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L-theanine adjunct to sertraline for major depressive disorder: A randomized, double-blind, placebo-controlled clinical trial

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ABSTRACT

Background: Unsatisfactory responses to major depressive disorder (MDD) therapeutics available necessitated up-to-date treatment approaches. This study sought to investigate the efficacy and tolerability of adjunctive L-theanine, a green tea constituent with neuropsychotropic effects, for MDD.

Methods: Sixty MDD (DSM-5) patients were equally assigned to receive sertraline (100 mg/d) plus either L-theanine (200 mg/d) or matched placebo in a six-week randomized, parallel-group, double-blind, placebo-controlled study. The participants were assessed using the Hamilton depression rating scale (HDRS) at baseline and weeks 2, 4, and 6. Changes in scores, early improvement, response and remission rates, and adverse events were compared between the groups.

Results: Twenty-five participants in each group, a total of 50 patients, completed the study. All baseline characteristics were similar between the groups. The general linear model repeated-measures analysis demonstrated a significant time-treatment interaction effect for HDRS during the trial (p-value = 0.014), indicating more remarkable symptom improvement in the L-theanine group. A greater reduction in HDRS scores was observed in the L-theanine group from baseline to weeks 2, 4, and 6 (p-values = 0.02, 0.03, and 0.01, respectively). All patients responded to sertraline plus L-theanine until week 6. L-theanine was superior to placebo regarding response to treatment and remission rates at week 6 (p-values = 0.05 and 0.02, respectively). The frequency of side effects was comparable between the groups.

Limitations: The small sample size and short study period were the limitations.

Conclusions: L-theanine adjunct to sertraline outperforms placebo in treating MDD in a safe manner. Further long-term, large-scale studies are recommended to confirm this evidence.

1. Introduction

Major depressive disorder (MDD), the most common psychiatric disorder worldwide, has considerable negative impacts on health and finances of society (Malhi and Mann, 2018). Its potential complications include psychosocial functioning limitation, interpersonal relationship disturbance, substance abuse, and suicide (Malhi and Mann, 2018; Proudman et al., 2021). Depression is estimated to affect the lives of 280 million people worldwide, and approximately one in five people experience a minimum of one episode of this disorder in their lifetime (Bromet et al., 2011; Cipriani et al., 2018; Proudman et al., 2021). MDD was introduced in the reports of the World Health Organization as one of the five leading causes of global disability-adjusted life years (DALY), and it is predicted that it will become the first cause by 2030 (Malhi and Mann, 2018; Mathers, 2008).

Currently, common treatments for depression include

Abbreviations: MDD, major depressive disorder; DALY, disability-adjusted life years; ECT, electroconvulsive therapy; HPA, hypothalamic–pituitary–adrenal; HDRS, Hamilton depression rating scale; DSM-V, Diagnostic and Statistical Manual of Mental Disorders (Structured Clinical Interview), Fifth Edition; FDA, Food and Drug Administration; MD, mean difference; SD, standard deviation; GLM, general linear model; CI, confidence interval; NNT, number needed to treat; SRDS, Self-Rating Depression Scale; AMPA, aminomethylphosphonic acid; NMDA, *N*-methyl-D-aspartate; BDNF, brain-derived neurotrophic factor.

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psychotherapy, pharmacotherapy, and electroconvulsive therapy (ECT) (Cipriani et al., 2018). MDD treatment is remarkably challenging due to the complex nature of MDD, a clinically significant delay in the onset of treatment efficiency and the partial response to treatment, concurrency with other chronic and acute physical and mental conditions, and intolerable adverse events by a single medication, which exists in about one-third of patients (Fava, 2009; Proudman et al., 2021). One of the ways to overcome the mentioned resistance is to add adjunct medicines, which are highly preferred due to their possible effectiveness, appropriate social acceptance, probable safety, and lower cost (Kessler et al., 2001).

