L-theanine as a promising agent on brain health-promoting foods – A review

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Abstract: With the aging of the population and the growing pressure of social competition, brain-related neurodegenerative diseases and mental disorders increasingly affect our quality of life and place a huge burden on health systems around world. L-theanine is a unique non-protein amino acid from tea leave, and now commercially available as a safe food ingredient in the market. This review summarizes the studies on the effects of L-theanine on various mental and brain conditions, including mental stress, anxiety, insomnia, depression, poor learning ability and memory, neurodegenerative diseases, and discusses its potential application in functional foods for brain health.

Keywords: L-theanine, brain diseases, functional food, brain health

1. Introduction

Tea is an ancient herbal beverage derived from the leaves of the plant *Camellia sinensis*, and currently ranked as the second most widely consumed drink in the world after water. The popularity of tea consumption is typically due to its pleasing astringent taste and refreshing boost as well as its widely acknowledged health benefits, including anti-aging, anti-diabetic, pro-metabolic, immune boosting, anti-depression effects (Rothenberg and Zhang, 2019; Sharangi, 2009). In recent years, increasing social competition pressure and aging population are associated with increasing risks of mental illness, such as depression, insomnia and anxiety, as well as neurodegenerative diseases, including dementia, Parkinson's disease and Alzheimer's disease (Rothenberg and Zhang, 2019; Deb et al., 2019). These mental conditions and brain diseases are more and more seriously affecting our life quality, and placing a huge burden on health systems around world, while the treatment options are still limited. Meanwhile, it is common knowledge that healthy diets, especially drinking tea, could exert beneficial effects on the mood, memory, attention and brain health. A recent epidemiological study conducted in a healthy Korean population, has demonstrated that tea consumption is inversely associated with the development of depression (Kim and Kim, 2018). Another study of people aged over 55 in Singapore suggested that long-term habitual tea consumption, even as less as one cup of tea per week, might reduce the risk of dementia via improving the memory and information-processing capacity (Feng et al., 2010). Among the numerous bioactive compounds presented in all major tea types, predominantly L-theanine, caffeine, catechins, flavonoids and their metabolites, are capable of functioning through various pathways simultaneously to improve mood and brain health (Rothenberg and Zhang, 2019; Dietz and Dekker, 2017). Therefore, the scientists are exploring tea or its purified compound as a natural dietary agent in the role of nutrition in mental health and preventive medicine (Gilbert, 2019).

L-theanine, also known as γ-glutamylethylamide, is first discovered and isolated by Sakato in the 1940s (Sakato, 1950). It is the most abundant non-proteinogenic amino acid, accounting for more than 50% of total amino acids in tea. L-theanine is water-soluble and considered as an important contributor to the distinctive aroma and the

‘umami’ taste of tea infusion (Guo et al., 2018). Accumulating evidence reveal that L-theanine administration is strongly related to various benefits on brain health, such as anti-stress and neuroprotective role through a number of potential routes (Deb et.al, 2019; Sharma et al., 2018; Hidese et al., 2019; Dramard et al., 2018; Ben et al., 2016). First, L-theanine is structurally similar to glutamic acid and glutamate (Fig. 1). Glutamate, synthesized from its precursor glutamine, is the most abundant amino acid in the brain and has been found to be involving in several important behavioral and physiological functions (William et al., 2020). The healthy functions of L-theanine intake can partially be associated with its ability of regulating the binding of glutamate and glutamate receptors in the brain (Debs et al., 2019). Second, chronic L-theanine administration is able to facilitate neurogenesis in the developing hippocampus. Third, L-theanine is effective in providing the protection against neuronal cell apoptosis in the brain (Ben et al., 2016) via reducing the oxidative stress-induced damages and downregulating the abnormal expression of inflammatory marker in the brain (Sumathi et al., 2016). Finally, animal and human studies suggest that L-theanine intake has a significant effect on the regulation of neurotransmitters like dopamine and serotonin, stimulating the production of alpha brain waves, decreasing blood pressure and heart rate (Yoto et al., 2012; Huneja, et al., 2013).

