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Research Article

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Tryptophan and HTP Supplementation in the Treatment of Cognitive and Mood Disorders: A Systematic Review and Meta-Analysis

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ABSTRACT

Introduction: Cognitive and mood disorders, which are increasingly prevalent due to stress, depression, and anxiety, necessitate effective treatmentswith minimal side effects. Tryptophan (TRP) and 5-hydroxytryptophan (5-HTP), serotonin precursors, are potential therapeutic options. Serotonindeficiency is linked to various cognitive and mood disorders. Previous studies on TRP and 5-HTP supplementation have shown mixed results,suggesting the need for a comprehensive review.

Method: A systematic review and meta-analysis were conducted following PRISMA guidelines, with studies sourced from PubMed, Scopus, and GoogleScholar between 2000 and 2023. Only randomized controlled trials (RCTs) involving adults and children with cognitive or mood disorders wereincluded. The exclusion criteriawere studies focused on specific disorders, those involving other mental disorders, or those not in English. The dataextracted focused on demographic information, supplement dosage, and outcome measures such as plasma glucose levels, BMI, depression status,and mood.

Results: Sixteen RCTs met the inclusion criteria. Meta-analysis revealed that TRP and 5-HTP supplementation significantly increased total plasmalevels and improved mood and depression scores. However, no significant impact was found on BMI or Mini-Mental State Examination (MMSE) score.High heterogeneity was observed across studies.

Conclusion: TRP and 5-HTP supplementation appear to effectively enhance mood and reduce depression symptoms in individuals with cognitive andmood disorders. However, the benefits on cognitive function are less clear, and further research is needed to confirm these findings and explore thevariability in responses.

Introduction

In modern society, the prevalence of cognitive and mood disorders has increased due to stress, depression and anxiety [1]. This increased the need to find and develop such elements that improve moods and effectively treat cognitive disorders without causing any side effects [2]. The fledgling field of nutritional psychotherapy presents some possibilities for clinical intervention for those suffering from anxiety and mood disorders. Supplementation with tryptophan (TRP) and 5-hydroxytryptophan (5-HTP) has been recommended as a possible therapeutic option for cognitive and mood disorders. TRP is an essential amino acid that must be acquired from daily food intake. TRP and 5-HTP acts precursors for serotonin. Serotonin is a neurotransmitter that is essential for the regulation of mood, cognition, and sleep.

A deficiency in serotonin has been associated with the development of a number of cognitive and mood disorders, such as depression, anxiety, and Alzheimer's disease [3]. Past studies have indicated that higher serotonin levels in the brain boost mood and lessen emotional disturbances in healthy people [4-6]. Dietary treatment for serotonin production in the brain has long been documented d, which has been ascribed to the higher uptake of TRP in the brain [7]. Several studies have been conducted to mimic symptoms of depression by using TRP-depleted models. A low-TRP diet could result in a 70% reduction in blood TRP levels within 4 to 6 hours. TRP has also been linked to the induction of a depressive state [8]. This decrease in TRP utilization in the brain is similar to the cognitive bias exhibited in sad persons in regard to memory and attention given to positive/negative information [9].

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Several factors, such as nutrition, stress, and the use of some pharmaceuticals, can influence the level of TRP in the body. 5-HTP is a metabolite generated from the breakdown of TRP, and it can pass through the blood–brain barrier more easily than TRP can. Several relatively small clinical trials have been conducted to evaluate the efficacy of TRP and 5-HTP supplementation for the treatment of cognitive and mood-related disorders. The findings of these trials have been inconsistent, with some indicating positive effects and others indicating no effect. Clinical studies have suggested that TRP and 5-HTP supplementation improve cognitive performance in both healthy persons and patients with cognitive impairments [10,11]. TRP supplementation increased attention and memory function in a study involving healthy individuals (Murphy et al., 2006). Another study revealed that 5-HTP supplementation enhanced cognitive performance in persons with Alzheimer's disease (James Meschino). TRP and 5-HTP supplementation has additionally been demonstrated in studies to enhance mood in individuals with mood disorders. TRP supplementation has been shown to lessen symptoms of depression in a study of people suffering from depression [12]. Another study showed that taking 5-HTP supplements enhanced mood in persons suffering from anxiety problems [13,14].

TRP and 5-HTP are usually well tolerated and nontoxic. However, some people may develop adverse effects such as nausea, vomiting, and diarrhea. Individual clinical research on the efficacy of TRP and 5-HTP supplementation for the treatment of cognitive and mood disorders has shown contradictory results [15,16]. A meta-analysis is a systematic review of several studies that could be used to collect information to produce a more reliable estimate of the effect as a whole. The primary objective of this meta-analysis was to investigate the beneficial effects of TRP and 5-HTP supplements for the treatment of cognitive and mood disorders. Several reports have evaluated the effectiveness of TRP and5-HTP for treating mood disorders and cognitive impairments. However, no single study has been conducted to systematically review the studies on the collective effects of both substances, TRP and 5-HTP, on cognitive and mood disorders. This meta-analysis also provides an overview of possible moderators of therapy response, such as the kind of cognitive or mood disorder, supplement dose and duration, and the occurrence of any adverse effects.