L-theanine (C7H14N2O3) is an alpha amino acid that exists naturally in green and black tea and some mushrooms. L-theanine is naturally synthesized from L-glutamic acid and is believed to modulate gamma-aminobutyric acid, serotonin, and dopamine levels (Türközü and Şanlier, 2017; Vuong et al., 2011). The beneficial effects of L-theanine on health, including relaxation, enhanced concentration, nerve protection, anti-tumor effects, immune system function adjustment, vascular function regulation, blood pressure modulation, suppression of weight gain and fat accumulation, and cold relief, have been investigated and demonstrated in several studies (Mu et al., 2015; Türközü and Şanlier, 2017). Studies suggest chronic L-theanine administration has multiple beneficial effects on depressive symptoms via mechanisms involving the hypothalamic–pituitary–adrenal (HPA) axis activity; inflammatory immune response; restoration of monoaminergic systems, which includes restoration of neurologically active gut microbiota; and restoration of neurogenesis/neuroplasticity (Rothenberg and Zhang, 2019; Vuong et al., 2011).

An open-label clinical trial by Hidese et al. showed that Hamilton depression rating scale (HDRS) scores decreased significantly after chronic administration of L-theanine. They stated that the study did not have a placebo group and to consolidate and confirm the effects, controlled studies with a placebo is needed (Hidese et al., 2017). Given the corroborative evidence, the acceleration of antidepressant effect onset and symptom improvement is assumed by prescribing adjunctive L-theanine therapy. In this six-week, randomized, double-blind, placebo-controlled clinical trial, effects of L-theanine as an adjunct to sertraline in treating MDD were investigated.

2. Materials and methods

2.1. Design and setting

This study is a six-week, randomized, double-blind, and placebo-controlled clinical trial conducted in the outpatient clinic of Roozbeh Psychiatric Hospital, Tehran University of Medical Sciences, Tehran, Iran, from July 2020 to November 2022. The study protocol was registered in the Iranian registry of clinical trials (IRCT: www.irct.ir; registration code: IRCT20090117001556N131). The protocol concurred with the Declaration of Helsinki (Association 2013) and its subsequent revisions. The Tehran University of Medical Sciences institutional ethics committee approved the protocol (approval code: IR.TUMS.VCR.REC.1398.1011). Written informed consent was obtained from all enrolled patients. All participants in this trial were informed that they were free to leave the study at any time without any consequences on their therapy.

2.2. Participants

Enrolled participants were outpatients of both genders aged between 18 and 60 years diagnosed with MDD according to the Diagnostic and Statistical Manual of Mental Disorders (Structured Clinical Interview), Fifth Edition (DSM-5) (American Psychiatric Association A. and Association, 2013). Patients with HDRS scores (Hamilton, 1960) higher than 19 were included.

Exclusion criteria were as follows: receipt of any antidepressant medication during the previous month, receipt of ECT during the last two months, presence of psychosis or diagnosis of other prominent mental disorders (e.g., bipolar I or II disorders, anxiety disorder, personality disorder, eating disorder, cognitive disorder, schizophrenia, and schizotypal personality disorder), suicidal ideation (score > 2 on the suicide item of the HDRS), depression due to other illnesses, alcohol or substance (except nicotine) abuse, any uncontrolled medical condition such as a history of thyroid disease, renal disease, cardiovascular problems, liver disorders, pregnancy, or lactation. The occurrence of exaggerated symptoms during the treatment period based on the therapist's clinical judgment resulted in exclusion. Also, life-threatening side effects and abnormal electrocardiograms excluded patients from the study. A board-certified psychiatrist assessed patients to ensure the presence of inclusion criteria and the absence of exclusion criteria. Because the participants were outpatients, extensive protective measures were required. Alternative standard care was provided immediately to those who left the study before completion.

