

Original citation:

Filipe Lopes Sakamoto, Rodrigo Metzker Pereira Ribeiro, Allain Amador Bueno, Heitor Oliveira Santos (2019) Psychotropic effects of L-theanine and its clinical properties: From the management of anxiety and stress to a potential use in schizophrenia, *Pharmacological Research*. 147, article no. 104395, <https://doi.org/10.1016/j.phrs.2019.104395>.

Permanent WRaP URL:

<https://eprints.worc.ac.uk/8508/>

Copyright and reuse:

The Worcester Research and Publications (WRaP) makes this work available open access under the following conditions. Copyright © and all moral rights to the version of the paper presented here belong to the individual author(s) and/or other copyright owners. To the extent reasonable and practicable the material made available in WRaP has been checked for eligibility before being made available.

Copies of full items can be used for personal research or study, educational, or not-for-profit purposes without prior permission or charge, provided that the authors, title and full bibliographic details are credited, a hyperlink and/or URL is given for the original metadata page and the content is not changed in any way.

Publisher's statement:

This is an Accepted Manuscript of an article published by Elsevier in *Pharmacological Research*, available online: <https://www.sciencedirect.com/science/article/abs/pii/S1043661819307790>. © 2019 Elsevier. Licensed under the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International. <http://creativecommons.org/licenses/by-nc-nd/4.0/>

A note on versions:

The version presented here may differ from the published version or, version of record, if you wish to cite this item you are advised to consult the publisher's version. Please see the 'permanent WRaP URL' above for details on accessing the published version and note that access may require a subscription.

For more information, please contact wrapteam@worc.ac.uk

Psychotropic effects of L-theanine and its clinical properties: from the management of anxiety and stress to a potential use in schizophrenia

Filipe Lopes Sakamoto¹, Rodrigo Metzker Pereira Ribeiro¹, Allain Amador Bueno², Heitor Oliveira Santos^{3*}

¹University of Western São Paulo, Presidente Prudente, São Paulo, Brazil

²College of Health, Life and Environmental Sciences, University of Worcester, United Kingdom

³ School of Medicine, Federal University of Uberlândia (UFU), Uberlandia, Minas Gerais, Brazil.

*Corresponding author: Heitor Oliveira Santos. Federal University of Uberlandia, Uberlandia, Minas Gerais, Brazil. Av. Para, nº1720 Bloco 2U Campus Umuarama, 38400-902.

E-mail adress: heitoroliveirasantos@gmail.com (H. O. Santos)

Abstract

Anxiety disorders are highly prevalent in modern societies, and are ranked the sixth most important contributor of non-fatal negative health outcomes. L-theanine is an amino acid naturally found in green tea (*Camellia sinensis*) and some other plant extracts, and recent clinical studies have proposed promising adjuvant effects of L-theanine for the negative impact of anxiety and psychological stress on health. In this integrative narrative review, we aimed to appraise and further discuss the effects of L-theanine administration on anxiety disorders and psychological stress. Published data suggests that L-theanine administered at daily doses ranging from 200 to 400 mg for up to 8 weeks are safe and induce anxiolytic and anti-stress effects in acute and chronic conditions. L-theanine at doses lower and higher than these may also show promising therapeutic potential; however, a more thorough investigation through randomized double-blind placebo-controlled crossover clinical trials are necessary to elucidate its effects for longer periods, providing further insights for meta-analyses and the development of recommendation guidelines. Additionally, animal studies investigating a higher dosage, its combination with other pharmacological compounds and associated metabolic comorbidities are recommended, as cases of hepatotoxicity associated with the consumption of green tea extract have been reported.

Keywords: anxiety; *Camellia sinensis*; green tea; L-theanine; psychological stress, schizophrenia.

Highlights

- L-theanine presents anxiolytic and anti-stress properties.
- Such effects cover acute and chronic conditions.
- 200 to 400 mg/d up to 8 weeks appears to be safe and effective.
- Further studies are required to further investigate the effects of L-theanine beyond this dosage and period.

1. Introduction

Anxiety and fear-related disorders include generalized anxiety disorder (GAD), panic disorder, agoraphobias, specific phobias, social anxiety disorder, associated or not with panic attacks [1,2], and are collectively ranked the sixth most important contributor of non-fatal negative health outcomes [2]. Anxiety is highly prevalent in patients suffering with co-occurring medical conditions, including metabolic syndrome and diabetes [3], cancer [4], HIV infection [5], and several other conditions. Anxiety is also highly prevalent in the general population: a study investigating subthreshold anxiety disorder in the general Dutch population has found a prevalence of 11.4% [6], whilst another study investigating self-evaluated anxiety in the general Norwegian population found that 6.6% of respondents reported current anxiety, and 21.7% of them reported lifetime anxiety [7]. Due to their high prevalence, anxiety disorders are considered as an epidemic and a Public Health concern [2,8].

Anxiety *per se* is a reaction commonly triggered by stress and general daily situations [9]. In the field of psychiatry, anxiety disorders are known to negatively influence the emotional state, and are characterized by anticipation of future or perceived threat, associated with behavioural manifestations that cause clinically significant distress, lasting six months or longer [10]. The symptoms of anxiety have a significant negative impact in daily activities for the affected individual as well as their peers, with the potential to decrease school performance and deteriorate social relationships [11]. Anxiety is also positively associated with other psychiatric disorders, such as attention deficit hyperactivity disorder (ADHD) [12].

Psychological stress can be defined as a physiological response to environmental stimuli that triggers the fight-or-flight response, associated with the feelings of strain and emotional pressure [13]. It often manifests itself when the affected individual no longer has the adaptive capacity to cope with the negative emotional response triggered by unpleasant or hostile social or environmental situations [14]. Stress is highly prevalent in modern societies; a study has reported

signs and symptoms of moderate to high stress in 59% of a population of working age seeking primary health care [15].

Psychological stress can be defined as acute, for example in anticipation to a surgical procedure, or chronic, for example in financial or family difficulties [16]. Both forms of stress have the potential to disrupt the nervous, endocrine and immune systems [13,17], yielding additional psychosomatic manifestations such as fear and anxiety [14,18]. Stressful life events are positively associated with short-, medium- and long-term health disorders [19–21], and act as catalysts for the exacerbation of anxiety symptoms, potentially leading to the full development of anxiety disorders [9].

Various families of drugs have been historically, and still currently, employed for the treatment and or management of anxiety, including benzodiazepines, barbiturates, antidepressants, antihistamines, opioids, sympatholytics, cannabis and several others, to name a few. Each family and their respective drugs however are known for their well-documented side effects, including toxicity, tolerability, tolerance, addiction and withdrawal issues, not covered in the present study.

In that regard however, the oral administration of L-theanine (γ -glutamylethylamide) has been proposed as an appealing nutraceutical compound for the management of anxiety [22]. L-theanine is a unique non-proteinaceous amino acid naturally occurring in tea plants, and considered a potential multifaceted supplement [23]. Therefore, the aim of the present integrative narrative review is to further discuss and debate the observed clinical findings and dose-related efficacy of L-theanine administration on parameters of anxiety and stress.

2. Methods

This integrative literature review was carried out based on Cochrane, MEDLINE and Web of Science databases. Specific key terms in English were employed to scrutinise relevant publications, and specific selection criteria were adopted for screening clinical trials and other relevant studies, as detailed in Figure

1. For this purpose, the literature search addressed human studies with more emphasis on clinical trials published in the last 15 years (from 2004 to 2019).

[Insert figure 1 here]

3. Anxiety and stress outcomes

Overall, several studies have shown that the administration of L-theanine improved anxiety and stress outcomes, alongside improvements in other manifestations such as depression and psychopathological symptoms (Table 1). Such findings were obtained through the employment of several validated psychometric tools, including the Hamilton Anxiety Rating Scale (HARS), Tension Anxiety Scores, Pittsburgh Sleep Quality Index (PSQI), Positive and Negative Syndrome Scale (PANSS) [24,25], and others.

Additionally, verbal memory and executive function were improved in individuals diagnosed with Major Depressive Disorder (MDD) supplemented with 250 mg of L-theanine and tested for the Brief Assessment of Cognition in Schizophrenia (BACS) [24]. Healthy individuals supplemented with 200 mg of L-theanine showed improvement in the tranquil–troubled subscale of the Visual Analogue Mood Scale (VAMS) [26].

An overall improvement in anxiety symptoms was often accompanied by improvements in biomarkers, including salivary α -amylase, cortisol, chromogranin A and immunoglobulin A [27–30]. White and colleagues, employing the technique of magnetoencephalography, found that posterior resting alpha activity was significantly higher in the high trait anxiety group receiving L-theanine as compared to the matched placebo group [29].