Methodology

Research Protocol

As stated in the Cochrane Handbook for Systematic Reviews, the following research question served as the basis for the current review: what are theexisting studies exploring the use of tryptophan and hydroxytryptophan supplementation for the treatment of cognitive and mood disorders? What arethe most common methods or supplements used to treat cognitive and mood disorders? What is the overall accuracy and sensitivity of the treatmentwhen using tryptophan and hydroxytryptophan supplements in combination with other supplements? What are the recommendation approaches? Byusing the research questions as a guide, quality papers and materials were culled from different databases.

Data Sources and Search Strategy

A systematic review and meta-analysis were carried out in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria. A systematic search of electronic databases, including PubMed, Scopus and Google Scholar, was conducted for studies investigating the effectiveness of TRP and 5-HTP supplementation for the treatment of cognitive and mood disorders, we searched for publication periods between 2000 and 2023. The inclusion criteria were randomized controlled trials, (RCTs), articles published in English, and studies that included adults and children with cognitive disorders. The excluded studies were published that focused on a specific type of cognitive or mood disorder (e.g., major depressive disorder, bipolar disorder) or included participants with other mental disorders or studies published in languages other than English. Animal studies were also excluded from the research.

Study Selection Criteria

A total of 972 RCTs were identified from the databases (PubMed and Scopus), and 8 RCTs were retrieved from the references of the articles. The study selection process was performed by two reviewers (AL & AA), first, the reviewers reviewed the title to remove duplicates from the studies. Second, the reviewer reviewed the abstracts of the remaining articles from stage one to exclude articles that were not relevant to the present study. The third step involved reading through the full text to assess the eligibility of the remaining articles and applying the exclusion criteria. After the third step, the third reviewer assessed the quality of the articles.

Quality Assessment

The Cochrane Handbook for Systematic Reviews of Interventions was followed and particularly focused on random sequence generation, allocation concealment, blinding, outcome assessment, and selective reporting of selected studies [17]. For RCTs, we used the Cochrane risk of bias (ROB) assessment tool, which is well described in the Cochrane Handbook of Systematic Reviews of Interventions version 6.0 [17]. This tool can detect five types of bias: performance bias, selection bias, detection bias, reporting bias, and attrition bias. The included RCTs could be considered to be of high, unclear, or low bias source based on these domains.

Data Extraction

A standardized data extraction form was used to extract relevant information from the included studies. The information extracted included only demographic information and outcome measures. The demographic variables extracted from the included studies were as follows: Author First Naming, Study Design, Supplemental (5—HTP, tryptophan, L-5-HTP and fluoxetine, DHA, EPA, vitamin E, TRP-rich egg, amino acids, A-LAC protein, BCCA supplement), amount of dosage received by the patients (100 mg, 200 mg, 150-400 mg and 0.5g), number of patients in both the follow-up period and outcomes reported. The outcomes of interest extracted from the included studies were the estimated total plasma ALB concentration, BMI, depression status, MMSE score and Mood score recorded in both the intervention group and control group.

Synthesis Analysis

We used a random-effects meta-analysis model to synthesize the data from the included studies. The potential moderators of treatment response were also investigated using subgroup analyses. This meta-analysis provides a more comprehensive and robust estimate of the effectiveness of TRP and 5-HTP

supplementation for the treatment of cognitive and mood disorders. We also expect our meta-analysis to identify potential moderators of treatment response, which could be used to guide future research and clinical practice.

Results

Study Selection

Out of the 980 articles generated from PubMed, Scopus, and Science Direct, 32 relevant articles were retrieved after removing duplicates. The remaining 32 articles were assessed for eligibility by two reviewers (AL & AA) through the reading of tiles and abstracts; 9 articles were removed during this process because outcomes were not reported and because the articles were conducted on other diseases of interest (patients with no history of cognitive or mood disorders). After the above stage, the full texts of the remaining 23 articles were screened, and 7 articles were excluded, mainly because the patients were not randomized into groups or because the study type was not a randomized controlled design. The remaining 16 articles were included in the review and considered for meta-analysis.

Study characteristics

The 16 RCTs included in the systematic review and meta-analysis were thoroughly examined, and the following data were extracted and are presented in Table 1: Author name, study design, and supplement reported in each of the studies (tryptophan, 5-HTP, L-5-HTP and fluoxetine, DHA 720 mg, EPA286 mg and BCCA supplemented with 2 gm of TRP), dosage of intervention reported in each study, number of patients allocated to the intervention group and control group, and period of treatment (follow-up period). The outcome measures included biochemical outcomes, such as total lymphocyte and high-density lipoprotein cholesterol (HDL-C) levels; body composition; BMI; nutritional status; cognitive status; depression status; mental health status; mood evaluation; and memory assessment.

Quality Assessment

Among the 16 RCTs, one trial had a high risk of bias under selection bias, one RCT had a high risk of bias under performance bias, and one had a risk of bias under detection bias (Rob Markus et al., 2001) [18,19]. A high risk of bias under incomplete outcome was recorded in three studies (Rondenelli et al., 2012) and the other biases recorded in five RCTs were the frequency of complications not reported in the studies and results not properly presented [19]. All RCTs were deemed to be of at least satisfactory quality and were therefore eligible for inclusion in the meta-analysis.

