Review

Micronutrients in the Treatment of ADHD: Speculation or Opportunity?

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Abstract: Attention Deficit Hyperactivity Disorder is a neurodevelopmental disorder characterised by core symptoms of impulsivity, locomotor hyperactivity, and inattention affecting around 5% of children and adolescents worldwide. Although this brain illness is wrongly considered a childhood disorder, increasing evidences suggest that it can persist into adulthood in about 65% of cases leading to significant clinical, socio-relational, and occupational disabilities. Pharmacological and non-pharmacological treatments currently available permit to achieve numerous benefits, in particular, if started early in childhood, however, quality of life of patients affected by ADHD could be compromised in any case in terms of self-esteem, ability to finalize projects, and personal satisfaction. In this study we evaluated the impact of micronutrient formulations on ADHD symptoms in both children and adults analyzing results of randomized, placebo-controlled trials.

Keywords: ADHD; micronutrients; neurodevelopment; disattention; hyperactivity

1. Introduction

Attention Deficit Hyperactivity Disorder (ADHD) is the most common neurodevelopmental disorder with an estimated worldwide prevalence around 5% in children and adolescents (1). The core symptoms of this disabling brain disorder consist of a persistent and inappropriate level of impulsivity, locomotor hyperactivity, and inattention (1). These core symptoms may all occur simultaneously with comparable level of severity (mixed subtype), but in many cases, ADHD patients can show a prevalence of inattention (subtype with predominant inattention) or impulsivity/hyperactivity (subtype with predominant impulsivity/hyperactivity) (1,2). In association to the core symptoms, patients affected by ADHD can develop a wide range of seconday, but no less impairing symptoms and disorders such as sleep and eating disorders, dyslexia, dyscalculia, social phobia, crippling shyness, inability to finalize personal and work projects, generalized and somatized anxiety, personality disorders, and mood instability (1). Although ADHD has long time been mistakenly considered a childhood disorder, considerable clinical evidences have shown that ADHD symptoms persist in adulthood in around 65% of cases causing significant clinical, socio-relational, and occupational disabilities (2). Furthermore, in some special populations such as people affected by psychiatric disorders and/or substance/alcohol use disorders, the prevalence of ADHD can increase to affect one in four/three patients (3,4). However, in adults, ADHD symptoms show a different presentation reflecting the structural brain change due to the neurodevelopment completion. ADHD symptoms should be considered fluid clinical manifestations within individuals across their lifespan rather than stable traits (1-4). In adulthood, the childhood hyperactivity or inattention can be replaced by both impulsivity and disorganization as well as psychiatric and substance use disorders may mask the clinical presentation making it difficult to detect the ADHD symptoms (1-4). Despite the large amount of evidences reported in the scientific literature,

 doi:10.20944/preprints202212.0215.v1

to date, the etiology and pathophysiology of ADHD are still incompletely understood (5). Studies of twins and adopted children display a high heritability for ADHD ranging from 60 to 90% (5). Anyhow, as for other psychiatric disorders, it became clear that ADHD etiology is explained for by a complex interaction of many genes each with a relatively small effect and by interactions between genes and environment (5). Among the environmental factors influencing the prevalence of ADHD, pre- and post-natal factors, such as maternal smoking, alcohol and substances use, low birth weight, premature birth as well as exposure to toxins, such as organo-phosphate pesticides, polychlorinated biphenyls, and zinc play a key role (6). Since the neurodevelopment process may be influenced by numerous environmental factors able to alter various signaling systems regulating the progressive sequence of developmental events, many studies have investigated the role of drugs, chemicals, and micronutrients in the development, evolution, and treatment of ADHD (7). Pharmacological treatments currently available include stimulant medicines (e.g. methylphenidate, dexamfetamine, and lisdexamfetamine) and non-stimulant medications (e.g. atomoxetine) (8,9) that can be associated to non-pharmacological therapies such as neurofeedback, cognitive training, cognitive behavioral therapy, child training, and parent training (10). Pharmacological treatments show a class effect of improving clinical response compared to placebo, however, inattentiveness and restlessness appear to be improved more than quality of life (8,9). If we analyze the effect of non-pharmacological treatments on patients affected by ADHD, the data emerged from the studies do not provide solid evidences to consider the non-pharmacological interventions as highly effective therapies for treating ADHD core symptoms. However, some of them, such as behavioral interventions or cognitive training may be effective for treating the socio-relational and occupational impairments (11,12). In order to improving the quality of life of patients affected by ADHD, numerous nutraceuticals, phytoceuticals, complementary, and alternative medicines have been tested in children, adolescents, and adults as unique or associate therapy (13,14). To date, there are very limited randomized, placebo-controlled trials (RCTs) investigating the effect of both nutraceuticals and phytoceuticals on the symptoms of ADHD (15). The data emerged from the currently available RCTs do not permit to recommend the use of omega-3 and omega-9 fatty acids, zinc, acetyl-L-carnitine, and Ginkgo biloba for treating the core symptoms of ADHD (15). Conversely, vitamin D at doses ranging between 1500 and 4000 IU per day is weakly recommended for adjunctive use in child ADHD (15). On the other hand, the information extracted from the studies in which authors tested a micronutrient formula containing various combined nutraceuticals and phytoceuticals in place of a single nutraceutical/ phytoceutical appear to be more encouraging (15). The aim of this paper is to summarize the data emerged from the studies in which authors have evaluated the effect of different micronutrient formulations on child and adult ADHD symptoms focusing our attention on the RCTs.