L-theanine can be daily supplemented through tea drinking, while the L-theanine content of tea varies considerably. Keenan et al. determined the amounts of L-theanine contained in commercially-available teas and found that a standard cup (200 mL) of green tea and black tea prepared under the regular brewing conditions contain around 8 and 25 mg L-theanine, respectively (Keenan et al., 2011). After L-theanine was orally administrated, it can be quickly absorbed and transported through the brush-border membrane by a common Na(+)-coupled co-transporter in the intestine and enters systemic circulation (Kitaoka et al., 1996). L-theanine reaches the peak serum concentration after approximately 50 min of administration, and most of L-theanine is thought to be hydrolyzed to ethylamine and glutamic acid (Van der Pijl et al., 2010; Scheid et al., 2012). Absorbed L-theanine freely passes the blood–brain barrier and reaches the brain tissue within 30 min, which is also confirmed by the changes of

resting-state α-wave activity in healthy volunteers after oral intake of L-theanine (Juneja et al., 1999). The concentration of L-theanine continuously increases and reaches its maximum level in the brain within 5 hours. Within 24 hours, L-theanine and its metabolites are gradually excreted by urine and completely eliminated from plasma and the brain (Scheid et al., 2012).

Explorations into the effects of natural compounds on mental and brain health attract growing scientific and industrial interests in the role of nutrition in mental health and preventive medicine. As the most important amino acid derived from tea leaves, L-theanine has long been considered to exert both short- and long-term beneficial effects on mental and brain health, without causing any significant side-effects. Meanwhile, with development of massive-production technology of L-theanine, it is now commercially produced at decreasing cost in the factories through biological transformation, chemical synthesis or directly isolation from tea leaves. As a result, L-theanine has great potential on developing functional foods or drinks, which can be daily consumed to improve mood and promote brain-health. These L-theanine enriched food products can be tastier with the addition of L-theanine, and provide an effective and cheap way to tackle anxiety, depression and prevent age-related brain diseases, all these conditions already cause a huge burden on health systems in our modern society. This review summarizes the studies on the effects of L-theanine on various mental and brain conditions, including mental stress, anxiety, insomnia, depression, poor learning ability and memory, neurodegenerative diseases, and discusses its potential use in functional foods for brain health.