Most of the studies appraised in our review recruited from 12 to 60 participants, were double-blinded and tested the effects of L-theanine in doses ranging from 15 to 400 mg [24–27,29,31–35]. In addition, two of the studies appraised [28,30] investigated the effects of L-theanine combined with tea intake. More recently however, in the opposite direction Sarris *et al* did not find improvements in anxiety scores based on HARS, nor in the severity of insomnia

based on the Insomnia Severity Index, after L-theanine supplementation (450-900 mg/d) in an 8-week double-blind placebo-controlled trial [36]. No significant cognitive effects were observed either.

[Insert table 1 here]

4. Blood pressure lowering effects

L-theanine may have the potential to lower blood pressure, possibly indirectly via reduction of the manifestations associated with stress, inhibiting cortical neural excitation and consequently attenuating sympathetic activity [35]. Two of the appraised studies have found decreased blood pressure in adults with high stress response after supplementation with 200 mg of L-theanine [33,35].

5. Major Depressive Disorder

Preclinical studies suggest that L-theanine has antipsychotic-like and possibly antidepressant-like effects. At molecular level, L-theanine appears to stimulate brain-derived neurotrophic factor (BDNF) in the hippocampus whilst agonistically acting on NMDA receptors, having also a modulatory effect on central monoaminergic neurotransmitter systems [38,39]. Regarding its clinical features, inhibition of the central nervous system mediated by the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) may be associated with the anxiolytic effects of L-theanine, and such association may be helpful for sleep disturbances, particularly in MDD individuals [24,31]. As discussed earlier, Hidese and colleagues found that L-theanine administration reduced depressive symptoms and improved cognitive function in MDD patients [24]. It is however worth noting that Hidese's study was open-labelled, thus caution may be necessary on its interpretation. Therefore, further investigations are imperative to elucidate the clinical effects of L-theanine across the MDD field.

6. A natural sleep aid

Overall, it is suggested that the intake of 200 mg of L-theanine at bedtime may improve sleep quality by anxiolysis rather than sedation, as the conventional pharmacological treatment for insomnia [40]. Said effects line up with improvements seen in several sleep quality parameters, including sleep monitored by actigraphy, obstructive sleep apnoea, sleep inventory questionnaire, dysfunctional arousal, autonomic nervous system assessment, and paediatric sleep questionnaire [40].

GABA in the central nervous system is primarily synthesized *in situ*; however, despite the acknowledged debate in the topic, some researchers suggest that the blood brain barrier is permeable to GABA [41,42]. In that sense, Kim and colleagues showed that there is a synergistic sleep enhancement effect of orally administered GABA/L-theanine mixture, whose combination has led to decreased sleep latency and improved NREM sleep in mice, when compared to their individual administration [43]. Taking into account the combination of L-theanine administration with other supplements which claim sleep-promoting effects, GABA for example, further studies are required to prove or disprove its clinical relevance.

The usefulness of L-theanine as sleep aid may reach the psychiatric field. For instance, L-theanine is considered a promising adjunct therapeutic tool for children and adolescents with ADHD-related sleep disturbances [44,45], a complex and challenging medical condition in young psychiatric patients [46]. Moreover, Ota *et al* reported improved sleep quality in schizophrenia patients after 250 mg/day of L-theanine for 8 weeks [47].

7. Schizophrenia and schizoaffective disorder

In addition to improvement in sleep quality, Ota and colleagues also observed that the daily administration of 250 mg/day of L-theanine for 8 weeks added to the patients' ongoing antipsychotic treatment was effective in ameliorating symptoms in schizophrenia. Interestingly, employing ¹H magnetic resonance spectroscopy (MRS), the researchers found that L-theanine modulated glutamate+glutamine concentrations in the frontal and parietal regions of the brain, which could be a possible mechanism underlying its therapeutic properties [47].

Ritsner and colleagues found in a double-blind randomized placebo-controlled clinical trial recruiting 60 patients diagnosed with chronic schizophrenia and schizoaffective disorder that L-theanine supplementation for 8 weeks combined with the respective ongoing antipsychotic treatment was able to significantly reduce anxiety and significantly improve general psychopathological scores [25]. Another publication [32] from the same research group, analysing a subset of 40 participants from the clinical trial referred above, observed improvements in circulating levels of brain-derived neurotrophic factor and cortisol to dehydroepiandrosterone sulfate ratio after L-theanine supplementation. The authors emphasized in both studies the beneficial effects of L-theanine alongside its safety and good tolerance at daily doses of 400 mg [25,32].

8. Discussion

Collectively, the aforementioned findings support a multifaceted potential of L-theanine supplementation in a wide clinical spectrum, from children and adolescents to adult subjects (table 1). The potential benefits appear to be promising for several psychological and psychiatric manifestations, encompassing the management of anxiety and stress alongside conditions such as sleep disturbances and even hypertension, as well as MDD, schizophrenia and schizoaffective disorder.

8.1. Pharmacodynamics

Structurally, L-theanine is a glutamate analogue, hence binding to the same glutamate receptors and therefore hindering the neuroexcitatory effects triggered by glutamatergic activation [48,49]. It is believed that L-theanine mediation on glutamatergic neurotransmission is the main pathway by which this non-proteinaceous amino acid is able to attenuate anxiety disorders and mitigate the negative outcomes of exposure to acute and chronic stress.

Putatively, the firstly observed mechanism of action of L-theanine was its antagonistic action by binding to NMDA, AMPA and kainate subtypes of ionotropic

glutamate receptors [50,51]. Interestingly however, an inhibitory effect of L-theanine on glutamine transporters was also identified [50,52], and this is believed to be another major mechanism of action of L-theanine in the central nervous system. So much so that Wakabayashi *et al* found that L-theanine increased BDNF in the hippocampus and yielded agonistic action upon NMDA receptors, suggesting that L-theanine may not be a full antagonist of the glutamate system only, possibly being a partial antagonist / agonist [38].

Glutamine is converted to glutamate via de-amination in the neuron mitochondrion, mediated by phosphate-activated glutaminase (PAG) [53]. The exact mechanism is yet to be fully elucidated, but it appears that L-theanine inhibits the uptake of glutamine by neurons [54], possibly via competition for the glutamine transporter Alanine-Serine-Cysteine transporter 2 (ASCT2), also known as SLC1A5 [55]. The proposed mechanisms of action are illustrated in Figure 2.

[Insert figure 2 here]

Furthermore, similarly to GABA administration, L-theanine was able to significantly increase the generation of alpha waves [31], which are more predominant in adults at rest with eyes closed, but also in relaxed conditions. In the same study [31], both GABA and L-theanine reduced the predominance of beta waves, but not at a statistically significant level. Beta waves are common in alert, awake adults, but also predominant in situations which demand intense mental effort. Corroborating such findings, studies employing animal models have found that the administration of L-theanine seems to increase GABA levels in the brain [43,49].

Studies have investigated the associations between L-theanine with dopamine and serotonin in rodents [51,59,60]. Yamada and colleagues have reported an increase of up to two-fold in dopamine levels induced by L-theanine perfusion in rat striatal brain [51]. Prior to that, Yokogoshi and colleagues had found significantly higher levels of dopamine in rat striatum after intragastric

administration of L-theanine, alongside higher levels of serotonin in striatum, hippocampus and hypothalamus, as compared to the saline-treated controls [60].

Ogawa *et al* in turn found in Wistar Kyoto rats, an animal model of treatment-resistant depression, that repeated administration of L-theanine induced an anxiolytic effect [61]. The researchers found significantly decreased glutamate and increased methionine levels in the cerebrospinal fluid after L-theanine administration, suggesting a positive modulation in hippocampal activity coupled with the anxiolytic action. Additionally, the L-theanine-treated rats showed increased neural activity when submitted to ¹⁸F-fluorodeoxyglucose positron emission tomography (PET) scanning [61]. More recently, Shen and colleagues [59] found in a rat model of depression that L-theanine oral administration not only improved depressive-like behaviours, it also increased dopamine and serotonin levels in the prefrontal cortex, nucleus accumbens and hippocampus, as compared to the control group.

Taken together, the neurochemical effects of L-theanine may be clinically appealing in the context of anxiety and stress. The supplementation of compounds with neurochemical properties for improvement of sleep quality, such as GABA [62,63] and melatonin [64], has been suggested. Such approaches are gaining more momentum in recent times; however, as claims are often associated with vested commercial interests, multi-centre randomized placebo-controlled double-blind crossover clinical trials are required to clarify the usefulness of such supplements. Figure 3 highlights gaps in knowledge in regards to the relationship between L-theanine and GABAergic, dopaminergic and serotonergic signalling pathways.

[Insert figure 3 here]

8.2. Pharmacokinetics

At the intestinal brush-border membrane, similarly to glutamine, L-theanine absorption is mediated by a common Na⁺-coupled co-transporter; however, its affinity to L-theanine is lower than that of glutamine [65]. Unno and colleagues

found in rats that the plasma concentration of orally administered L-theanine peaked at 30 minutes [66]. Also in rats, two separate studies from the same research group [60,67], detected the presence of L-theanine in neural tissue after its intragastric administration, and that this transport occurred via a leucine-preferring transport system. In liver and serum, L-theanine concentrations started to decrease after 1 hour of its administration, whereas in the brain it peaked at 5 hours, when it started to decrease [67], and total clearance observed after 24 hours [67].