2. Materials and Methods

A systematic search for studies in english language was conducted using the Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Health Technology Assessment Database, Allied and Complementary Medicine (AMED), PsycINFO, Ovid MEDLINE(R), and EMBASE. Search terms used were: ADHD OR child ADHD OR adolescent ADHD OR adult ADHD OR attention deficit OR child attention deficit OR adolescent attention deficit OR adult attention deficit OR attentional deficit OR child attentional deficit OR adolescent attentional deficit OR adult attentional deficit AND multivitamin OR micronutrient OR herbal OR herbal medicine OR plant medicine OR phytomedicine OR supplement OR vitamin OR mineral OR nutrient OR food supplement OR meal replacement OR nutritional supplement OR health supplement OR omega 3 OR fish oil OR alpha lipoic acid OR alpha linolenic acid OR alpha linoleic acid OR eicosapentaenoic OR docosahexaenoic OR fatty acid OR amino acid OR taurine OR S-adenosyl-methionine OR creatine OR acetylcysteine OR cysteine OR probiotic OR tryptophan OR tocopherol OR alphatocopherol OR carotene OR retinol OR thiamine OR

 doi:10.20944/preprints202212.0215.v1

riboflavin OR niacin OR niacinamide OR nicotinic acid OR pantothenic OR pyridox OR biotin OR methylfolate OR 5-MTH OR levomefolic acid OR folate OR folinic acid OR folic acid OR inositol OR cyanocobalamin OR methylcobalamin OR cobalamin OR ascorbic acid OR cholecalciferol OR iron OR ferrous OR tocopherols OR trace element OR calcium OR phosphorus OR magnesium OR potassium OR manganese OR zinc OR selenium OR boron OR chromium OR lycopene OR isoflav OR flavonoid OR bioflavonoid OR carnitine OR st John's wort OR kava OR ginseng OR saffron OR curcumin OR valerian OR ginkgo OR rhodiola OR Bacopa monniera OR Centella asiatica OR Crocus sativus OR Curcuma longa OR Hypericum perforatum OR Galphimia OR Ginkgo biloba OR Lavandula OR Matricaria spp. OR Panax ginseng OR Passiflora incarnata OR Piper methysticum OR Rhodiola rosea OR Valeriana OR Withania somnifera. All RCTs in which was used a mixture of nutraceuticals and/or phytoceuticals either as adjunctive treatment or monotherapy was included. No restrictions were placed on the dosage or standardisation of micronutrient formulations used. We included all RCTs performed on children, adolescents, and adults, due to the natural evolution of the disorder. Only studies with a duration greater than four weeks were considered for our analysis. In order to minimise Type I error, RCTs with less than 10 participants per arm were excluded.