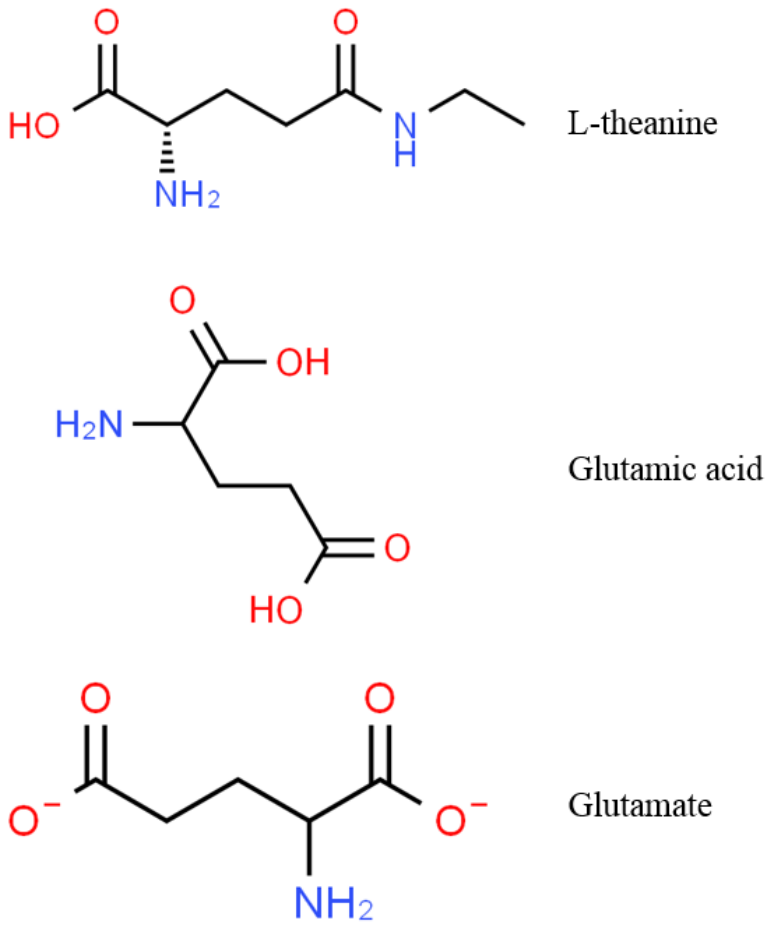

Fig. 1 Chemical structure of L-theanine, glutamic acid and glutamate

2. Health benefits of L-theanine on mental illness

2.1. Relieving stress and anxiety

Drinking tea has long been considered to be less stimulating and more relaxing than drinking coffee, even both of tea and coffee contain sufficient caffeine to induce alertness. This effect has been suggested to be due to the abundant existence of a unique amino acid L-theanine in tea. After tea consumption, L-theanine is quickly absorbed in the small intestine and transported across blood-brain barrier into the brain (Dassanayake et al., 2020). The beneficial effects of L-theanine on stress and anxiety have been extensively investigated and proven in the animals. For instance, an eight-week study examined the effects of L-theanine administration (25-50 mg twice daily) on the anxious dogs fearing unfamiliar human beings. The results suggest that L-theanine is effective for treating anxiety-related behaviors without causing any side

effects (Araujo et al., 2010). The similar anti-anxiety effect was confirmed in mice suffered chronic restraint stress produced by restraining in the polypropylene tubes. L-theanine (2 and 4 mg/kg) was administered orally followed by acute immobilized stress. Continuous consumption of L-theanine significantly ameliorate chronic stress-induced disorders, such as cognitive impairments and increased oxidative stress (Tian et al., 2013). In a recent human study, after four-week L-theanine administration (200 mg daily), the stress-related symptoms, Self-rating Depression Scale, State-Trait Anxiety Inventory-trait, and Pittsburgh Sleep Quality Index (PSQI) scores decreased, indicating that L-theanine has the potential to be a novel nutraceutical ingredient for promoting mental health in the general population with stress-related ailments (Hidese et. al., 2019).

Research indicates that L-theanine is able to relieve stress and anxiety by stimulating production of α-brain wave (Bryan, 2008), which is indicative of wakeful relaxation and decreased anxiety, as well as improved creativity, learning and concentration (Lardner, 2014; Gomez-Ramirez et al., 2007). Eight female university students, divided into high and low-anxiety groups, received a dose of oral administration of L-theanine (200 mg). After 30 mins, significantly increased α-brain wave activity in the occipital and parietal regions of the brains was detected in both groups using electroencephalography (EEG). The emission intensity of α-brain wave in the high-anxiety group was greater than that of low-anxiety group (Kobayashi et al., 1998). To investigate this effect at more realistic dietary levels of L-theanine, EEG was measured at 0, 45, 60, 75, 90 and 105 mins after ingestion of 50 mg L-theanine in the healthy young participants (n=16), who were resting with their eyes closed during EEG recording. The results showed that, compared with that of placebo (n=19), α-brain wave activity in the L-theanine group was significantly increased linearly with time (Nobre et al., 2008). When people are engaged in acute stress tasks such as the mental arithmetic and the public speaking, the physiological parameters, i.e. the heart rate and blood pressure, will be evaluated due to increased stress. L-theanine is found to be able to help regulate these stress-related physiological parameters, which further contributes to its anti-anxiety effect. In the healthy participants with induced high-stress, oral intake

of 200 mg L-theanine could attenuate the rise in heart rate, salivary immunoglobulin A responses (Kimura et al., 2007) and blood pressure (Yoto et al., 2012), suggesting that L-theanine could reduce stress and anxiety by inhibiting cortical neuron excitation.

2.2. Improving sleep quality

A lack of sleep is associated with an increased risk of various diseases and also responsible for compromised social behaviors, leading to a poor quality of life and negative socioeconomic consequences (Rao et al., 2015). As sleep inducers and sedatives always lead to undesired addiction and numerous side effects, such as drowsiness, decreased alertness and depression, L-theanine attracts increasing attention for its potential as a safe natural sleep aid.