8.3. L-theanine vs. green tea

There are more than 300 types of tea derived from *Camellia sinensis* L., commonly being classified into three main categories: green tea (non-fermented), oolong tea (semi-fermented) and black tea (fermented) [68]. L-theanine content in dry extract is circa 1 to 2%, with approximately 25 to 60 mg of L-theanine in a typical 200 mL cup of tea [69]. However, as green tea is unfermented, it contains higher amounts of L-theanine than oolong or black tea; the extent of fermentation is a factor for lower L-theanine concentrations [70,71].

Several studies have identified health benefits associated with the consumption of green tea, including improvements in cognitive decline, depression and psychological disturbances [72–74]. However, we found only three studies [28,30,37] that have investigated the effects of green tea intake on parameters of anxiety and stress. Not only that, very little is known about the other constituents of green tea in this field. For instance, we did not find any study that performed a specific intervention with epigallocatechin gallate (EGCG), an important component of green tea that may possess relevant antioxidant properties upon diseases of the nervous system [75].

8.4. Cognitive systems: nootropic and adaptogenic effects

Nootropics, colloquially known as “smart drugs”, have been tested for the treatment of cognitive deficits [76], and are currently gaining more questionable popularity in the lay, off-label background as cognitive enhancers. Along the same

lines, adaptogens are compounds proposed for attention improvement in stressful situations [77]. Nootropic and adaptogenic compounds include several herbal medicines, and their alleged effects are thought to influence cognitive systems, including short-term memory and memory processing.

Green tea extract may modulate human brain activity in the dorsolateral prefrontal cortex (DLPFC), an area of the frontal lobe associated with the processing of working memory. In a double-blind study, Borgwardt *et al* subjected 12 healthy volunteers to functional magnetic resonance imaging, performing a working memory test following administration of 250 or 500 mL of a milk whey mixture drink enriched with 0.05% standardized green tea extract, or the same drink without green tea as control. Through a controlled repeated measures within-subject design, each volunteer was scanned four times with a 1-week interval between scans. The researchers found that the administration of green tea extract increased activation in the DLPFC in a dose dependant manner, compared with the placebo administration [78]. In another study from the same University and employing comparable design, Schmidt *et al* showed that 250 or 500 mL of milk whey-based drink containing 2.75 g/L of green tea extract increased working memory by modulating the connectivity between the right superior parietal lobe and the middle frontal gyrus [79]. However, the doses of green tea employed probably contain low amounts of L-theanine.

A recent experimental study showed that C57BL/J male mice subjected to chronic restraint-induced stress showed restored levels of TNF- α , IL-6, noradrenaline and 5-HT in the prefrontal cortex, restored plasma corticosterone levels, alongside improved memory and hippocampal apoptosis after L-theanine administration [80]. Interestingly however, in a double-blind randomized cross-over study, the administration of 100 mg of L-theanine reduced error rate but did not influence alpha wave activity in 27 volunteers on two-hour sessions of the Sustained Attention to Response Task (SART) test [81]. The inconclusiveness of such findings justify further investigations into the potential role of L-theanine as a nootropic and adaptogenic compound.

8.5. Toxicity issues

Experimentally induced toxicity by high dose administration of green tea extract has been observed in rats [82] and dogs [83]. Additionally, a study on Swiss albino mice found that L-theanine administration enhanced the toxic effects of strychnine [84]. Cases of liver injury associated with the consumption of green tea have been reported in the medical literature [85–88]. Despite its low prevalence, as far as it is known, such cases were observed in individuals consuming high volumes of green tea for long periods, in individuals who combined green tea with other plant extracts, multicomponent mixtures or other drugs, and in individuals with history of liver disease. On those grounds, the risk of toxicity induced by green tea intake or L-theanine supplementation is small but should not be neglected. This is particularly relevant in individuals on therapies employing other pharmacological agents, in which metabolite interaction can influence the pharmacokinetics and pharmacodynamics of the compounds involved. Such relevance medically justifies the development of further studies on animal models.

9. Conclusion

L-theanine administration at daily doses of 200 to 400 mg appears to confer anxiolytic and stress-reducing effects. Acute effects of L-theanine are observed few hours after its intake, and its chronic effects also appear to be positive. However, an important limitation of the studies so far available refer to their short intervention period, no longer than eight weeks. The effects of L-theanine administration seem be proportional to the magnitude of anxiety and stress. To the best of our knowledge, no side effects or adverse reactions of L-theanine supplementation at daily doses of 200 to 400 mg for up to eight weeks have been reported so far. L-theanine at doses lower and higher than those may also be a promising adjuvant in the broad clinical spectrum. Additional multi-centre randomized placebo-controlled double-blind crossover clinical trials are required in order to further investigate the safety and effectiveness of L-theanine intake in dosages higher than the ones so

far investigated, and for longer periods, hence expanding the evidence for meta-analyses and recommendation guidelines.

Conflicts of interest

The authors declare that this research was conducted in the absence of any commercial or financial relationship that could possibly be construed as a potential conflict of interest.

Acknowledgment

The authors did not receive any specific funding for this study.

References

- [1] C.S. Kogan, D.J. Stein, M. Maj, M.B. First, P.M.G. Emmelkamp, G.M. Reed, The Classification of Anxiety and Fear-Related Disorders in the ICD-11, *Depress Anxiety*. 33 (2016) 1141–1154. doi:10.1002/da.22530.
- [2] W.H. Organization, Depression and other common mental disorders: global health estimates, (2017). <https://apps.who.int/iris/handle/10665/254610> (accessed February 11, 2019).
- [3] A. Shinkov, A.-M. Borissova, R. Kovatcheva, J. Vlahov, L. Dakovska, I. Atanassova, P. Petkova, Increased prevalence of depression and anxiety among subjects with metabolic syndrome and known type 2 diabetes mellitus - a population-based study, *Postgrad Med*. 130 (2018) 251–257. doi:10.1080/00325481.2018.1410054.
- [4] F. Mols, D. Schoormans, I. de Hingh, S. Oerlemans, O. Husson, Symptoms of anxiety and depression among colorectal cancer survivors from the population-based, longitudinal PROFILES Registry: Prevalence, predictors, and impact on quality of life, *Cancer*. 124 (2018) 2621–2628. doi:10.1002/cncr.31369.
- [5] G. Tesfaw, G. Ayano, T. Awoke, D. Assefa, Z. Birhanu, G. Miheretie, G. Abebe, Prevalence and correlates of depression and anxiety among patients with HIV on-follow up at Alert Hospital, Addis Ababa, Ethiopia, *BMC Psychiatry*. 16 (2016) 368. doi:10.1186/s12888-016-1037-9.
- [6] R.C. Bosman, M. Ten Have, R. de Graaf, A.D. Muntingh, A.J. van Balkom, N.M. Batelaan, Prevalence and course of subthreshold anxiety disorder in the general population: A three-year follow-up study, *J Affect Disord*. 247 (2019) 105–113. doi:10.1016/j.jad.2019.01.018.
- [7] T. Bonsaksen, T. Heir, Ø. Ekeberg, T.K. Grimholt, A. Lerdal, L. Skogstad, I. Schou-Bredal, Self-evaluated anxiety in the Norwegian population: prevalence and associated factors, *Arch Public Health*. 77 (2019) 10. doi:10.1186/s13690-019-0338-0.
- [8] M.J. Friedrich, Depression Is the Leading Cause of Disability Around the World, *JAMA*. 317 (2017) 1517–1517. doi:10.1001/jama.2017.3826.
- [9] D.W. Grupe, J.B. Nitschke, Uncertainty and anticipation in anxiety: an integrated neurobiological and psychological perspective, *Nat. Rev. Neurosci*. 14 (2013) 488–501. doi:10.1038/nrn3524.
- [10] American Psychiatric Association, *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*, American Psychiatric Association, 2013. doi:10.1176/appi.books.9780890425596.
- [11] L. Mazzone, F. Ducci, M.C. Scoto, E. Passaniti, V.G. D'Arrigo, B. Vitiello, The role of anxiety symptoms in school performance in a community sample of children and adolescents, *BMC Public Health*. 7 (2007) 347. doi:10.1186/1471-2458-7-347.
- [12] J.D. Pedraza, B. Coffey, Obsessive-Compulsive Disorder and Comorbid Attention-Deficit/Hyperactivity Disorder: A Complex Diagnostic Disentanglement and Treatment, *J Child Adolesc Psychopharmacol*. 23 (2013) 419–422. doi:10.1089/cap.2013.2362.
- [13] J.M.F. Hall, D. Cruser, A. Podawiltz, D.I. Mummert, H. Jones, M.E. Mummert, Psychological Stress and the Cutaneous Immune Response: Roles of the HPA Axis