2.3. Intervention

Patients were randomly assigned to either the placebo group or the experimental group (1:1). The patients received sertraline (Sobhan Co.) 100 mg daily in a similar manner, regardless of the group they were assigned to. The participants in the intervention group received one 200 mg L-theanine tablet (produced by ACER) daily for six weeks, and the other group received matched placebo for six weeks. The US Food and Drug Administration (FDA) has classified L-theanine as a safe substance (generally considered safe). Based on calculations from recent studies, an acceptable safe and effective dose of L-theanine is up to 1200 mg daily (Mu et al., 2015; Rothenberg and Zhang, 2019). No other psychiatric medications were allowed during this study.

2.4. Outcomes

The participants were assessed at baseline and weeks 2, 4, and 6 after the intervention using the 17-point HDRS. The primary outcome was comparing changes in HDRS scores at each time point between study arms. The secondary outcomes included early response rate ($\geq$20 % reduction in HDRS score within the first two weeks), treatment response rate ($\geq$50 % reduction in HDRS score), remission rate (HDRS score ≤ 7), time to response treatment, and adverse events (Ghajar et al., 2017; Jafarinia et al., 2016).

2.5. Tolerability

According to studies, using L-theanine does not lead to serious side effects (Mu et al., 2015; Rothenberg and Zhang, 2019; Türközü and Şanlier, 2017). In this study, a psychiatrist carefully monitored adverse events at baseline and each follow-up visit (weeks 2, 4, and 6). A 25-item checklist was used to investigate any possible adverse effects in this study (Abbasi et al., 2010; Arabzadeh et al., 2015). Moreover, one of the team members recorded any adverse events by calling the patients at least once a week. All patients were provided a 24-h medical helpline phone number for medical advice related to adverse effects.

2.6. Sample size

Assuming a standard deviation (SD) of 3.5 in the HDRS score using a two-tailed *t*-test of difference between means and a mean difference (MD) of 3.5 in the HDRS score between the intervention and placebo groups with a power of $1\text{-}\beta = 0.85$, a two-sided significance level of 5 %, and an attrition rate of 20 %, and to ensure a sufficient sample size and increase generalizability of the results, 30 patients were planned in each group.

2.7. Randomization, blinding, and medication allocation

Patients were randomized according to a permuted blocked randomization method (blocks of 4, allocation ratio 1:1) to receive two types of treatment using a computer-generated code. Tablet preparations were made considering tablets similar in color, size, shape, and taste but wholly indistinguishable and were kept in sealed, opaque envelopes until the allocation time. The enrolled patients, healthcare providers, outcome assessors, and statisticians were all blinded to the allocation. In addition, two separate groups performed random assignments and clinical assessments.

2.8. Statistical analysis

All data analysis was performed using SPSS® 26 (IBM Corporation, Armonk, NY, USA). Continuous and categorical variables were presented as means and standard deviations and frequency counts and percentages, respectively. For the interpretation of results, p-values$\leq$0.05 were considered statistically significant, except for the primary outcome analysis, for which p-values$\leq$0.0167 were considered statistically significant using a Bonferroni correction for each of the three tests because it was a comparison of treatment groups at three time points. Continuous variables like age, disease duration, and HDRS score were compared between groups by independent-sample t-tests or Mann-Whitney U tests, and categorical variables, i.e., marital status, gender, literacy rate, early improvement rate, response rate, remission rate, and side effects were compared using Fisher's exact test or chi-squared test. The comparison of changes in HDRS scores between the study groups during the study period were performed via ANOVA analysis with repeated measures of the general linear model (GLM), corrected for non-sphericity by the Greenhouse-Geisser test. Two treatment arms were considered the between-subjects factor, and three screening sessions were considered the within-subjects factor. For comparing the time needed to respond to treatment between the two groups, Kaplan-Meier estimates with the log-rank test were used.