3. Results

Considering the selection criteria used to search for articles, we found three studies eligible for our analysis. Overall, patients were recruited from 2009 to 2020. In the first 2 studies, patients were recruited in New Zealand, while in the third trial, patients were recruited in both United States of America and Canada. The trials duration ranged between 8 and 10 weeks and, apart from patients recruited in Canada, at baseline and study completion all patients enrolled were tested for haematological and biochemical variable which included thyroid function, prolactin, glucose, homocysteine, iron, zinc, copper, vitamin D, vitamin B12, folate, alanine aminotransferase (ALT), aspartame aminotransferase (AST), urinalysis, and urine drug screen. In 2014, Rucklidge et al. in a double-blind, randomised, placebo-controlled eight-weeks trial have evaluated the effect of fifteen tablets of a micronutrient formulation (Table 1) on adult ADHD symptoms in a sample of forty-two patients compared to a sample of thirty-eight patients who received placebo (16). Four patients in the micronutrient group and two in the placebo group dropped out of the study. In none of the cases the study was interrupted due to the development of significant adverse effects (16). The two groups were homogeneous for socio-demographic and clinical characteristics apart from the gender ratio and the presence of anxiety disorders. In particular, in the placebo group there was a male predominance while in the micronutrient group there was a higher prevalence of patients affected by anxiety disorders (16). Considering the pharmacological history of patients involved in the study, 17.5% of the sample had received an ADHD treatment as a child with stimulant or nonstimulant medicines, and 51.3% had a history of taking psychiatric medicines. In particular, 16.3% had been prescribed a stimulant madication, 25% had been prescribed a prychiatric medicine other than a stimulant, and 10% had been prescribed a combination of drugs (16). Authors found a significant difference between groups on the self and observed Conners Adult ADHD Diagnostic Interview (CAARS) for DSM-IV total subscales score, but not on the clinician CAARS ratings. However, when authors analyzed the Clinical Global Impression Improvement (CGI-I) and Clinical Global Impression ADHD (CGI-ADHD) scores, they found the rated ADHD symptoms and global change as more improved in the micronutrient group if compared to the placebo group. No group difference was found in the Montgomery-Asberg Depression Rating Scale (MADRAS) and Longitudinal Interval Follow-up Evaluation Range Impaired Functioning Tool (LIFE-RIFT). When authors analyzed the MADRAS score for the subsample of patients with moderate or severe depression at baseline (11 patients), they found significant differences favouring the micronutrient group. Otherwise, the micronutrient group showed greater overall improvement based on the Global Assessment of Functioning (GAF). No significant adverse effects were

 doi:10.20944/preprints202212.0215.v1

reported in both samples. Finally, patients in the micronutrient group showed significant change in vitamin D, vitamin B12, and folate levels if compared to the placebo group. Only B12 levels increased beyond the reference range in the micronutrient group. A 1-year follow up study showed that, although there was a significant regression in psychiatric functioning from the end of the trial, patients who stayed on micronutrients treatment maintained the benefits compared to patients who had stopped taking since outcomes remained significantly improved from baseline (17). In 2018, Rucklidge et al. in a fully blinded, randomized, placebo-controlled 10-weeks trial have evaluated the effect of twelve tablets of a micronutrient formulation (Table 2) on child ADHD symptoms in a sample of forty-seven patients compared to a sample of forty-six patients who received placebo (18). Two patients in each group did not complete the trial. No difference between groups was found in socio -demographic and clinical characteristics apart from a higher prevalence of generalized anxiety disorder in the micronutrient group if compared to the placebo group. Overall, 32% of the sample had a past history of psychiatric medicine use. In particular, 22% had been prescribed a stimulant medication, 2% had been prescribed a psychiatric medicine other than a stimulant, and 8% had been prescribed a combination of drugs. When authors analyzed the CGI-I-Overall scores, they found a significant improvement in all areas of functioning in the micronutrient group if compared to the placebo group. Differently, no between group differences were observed for ADHD ratings on the ADHD Rating Scale IV (ADHD-RS-IV) clinician version and Child Mania Rating Scale (CMRS) parent version. Authors found a significant difference between groups in the score of the CGI-I-ADHD, CGI-I-Mood, and Children's Global Assessment Scale (C-GAS). Particularly, the significant improvement in the clinician rated CGI-I-ADHD found in the micronutirent group was largely due to a greater improvement in the inattentive symptoms rather than the hyperactivity/impulsivity symptoms. Otherwise, teacher ratings of ADHD symptoms showed no group differences across all dimensions of ADHD. Additionally, authors found significant group differences on the Strengths and Difficulties Questionnaire (SDQ)–Parent Conduct Problems Subscale and Behaviour Rating Inventory of Executive Function Teacher (BRIEF)-Teacher Emotional Control Subscale. No significant differences between groups were found in the other subscales of the SDQ and BRIEF. No significant adverse effects were reported in both samples. Finally, patients in the micronutrient group showed significant change in vitamin D, vitamin B12, and folate levels if compared to the placebo group. Only B12 levels increased beyond the reference range in the micronutrient group. A 1-year follow up study of patients who had participated in the trial showed that 84% of those who had continued micronutrients treatment were identified as "Much" or "Very Much" improved overall relative to baseline functioning, compared to 50% of those who switched to psychiatric medications and 21% of those who discontinued treatment (19). In 2022, Johnstone et al. in a placebo-controlled, randomized, fully blinded, 8-weeks trial evaluated the effect of nine to twelve tablets of a micronutrient formulation (Table 2) on child ADHD symptoms in a sample of seventy-one, 6-12- years, non-treated patients compared to a sample of fifty-five, 6-12-years, non-treated patients who received placebo (20). No difference between groups have been found analyzing the socio-demographic and baseline clinical characteristics. Using the CGI-Severity (CGI-S) at baseline, 56% of the participants were rated as "moderately ill" and 43% as "markedly/serverely ill". 56% of patients in the micronutrient subgroup with a severe illness compared to 22% of those in the placebo subgroup had illness severity reduced on the CGI-S. The analysis of intention to treat (ITT) population based on blinded CGI-I, showed that patients in the micronutrient group were 3 times as likely to be responders (54%) if compared to those in the placebo group (18). No significant differences between groups were found on the parent rated Child and Adolescent Symptom Inventory 5 (CASI-5) score. On the adult/teacher CASI subscales, authors found no significant difference between groups apart from the Peer Conflict subscale. During the 8-weeks, participants in the micronutrients group grew 6 millimeters more on average than those in the placebo group. On the CGI-S, the illness severity of 3 patients in the placebo group