In an animal study, low doses (22.5 and 37.5 mg/Kg) of L-theanine were found to attenuate the caffeine-induced sleep disturbances in rats through significantly promoting the slow-wave sleep. However, this effect is not dose-dependent and excessive L-theanine (i.e. 75 and 150 mg/Kg) intake may have the opposite effect and worsen sleep quality (Jang et al., 2015). The long-term effects of L-theanine administration on the sleep quality were examined in healthy adults (n=30), and four-week administration of L-theanine (200 mg daily) could significantly improve sleep quality via reducing sleep latency, sleep disturbance, and use of sleep medication, compared with the placebo administration (Hidese et al., 2019). L-theanine also exhibits promising effects on improving sleep quality in the population associated with mental illness. Sleep deprivation is commonly found among the population diagnosed with attention-deficit/hyperactivity disorder (ADHD). Lyon and co-workers (Lyon et al., 2011) investigated the efficacy and safety of L-theanine (400 mg per day, six weeks) as an aid to improve objective sleep quality in 98 boys with ADHD. It was found that, compared with the placebo group, L-theanine administration could significantly improve sleep percentage and sleep efficiency scores, along with a non-significant trend for less activity during sleep. However, it was noticeable that sleep latency remained unchanged in this study. Moreover, daily high dose (400 mg) of L-theanine administration was well tolerated without causing any significant adverse events.

Unlike many sleep inducers, L-theanine is suggested to be used during the daytime

due to its capacity on promoting relaxation and attention without drowsiness. It can effectively improve sleep quality through anxiolysis, which is required for the initiation of high-quality sleep. The studies indicate that L-theanine does not directly induce sleep but rather prepares the body and mind to enter sleep efficiently. Moreover, in a recent study, it was found that GABA/L-theanine mixture has a positive synergistic effect on sleep quality and duration in ICR mice (Kim et al., 2019). The results showed that, compared with GABA or L-theanine alone, GABA/L-theanine mixture (100/20 mg/Kg) could decrease sleep latency by 20.7% and 14.9%, and increase sleep duration by 87.3% and 26.8%, respectively.

2.3. Alleviating depression

In the modern society, depression is the most common psychiatric illness in the population, associated with impaired social function and increased suicide risks. Due to low efficiency and intolerable side effects caused by many antidepressants, this mental illness is becoming one of the most serious global health burden (Hidese et al., 2017). It has been found that L-theanine could be used as one of the natural herbal medicines for the potential application in mental diseases. Antidepressant-like effects of 10-day administration of L-theanine at doses of 1, 4 and 20 mg/Kg were confirmed in the depressed mice model induced by physical (forced swim, tail suspension) or reserpine treatments (Yin et al., 2011). Further research has demonstrated that, using the rats with depression as animal model, L-theanine (2 mg/kg) administration for 21 days could ameliorate behavioral disorders, and significantly increased circulating monoamine neurotransmitters, including serotonin (5-HT), norepinephrine (NE) and dopamine (DA) in limbic-cortical-striatal-pallidal-thalamic-circuit related brain regions (Shen et al., 2019). Moreover, after L-theanine is transported into the brain, it is able to induce the expression of brain-derived neurotrophic factor (BDNF) protein in the hippocampus, and exert the agonistic action on the *N*-methyl-D-aspartate (NMDA) receptor, which at least partially contributes to its antidepressant effect (Wakabayashi et al., 2012). Besides the promising results obtained from animal experiments, in an open-label clinical trial, the anti-depressive effects of chronic (8 weeks) L-theanine administration (250 mg daily) was investigated in 20 patients with major depressive

disorder. The result suggests that continuous L-theanine administration exerts multiple beneficial effects on depressive symptoms, as well as anxiety, sleep disorder and cognitive impairments in patients, without causing side effects (Hidese et al., 2017).