Studies Included in the Meta-Analysis

The first outcome was the total plasma ALB concentration. Across all the RCTs, six studies reported the effect of supplementation on patients' cognitive and mood disorders. The pooled random effects meta-analysis showed that, supplementation (tryptophan) had a highly significant effect on the plasma total level (MD = 4.40, 95% confidence interval; -3.86, 12.66; z score = 1.04; p value = 0.00). High, moderately significant heterogeneity was found among the studies (I2 = 97.54, p value = 0.00).

Second, a random effect meta-analysis was conducted on RCTs that presented data on body composition and were deemed to be of at least satisfactory quality (Figure 4) (Rondenelli et al., 2012; Lieben et al., 2016; Tsuijita et al., 2019) [12]. The pooled meta-analysis revealed that Tryptophan supplementation had no significant effect on the body mass index of patients after administration compared with that of the placebo (MD = -0.46, 95% confidence interval; -2.84; 1.92, p value = 0.70). High and moderate heterogeneity was observed among the studies (I2 = 84.65, P value = 0.00).

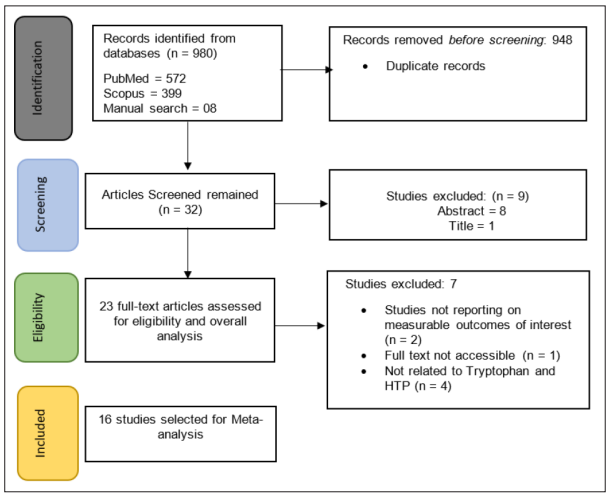
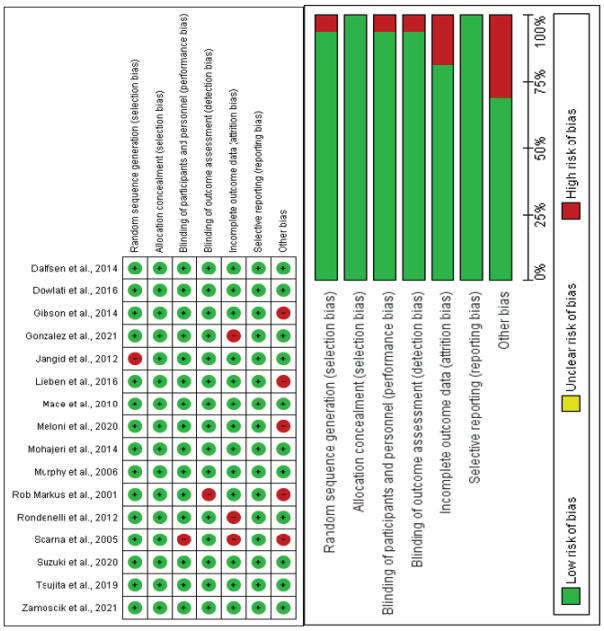


Figure 1: PRISMA flow chart



In the random effect meta-analysis of cognitive assessment and mood disorders, three outcomes were analyzed: Mini Mental Scale (MMSE) score, mood state, and depression status. In assessing differences in depression, Datfsen et al., Murphy et al., Meloni et al., and Dowlat et al., 2020, the Beck Depression Scale (BDI) was used, while some RCTs reported on the GHQ, HAM-D, EDSS, and CESD scores [20-23]. The pooled meta-analysis in revealed a significant reduction in depression (SM = -0.13, 95% confidence interval; -2.84 to 1.36, p value = 0.00). The percentage of heterogeneity among the studies was found to be significant and high (I2 = 85.99, p value = 0.00).