- and the Sympathetic Nervous System in Atopic Dermatitis and Psoriasis, *Dermatol Res Pract.* 2012 (2012) 403908. doi:10.1155/2012/403908.
- [14] K. Kagias, C. Nehammer, R. Pocock, Neuronal responses to physiological stress, *Front Genet.* 3 (2012) 222. doi:10.3389/fgene.2012.00222.
- [15] L. Wiegner, D. Hange, C. Björkelund, G. Ahlborg, Prevalence of perceived stress and associations to symptoms of exhaustion, depression and anxiety in a working age population seeking primary care--an observational study, *BMC Fam Pract.* 16 (2015) 38. doi:10.1186/s12875-015-0252-7.
- [16] L. Yang, Y. Zhao, Y. Wang, L. Liu, X. Zhang, B. Li, R. Cui, The Effects of Psychological Stress on Depression, *Curr Neuropharmacol.* 13 (2015) 494–504. doi:10.2174/1570159X1304150831150507.
- [17] S.C. Segerstrom, G.E. Miller, Psychological stress and the human immune system: a meta-analytic study of 30 years of inquiry, *Psychol Bull.* 130 (2004) 601–630. doi:10.1037/0033-2909.130.4.601.
- [18] G. C, D. R, C. MF, K. L, K. MA, Acute stress potentiates anxiety in humans, *Biol Psychiatry.* 62 (2007) 1183–1186. doi:10.1016/j.biopsych.2007.06.007.
- [19] N. Bergmann, S. Ballegaard, J. Krogh, P. Bech, Å. Hjalmarson, F. Gyntelberg, J. Faber, Chronic psychological stress seems associated with elements of the metabolic syndrome in patients with ischaemic heart disease, *Scand. J. Clin. Lab. Invest.* 77 (2017) 513–519. doi:10.1080/00365513.2017.1354254.
- [20] P.J. Lang, L.M. McTeague, M.M. Bradley, Pathological anxiety and function/dysfunction in the brain's fear/defense circuitry, *Restor. Neurol. Neurosci.* 32 (2014) 63–77. doi:10.3233/RNN-139012.
- [21] C. Stefanaki, P. Pervanidou, D. Boschiero, G.P. Chrousos, Chronic stress and body composition disorders: implications for health and disease, *Hormones (Athens).* 17 (2018) 33–43. doi:10.1007/s42000-018-0023-7.
- [22] W. Mu, T. Zhang, B. Jiang, An overview of biological production of L-theanine, *Biotechnol. Adv.* 33 (2015) 335–342. doi:10.1016/j.biotechadv.2015.04.004.
- [23] R. Adhikary, V. Mandal, l-theanine: A potential multifaceted natural bioactive amide as health supplement, *Asian Pacific Journal of Tropical Biomedicine.* 7 (2017) 842–848. doi:10.1016/j.apjtb.2017.08.005.
- [24] S. Hidese, M. Ota, C. Wakabayashi, T. Noda, H. Ozawa, T. Okubo, H. Kunugi, Effects of chronic l-theanine administration in patients with major depressive disorder: an open-label study, *Acta Neuropsychiatr.* 29 (2017) 72–79. doi:10.1017/neu.2016.33.
- [25] M.S. Ritsner, C. Miodownik, Y. Ratner, T. Shleifer, M. Mar, L. Pintov, V. Lerner, L-theanine relieves positive, activation, and anxiety symptoms in patients with schizophrenia and schizoaffective disorder: an 8-week, randomized, double-blind, placebo-controlled, 2-center study, *J Clin Psychiatry.* 72 (2011) 34–42. doi:10.4088/JCP.09m05324gre.
- [26] K. Lu, M.A. Gray, C. Oliver, D.T. Liley, B.J. Harrison, C.F. Bartholomeusz, K.L. Phan, P.J. Nathan, The acute effects of L-theanine in comparison with alprazolam on anticipatory anxiety in humans, *Hum Psychopharmacol.* 19 (2004) 457–465. doi:10.1002/hup.611.
- [27] K. Kimura, M. Ozeki, L.R. Juneja, H. Ohira, L-Theanine reduces psychological and physiological stress responses, *Biol Psychol.* 74 (2007) 39–45. doi:10.1016/j.biopsycho.2006.06.006.

- [28] K. Unno, H. Yamada, K. Iguchi, H. Ishida, Y. Iwao, A. Morita, Y. Nakamura, Anti-stress Effect of Green Tea with Lowered Caffeine on Humans: A Pilot Study, *Biol. Pharm. Bull.* 40 (2017) 902–909. doi:10.1248/bpb.b17-00141.
- [29] D.J. White, S. de Klerk, W. Woods, S. Gondalia, C. Noonan, A.B. Scholey, Anti-Stress, Behavioural and Magnetoencephalography Effects of an L-Theanine-Based Nutrient Drink: A Randomised, Double-Blind, Placebo-Controlled, Crossover Trial, *Nutrients*. 8 (2016). doi:10.3390/nu8010053.
- [30] A. Yoto, S. Murao, Y. Nakamura, H. Yokogoshi, Intake of green tea inhibited increase of salivary chromogranin A after mental task stress loads, *Journal of Physiological Anthropology*. 33 (2014) 20. doi:10.1186/1880-6805-33-20.
- [31] A.M. Abdou, S. Higashiguchi, K. Horie, M. Kim, H. Hatta, H. Yokogoshi, Relaxation and immunity enhancement effects of gamma-aminobutyric acid (GABA) administration in humans, *Biofactors*. 26 (2006) 201–208.
- [32] C. Miodownik, R. Maayan, Y. Ratner, V. Lerner, L. Pintov, M. Mar, A. Weizman, M.S. Ritsner, Serum levels of brain-derived neurotrophic factor and cortisol to sulfate of dehydroepiandrosterone molar ratio associated with clinical response to L-theanine as augmentation of antipsychotic therapy in schizophrenia and schizoaffective disorder patients, *Clin Neuropharmacol.* 34 (2011) 155–160. doi:10.1097/WNF.0b013e318220d8c6.
- [33] P.J. Rogers, J.E. Smith, S.V. Heatherley, C.W. Pleydell-Pearce, Time for tea: mood, blood pressure and cognitive performance effects of caffeine and theanine administered alone and together, *Psychopharmacology (Berl.)*. 195 (2008) 569–577. doi:10.1007/s00213-007-0938-1.
- [34] K. Unno, N. Tanida, N. Ishii, H. Yamamoto, K. Iguchi, M. Hoshino, A. Takeda, H. Ozawa, T. Ohkubo, L.R. Juneja, H. Yamada, Anti-stress effect of theanine on students during pharmacy practice: positive correlation among salivary α -amylase activity, trait anxiety and subjective stress, *Pharmacol. Biochem. Behav.* 111 (2013) 128–135. doi:10.1016/j.pbb.2013.09.004.
- [35] A. Yoto, M. Motoki, S. Murao, H. Yokogoshi, Effects of L-theanine or caffeine intake on changes in blood pressure under physical and psychological stresses, *J Physiol Anthropol.* 31 (2012) 28. doi:10.1186/1880-6805-31-28.
- [36] J. Sarris, G.J. Byrne, L. Cribb, G. Oliver, J. Murphy, P. Macdonald, S. Nazareth, D. Karamacoska, S. Galea, A. Short, C. Ee, Y. Birling, R. Menon, C.H. Ng, L-theanine in the adjunctive treatment of generalized anxiety disorder: A double-blind, randomised, placebo-controlled trial, *J Psychiatr Res.* 110 (2019) 31–37. doi:10.1016/j.jpsychires.2018.12.014.
- [37] A. Kardashev, Y. Ratner, M.S. Ritsner, Add-On Pregnenolone with L-Theanine to Antipsychotic Therapy Relieves Negative and Anxiety Symptoms of Schizophrenia: An 8-Week, Randomized, Double-Blind, Placebo-Controlled Trial, *Clin Schizophr Relat Psychoses*. 12 (2018) 31–41. doi:10.3371/CSRP.KARA.070415.
- [38] C. Wakabayashi, T. Numakawa, M. Ninomiya, S. Chiba, H. Kunugi, Behavioral and molecular evidence for psychotropic effects in L-theanine, *Psychopharmacology (Berl.)*. 219 (2012) 1099–1109. doi:10.1007/s00213-011-2440-z.
- [39] C. Yin, L. Gou, Y. Liu, X. Yin, L. Zhang, G. Jia, X. Zhuang, Antidepressant-like effects of L-theanine in the forced swim and tail suspension tests in mice, *Phytother Res.* 25 (2011) 1636–1639. doi:10.1002/ptr.3456.