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 13 December 2022 doi:10.20944/preprints202212.0215.v1

worsened compared to none in the micronutrient group. No significant adverse effects were reported in both samples. No concerning blood or urine values were detected from baseline to study completion. One child on placebo group had AST and ALT values above the reference range at baseline that fell to within range at the study completion measurement. 4 children in the micronutrient group increased the AST and ALT values after treatment, but the variation was not statistically significant.

Table 1. Ingredients.

Vitamin A	5760 IU	Selenium	204 µg
Vitamin C	600 mg	Copper	7.2 mg
Vitamin D	**1440 IU**	Manganese	9.6 mg
Vitamin E	360 IU	Chromium	624 µg
Thiamin	18 mg	Molybdenum	144 µg
Riboflavin	13.5 mg	Potassium	240 mg
Niacin	90 mg	Choline bitartrate	540 mg
Vitamin B6	36 mg	dl-Phenylalanine	360 mg
Folic acid	1440 µg	Citrus bioflavonoids	240 mg
Vitamin B12	900 µg	Inositol	180 mg
Biotin	1080 µg	Glutamine	180 mg
Pantothenic acid	21.6 mg	Methionine	60 mg
Calcium	1320 mg	Grape seed	45 mg
Iron	13.7 mg	Ginkgo biloba	36 mg
Phosphorus	840 mg	Germanium sesquioxide	20.7 mg
Iodine	204 µg	Boron	2400 µg
Magnesium	600 mg	Vanadium	1194 µg
Zinc	48 mg	Nickel	29.4 µg

Table 2: Ingredients.

Vitamin A	384 IU	Selenium	13.6 µg
Vitamin C	40 mg	Copper	0.5 mg
Vitamin D	200 IU	Manganese	0.6 mg
Vitamin E	24 IU	Chromium	42 µg
Vitamin K (d-alpha tocopheryl succinate)	6 µg	Molybdenum	10 µg
Vitamin K (menaquinone-7)	2 µg	Potassium	16 mg
Thiamin	4 mg	Choline bitartrate	36 mg
Riboflavin	1.2 mg	Alpha-lipoic acid	33.3 mg
Niacin	6 mg	Mineral wax	12.5 mg
Vitamin B6	4.7 mg	Acetylcarnitine	4 mg
Folic acid	53.3 µg	Inositol	12 mg
Vitamin B12	60 µg	Cysteine	2 mg
Biotin	72 µg	Methionine	2 mg
Pantothenic acid	2 mg	Grape seed	3 mg
Calcium	88 mg	Ginkgo biloba	2.4 mg

 doi:10.20944/preprints202212.0215.v1

Iron	0.9 mg	Germanium sesquioxide	1.4 mg
Phosphorus	56 mg	Boron	0.2 mg
Iodine	14 µg	Vanadium	0.1 mg
Magnesium	40 mg	Lithium orotate	0.07 mg
Zinc	3.2 mg	Nickel	0.002 mg