Table 1: Demographic characteristics of the included studies

Study	Type	Supplement	Dosage	N (treated group)	N (Control group/ placebo)	Treatment period (days)	Outcome
Zamoscik et al. (2021)	Randomized controlled trial	5-HTP	200 mg at t1or t2, only order differed	38	39	4 weeks	• With 5-HTP, immoral behavior without negative consequences was rated as more reprehensible. • Additionally, during story reading, activation in insula and supramarginal gyrus was increased after TRP intake. • No significant effects of TRP on emotion recognition were identified for the whole sample. • Importantly, emotion recognition ability decreased with age which was for positive emotions compensated by TRP. • Improved recognition of positive emotions with TRP in older participants supports the use of a TRP-rich diet to compensate forage-related decline in social-cognitive processes.
Tsujita et al., (2019)	Randomized, double-blind, placebo-controlled	Tryptophan	Treatment:100 mg of TRP, 4 mg of vitamin B6, and 4 mg of nicotinamide as active components, with 117mg of lactate and 5 mg of calcium stearate as additives -Placebo: 270mg lactate	15 -Mild to moderate: 6) - Severe (9)	15 -Mild to moderate:(8) - Severe (7)	7 days, twice daily between meals	• The CES-D score significantly improved following both treatments in the severe depression subgroups, while the POMS depression score was significantly improved only in the TRP severe depression subgroup. • There was no significant change in ANS activity or plasma total TRP in any group. • TRP, vitaminB6, and nicotinamide-containing supplements loading between meals can quickly improve depressed mood in quite low dose in young adults with severe subclinical depression
Jangid etal., (2012)	Randomized, double-blind, parallel group study	L-5-HTP & fluoxetine	-L-5-HTPcapsules150-400mg with time -Fluoxetine20-40mg capsules with time	-N=34 in L-5-HTP - N=36 in fluoxetine			Both treatment groups showed significant and nearly equal reduction in HAM-D scores beginning at week two and continuing through week eight. • Twenty-two patients (73.33%) in the l-5-HTPgroup and 24patients (80%) in the fluoxetine group showed positive response at the end of the study. • l-5-HTP has definitely got antidepressant effect in patients of depression. • Antidepressant effect was seen within 2 weeks of treatment and was apparent in all degrees of depression. • The therapeutic efficacy of l-5-HTPwas considered as equal to that of fluoxetine.

Mohajeriet al., (2014)	Randomized, placebo-controlled, parallel trial	Tryptophan	0.5 g twice per d	N=29	N=30	19 days	• The results for the Affective Go/No-Go Task exhibited a slowing of responses to negative words, suggesting reduced attention to negative emotional stimuli. • The results for the Facial Emotional Expression Rating Task also supported a shift away from attention to negative emotions and a bias toward happiness. • An increase in arousal-like symptoms, labeled 'high energy', shorter reaction times and a slight benefit to sustained attention were observed in the treated subjects. • Finally, when the supplement was taken 60-90min before bedtime, a feeling of happiness before going to bed
Murphy et al., (2006)	Randomized, double-blind intervention	Tryptophan	1 g 3x a day	N=19	N=19	14 days	• TRP increased the recognition of happy facial expressions and decreased the recognition of disgusted facial expressions in female, but not male, volunteers. • TRP also reduced attentional vigilance toward negative words and decreased baseline startle responsivity in the females. • These findings provide evidence that TRP supplementation in women induces a positive bias in the processing of emotional material that is reminiscent of the actions of serotonergic antidepressants. • This highlights a key role for serotonin in emotional processing and lends support to the use of TRP as a nutritional supplement in people with mild depression or for prevention in those at risk. • Future studies are needed to clarify the effect of tryptophan on these measures in men.
Rondanelli et al., (2012)	Randomized, double-blind, placebo-controlled trial	Composition of two capsules: DHA 720 mg, EPA 286 mg, vitamin E 16 mg, soy phospholipids 160 mg (phosphatidylinositol, phosphatidylcholine, and phosphatidylethanolamine), tryptophan 95 mg, and melatonin 5 mg.	Two capsules, orally, once a day, 1hour before bed time	N=11	N=14	12 weeks	• After 12weeks, a significant treatment effect for the MMSE and a positive trend for the semantic verbal fluency was found in the supplement group. • A significant treatment effect was determined for the olfactory sensitivity assessment • As regards the nutrition evaluation, after 12weeks of treatment the supplemented group showed an improvement in the MNA score with a significant difference relative to placebo. • Older adults with MCI had significant improvements in several measures of cognitive function when supplemented with an oily emulsion of DHA-phospholipids containing melatonin and tryptophan for 12weeks, compared with the placebo