- [40] T.P. Rao, M. Ozeki, L.R. Juneja, In Search of a Safe Natural Sleep Aid, *J Am Coll Nutr.* 34 (2015) 436–447. doi:10.1080/07315724.2014.926153.
- [41] W. Löscher, H.H. Frey, Transport of GABA at the blood-CSF interface, *J. Neurochem.* 38 (1982) 1072–1079.
- [42] N. Shyamaladevi, A.R. Jayakumar, R. Sujatha, V. Paul, E.H. Subramanian, Evidence that nitric oxide production increases gamma-amino butyric acid permeability of blood-brain barrier, *Brain Res. Bull.* 57 (2002) 231–236.
- [43] S. Kim, K. Jo, K.-B. Hong, S.H. Han, H.J. Suh, GABA and l-theanine mixture decreases sleep latency and improves NREM sleep, *Pharm Biol.* 57 (2019) 65–73. doi:10.1080/13880209.2018.1557698.
- [44] M.R. Lyon, M.P. Kapoor, L.R. Juneja, The effects of L-theanine (Suntheanine®) on objective sleep quality in boys with attention deficit hyperactivity disorder (ADHD): a randomized, double-blind, placebo-controlled clinical trial, *Altern Med Rev.* 16 (2011) 348–354.
- [45] K. Singh, A.W. Zimmerman, Sleep in Autism Spectrum Disorder and Attention Deficit Hyperactivity Disorder, *Seminars in Pediatric Neurology.* 22 (2015) 113–125. doi:10.1016/j.spen.2015.03.006.
- [46] M. Davidovitch, G. Koren, N. Fund, M. Shrem, A. Porath, Challenges in defining the rates of ADHD diagnosis and treatment: trends over the last decade, *BMC Pediatr.* 17 (2017). doi:10.1186/s12887-017-0971-0.
- [47] M. Ota, C. Wakabayashi, N. Sato, H. Hori, K. Hattori, T. Teraishi, H. Ozawa, T. Okubo, H. Kunugi, Effect of L-theanine on glutamatergic function in patients with schizophrenia, *Acta Neuropsychiatr.* 27 (2015) 291–296. doi:10.1017/neu.2015.22.
- [48] A.L. Lardner, Neurobiological effects of the green tea constituent theanine and its potential role in the treatment of psychiatric and neurodegenerative disorders, *Nutr Neurosci.* 17 (2014) 145–155. doi:10.1179/1476830513Y.0000000079.
- [49] P.J. Nathan, K. Lu, M. Gray, C. Oliver, The neuropharmacology of L-theanine (N-ethyl-L-glutamine): a possible neuroprotective and cognitive enhancing agent, *J Herb Pharmacother.* 6 (2006) 21–30.
- [50] T. Kakuda, Neuroprotective effects of theanine and its preventive effects on cognitive dysfunction, *Pharmacol. Res.* 64 (2011) 162–168. doi:10.1016/j.phrs.2011.03.010.
- [51] T. Yamada, T. Terashima, T. Okubo, L.R. Juneja, H. Yokogoshi, Effects of theanine, r-glutamylethylamide, on neurotransmitter release and its relationship with glutamic acid neurotransmission, *Nutr Neurosci.* 8 (2005) 219–226. doi:10.1080/10284150500170799.
- [52] T. Kakuda, E. Hinoi, A. Abe, A. Nozawa, M. Ogura, Y. Yoneda, Theanine, an ingredient of green tea, inhibits [3H]glutamine transport in neurons and astroglia in rat brain, *J. Neurosci. Res.* 86 (2008) 1846–1856. doi:10.1002/jnr.21637.
- [53] L. Hertz, The Glutamate-Glutamine (GABA) Cycle: Importance of Late Postnatal Development and Potential Reciprocal Interactions between Biosynthesis and Degradation, *Front Endocrinol (Lausanne).* 4 (2013) 59. doi:10.3389/fendo.2013.00059.
- [54] Y. Yoneda, An L-Glutamine Transporter Isoform for Neurogenesis Facilitated by L-Theanine, *Neurochem. Res.* 42 (2017) 2686–2697. doi:10.1007/s11064-017-2317-6.
- [55] Y. Kanai, B. Cléménçon, A. Simonin, M. Leuenberger, M. Lochner, M. Weisstanner, M.A. Hediger, The SLC1 high-affinity glutamate and neutral amino acid transporter family, *Mol. Aspects Med.* 34 (2013) 108–120. doi:10.1016/j.mam.2013.01.001.

- [56] T.A. Baskerville, A.J. Douglas, Dopamine and Oxytocin Interactions Underlying Behaviors: Potential Contributions to Behavioral Disorders, *CNS Neuroscience & Therapeutics*. 16 (2010) e92–e123. doi:10.1111/j.1755-5949.2010.00154.x.
- [57] C. Chiapponi, F. Piras, F. Piras, C. Caltagirone, G. Spalletta, GABA System in Schizophrenia and Mood Disorders: A Mini Review on Third-Generation Imaging Studies, *Front. Psychiatry*. 7 (2016). doi:10.3389/fpsyt.2016.00061.
- [58] S.N. Young, M. Leyton, The role of serotonin in human mood and social interaction. Insight from altered tryptophan levels, *Pharmacol. Biochem. Behav.* 71 (2002) 857–865.
- [59] M. Shen, Y. Yang, Y. Wu, B. Zhang, H. Wu, L. Wang, H. Tang, J. Chen, L-theanine ameliorate depressive-like behavior in a chronic unpredictable mild stress rat model via modulating the monoamine levels in limbic-cortical-striatal-pallidal-thalamic-circuit related brain regions, *Phytother Res.* 33 (2019) 412–421. doi:10.1002/ptr.6237.
- [60] H. Yokogoshi, M. Kobayashi, M. Mochizuki, T. Terashima, Effect of theanine, *r*-glutamylethylamide, on brain monoamines and striatal dopamine release in conscious rats, *Neurochem. Res.* 23 (1998) 667–673.
- [61] S. Ogawa, M. Ota, J. Ogura, K. Kato, H. Kunugi, Effects of L-theanine on anxiety-like behavior, cerebrospinal fluid amino acid profile, and hippocampal activity in Wistar Kyoto rats, *Psychopharmacology (Berl.)*. 235 (2018) 37–45. doi:10.1007/s00213-017-4743-1.
- [62] E. Boonstra, R. de Kleijn, L.S. Colzato, A. Alkemade, B.U. Forstmann, S. Nieuwenhuis, Neurotransmitters as food supplements: the effects of GABA on brain and behavior, *Front Psychol.* 6 (2015). doi:10.3389/fpsyg.2015.01520.
- [63] F. Jie, G. Yin, W. Yang, M. Yang, S. Gao, J. Lv, B. Li, Stress in Regulation of GABA Amygdala System and Relevance to Neuropsychiatric Diseases, *Front Neurosci.* 12 (2018). doi:10.3389/fnins.2018.00562.
- [64] M. Beaumont, D. Batéjat, C. Piérard, P. Van Beers, J.B. Denis, O. Coste, P. Doireau, F. Chauffard, J. French, D. Lagarde, Caffeine or melatonin effects on sleep and sleepiness after rapid eastward transmeridian travel, *J. Appl. Physiol.* 96 (2004) 50–58. doi:10.1152/jappphysiol.00940.2002.
- [65] S. Kitaoka, H. Hayashi, H. Yokogoshi, Y. Suzuki, Transmural potential changes associated with the in vitro absorption of theanine in the guinea pig intestine, *Biosci. Biotechnol. Biochem.* 60 (1996) 1768–1771. doi:10.1271/bbb.60.1768.
- [66] T. Unno, Y. Suzuki, T. Kakuda, T. Hayakawa, H. Tsuge, Metabolism of theanine, gamma-glutamylethylamide, in rats, *J. Agric. Food Chem.* 47 (1999) 1593–1596.
- [67] T. Terashima, J. Takido, H. Yokogoshi, Time-dependent changes of amino acids in the serum, liver, brain and urine of rats administered with theanine, *Biosci. Biotechnol. Biochem.* 63 (1999) 615–618.
- [68] S. Sang, J.D. Lambert, C.-T. Ho, C.S. Yang, The chemistry and biotransformation of tea constituents, *Pharmacol. Res.* 64 (2011) 87–99. doi:10.1016/j.phrs.2011.02.007.
- [69] A.C. Nobre, A. Rao, G.N. Owen, L-theanine, a natural constituent in tea, and its effect on mental state, *Asia Pac J Clin Nutr.* 17 Suppl 1 (2008) 167–168.
- [70] Y. Ying, J.W. Ho, Z.Y. Chen, J. Wang, Analysis of Theanine in Tea Leaves by HPLC with Fluorescence Detection, *Journal of Liquid Chromatography & Related Technologies.* 28 (2005) 727–737. doi:10.1081/JLC-200048894.
- [71] A. Alcázar, O. Ballesteros, J.M. Jurado, F. Pablos, M.J. Martín, J.L. Vilches, A. Navalón, Differentiation of green, white, black, Oolong, and Pu-erh teas according to