3. Results

3.1. Participants

The flow chart of the number of participants approached, screened, and included in the study is illustrated in Fig. 1. A total of 80 participants were screened for the eligibility criteria, and 68 patients met the inclusion criteria, among whom eight dropped out of the study. In the screening process, five patients were older than 60, three refused to participate, seven had HDRS scores <19, one had suicidal thoughts, three were diagnosed with a comorbidity, and one had received an antidepressant in the previous month. As a result, 60 patients were enrolled in the study and randomized into either (i) L-theanine + sertraline group or (ii) placebo + sertraline group. As shown in Table 1, the two groups were matched in gender and age at baseline, and no statistically significant difference in HDRS scores was observed between the two groups at baseline (26.88 ± 3.03 vs. 26.52 ± 3.77 for L-theanine and placebo groups, respectively, p-value = 0.71).

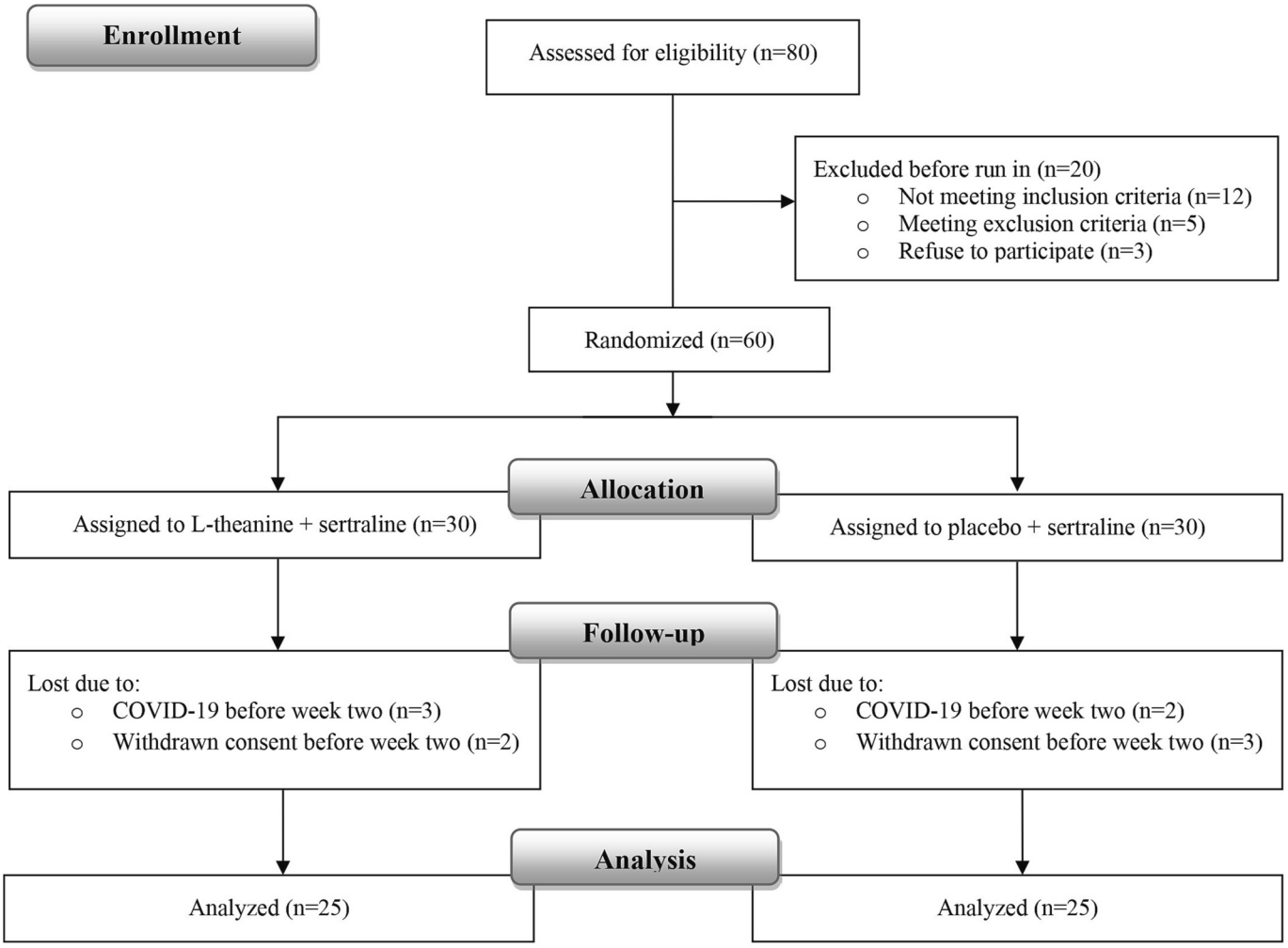

Fig. 1. Flow diagram representing case selection for the trial program.

Table 1
Comparison of participants' baseline characteristics between the two groups using independent t-test and chi-square test.

Item		L-theanine + sertraline group (n = 25)	Placebo + sertraline group (n = 25)	*p*-value
Age, mean ± SD		34.44 ± 5.79	32.52 ± 6.47	0.27
Gender, Female (%)		13 (52 %)	9 (36 %)	0.39
Duration of illness, mean ± SD years		2.58 ± 1.43	2.88 ± 1.17	0.42
Marital status, N (%)	Single	9 (36 %)	11 (44 %)	0.77
	Married	16 (64 %)	14 (56 %)	
	Divorced	0	0	
Educational status, N (%)	Primary school	1 (4 %)	2 (8 %)	0.86
	High school	7 (28 %)	8 (32 %)	
	Diploma	10 (40 %)	10 (40 %)	
	Higher education	7 (28 %)	5 (20 %)	
Occupational status, N (%)	Employed	3 (12 %)	6 (24 %)	0.70
	Unemployed	4 (16 %)	2 (8 %)	