Dowlati etal., (2020)	Open-label study	Tryptophan + Other supplements	2 g oftryptophan,10 g of tyrosine, and blueberry juice with blueberry extract	N=21	N=20	Postpartum day 5	• Postpartum blues (PPB)severity was quantitated by the elevation in depressed mood on a visual analog scale following the sad mood induction procedure (MIP). • Following the MIP, there was a robust induction of depressed mood in the control group, but no effect in the supplement group [43.85 ± 18.98 mm vs. 0.05 ± 9.57 mm shift; effect size:2.9; F (1,39) =88.33, P < 0.001]. • This dietary supplement designed to counter functions of elevated MAO-A activity eliminates vulnerability to depressed mood during the peak of PPB.
Gonzalezet al.,(2021)	Randomized	Tryptophan	2 capsules with 500 mg of tryptophan	N=113	N=25	15 days	• Here we provide evidence that tryptophan supplementation has an uneven effect on mood improvement in the general population.
Meloni et al., (2020)	Randomized, double-blind placebo-Controlled crossover trial	5-HTP	50 mg of 5-HTP daily	N=25	N=25	4 weeks	• Repeated-measures analysis revealed a significant improvement of depressive symptoms during the 50-mg 5-HTPtreatmentcompared with placebo as assessed by the Hamilton Depression Rating Scale (HDRS). • No effect of5-HTP was seen on apathy symptoms assessed by the Hamilton Depression Rating Scale (HDRS) and Apathy Scale (AS). • This study provides preliminary evidence of clinical benefit of 5-HTPfor treating depressive symptoms in PD. Larger studies with a longer treatment duration are needed to corroborate these early findings.
Gibson et al. (2014)	Randomized controlled trial	TRP-rich egg-white protein hydrolysate	2 or 4 g of TRP-rich protein hydrolysate product or3.11 g case in hydrolysate as a control.	2g (N = 20); 4g (N = 21)	N=19		• The TRP-rich protein hydrolysate produced the expected dose-dependent increase in the ratio of plasma TRP to competing large neutral amino acids. TRP-rich protein hydrolysate (2 g only) prevented both the decline in wellbeing and increase in fatigue seen over the test session in the control group. • This treatment dose resulted in a significant shift in emotional processing toward positive words and reduced negative bias in assessing negative facial expressions. • Effects on cognition were small and not statistically reliable and are not reported here. However, there was no evidence for any adverse effects. • Consumption of a low dose of TRP-rich protein hydrolysate may have beneficial effects on emotional function that could promote feelings of wellbeing, possibly conferring resistance to deterioration in mood in healthy subjects or Depressive episodes.

Suzuki et al., (2020)	Randomized, placebo-controlled trial	Ingestion of seven selected essential amino acids as agranular powder, namely, leucine, phenylalanine, and lysine supplemented with isoleucine, histidine, valine, and tryptophan	3 g (3gIG) or6 g (6gIG) of the selected amino acids	N=35 (3gIG) & N=35(6gIG) &	N=35	3 months	• The numbers of participants excluding dropouts were 35 in PCG and 3gIG and 33 in6gIG. Analysis of covariance revealed that the6gIG showed significantly improved cognitive function (Trail Making Test B), social interaction and psychological health scores after ingestion compared to the PCG (multiplicity adjusted $p < 0.05$). • Current findings suggested that ingestion of the seven essential amino acids led to improved attention and cognitive flexibility and psychosocial functioning, which is expected to prevent cognitive decline.
Mace et al., (2010)	Double-blind, placebo-controlled, counterbalanced, crossover, randomized design	The placebo comprised a drink with amino acids balanced to match human milk; ATD was the same mixture without tryptophan (TRP). The composition of amino acids was, as per Young, et al., (1985), whisked with 250 g water. Men received 104.4 g foreach treatment and woman received 80% of this dose, based on the premise that females have a nearly 20%lower average weight (Ellenbogen, et al., 1996).	NA	N=20 (20patients withPD)	N=35 (Healthy patients)	Crossovertreat-ment1-weekapart	• In a visual recognition task, ATD improved performance in the PD but not in the control group. In terms of psychomotor speed, there was also a group-specific effect with reduced latency of response during ATD in the PD group but increased latency in the control group. ATD has subtle neuropsychological effects, which differ significantly between PD and healthy control subjects. This suggests that the dopaminergic and cholinergic deficit of PD significantly modulates the effects of serotonin depletion, resulting in positive effects in some domains. Further investigation on the effects of specific serotonin antagonists maybe merited in PD.
RobMarkus et al., (2001)	Double-blind, placebo-controlled study	The milk shakes for the experimental diet contained 20 g tryptophan-enriched (4.8 g/100 gtryptophan) A-LAC protein and the milk shake of the placebo diet contained 20 g (1.4 g/100 g tryptophan) sodium caseinate.	NA	N=14	N=14	2 days	• Evening α-lactalbumin in take caused a 130%increase in TRP: LNAA before bedtime and modestly but significantly reduced sleepiness and improved brain-sustained attention processes the following morning. Only in poor sleepers was this accompanied by improved behavioral performance. • Evening dietary increases in plasma tryptophan availability for up take into the brain enhance sustained alertness early in the morning after an overnight sleep, most likely because of improved sleep.