2.4. Enhancing learning ability and memory

It has been shown that L-theanine intake has a significant effect on the release or reduction of neurotransmitters like dopamine and serotonin, which are closely related to learning ability and memory (Juneja et al., 1999). Animal studies demonstrated that L-theanine administration is strongly related to the enhancement of cognitive, especially concerning learning and memory. A relatively high-dose (180 mg daily) of L-theanine was administered to weanling male Wistar rats for 4 months, and the rats showed improved learning ability and memory through the Operant test and Avoidance tests (Juneja et al., 1999). Chronic L-theanine intake also contributes to the postnatal development of hippocampal function in young rats fed with water containing 0.3% L-theanine (estimated to be around 4 mg/Kg daily) for weeks. The results demonstrated that chronic L-theanine administration is able to facilitate neurogenesis in the developing hippocampus via inducing the production of brain-derived neurotropic factor (BDNF) protein, and thus improve recognition memory (Takeda et al., 2011).

It was also found that low dose of L-theanine (i.e. one cup of tea, 25 mg L-theanine) could not exhibit significant acute effect on attention and learning ability in human (Kahathuduwa et al., 2017). There doses (100, 200 and 400 mg) of L-theanine and a placebo were consumed by 27 healthy young adults in a double-blind, placebo-controlled, counter balanced, 4-way crossover study. Compared to the placebo, L-theanine intake can improve attention in a dose-dependent manner (Dassanayake et al., 2020). Recent studies demonstrated that intake both caffeine and L-theanine through daily tea consumption contributes to the enhancement of cognitive, especially concerning learning and memory. Therefore, it is becoming popular to determine and compare the effects of L-theanine, caffeine or their combination on the learning and memory in human. In a randomized 4-way crossover human study, after 9 healthy participants took 200 mg of L-theanine, 160 mg of caffeine, their combination, or the placebo and rested for 60 mins, a functional magnetic resonance imaging (fMRI) scan

was performed during they performed a visual color stimulus discrimination task. It is confirmed that oral intake of L-theanine alone or in combination with caffeine were able to decrease fMRI responses to distractor stimuli in brain regions, and L-theanine and caffeine could exert a synergistic effect. The findings suggest that L-theanine helps human brain to attend to targets more efficiently through decreasing neural resource allocation to process distractors (Kahathuduwa et al., 2018). A recent study extended the findings by investigating effects of L-theanine (2.5 mg/Kg), caffeine (2.0 mg/Kg) and their combination on sustained attention and inhibitory control in boys with attention deficit hyperactivity disorder (ADHD). It is notable that caffeine or L-theanine alone worsened or had a trend of worsening inhibitory control among boys with ADHD. However, L-theanine-caffeine combination showed therapeutic potential on ADHD-associated impairments in sustained attention, inhibitory control and overall cognitive performance, partly through inhibiting mind wandering (Kahathuduwa et al., 2020). Besides purified caffeine, green tea extract could also be combined with L-theanine to enhance the effects on attention and cognitive. The beneficial effects of 16-week administration of a combination of green tea extract (1440 mg daily) and L-theanine (240 mg daily) was examined among 91 subjects with mild cognitive impairment (MCI) in a randomized, double-blind, placebo-controlled study. In the treatment group, the brain theta waves, an indicator of cognitive alertness, were noticeably increased in the temporal, frontal, parietal, and occipital areas. The supplementation of the combination improved memory and selective attention among MCI patients (Park et al., 2011). L-theanine is known to improve learning ability through enhancing attention. Considering all research, although the underlying mechanisms are complex and mostly unknown, it is clear that high dose of L-theanine (i.e. 200-400 mg daily), especially when it is combined with caffeine or tea extract, has acute and chronic beneficial effects in healthy human and the patients with impaired learning ability and memory.

2.5. Decreasing the risks of neurodegenerative diseases

Aging is a major cause for neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease, which are characterized by the progressive degeneration of the structure and function of the central nervous system or peripheral nervous system.

Along with the increasing number of human population older than 60 years, these neurodegenerative diseases lead to a significant social and economic burden (Zhu et al., 2018). Moreover, it remains a challenge of treating and managing these diseases using currently marketed therapeutic drugs due to their modest benefits and multiple side effects (Kulisevsky et al., 2014).

