-theanine lowers blood pressure in humans, extends lifespan in worms and mice under stressful conditions, and suppresses tumor growth in mice, but no studies have tested whether it prevents age-related diseases.

**Safety:** No clinical data exist for long-term supplementation of L-theanine at doses higher than what is found in tea.



**What is it?** Green tea (including sencha, matcha, and gyokuro), black tea, and oolong tea are all derived from the same plant, *Camellia sinensis*, a perennial evergreen shrub. L-theanine is an amino acid analogue structurally similar to glutamate and is contained in green, black, and oolong tea, comprising about 1-3% of the dry weight of tea leaves [1]. A single cup of liquid tea contains 5-85 mg of L-theanine, depending on the type, quality, and preparation of the tea. L-theanine readily crosses the blood-brain-barrier [2] and is traditionally used as a relaxation-promoting agent [3]. Animal studies have shown that L-theanine inhibits glutamate receptors while increasing dopamine release, gamma-aminobutyric acid (GABA) concentrations, and serotonin levels in the brain [2; 4; 5; 6].

**Neuroprotective Benefit:** While some positive short-term effects on memory, attention, and relaxation have been observed in healthy adults, long-term effects on brain health are unknown.

Types of evidence:

- 1 meta-analysis based on 10 randomized controlled trials (RCTs) testing acute effects of L-theanine in healthy adults
- 1 double-blind RCT in MCI subjects examining the effects of green tea extract with L-theanine
- 3 RCTs not included in the meta-analysis that also tested acute effects of L-theanine
- 2 RCTs examining L-theanine effects on brain alpha-band activity
- 1 open-label study in people with major depressive disorder
- 1 review
- 6 laboratory studies

**Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function?** Most studies with L-theanine have examined its acute nootropic effects. It is often used in combination with other supplements such as caffeine and green tea extract. It appears to have synergistic effects with caffeine.

Human research to suggest protection from cognitive decline or dementia: None available.

Human research to suggest benefits to patients with dementia: None available.

Human research for short-term cognitive function: IMPROVEMENT BUT MIXED AND MODEST.

In a double-blind RCT in 91 patients with MCI, the combination of green tea extract and L-theanine (1680 mg of the supplement LGNC-07, which contained 240 mg of L-theanine) for 16 weeks did not



significantly affect memory or attention at the end of the trial but marginal improvement in memory was observed at the 8-week time point [7]. However, in a subgroup who had relatively severe baseline impairment (MMSE scores of 21-23), significant improvements in memory and attention were observed. Brain theta waves were increased in the temporal, frontal, parietal, and occipital cortex after 3 hours, suggestive of cognitive alertness.

A combination of L-theanine and caffeine was reported to improve alertness and attentional switching accuracy in a meta-analysis of 10 acute RCTs in healthy adults [8]. However, the majority of the attention-enhancing effects were attributed to caffeine. L-theanine may interact with caffeine, improving attention and ability to ignore distractions, and together, enhance performance on cognitively demanding tasks [9]. In an RCT of 16 healthy adults, L-theanine alone did not affect attentional focus, but L-theanine (100 mg) combined with caffeine (50 mg) showed improvement in target detection and discrimination [10].

It is possible that L-theanine may have effects independently of caffeine. In an RCT crossover study of 20 healthy adult males, recognition visual reaction time significantly improved with L-theanine (200 mg), caffeine (160 mg), or a theanine-caffeine combination, but not with a single cup of tea or placebo [11].

While these studies suggest modest benefit, some others report mixed effects. In a double-blind RCT crossover study, L-theanine partly attenuated the beneficial effects of caffeine on cognition and mood [12]. For example, the caffeine group had a higher number of responses and faster reaction times on the Stroop test compared to the placebo group; these benefits were not seen in the L-theanine group. However, errors on the Stroop test were significantly lower in the L-theanine group compared to the theanine-caffeine combination group. Thus the calming effects of L-theanine may improve accuracy at the expense of speed.

**Brain wave activity:** INCREASED. Several EEG studies have shown that L-theanine increases alpha activity, indicative of a state of wakeful relaxation [3; 13; 14]. L-theanine increases attention-related anticipatory alpha activity while decreasing background alpha activity, potentially improving focus [13]. A double-blind RCT of 34 healthy adults under cognitive stress (multitasking) showed that an L-theanine-based nutrient drink (containing 200 mg of L-theanine, 25 mg of alpha GPC, 1 mg of phosphatidylserine, and 10 mg of chamomile) also increased alpha activity while decreasing stress [15]. However, changes in alpha activity were not correlated with subjective stress or cortisol levels. The functional relevance of alpha activity changes is not yet clear.



**Mood:** INCONCLUSIVE. L-theanine may have a role in regulating anxiety due to its effects on the serotonin and GABA systems [2; 5]. In an open-label uncontrolled study in patients with major depressive disorder, L-theanine administration improved mood, verbal memory, and executive function [16], but a placebo-controlled study is required to confirm these effects.