Dalfsen et al., (2014)	Well-Balanced experimental design	tryptophan (3.0 g/day)	NA	Homozygous S-allele (n =57) and L-allele (n =54) genotypes with high and low chronic stress vulnerability (neuroticism)	NA	NA	• Although high neuroticism was significantly related to a higher frequency of stressful life events and daily hassles, it did not interact with the 5-HTTLPRgenotype on general past sleep quality. However, as expected, a 7day period of tryptophan administration was exclusively associated with better sleep quality scores in the S'/S' genotype with high trait neuroticism. • Current findings suggest that 5-HTTLPRdoes not directly interact with stress vulnerability in order to influence sleep quality. Instead, based on current and previous findings, itis suggested that the S'/S' 5-HTTLPRgenotype promotes the risk for stress-related sleep disturbances because of an increased susceptibility to the depressogenic consequences of stress. Accordingly, by way of reducing depressive symptomatology, tryptophan augmentation may particularly improve sleep quality in stress-vulnerable individuals carrying the 5-HTTLPR S-allele.
Scarna et al., (2005)	Randomized, double-blind	BCCA supplement + 2 gm TRP	60-g mixture of branched chain amino acids (BCAAs)	N-17(BCCP/TRP)	N=15 (Placebo)	NA	• Relative to placebo, the BCAA/TRP mixture substantially lowered the ratio of TYR+ PHE: BCAA and increased plasma prolactin. The ratio of TRP:BCAA was also lowered but toa lesser extent. The BCAA/TRP mixture produced significant changes in a task of decision-making where volunteers showed reduced discrimination between gambles with large and small losses. • A 62 g BCAA/TRP mixture decreases the availability of TYRand PHE for brain catecholamine synthesis and increases plasma prolactin consistent with lowered brain dopamine function. Addition of 2 g TRP to the 60 g BCAA mixture does not prevent a reduction of the ratio TRP:BCAA relative to placebo. The effects of the BCAA/TRP mixture on decision-making suggest a general action of dopamine pathways on the processing of emotional information in risky choice, including punishment-related cues, consistent with suggestions that dopamine mechanisms mediate behavioral responses to aversive as well as appetitive stimuli in instrumental conditioning.
Lieben et al., (2016)	Double-blind, placebo-controlled, crossover study	Whey protein mixture with4 different amounts of TRP	NA	N=15 (MSpatients withdepressedmood)	N=17 (MSpatientswithoutdepressedmood)	NA	• A fast, transient and dose-dependent increase of total plasma TRP and TRP/ΣLNAA ratio was found. Ratings of negative mood decreased overtime, independent of the TRP dose. Relative to whey-only, immediate word recall and delayed recognition improved after ingestion of the lowest added TRP dose and was mainly due to better recollection for positive loaded words. Executive functions were not affected by a difference in TRP availability. • A moderate addition of TRP to whey protein enhances memory processes without improving the mood state in MS.

The random effects meta-analysis included the Mini-Mental State Examination (MMSE) and the Mood Examination. For the MMSE, data were extracted from five RCTs (Murphy et al., 2006), and pooling resulted in a no significant impact on the MMSE score (MD = -0.39, 95% confidence interval; -0.46 to 1.95, z score = 0.90, p value = 0.43) (Figure 6) [24,22-26]. For the Mood Examination, significant results were found (MD = -0.01, 95% confidence interval; -0.51 to 0.74, z score = -1.07, p value = 0.00) (Figure 7).