Increasing evidence suggests that L-theanine, as a safe food ingredient for long-term consumption, has a potential to reverse the pathophysiological changes associated with neurodegenerative disease through complex mechanisms, including stimulating the status of antioxidants in the brain, downregulating the expression of inflammatory cytokines, preserving striatal neurotransmitters homeostasis, and preventing glutamate excitotoxicity. Although glutamate is the principal excitatory neurotransmitter in brain and involved in important brain functions, excessively released glutamate into the extracellular space leads to over activation of glutamate receptors, AMPA receptor, Kainate receptor, and NMDA receptor (Balkhi et al., 2014). Over activation of glutamate receptors results in a phenomenon called 'neuronal excitotoxicity', which is responsible for neuronal cell death or damage. L-theanine is structurally similar to glutamate and glutamine, and thus capable of binding to all the three glutamate receptors subtypes and performing its neuroprotective effects through down-regulation of glutamate excitotoxicity (Debs et al., 2019). It was found that in an in vitro model of Alzheimer's disease, L-theanine significantly attenuated L-glutamate-induced apoptosis probably through blunting NMDA receptor-related pathways, modulating JNK-related cell signaling pathways as well as decreasing production of nitric oxide via down-regulating protein levels of inducible nitric oxide synthase (iNOS) and neuronal nitric oxide synthase (nNOS) (Di et al., 2010). In the rats with induced oxidative damage in the brain, oral administration of L-theanine (200 mg/Kg) increased the status of antioxidants, decreased the levels of lipid peroxide, nitric oxide and increased the activities of creatine kinase (CK), acetylcholinesterase (AchE), and ATPases in the hippocampus, cerebellum and cerebral cortex (Sumathi et al., 2016). Similarly, another animal study also found that treatment with L-theanine (25-50 mg/kg) significantly and dose dependently prevented 3-NP-induced striatal toxicity (Huntington disease-like

neuropathology) in rats by inhibiting detrimental nitric oxide production, decreasing proinflammatory cytokines levels and restoring striatal GABA, glutamate and catecholamine levels (Jamwal and Kumar, 2017). Moreover, intraperitoneal injection of L-theanine (100 or 200 mg/kg/day) in mice for 8 weeks was also found to be able to reduce Cadmium (Cd)-induced brain injury, a factor leading to neurological degenerative disorders. L-theanine significantly reduced Cd level in the mouse brain and plasma, and thus inhibited Cd-induced neuronal cell death in the mouse cortex and hippocampus. L-theanine suppressed the activation of glycogen synthase kinase-3b (GSK-3b) and thus inhibited tau protein hyperphosphorylation, which greatly attributes to Cd-induced cytotoxicity. Meanwhile, L-Theanine also improved the status of antioxidants in the mouse brain, by elevating the levels of glutathione (GSH) and activities of superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GSH-Px) (Ben et al., 2016)

3. Potential in functional foods

In modern society, an increasing number of people are facing much fiercer stress and anxiety from their daily work, study and life. Meanwhile, the incidence of neurodegenerative diseases is rapidly increasing in this so-called aging society. Both stress-induced mental illness and aging-related neurodegenerative diseases cause huge economic burden and significantly negative effects on the daily life. Therefore, the functional foods designed to enhance the mood and keep the brain healthy have recently attracted growing interest. L-theanine, a natural tea component, is emerging as one of the most popular ingredients in functional foods and drinks since its appealing taste and multiple roles in improving mood state and brain health. Although certain amount of L-theanine (around 20-100 mg) can be consumed through daily tea drinking, there are still many people don't have tea drinking habits. Even for tea drinkers, the studies suggest that a much higher dose of pure L-theanine is needed to exert maximum effectiveness on brain health (Deb et al., 2019; Kahathuduwa et al., 2017). Based on the findings of L-theanine, we suggest that integrating of commercial L-theanine in food matrix will provide a convenient delivery method, in which L-theanine can be easily accessible and bioavailable in concentrations sufficient to produce the desired physiological effects.