	Housewife	11 (44 %)	11 (44 %)	
	Student	7 (28 %)	6 (24 %)	
Smoking, Yes (%)		9 (36 %)	8 (32 %)	0.76
Baseline HDRS score, mean ± SD		26.88 ± 3.03	26.52 ± 3.77	0.71

SD, standard deviation; HDRS, Hamilton depression rating scale.

3.2. Outcomes

Table 2 provides the descriptive statistical overview of the HDRS scores at baseline and weeks 2, 4, and 6 within and between the L-theanine and placebo groups and changes from the baseline. At weeks 4 and 6, the HDRS score was significantly lower in patients in the L-theanine group (MD [95 % confidence interval (CI) = −2.68, (−4.84, −0.51)], *p*-value = 0.01 and MD [95 % CI = −2.76 (−4.01, −1.50)], *p*-value = 0.00, respectively). Reduction in HDRS scores compared to baseline was comparable between the two groups, with a trend for a greater reduction in the L-theanine group at weeks 2, 4, and 6 (Table 2 and Fig. 2).

Table 2
Comparison of score changes between the two groups using independent t-test.

HDRS score	L-theanine + sertraline group (n = 25)	Placebo + sertraline group (n = 25)	Mean difference (95 % CI)	t(50)	*p*-value
Baseline, mean ± SD	26.88 ± 3.03	26.52 ± 3.77	0.36 (−1.58, 2.30)	0.37	0.71
Week 2, mean ± SD	19.88 ± 4.08	21.56 ± 3.27	−1.68 (−3.78, 0.42)	−1.60	0.11
Week 4, mean ± SD	12.72 ± 4.18	15.40 ± 3.36	−2.68 (−4.84, −0.51)	−2.49	0.01[a]
Week 6, mean ± SD	6.48 ± 1.87	9.24 ± 2.48	−2.76 (−4.01, −1.50)	−4.43	0.00[a]
Changes from baseline to week 2, mean ± SD	7 ± 2.53	4.96 ± 3.71	−2.04 (−3.85, −0.23)	−2.26	0.02[a]
Changes from baseline to week 4, mean ± SD	14.16 ± 4.24	11.12 ± 5.41	−3.04 (−5.81, −0.27)	−2.20	0.03[a]
Changes from baseline to week 6, mean ± SD	20.4 ± 3.24	17.28 ± 4.93	−3.12 (−5.49, −0.74)	−2.64	0.01[a]

HDRS, Hamilton depression rating scale; SD, standard deviation; CI, confidence interval.
[a] Significant.