***Mechanisms of action for neuroprotection identified from laboratory and clinical research:*** Preclinical data suggest that L-theanine acts on the central nervous system by potentiating GABA, dopamine, and serotonin responses. Neuroprotective effects may be mediated by its antagonistic effects on glutamate receptors (AMPA, kainite, NMDA, and group 1 metabotropic glutamate receptors) [4; 5]. For example, theanine has been shown to inhibit neuronal death from exposure to glutamate and this effect was abolished by blocking the group I metabotropic glutamate receptors (mGluRs) [17].

**Alzheimer's:** In rats, L-theanine attenuated A $\beta$ 42-induced memory impairment, reduced neuronal death in the cortex and hippocampus, and inhibited the A $\beta$ 42-induced activation of ERK, p38 MAPK, and NF $\kappa$ B [18]. L-theanine also reduced oxidative damage to proteins and lipids while elevating glutathione levels in the brain. L-theanine-treated rats have 20% lower oxidation levels in the cortex compared to untreated controls [19]. These changes were accompanied by increased levels of PLC- $\beta$ 1 and PLC- $\gamma$ 1 in the cortex. In cell culture, rotenone- and dieldrin-induced apoptosis and DNA fragmentation are partially prevented with L-theanine treatment [20]. L-theanine appeared to exert its neuroprotective effects by suppressing heme oxygenase-1 and restoring ERK1/2 phosphorylation, BDNF production, and GDNF production.

**Stress:** Positive effects of L-theanine on cognitive functions have been observed in a rodent model of stress [21]. Restraint stress for 3 weeks significantly impaired cognitive performance in mice while increasing corticosterone levels. L-theanine reversed the cognitive impairments and oxidative damage while restoring healthy levels of corticosterone and catecholamines in the brain and serum.

**Ischemia:** In a mouse ischemia model, L-theanine treatment reduced cerebral infarct size and this neuroprotective effect was prevented by a GABA-A receptor antagonist, suggesting that neuroprotective effects of theanine is partly mediated by GABA-A receptors [22].

**APOE4 interactions:** It is unknown whether L-theanine has different effects in ApoE4 carriers versus non-carriers. Some studies have examined the interactions between ApoE status and caffeine intake from tea or coffee [23], which have produced inconclusive results.

**Aging and related health concerns:** L-theanine lowers blood pressure in humans, extends lifespan in worms and mice under stressful conditions, and suppresses tumor growth in mice, but no studies have tested whether it prevents age-related diseases.

*Types of evidence:*

- 2 RCTs examining acute effects on blood pressure
- 1 RCT in boys with ADHD on sleep quality
- 1 open-label study on sleep quality in patients with major depressive disorder
- 4 laboratory studies (2 laboratory studies on lifespan, 2 *in vitro/vivo* studies on cancer)

**Lifespan:** EXTENSION. In *C. elegans*, L-theanine (at 100 nM, 1  $\mu$ M, and 10  $\mu$ M) promotes resistance from paraquat toxicity and extends lifespan by up to 4.4% [24]. In a mouse model of psychosocial stress, L-theanine consumption (20  $\mu$ g/ml, 5-6 mg/kg) prevented the shortening of lifespan, cerebral atrophy, learning impairment, and oxidative damage of cerebral DNA [25]. However, no effect of L-theanine on lifespan was observed in control mice that were not exposed to psychosocial stress. Both of these studies show that L-theanine has lifespan-extending properties when the organism is under harmful insults. L-theanine does not appear to be as beneficial in healthy animals.

**Cancer:** SUPPRESSION. Theanine and theanine derivatives were shown in two studies to suppress growth of cervical tumors, lung cancer, and leukemia in cell culture systems as well as in tumor-bearing mice [26; 27]. Both of these studies showed that suppression of cancer growth with L-theanine and its derivatives (TBrC, TFC, and TNC) occurred without toxicity to the mice. TFC and TNC suppress cancer growth by targeting the EGFR/VEGFR-Akt/NF-kB pathways [27].

**Blood pressure:** DECREASE. A double-blind RCT of 48 adults tested the acute effects of L-theanine (200 mg), caffeine (250 mg), and the combination, and found that while caffeine increased blood pressure and alertness, theanine attenuated this increase in blood pressure without affecting caffeine's positive effects on alertness [28]. A smaller RCT of 14 adults showed a similar effect of L-theanine on blood pressure, though the effect was limited to high stress-response adults [29]. Preclinical studies have shown that L-theanine activates ERK and endothelial nitric oxide synthase (eNOS), resulting in enhanced NO production and dilation of arteries [30].

