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Complementary medicines (herbal and nutritional products) in the treatment of Attention Deficit Hyperactivity Disorder (ADHD): A systematic review of the evidence☆

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Omega-3

Summary
Overview: Complementary and Alternative Medicines (CAMs) are frequently given to children and adolescents for reputed benefits in the treatment of hyperkinetic and concentration disorders such as Attention Deficit Hyperactivity Disorder (ADHD). In such vulnerable populations high quality evidence is required to support such claims.
Aims: The aim of the paper is to assess the current evidence of herbal and nutritional interventions for ADHD using a systematic search of clinical trials meeting an acceptable standard of evidence.
Methods: PubMed, PsycINFO, Cochrane Library and CINAHL were searched up to May 26th, 2011 for randomised, controlled clinical trials using CAM products as interventions to treat ADHD. A quality analysis using a purpose-designed scale, and an estimation of effect sizes (Cohen's *d*) where data were available, were also calculated.
Results: The review revealed that 16 studies met inclusion criteria, with predominant evidentiary support found for zinc, iron, *Pinus marinus* (French maritime pine bark), and a Chinese herbal formula (Ningdong); and mixed (mainly inconclusive) evidence for omega-3, and L-acetyl carnitine. Current data suggest that *Ginkgo biloba* (ginkgo), and *Hypercium perforatum* (St. John's wort) are ineffective in treating ADHD.

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Conclusion: The research suggests only some CAMs may be beneficial in ADHD, thus clinicians need to be aware of the current evidence. Promising candidates for future research include *Bacopa monniera* (brahmi) and *Piper methysticum* (kava), providing potential efficacy in improving attentional and hyperkinetic disorders via a combination of cognitive enhancing and sedative effects.

Contents

Introduction

The number of children diagnosed with Attention Deficit Hyperactivity Disorder (ADHD) has grown markedly since being recognised as a specific disorder in the 1970s. The prevalence rate of ADHD within Western cultures is approximately 5%, and remains the most common psychiatric illness among young children, with an estimated 50% of these children retaining ADHD symptoms for the rest of their lives.[1,2] The economic consequences of ADHD persisting into adulthood are significant, with one U.S. analysis finding an average of 35 days of annual lost work performance, representing 120 million days of annual lost work in the labor force, equivalent to $19.5 billion lost human capital.[3]

The aetiology of ADHD and the dysfunction of the neuro-circuitry within prefrontal cortex have two potential theories; maturational lag,[4] or developmental deviation.[5,6] A lag in developmental maturation delineates that normal maturing of the prefrontal cortex is delayed and depending on the severity of symptoms of the child, will gradually match the maturation level of normal peers.[7] Developmental deviation has been found in electroencephalograph (EEG) studies that have revealed that despite age changes, ADHD symptoms and associated cognitive differences remain resilient as maturation continues, and is on an abnormal developmental path to peers.[5,6] There has been extensive research into the causes of ADHD including its high heritability and genetic influences that predispose a child to deficits in dopamine and serotonin transmission.[8] Other causes have been attributed to harmful exposure to the foetus/child in the prenatal, perinatal, postnatal and early childhood phases.[9] In utero exposure to excess alcohol, tobacco and lead have been linked to an increased risk of ADHD,[10] while studies on diet have found that ADHD symptoms may become exacerbated when certain additives or food preservatives are consumed.[11]

Diagnostic tools used to establish a diagnosis of attention deficit hyperactivity/impulsivity disorder involve the clear understanding that symptoms have been present and persistent for a minimum of six months prior to the age of seven, are considered maladaptive, not consistent with the child's developmental level, and cannot be explained by other psychiatric or medical disorders.[12] Symptoms relating to ADHD include inattentiveness in the classroom or at home; or an inability to carry out simple instructions or sustain task attention which can result in careless mistakes in school work and reduce motivation for subsequent participation. Hyperactivity and/or impulsivity diagnosis include symptoms of restlessness that exist in the hands or feet during times of sitting or sleeping and running, moving erratically or talking excessively which cause disruption in an otherwise calm environment.[12] Comorbidity is common in ADHD, with strong links to oppositional defiance disorder and learning disorders in children; and major depressive disorder, anxiety disorders, social dysfunction and substance abuse in adults.[13,14] Academic issues surrounding ADHD in childhood are linked to a higher drop-out rate from secondary (high) school with fewer than 5% completing a university degree.[15] A large proportion of ADHD adults are found to be unemployed[15] with a significant number of those with employment taking considerable amounts of unpaid leave.[17]