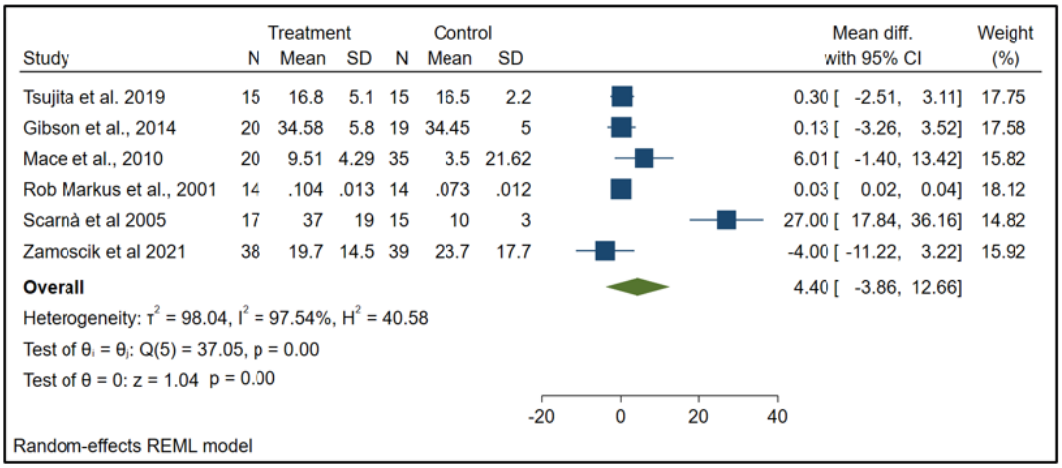


Figure 4: Forest plot of body mass index

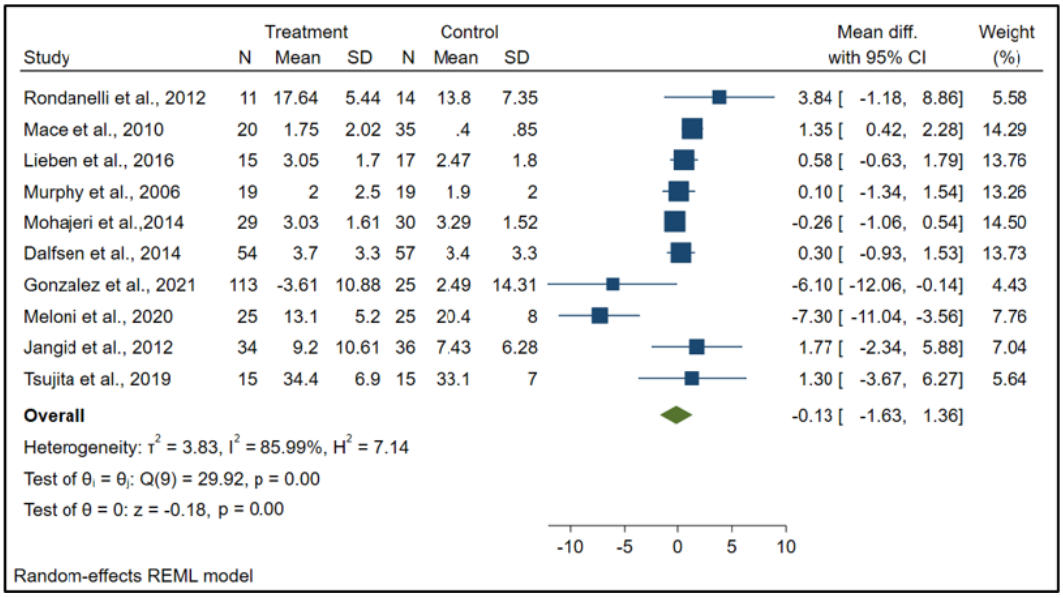


Figure 5: Forest plot of depression status

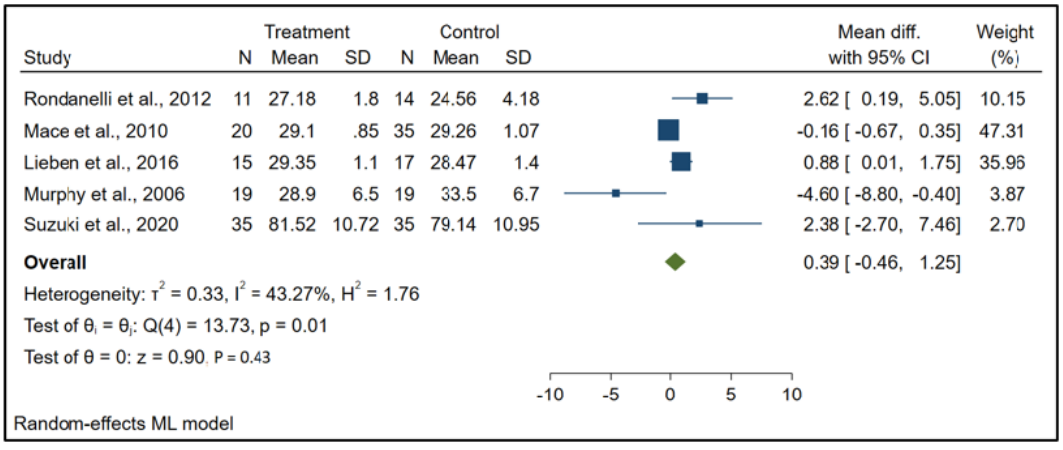


Figure 6: Forest plot of the Mini Mental Scale

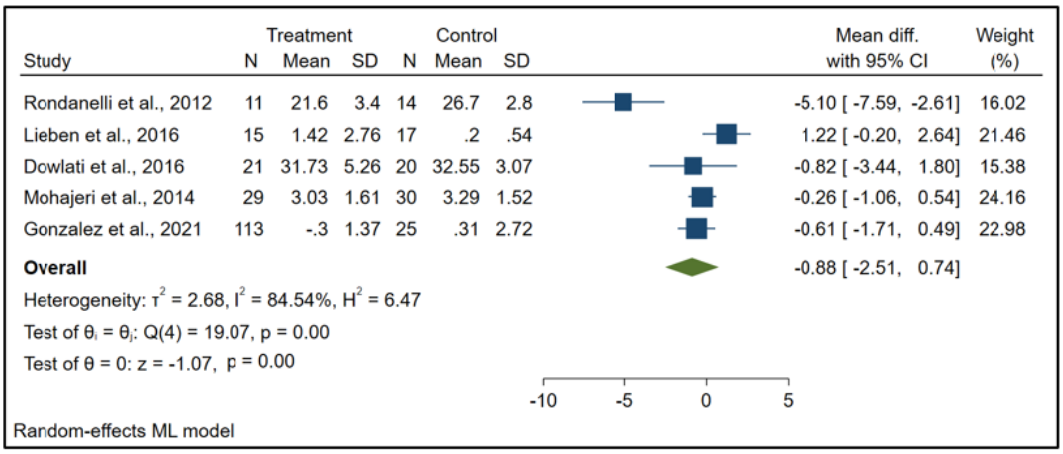


Figure 7: Forest plot of the Mood Assessment

Risk of Bias Across Studies

To examine the publication bias in all RCTs included in the meta-analysis of total plasma ALB concentration, BMI, depression status, MMSE score and Mood assessment score, a visual inspection was performed using a funnel plot Overall, the funnel plot displayed a symmetrical shape, implying no evidence of publication bias. For the analysis of total plasma level levels, BMIs and mood assessments, due to the small number of studies, one outlier was noted, in both directions, suggesting true heterogeneity rather than publication bias (Figure 8a).