- their free amino acids content, *J. Agric. Food Chem.* 55 (2007) 5960–5965. doi:10.1021/jf070601a.
- [72] D.A. Camfield, C. Stough, J. Farrimond, A.B. Scholey, Acute effects of tea constituents L-theanine, caffeine, and epigallocatechin gallate on cognitive function and mood: a systematic review and meta-analysis, *Nutr. Rev.* 72 (2014) 507–522. doi:10.1111/nure.12120.
- [73] X. Dong, C. Yang, S. Cao, Y. Gan, H. Sun, Y. Gong, H. Yang, X. Yin, Z. Lu, Tea consumption and the risk of depression: a meta-analysis of observational studies, *Aust N Z J Psychiatry.* 49 (2015) 334–345. doi:10.1177/0004867414567759.
- [74] X. Liu, X. Du, G. Han, W. Gao, Association between tea consumption and risk of cognitive disorders: A dose-response meta-analysis of observational studies, *Oncotarget.* 8 (2017) 43306–43321. doi:10.18632/oncotarget.17429.
- [75] S. Kuriyama, A. Hozawa, K. Ohmori, T. Shimazu, T. Matsui, S. Ebihara, S. Awata, R. Nagatomi, H. Arai, I. Tsuji, Green tea consumption and cognitive function: a cross-sectional study from the Tsurugaya Project 1, *Am. J. Clin. Nutr.* 83 (2006) 355–361. doi:10.1093/ajcn/83.2.355.
- [76] L. Colucci, M. Bosco, A.R. Ziello, R. Rea, F. Amenta, A.M. Fasanaro, Effectiveness of nootropic drugs with cholinergic activity in treatment of cognitive deficit: a review, *J Exp Pharmacol.* 4 (2012) 163–172. doi:10.2147/JEP.S35326.
- [77] A. Panossian, G. Wikman, Effects of Adaptogens on the Central Nervous System and the Molecular Mechanisms Associated with Their Stress—Protective Activity, *Pharmaceuticals (Basel).* 3 (2010) 188–224. doi:10.3390/ph3010188.
- [78] S. Borgwardt, F. Hammann, K. Scheffler, M. Kreuter, J. Drewe, C. Beglinger, Neural effects of green tea extract on dorsolateral prefrontal cortex, *Eur J Clin Nutr.* 66 (2012) 1187–1192. doi:10.1038/ejcn.2012.105.
- [79] A. Schmidt, F. Hammann, B. Wölnerhanssen, A.C. Meyer-Gerspach, J. Drewe, C. Beglinger, S. Borgwardt, Green tea extract enhances parieto-frontal connectivity during working memory processing, *Psychopharmacology (Berl).* 231 (2014) 3879–3888. doi:10.1007/s00213-014-3526-1.
- [80] B.V.S. Chandrasekhar, E. P, S.U. Maheswari, D. Rajukumar, A Focus on the Effect of L-Theanine on Improving Depression and Cognition in C57BL/J Male Mice Subjected for Chronic Stress Induced Neuroinflammation, *Biomedical and Pharmacology Journal.* 10 (2017) 1015–1027. <http://biomedpharmajournal.org/vol11no2/a-focus-on-the-effect-of-l-theanine-on-improving-depression-and-cognition-in-c57blj-male-mice-subjected-for-chronic-stress-induced-neuroinflammation/> (accessed August 1, 2019).
- [81] J.J. Foxe, K.P. Morie, P.J. Laud, M.J. Rowson, E.A. de Bruin, S.P. Kelly, Assessing the effects of caffeine and theanine on the maintenance of vigilance during a sustained attention task, *Neuropharmacology.* 62 (2012) 2320–2327. doi:10.1016/j.neuropharm.2012.01.020.
- [82] D. Wang, J. Meng, K. Xu, R. Xiao, M. Xu, Y. Liu, Y. Zhao, P. Yao, H. Yan, L. Liu, Evaluation of oral subchronic toxicity of Pu-erh green tea (*camellia sinensis* var. *assamica*) extract in Sprague Dawley rats, *J Ethnopharmacol.* 142 (2012) 836–844. doi:10.1016/j.jep.2012.06.011.
- [83] K.-M. Wu, J. Yao, D. Boring, Green tea extract-induced lethal toxicity in fasted but not in nonfasted dogs, *Int. J. Toxicol.* 30 (2011) 19–20. doi:10.1177/1091581810387445.

- [84] X.-C. Yu, B.-L. Wu, J.-C. Gao, W. Yang, Theanine enhanced both the toxicity of strychnine and anticonvulsion of pentobarbital sodium, *Drug Chem Toxicol.* 39 (2016) 217–223. doi:10.3109/01480545.2015.1080264.
- [85] A. Javaid, H.L. Bonkovsky, Hepatotoxicity due to extracts of Chinese green tea (*Camellia sinensis*): a growing concern, *J. Hepatol.* 45 (2006) 334–335; author reply 335–336. doi:10.1016/j.jhep.2006.05.005.
- [86] M. Jimenez-Saenz, M.D.C. Martinez-Sanchez, Acute hepatitis associated with the use of green tea infusions, *J. Hepatol.* 44 (2006) 616–617. doi:10.1016/j.jhep.2005.11.041.
- [87] G. Mazzanti, A. Di Sotto, A. Vitalone, Hepatotoxicity of green tea: an update, *Arch. Toxicol.* 89 (2015) 1175–1191. doi:10.1007/s00204-015-1521-x.
- [88] R. Teschke, L. Zhang, L. Melzer, J. Schulze, A. Eickhoff, Green tea extract and the risk of drug-induced liver injury, *Expert Opin Drug Metab Toxicol.* 10 (2014) 1663–1676. doi:10.1517/17425255.2014.971011.

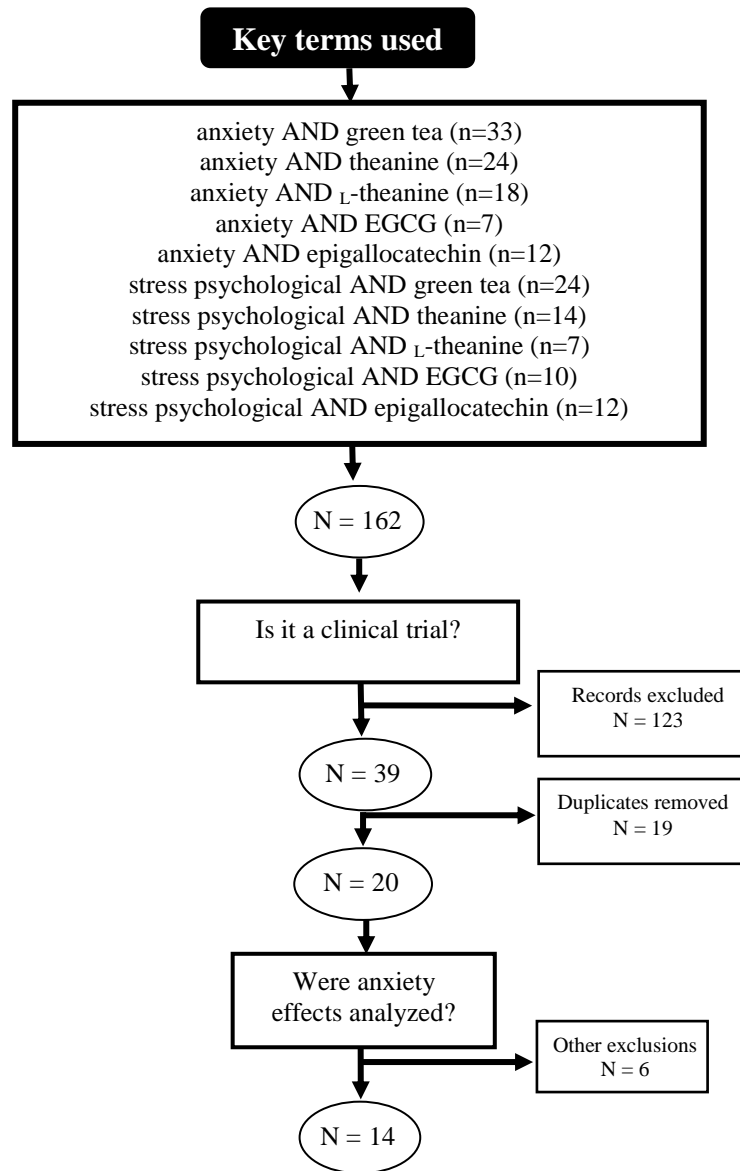


Figure 1. Flowchart diagram illustrating the selection process of included studies.