In terms of between-subject effects, a significant effect of treatment was detected according to GLM repeated measures ($F = 6.53$, df = 1, *p*-value = 0.014) (Table 3).

Table 4 shows a significant difference between L-theanine and placebo groups regarding early improvement rate (24 % versus 64 %; respectively, *p*-value = 0.04). At week 6, the number of patients responding to treatment was significantly higher in the L-theanine group than in the placebo group (100 % versus 84 %, *p*-value = 0.05). However, the difference was not significant at week 6 (40 % in the L-theanine group versus 64 % in the placebo group, *p*-value = 0.15). The remission rate was significantly higher in the L-theanine group (68 %) compared with the placebo group (32 %) at the study endpoint (*p*-value = 0.02).

Number needed to treat (NNT) analysis revealed that 2.8 patients needed an experimental treatment (rather than the control treatment) for additional patients to experience remission at six weeks.

According to Kaplan-Meier estimates, there was no difference in time to treatment response in the L-theanine and placebo groups (4.80 ± 0.20 vs. 5.14 ± 0.22 weeks, respectively; each log-rank *p*-value = 0.25). The time required for patient remission in the L-theanine group also showed no difference compared to the placebo group (5.76 ± 0.16 vs. 6.00 ± 0.00 weeks, respectively; each log-rank *p*-value = 0.32).

3.3. Adverse effects

Loss of appetite, abdominal pain, headache, diarrhea, and vomiting were the most common adverse effects in both groups (Table 5). No severe or unexpected side effects were identified. There was no statistically significant difference in the incidence of side effects between the two groups (*p*-value>0.05 for all items).

4. Discussion

The results of this six-week clinical trial determined that 200 mg/day of L-theanine adjunct to sertraline is superior to adjunctive placebo in reducing depressive symptoms in a significant number of MDD patients. This deduction was obtained based on the greater reduction of HDRS scores and higher response and remission rates in the L-theanine plus sertraline arm by considering random assignment and non-different baseline characteristics. Also, L-theanine was safe and well tolerated in these patients.

Earlier animal studies provided prospects for this clinical study. In previous preclinical studies, L-theanine improved behavioral depression induced by chronic psychosocial stress in male mice (Unno et al., 2011) and depressive-like behaviors in the chronic unpredictable mild stress in the rat model (Shen et al., 2019). It also suppressed depressant behavior in the stress-loaded mice model (Unno et al., 2020). Moreover, Hidese et al., in an open-label and uncontrolled clinical study, reported a significant reduction in HDRS scores in 20 patients with MDD following the administration of L-theanine 250 mg daily (Hidese et al., 2017). Another clinical trial on 30 participants without a major psychiatric illness reported the beneficial effects of L-theanine 200 mg daily on reducing the Self-Rating Depression Scale (SRDS) compared to placebo (Hidese et al., 2019).

On the contrary, Cicero et al., by prescribing a daily combined nutraceutical containing 100 mg of L-theanine to 30 elderly subjects with basal Mini-Mental State Examination scores between 20 and 27, did not report a significant difference in SRDS between the intervention and placebo groups (Cicero et al., 2017). When deducing this finding, in addition to the apparent characteristics of this study, including small number of cases, combined nature of the intervention, and low dose of L-theanine, the factors of the included subjects and their diagnoses should be considered. In this regard, there are studies that consider the antidepressant effects of L-theanine dependent on stress loading (Unno et al., 2020) and the presence of chronic unpredictable mild stress (Zhu et al., 2022).