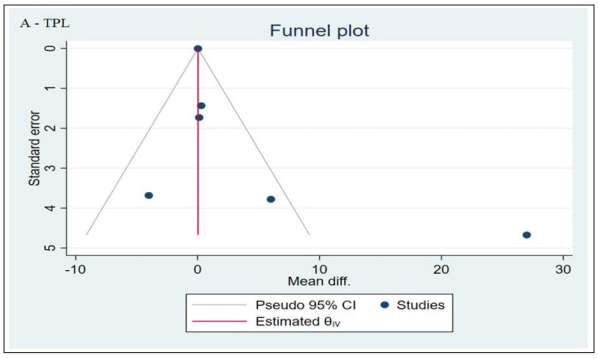


Figure 8: Funnel plot of the studies included in the meta-analysis of total plasma levels.

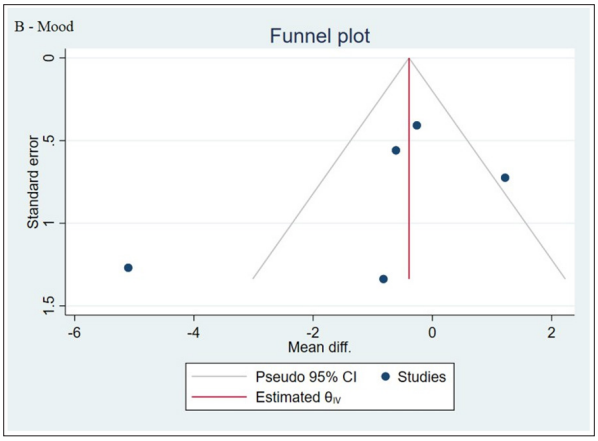


Figure 9: Funnel plot of the studies included in the meta-analysis of the Mood Assessment.

Discussion

Tryptophan and 5-HTPare biogenic amines that are produced from 5-HTP and serve as neurotransmitters in the brain and enteric nervous system [27]. Unlike 5-HTP in the enteric nervous system, which controls gastrointestinal secretion and motility, 5-HTP in the brain is involved in the modulation of mood and cognition. The blood–brain barrier prevents 5-HT from crossing under normal physiological circumstances. More than 90% of the 5-HTP in the body is created in gut mucosal enterochromaffin cells. According to O'Mahony et al., decreased central 5-HTP availability is a major factor in developing depression. Early research suggested that tryptophan and 5-HTP may be equally effective as some antidepressants for the treatment of mild-to-moderate depression and improved cognitive mood [21,28].

The present systematic review and meta-analysis showed that the administration of tryptophan and HTP supplements to patients with cognitive and mood disorders could significantly increase the total plasma level, and improve the Beck Depression Inventory (CES-D), EDSS and Goldberg General Health Questionnaire (GHQ) scores following treatment with tryptophan and HTP and improve mood. We could not perform a meta-analysis on the nutritional status of the patients or on two biochemical outcomes (HDL cholesterol and total lymphocytes) or short/long memory assessments due to the small number of RCTs reporting these out comes. Regarding cognitive improvement, our meta-analysis showed that older adults and children had significant improvements in reported depression scales and mood assessments as a measure of cognitive function when supplemented with tryptophan and HTP for 12 weeks of follow-up. In fact, it has been confirmed that this dietary supplement significantly reduces exposure to sadness post-delivery and eliminates the chance of postpartum depression [29].

In addition, the results of the meta-analysis are consistent with those of previous studies [20]. One study analyzed the depressive status of 138 healthy participants through the administration of daily 1 g of tryptophan or placebo supplementation and revealed that tryptophan not only has an uneven effect on mood improvement but also helps to improve other cognitive functions. With regard to the impact of the supplement on the Mini-Mental Health Scale score, we found an insignificant effect. This might be due to variations in dose and time of administration. Rob

Markus et al. examined the effect of tryptophan, which is rich in α-lactalbumin, on 14 healthy participants. The study showed that evening intake of tryptophan, which is rich in α-lactalbumin, resulted in 130% improvement in mental health and improved brain performance.

In line with the results of our meta-analysis, a reduction in body mass index was found after the administration of 5-HTP. Importantly, the intake of 5- HTP could help in the regulation of feeding behavior [30]. Empirical results have shown that the intake of 5-HTP and tryptophan support the role of serotonin in the regulation of feeding, aiding in raising brain 5-HT levels and resulting in decreased food intake, which eventually reduces BMI [31,32].

Limitations of the study

The limitations of this research include the fact that there are no previous systematic reviews or meta-analyses on the use of 5-HTP or tryptophan for the treatment of cognitive and mood disorders; therefore, this work cannot be considered exhaustive [33-40]. Second, the search limit was limited to studies published after 2000, and studies written in English could have limited our results, otherwise, relevant studies written in other languages might significantly improve our results. As a matter of fact, meta-analysis of nutritional status and some biochemical outcomes would have been possible. The strengths of this study lie in the search strategy and PICO format, which allowed for the generation of relevant literature that was deemed to be of good quality [41-51].

In conclusion we showed that, compared with the placebo, regular intake of 5-HTP and tryptophan significantly improved cognitive and mood disorders.

Declarations

Ethical statement

No ethical approval was deemed necessary for this study according to our national regulations.

Conflicts of interest

The authors have no conflicts of interest to disclose.

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