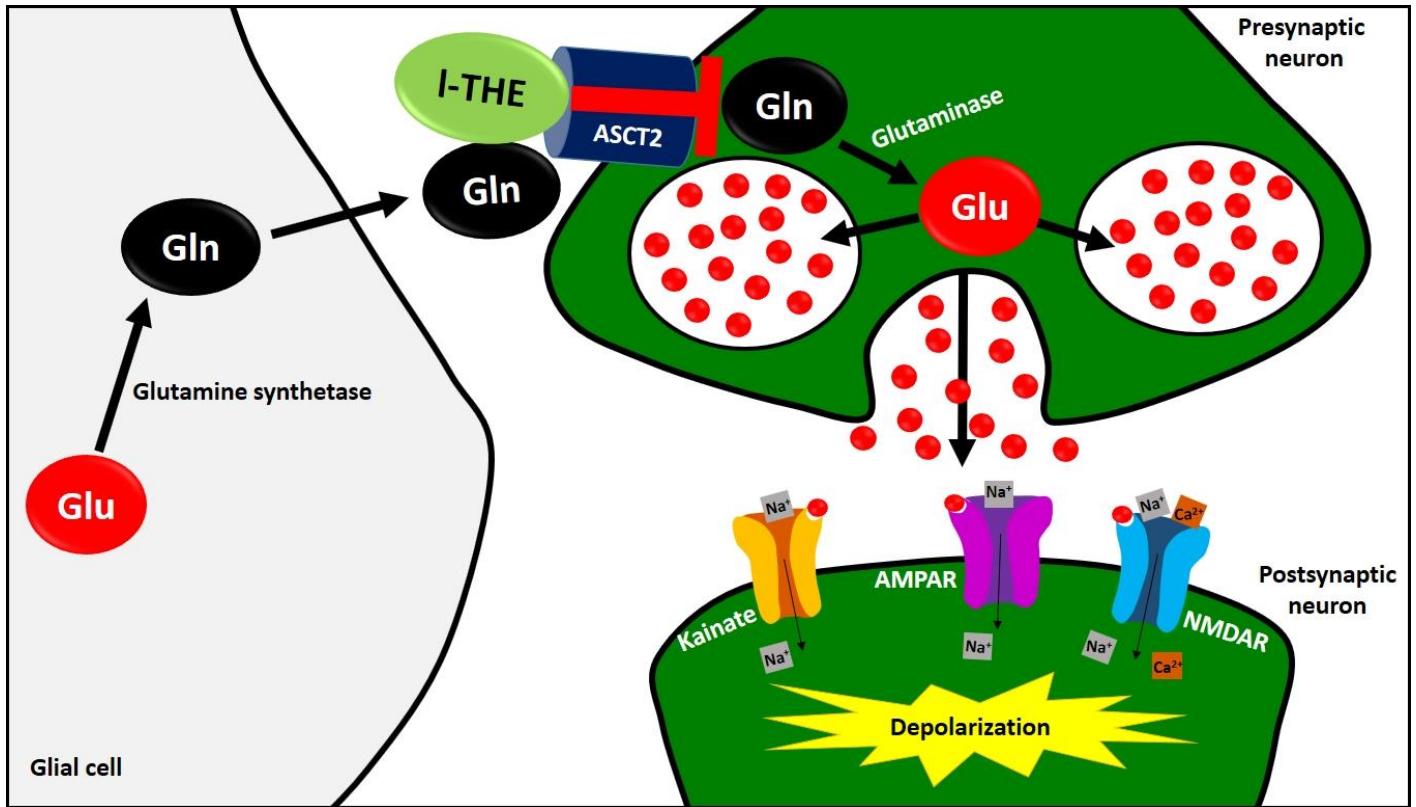


Figure 2. Antagonistic action of L-theanine *versus* glutamine at the ASCT2 transporter attenuates glutamatergic activation, via reduced presynaptic production of glutamate, and consequently suppressed binding to its ionotropic NMDA, AMPA and kainate postsynaptic receptors. Influx of depolarizing Na⁺ and Ca²⁺ currents is hindered, triggering a decreased depolarization pattern. AMPAR: α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; Gln: glutamine; Glu: glutamate; I-THE: L-theanine; NMDAR: N-methyl-D-aspartate receptor.

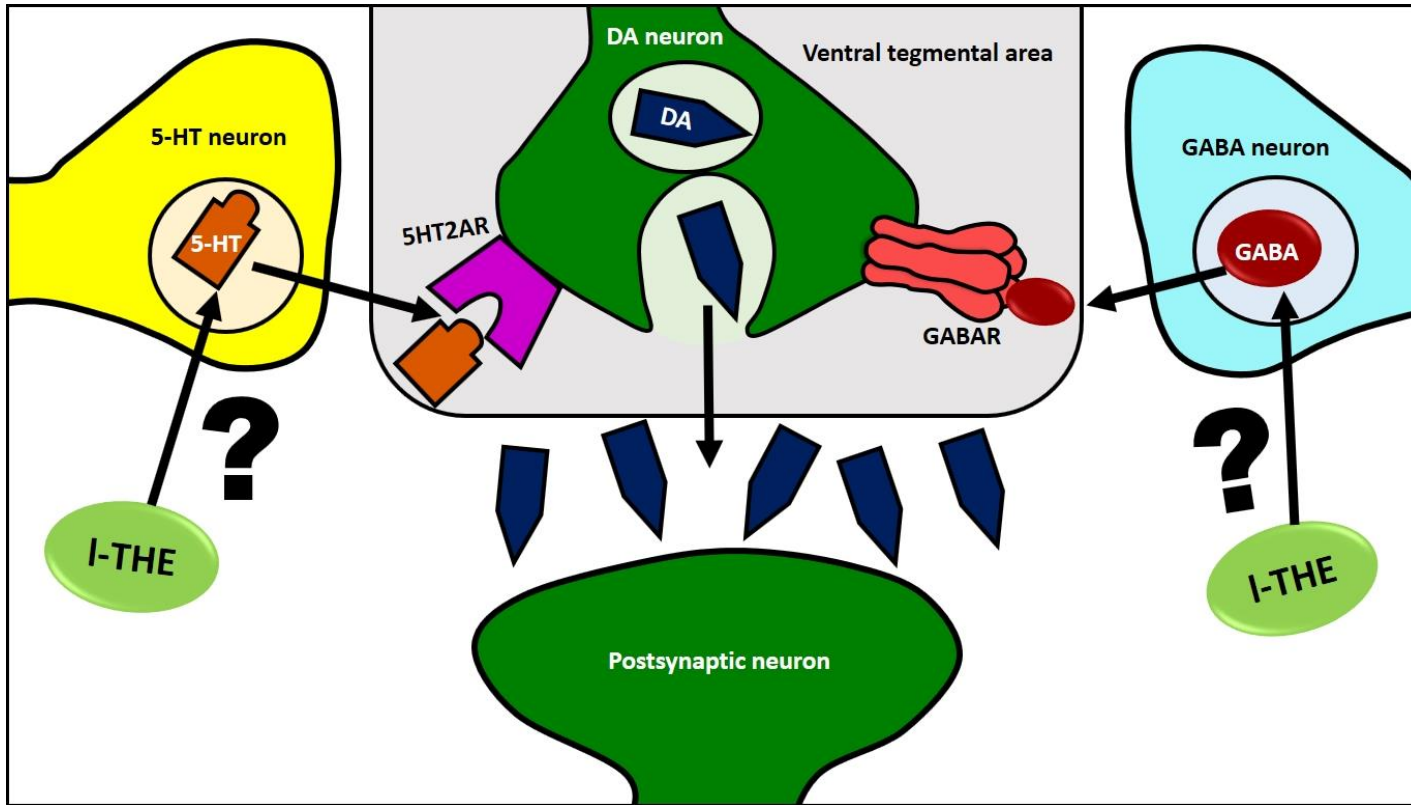


Figure 3. L-theanine appears to increase dopamine levels. Likewise, L-theanine may increase serotonin and GABA concentrations, which are neurotransmitters associated with dopaminergic circuitry. The neurophysiological roles of the three neurotransmitters corroborate the clinical findings in behavior and mood, including stress, fear and social interactions [62–64]. However, the exact mechanism through which L-theanine increases serotonin, GABA and dopamine levels remains an area for future investigation. DA:

dopamine; GABA: gamma-aminobutyric acid; GABAR: gamma-aminobutyric acid receptor; L-THE: L-theanine; 5-HT: serotonin; 5HT2AR, serotonin 2A receptor.