Besides its well-known functional effects on brain health, L-theanine has several advantages to be applied in functional foods. First, the safety of L-theanine has been well acknowledged. It was first allowed to be used as a common food additive in Japan in 1964, and then considered as a "generally recognized as safe" compound in USA since 1985. The result of a chronic toxicity test in mice indicated that even maximum tolerated dose of L-theanine (5% of the diet) is safe and non-poisonous (Fujii and Inai, 2008). Second, unlike dietary fiber and alkaloid, which could cause unpleasant flavor or taste after incorporating in the food matrix, L-theanine provides the distinctive aroma and the 'umami' taste to the food, making it more delicious. Third, L-theanine remains stable in the food processing conditions, such as a high temperatures of 121 ºC or an acid solution (pH 3.0 to 6.6), and able to be stored at room temperature for 12 months (Juneja et al., 1999). Third, pure L-theanine with reasonable cost is mass-produced in the factories and commercially available in the market.

Nowadays, increasing functional food products fortified with L-theanine have been developed and widely accepted by more and more consumers. The recommended dose of L-theanine in the food products ranges from 50-200 mg, which can be taken once or twice daily. In case of severe anxiety or stress conditions, 600-800 mg of L-theanine intake may be considered in increments of 100 mg to 200 mg spaced over the day. Functional beverage fortified with L-theanine may be the most convenient way to deliver the sufficient dose of L-theanine due to it is soluble and stable in the solution. In a recent study, the anti-stress effects of L-theanine-based nutrient beverage (200 mg of L-theanine) was investigated in a human trial. The results indicated that L-theanine drink significantly reduced subjective stress response a cognitive stressor, while no differences in cognitive performance were observed. This functional drink was also found to be more helpful to the participants with higher trait anxiety according to resting state MEG recordings (White et al., 2016). L-theanine can also be easily incorporated into solid food matrix, such as tropical fruit-flavored chewable tablet, gummy candy, and chocolate. A chocolate product (40 g) containing 60% cacao and 0.32% L-theanine was developed, and L-theanine was found to be able to reverse the acutely increased blood pressure stimulated by cacao ingestion in human. More interestingly, this study

suggests the possibility for the treatment of hypertension through long-term administration of the combination of cacao and L-theanine at higher doses (Montopoli et al., 2015).

Several natural compounds have been found to exhibit significant synergistic effects after being combined with L-theanine in the functional foods. For instant, caffeine is usually taken with L-theanine at a highly recommended ratio of 2:1 (L-theanine : caffeine) to improve attention and study ability. The combination of L-theanine and tea extract containing both caffeine and L-theanine is also popular, and the proportion of each compound should be calculated to adjust the ratio of L-theanine to caffeine to be 2:1. If this L-theanine product is taken before the meal, the effects should be noticed in around 30 min and may last 8 to 10 hours.

Forementioned L-theanine products have relatively simple food matrix, while the complex food matrix might have an impact on the pharmacokinetics and absorption rate of L-theanine. The physiological responses of a single intake of mango sorbet containing 200 mg of L-theanine was determined in the healthy participants (n=18) in a randomized, double-blind, placebo-controlled trial. It is notable that, this study found that L-theanine incorporated in this mango sorbet product showed no significant effects on blood pressure, heart rate or heart rate variability (William et al., 2020). Therefore, to realize the desired physiological effects, the impact of the composition of other food matrices like sugar, fat, protein, dietary fiber and concomitantly ingested meals on the pharmacokinetic behavior of L-theanine is needed to be extensively studied in future research.

4. Conclusion

With the pressures of an aging population and growing social competition, the search for safe natural products that can improve mood and prevent brain diseases is of great social importance. L-theanine has long been considered as a safe functional food ingredient worldwide, and now commercially produced by the factories. Research on the benefits of L-theanine intake on mental and brain health is ramping up, and the results from both clinical, animal and cell studies show that L-theanine has good

pharmacological effects in relieving stress, anti-anxiety, anti-depression, promoting sleep, improving learning ability and memory, protecting against neurodegenerative diseases. Considered its stability during the food processing and storage, L-theanine shows a great potential in the development of functional foods designed for the brain health, such as sleep aid, attention improvement and preventing brain disease. However, researchers still need to strengthen the understanding of the mechanisms of L-theanine intake in promoting mood and brain health, as well as the optimal doses required to produce short- and long-term therapeutical effects. Meanwhile, as integrated as part of a food matrix, the interaction among L-theanine and other food compounds and concomitantly ingested meals in humans has only been partially investigated to date.

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