**Sleep:** IMPROVEMENT. In a double-blind RCT of 93 boys diagnosed with attention deficit hyperactivity disorder (ADHD), L-theanine treatment (400 mg/day, Suntheanine<sup>®</sup>) for 6 weeks was associated with higher sleep efficiency (% of night spent sleeping restfully) and fewer bouts of nocturnal motor activity



compared to placebo [31]. The L-theanine group had on average ~5% greater sleep efficiency and ~10% fewer nocturnal motor activities compared to controls. Sleep quality was also improved with L-theanine (250 mg/d) in patients with major depressive disorder, but it was an open-label study and placebo-controlled studies are required to confirm these effects [16]. It is unknown whether L-theanine has beneficial effects on sleep in healthy adults.

**Safety:** No clinical data exist for long-term supplementation of L-theanine at doses higher than what is found in tea.

*Types of evidence:*

- 2 Cochrane meta-analyses based on 14 and 11 RCTs examining the effects of green tea (not L-theanine specifically) on weight loss and cardiovascular disease prevention, respectively
- 2 RCTs examining the effects of L-theanine, 1 in boys with ADHD and 1 in people with schizophrenia
- 3 rodent studies (1 toxicity/toxicokinetics study and 2 cancer studies)

No clinical data exist for long-term safety of L-theanine supplementation. Two Cochrane meta-analyses of green tea consumption (beverage or extract for at least 3 months), one in overweight adults and another in healthy adults, have reported that side effects from green tea are mild [32; 33]. No significant differences in adverse events were observed between green tea and placebo groups.

Two RCTs have tested the effects of L-theanine specifically. L-theanine treatment (400 mg/day) for 6 weeks was well-tolerated with no significant adverse events in 98 boys diagnosed with ADHD [31]. In another double-blind RCT, L-theanine (400 mg/day) with oral pregnenolone (50 mg/day) for 8 weeks was well-tolerated in patients with schizophrenia [34]. However, L-theanine was not tested by itself and the full text of this article was unavailable, so details of adverse events could not be evaluated. Larger, long-term studies are needed to evaluate long-term safety of L-theanine supplementation.

In a rat toxicity and toxicokinetic study, L-theanine was administered at 0, 1500, 3000, and 4000 mg/kg/day for 13 weeks [35]. No consistent statistically significant treatment-related adverse effects were found on behavior, morbidity, mortality, pathology, body weight, food consumption, clinical chemistry, hematology, or urinalysis. The no-observed-adverse-effect-level was 4000 mg/kg/day, the highest dose tested.

Interactions with drugs have not been well-studied. Because of its blood pressure-lowering properties, theoretically, concomitant use of blood pressure medications may be dangerous. Clinical data suggest that L-theanine inhibits the stimulant effects produced by caffeine [28; 29].

**Sources and dosing:** Clinical trials examining the effects of L-theanine on cognitive function, blood pressure, and sleep have used doses ranging from 12-400 mg/d, with the majority of studies using 200 mg/d [8; 11; 15]. In a rat toxicity study, the no-observed-adverse-effect-level was 4000 mg/kg/d, the highest dose tested [35]--the human equivalent dose while accounting for differences in body surface area is 645 mg/kg/d.

A single cup (200 ml) of liquid tea can contain 5 to 85 mg of L-theanine depending on the type of tea. Matcha is powdered Japanese green tea, where the tea powder is mixed with hot water and contains ~36 mg of L-theanine per serving (80 ml). Gyokuro is a type of green tea that is produced from shading the tea leaves, increasing theanine and caffeine production while inhibiting catechin levels, and contains 85 mg of L-theanine per cup. Sencha, the most common type of green tea in Japan (and the US), contains 8~25 mg in a cup. Black tea contains about 10~35 mg per cup [36]. The amount of L-theanine varies, with higher levels typically found in higher quality tea.

L-theanine is more bioavailable than its optical isomer D-theanine [37]. In an analysis of commercially available products labeled as L-theanine, 5 out of 6 contained significant amounts of D-theanine. Only Suntheanine® contained pure (>99%) L-theanine enantiomer [38].

**Research underway:** A clinical trial is testing whether a brain health supplement (BBG-1001) that contains green tea extract, turmeric, fish oil, and vitamin D can slow cognitive decline in people with mild cognitive impairment ([NCT02741804](#)). This study is scheduled to be completed in May 2019. Another clinical trial is testing the effects of a dietary supplement SPRINT (200 mg of L-theanine, 100 mg of caffeine, 40 mg of vinpocetine, 300 mg of L-tyrosine, 0.06 mg of pyridoxine, and 20 mg of cobalamin) on cognitive function in healthy young adults ([NCT02857829](#)). This study has not started recruiting participants yet.

#### Search terms:

Pubmed, Google: Green tea, L-theanine, matcha

- + cognitive, + memory, + *dementia*, + meta-analysis, + systematic review, + clinical trial, + ApoE4, + cancer, + cardiovascular, + lifespan, + safety



Clinicaltrials.gov:

- Green tea, L-theanine, matcha

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