In line with the benefits observed in this study, evidence of L-

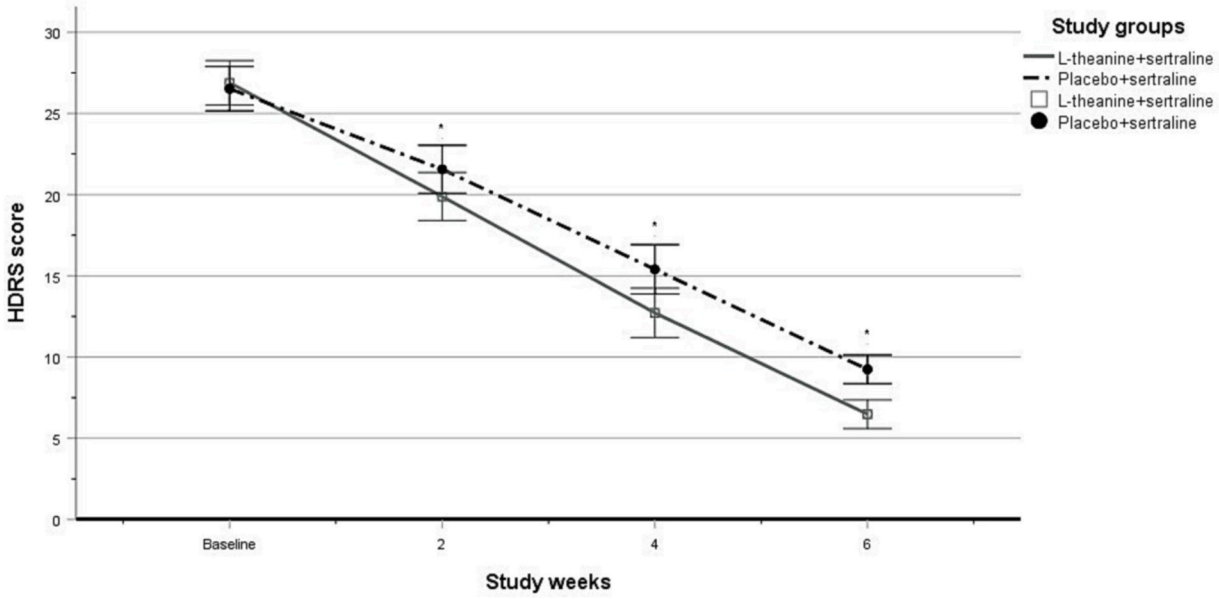

Fig. 2. Repeated measure analysis for comparison of effects of the two treatments on the Hamilton depression rating scale (HDRS) scores. Error bars represent ±2 standard errors. * shows a significant *p*-value obtained from the independent sample *t*-test comparing the score change from baseline to each time point between the two groups.

Table 3
Results of the general linear model repeated-measures analysis (between-subjects).

Source	Type III sum of squares	df	Mean square	F	*p*-value
Intercept	15,025.111	1	15,025.111	2748.758	0.000[a]
Treatment	35.701	1	35.701	6.531	0.014[a]
Error	262.375	48	5.466		

[a] Significant.

Table 4
Comparison of response to treatment and remission rates at different study points between the two groups using chi-square tests.

Item	L-theanine + sertraline group (n = 25)	Placebo + sertraline group (n = 25)	*p*-value
Number (%) of early improvers	6 (24 %)	16 (64 %)	0.04[a]
Number (%) of responders at week 2	1 (4 %)	1 (4 %)	0.75
Number (%) of responders at week 4	10 (40 %)	16 (64 %)	0.15
Number (%) of responders at week 6	25 (100 %)	21 (84 %)	0.05[a]
Number (%) of remitters at week 2	0	0	[b]
Number (%) of remitters at week 4	2 (8 %)	0	0.49
Number (%) of remitters at week 6	17 (68 %)	8 (32 %)	0.02[a]

[a] Significant.
[b] No statistics are computed.

Table 5
Frequency of adverse events in the two study groups.