4. Discussion

ADHD is an underestimated, littel known, and disabling neurodevelopmental disorder associated to high risk of comorbid psychiatric disorders and drug/alcohol addiction, as well as to low socio-occupational functioning, low self-esteem, and suicidal behaviors (21). Notwithstanding the negative results emerged from the clinical trials in which authors have tested the efficacy of micronutrients on the child and adult ADHD symptoms performed in the 1970s and 1980s (22-24), recent and more encouraging evidences have reiterated the need to deepen the studies on the efficacy of micronutrients in the treament of adult and child ADHD and clarify the role of the nutritional factors in the development and evolution of the brain neurodevelopmental disorders (25,26). In 2011, Rucklidge et al. designed an 8-weeks open label study in which they evaluated the effect of a 36-ingredient micronutrient formula on the neurocognitive functioning of 14 adults affected by ADHD and severe mood disregulation. The sample was compared with a group of 14 adult people without a diagnosis of ADHD. Authors found a significant improvement in the ADHD group if compared to the placebo group across a range of verbal abilities including verbal learning, verbal cognitive flexibility verbal cognitive fluency, and verbal inhibition (25) No significant difference between grups was found in visual-spatial memory, reaction time, working memory, and rapid naming (25). In 2015, Gordon et al. in an open label reversal study have evaluated the effect of a 36-ingredient micronutrient formula on ADHD symptoms of 14 medication-free children for a 6 months period. Authors found significant improvement on the clinician-rated CGI global functioning and some SDQ subscales including emotional symptoms, conduct problems, and prosocial behaviours. No significant adverse effect were reported by participants (26). Although limited, scientific literature evidences suggest greater efficacy of a micronutrient formulation rather than a single high-dose micronutrient (27,28). The mechanism of action of a micronutrient formulation on the symptoms of ADHD is unknown, however, some clinical evidences suggest that the serum nutrient levels have limited value for identifying responders from non-responders except for a potential correlation between low baseline levels of copper and vitamin D and high baseline levels of ferritin with a better response to some outcomes (29). Clinical studies have shown no childhood risk factors, demographic variables or pathological correlates that contraindicated micronutrient treatment (29). Differently, severe symptoms at baseline and a high number of developmental risk factors predicted a good treatment response (29). Micronutrients formulation could improve the western diet nutrient deficiencies (30), genetic errors of metabolism (31), and microbiome composition (32). Furthermore, micronutrients may promote the production of adenosine triphosphate (ATP) by mitochondria, since a deficient ATP production could be correlated to individual response variability in patients affected by ADHD (33). Additionally, micronutrients administration meight promote the regulation of homocysteine metabolism, neurotransmitters synthesis and, consequently, the stabilization of anxiety and mood (16). Overall, the randomized, placebo-controlled trials mentioned in our work have involved thirty-eight adults and one hundred and six children. All adults were enrolled in New Zealand, while approximately 33% of children were enrolled in New Zealand and approximately 67% in North America. As regards the results obtained on patients affected by adult ADHD, the only eight-week RCT showed a significant clinical improvement based on the CGI evaluation, but not on the CAARS. However, the assessment appears to be lacking of tests evaluating the various symptomatological dimensions of ADHD and secondary symptoms,