Graphical abstract

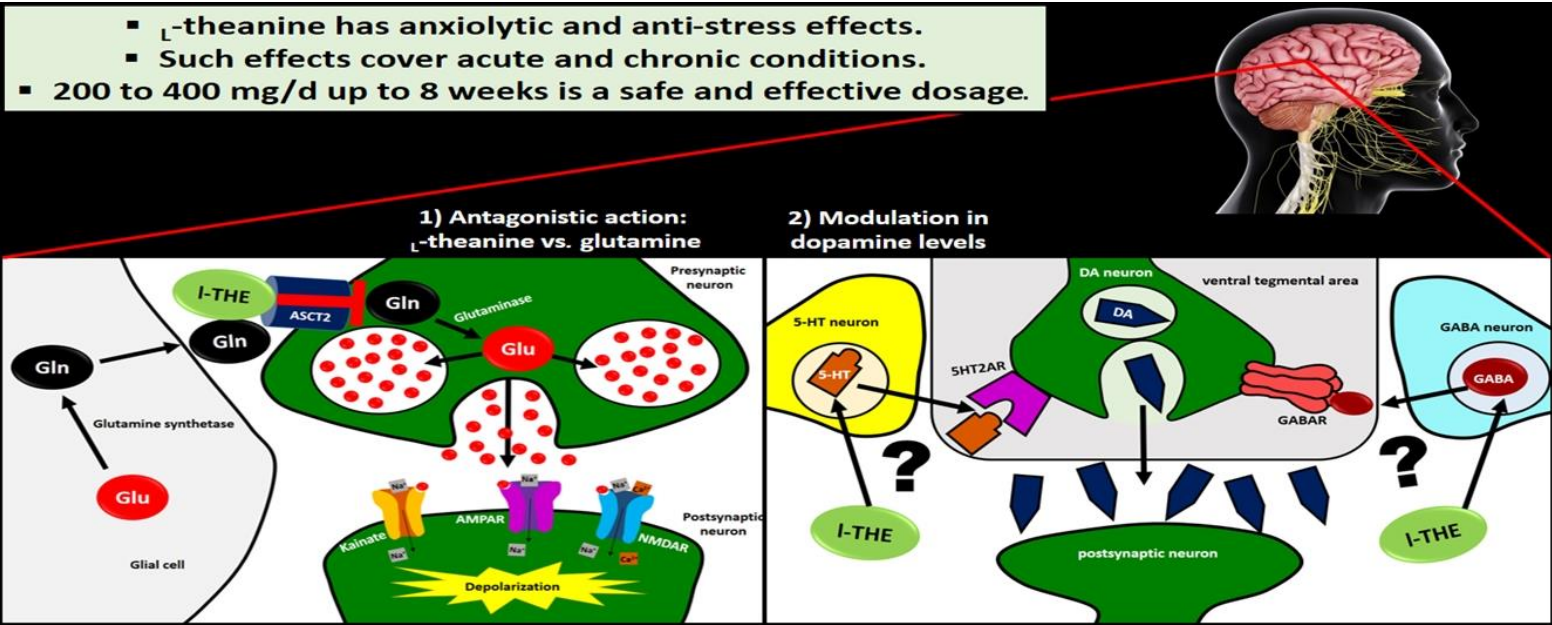


Table 1. Clinical effects of L-theanine administration on anxiety and stress outcomes

Authors	Subjects	Study Design (period of intervention)	Daily dose	Anxiety and stress outcomes
Sarris et al. 2019 [36]	46 participants with a DSM-5 diagnosis of GAD	Double-blind, placebo-controlled trial (8 weeks) with 1-week pre-study and 2-week post-study single-blinded observational periods	450–900 mg L-theanine	L-theanine did not outperform placebo for anxiety reduction on the HARS, nor insomnia severity on the Insomnia Severity Index. No significant cognitive effects were found. L-theanine-treated participants self-reported greater sleep satisfaction than placebo.
Kardashev et al. 2018 [37]	40 chronic schizophrenia and schizoaffective disorder patients	Double-blind, placebo-controlled trial (8 weeks)	400 mg L-theanine + 50 mg oral pregnenolone	Supplementation was associated with reduction of anxiety scores including anxious mood, tension, and cardiovascular symptoms, and elevation of general functioning. Negative symptoms including blunted affect, alogia, and anhedonia significantly improved with moderate effect sizes compared to control group.
Unno et al., 2017 [28]	20 college students	Pilot study, randomized into low-caffeine green tea or placebo barley tea groups (17 d)	15 mg of L-theanine/500 mL of low-caffeine green tea	sAA level increased significantly in the placebo group but not in the low-caffeine green tea group. There was no difference in STAI values between groups.
Hidese et al., 2017 [24]	20 patients with MDD	Open-label study (8 weeks)	250 mg L-theanine	HAMD-21 score was reduced. Anxiety-trait scores decreased in the STAI test. PSQI scores also decreased. Regarding cognitive functions, response latency and error

				rate decreased in the Stroop test; verbal memory and executive function were enhanced in the BACS test.
White et al., 2016 [29]	36 health adults	Acute double-blind, placebo-controlled, crossover trial (analysis performed 1 and 3 h post-dose)	200 mg of L-theanine + 25 mg of alpha glycerylphosphorylcholine + 1 mg of phosphatidylserine + 10 mg of micronized chamomile	Subjective stress response to a multitasking cognitive stressor significantly reduced 1 h after compared to placebo. Salivary cortisol response to stressor was reduced 3 h after following active treatment. No treatment-related cognitive performance changes were observed. Resting state alpha oscillatory activity was significantly increased in posterior MEG sensors after active treatment compared to placebo 2 h post-dose.
Yoto et al., 2014 [30]	18 healthy college students	Cross-over study, randomized into ordinary green tea, shaded white tea and warm water	17 mg of L-theanine in the green tea test 52 mg of L-theanine in the shaded white test	Salivary chromogranin A concentration increased after mental tasks, but intake of green tea inhibited this increase; the anti-stress effect was even greater after consumption of shaded white tea. Shaded white tea intake also lowered total mood disturbance (TMD) score on the profile of mood states (POMS).
Unno et al., 2013 [34]	20 healthy college students	Single-blind placebo controlled study (17 d)	200 mg mg of L-theanine 2 x/d	sAA level in the morning was higher than in L-theanine group compare with the placebo group. Subjective stress was significantly lower in the Ltheanine group than in the placebo group. Higher sAA level was correlated to shorter sleeping time in both groups.
Yoto et al., 2012 [35]	14 healthy college students	Acute cross-over study randomized into L-	200 mg of L-theanine 100 mg of caffeine	After mental tasks L-theanine significantly inhibited blood pressure increase in a high response group and reduced

		theanine + placebo, caffeine + placebo, or placebo only (analysis performed min post-dose)		the tension-anxiety scores compared with placebo.
Miodownik et al., 2011 [32]	60 schizophrenia and schizoaffective disorder patients	Double-blind, randomized, placebo- controlled trial (8 weeks)	400 mg of L-theanine	Circulating levels of BDNF and cortisol/DHEAS ratio were significantly associated with L-theanine intake. Variability of serum BDNF levels accounted for 26.2% of the total variance in reduction of dysphoric mood and 38.2% in anxiety scores. Cortisol/DHEAS ratio changed for 30% to 34% of the variance in activation factor and dysphoric mood scores and for 15.9% in anxiety scores.
Ritsner et al., 2011 [25]	40 schizophrenia and schizoaffective disorder patients	Double-blind, randomized, placebo- controlled trial (8 weeks)	400 mg of L-theanine	Compared with placebo, L-theanine intake was associated with reduction of anxiety measured by the HARS, and positive and general psychopathology scores measured by the PANSS 3-factor dimensional model. According to the 5-dimension model of psychopathology, L-theanine produced significant reductions on PANSS positive and activation factor scores compared to placebo.
Rogers et al., 2008 [33]	48 healthy adult participants	Acute double-blind, placebo-controlled study, randomized into L- theanine, caffeine, both	200 mg of L-theanine 250 mg of caffeine	L-theanine antagonized the effect of caffeine on blood pressure but did not significantly affect jitteriness, alertness or other aspects of mood, whereas caffeine increased self-rated alertness and jitteriness and blood

			or neither of these (analysis performed 40 min post-dose).		pressure. L-theanine slowed overall reaction time on the visual probe task
Kimura et al., 2007 [27]	12 healthy college students	Acute	double-blind, randomized, placebo-controlled trial (mental arithmetic task performed in each 5 min up to 20 min post-dose)	200 mg of L-theanine	L-theanine intake decreased heart rate and salivary immunoglobulin A responses to acute stress task when compared to placebo. These results were likely attributable to attenuation of sympathetic motor activation.
Abdou et al., 2006 [31]	13 healthy volunteers	Acute	crossover-test for L-theanine, GABA and placebo with 7-day intervals (3 measurements at 0, 30, and 60 min after each administration)	200 mg of L-theanine of GABA	L-theanine and GABA increased alpha wave generation ratio compared to placebo.
Lu et al., 2004 [26]	16 healthy subjects	Acute	double-blind repeated measures design by which all subjects were tested for alprazolam, L-theanine or placebo (under a relaxed and experimentally induced anxiety	200 mg of L-theanine 1 mg of alprazolam	L-theanine showed some evidence for relaxing effects on the tranquil-troubled subscale of the VAMS. Neither L-theanine nor alprazolam had any significant anxiolytic effects during the experimentally induced anxiety state.

condition, the effects
were assessed between -
1 h and 5 h after
administration)

Alpha GPC, L-alpha glycerylphosphorylcholine; BACS, brief assessment of cognition in schizophrenia; BDNF, brain derived neurotrophic factor; DHEA, dehydroepiandrosterone; DHEAS, dehydroepiandrosterone sulfate; DSM-5, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; HARS, Hamilton anxiety rating scale; GABA, gamma-aminobutyric acid; GAD, generalized anxiety disorder; MEG, magnetoencephalography; PANSS, positive and negative syndrome scale; PSQI, Pittsburgh sleep quality index; sAA, salivary alpha amylase; VAMS, visual analogue mood scale; STAI, state-trait anxiety inventory.