Adverse effects	L-theanine + sertraline group (n = 25)	Placebo + sertraline group (n = 25)	*p*-value
Diarrhea, No (%)	4 (16 %)	2 (8 %)	0.66
Vomiting, No (%)	4 (16 %)	2 (8 %)	0.66
Headache, No (%)	4 (16 %)	3 (12 %)	1
Abdominal pain, No (%)	5 (20 %)	3 (12 %)	0.70
Loss of appetite, No (%)	5 (20 %)	3 (12 %)	0.70

theanine action with mechanisms related to depression, including monoaminergic, glutamatergic, and inflammatory systems, has been reported. It has been observed that its administration leads to increases in monoamine neurotransmitters, including serotonin, norepinephrine, and dopamine in cortical-striatal-pallidal-thalamic-circuit-related brain regions in rats (Shen et al., 2019). In the glutamatergic system, L-theanine inhibits the extracellular combination of glutamine with neurons through its antagonistic effect on aminomethylphosphonic acid (AMPA) and kainate receptors (Türközü and Şanlier, 2017). It also interacts with the *N*-methyl-D-aspartate (NMDA) receptor (Wakabayashi et al., 2012). In addition, in the inflammatory system, brain-derived neurotrophic factor (BDNF) expression is reduced, and tryptophan is converted to kynurenine through the effects of cytokines (Kohler et al., 2016). Regarding this, evidence suggests that BDNF increases circulating levels through induction in the hippocampus (Wakabayashi et al., 2012) and modulates kynurenine levels (Unno et al., 2020).

L-theanine was found to be safe and tolerable in depressed patients in this study and did not differ from placebo in terms of side effects. Previous clinical trials had also achieved such a finding (Cicero et al., 2017; Hidese et al., 2019; Hidese et al., 2017; Ritsner et al., 2011). Moreover, acute and chronic toxicity tests have considered even excessive L-theanine consumption to be safe (Türközü and Şanlier, 2017). Although according to FDA recommendations, its daily consumption should not exceed 1200 mg (Türközü and Şanlier, 2017; Vuong et al., 2011).

The words "efficacy" or similar may be used subsequent to obtaining *p*-values <0.05 in studies, but this does not necessarily justify the clinical relevance of medication-placebo differences (Hengartner and Plöderl, 2018). A reduction of at least seven points or an effect size of 0.75 in the HDRS score is required for clinician-detectable minimal improvement, and less than this, although achieving statistical significance, has a small effect size (Hengartner and Plöderl, 2018; Moncrieff and Kirsch, 2015). In this study, the effect size (*d*) for the primary outcome (differences of

medication adjunct to L-theanine and medication adjunct to placebo) was 0.747, which was in the range of intermediate to large (Cohen, 2013) and desired (Hattie, 2009) effects. The small effect size issue is still debated for even approved medications (Hengartner and Plöderl, 2018; Moncrieff and Kirsch, 2015) and adjunctive treatments may increase their effect size synergistically or through different pathways (Sarris et al., 2016).

5. Limitations

Despite the significant advantages of this investigation, including a high-quality design, precise adjustment of baseline clinical characteristics, and intervention with a molecule rather than an uncharacterized plant, there are limitations that should be noted. The sample size is relatively small, and the duration of the study is relatively short. Another limitation is the examination of L-theanine alone, which was not conducted due to ethical considerations. Moreover, the lack of patient follow-up after the treatment period is another limitation.

6. Conclusions

L-theanine at a dose of 200 mg daily adjunct to sertraline outperforms adjunctive placebo in the treatment of depression. It is also safe and tolerable. Further high-quality, large-scale, long-term studies with follow-up of patients after the treatment period are recommended.

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Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

CRediT authorship contribution statement

SA: conceptualization, project administration, supervision, funding acquisition, methodology, and analysis; FK: data curation, investigation and analysis; AS, MAB, HA and FAB: writing original draft and formal analysis. All authors read and approved the final manuscript.

Conflict of interest

The authors had no competing interests.

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