 doi:10.20944/preprints202212.0215.v1

also through the use of neurocognitive measurements. Furthermore, there was no measurement of patient expectations and this is an important limitation considering that patient expectations can greatly influence the placebo effect intensity (34). MADRAS score resulted significant improved in patients with severe depression at baseline, but not in all the sample. However, patients with MADRAS score ≥ 20 were 11, less than 1 in 3, too few in absolute terms and compared to the sample to generalize the results. The data of GAF score improvement and absence of significant side effects are very interesting and require further investigations. It is also important to underline that the majority of participants had a history of specific or nonspecific psychopharmacological treatments and this is an important limitation when authors have to investigate the effect of a new treatment on the symptoms of a disese. As regards the effect of micronutrients on the child ADHD symptoms, in the first study, in which the sample was composed of patients with (1 in 3) and without (2 in 3) a history of specific or non-specific psychopharmacological treatmentes, the results showed a clinical impovement based on the CGI and C-GAS scales, particularly regarding the inattentive symptoms rhater than those of impulsivity and hyperactivity. Furthermore, teachers and parent observed a significant impovement on emotional control and conduct problems, repectively. In the study, authors did not perform a clinical specific assessment for the ADHD dimensions, for example using neurocognitive tests. Interpersonal expectancy effects are less thoroughly understood in children than in adults, however, parent expectancies should have been assessed to better interpret the role of the induced placebo effect. In the other study, all 71 patients were medication free and were recruited in 2 north americans centers, one in Canada and one in the United States of America. Authors found a significant improvement based on the CGI tests, but in the study were not administered neurocognitive tests to assess all specific dimensions of ADHD and secondary symptoms. This assessment is really important to optimize the results emerged from the global evaluations scales. Furthermore, parent expectancies were not assessed to better interpretate the role of the induced placebo effect. In both studies performed on child ADHD patients were not reported significant adverse effects. Overall, the clinical trials evaluated in our article can be considered as innovative studies that can shed light on the role of nutraceuticals in the treatment of ADHD symptoms in both children and adults. Scientific litterature shows that the use of single nutraceuticals appear to be low effective in both adult and child ADHD while the studies on the role of micronutrients formulation are still very limited though worthy of further clinical investigations. The clinical results emerged from the analysis of the scores obtained by adult and child patients treated with formulations of micronutrients in the global assessment tests (CGI) appear to be interesting and constitute the scientific basis and stimulus for further, more extensive, and methodologically more refined studies. However, the lack of a psychoneurocognitive assessment of all the core and secondary dimensions of ADHD in both adults and children, makes the interpretation and generalization of outcomes more complicated. Other limitations are the small size of the samples involved in the trials as well as the absence of patients and parent expectations assessment. These factors can significantly affect the interpretation of the data, producing false positives, especially in the short term evaluations. The risk of type I error from multiple measurements, lack of a large multicentricity as well as the presence, in many cases, of other pharmacological therapies, may produce furher distortions in the data interpretation. On the other hand, the absence of significant side effects is reassuring, even in those patients who continued to take the treatment in the 1-year follow-ups. 1-year follow-ups have shown that few patients continue to take the therapy in the long term, highlighting how the high number of capsules to be taken and the economic cost are the main causes of treatment discontinuation. In conclusion, the results emerging from the 3 trials, despite the many limitations, represent an important stimulus for further and more extensive studies due to a certain potential efficacy in the absence of significant side effects. Future studies will also have to investigate the correlation between clinical improvements and effects of single substances present in the formulations in order to be able to create essential and effective products to

 doi:10.20944/preprints202212.0215.v1

reduce the number of capsules to be taken and costs. Moreover, the future trials will have to compare the effect of micronutrient formulations to that of conventionale medicines used for treating the ADHD symptoms (stimulants and non-stimulants) in drug naive patients.

5. Conclusions

Despite the long history of assumption during centuries and the recent increase in demand worldwide, there is still scepticism, also among clinicians, associated with the use of nutraceuticals for the treatment of psychiatric disorders. Socially, the use of nutraceuticals is better considered if compared to the conventional medicines when the therapy is referred to children and adolescent, but the general consideration is often very limited (35). The principal reason is due to the incorrect results or wrong results interpretation emerged from poorly designed and controlled trials performed in the past decades. However, in the last years, new and well designed controlled trials have given new impetus to research on nutraceuticals for the treatment of various psychiatric disorders. Despite the excitement from some positive results, the evidences of nutraceutical treatment in short term studies for ADHD appear to be modest compared with those emerged from trials with stimulant and nonstimulant medicines. The only nutraceutical currently recommended for adjunctive use in the treatment of child ADHD is represented by the vitamin D at doses ranging between 1500 and 4000 IU per day. Other RCTs performed to study the effect of some nutraceuticals such as omega-3 and omega-9 fatty acids, zinc, acetyl-L-carnitine, and Ginkgo biloba on the symptoms of adult and child ADHD, have not provided positive results. The RCTs analyzed in our work appear innovative and interesting because they are the first to investigate the effect of a nutraceutical formulation in substitution of a single nutraceutical. Albeit modest, the data emerged deserve to be explored with further, larger, and multicenter controlled studies in order to confirm and better interpret the positive results. Future studies should use a neuropsychocognitive assessment to objectively investigate all primary and secondary symptoms of ADHD. Furthermore, they will have to correlate the clinical benefits with the individual substances present in the formulations in order to reduce the number of nutraceuticals to be included, and consequently, the number of capsules to be ingested and costs. Finally, future studies will have to directly compare the effects of nutraceuticals with those of conventional stimulant and nonstimulant drugs in drug-naive patients.

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Funding: This research received no external funding.

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Acknowledgments: In this section, you can acknowledge any support given which is not covered by the author contribution or funding sections. This may include administrative and technical support, or donations in kind (e.g., materials used for experiments).

Conflicts of Interest: The authors declare no conflict of interest.

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