Conventional treatment options usually include either in isolation or in combination, a pharmaceutical component, a behavioural component, and a psychosocial component. Pharmacotherapies which inhibit the re-uptake of noradrenline and dopamine such as the psychostimulants methylphenidate and dextroamphetamine, and non-stimulating pre-frontal cortex noradrenaline re-uptake inhibitor atomoxetine, are the standard Western treatment of ADHD.[2] Selective serotonin reuptake inhibitors (SSRIs) and other antidepressants are also used with varying degrees of success. A third of ADHD patients who take stimu-

lants for ADHD report significant adverse effects including anorexia, weight loss, abdominal pains, sleep disturbances, headaches, irritability, depressed mood and appetite,[16–20] with some reports of stimulant induced psychosis.[21]

Increasing apprehension regarding stimulant medication and the ramifications of its use on children has led to the investigation and acknowledgment of alternative therapeutic medications.[22] More than 50% of parents of children diagnosed with ADHD treat their children's symptoms using one or more Complementary or Alternative Medicines (CAMs) including vitamins, but few disclose this to their child's paediatrician.[23] Many individuals diagnosed with ADHD use CAMs alone or adjunctively with conventional pharmacological treatments, with one study of 822 children with diagnosed or suspected ADHD revealing 12 percent had used CAMs.[24] Due to the prevalent use of CAMs by children with ADHD, evidence is required to support claims of efficacy, especially as this is a vulnerable group. Previous publications have explored this area, however to date no comprehensive systematic review has been conducted, assessing the quality of studies and the strength of their clinical effects (effect sizes). Thus, the purpose of this paper is to present a systematic review of CAM natural products used for treating ADHD.

Methods

The electronic databases MEDLINE (PubMed), CINAHL, PsycINFO, and The Cochrane Library were accessed up to May 26th, 2011 (see Fig. 1 for systematic review flowchart). PubMed was searched using ADHD search terms in combination with specific CAMs (herbal and nutritional medicine) interventions (see Appendix 1 for intervention search term list). Papers that met the inclusion criteria were human randomised controlled trials (RCTs) of sufficient methodological rigor.

Inclusion criteria:

(1) Sample consisting of children or adolescents (aged 5—17) or adults (aged 18—65)
(2) Primary diagnosis of ADHD, or marked level of attention or hyperactivity on recognised scale
(3) Randomised and controlled design, or CAMs vs. a positive control (e.g. a psychostimulant)
(4) Sample size $\geq$20 (10 if a cross-over study)
(5) Duration of intervention $\geq$1 week
(6) Have measurable outcomes on attention or hyperactivity scale
(7) Rating on quality scale of 5 (see below for details of scale)
(8) Full paper in English

All other papers that did not meet these criteria were excluded. Each paper was analysed for methodological quality using a purpose-designed scale based on the Jadad scale[25] (as first used in Sarris and Byrne,[26] and in subsequent reviews e.g. Pase et al.[27]). The Jadad scale uses three primary quality factors — randomisation, blinding and reported withdrawals. The modified augmented version also assesses other methodological factors — exclusion criteria, intervention used, control used, and data reporting to provide a quality total out of ten. Quality assessment of the papers was independently rated to assess inter-rater reliability. Effect sizes were reported in all placebo-controlled studies where the results were significant (small clinical effect = 0.2, medium = clinical effect 0.5, large clinical effect = 0.8). We calculated an effect size as Cohen's *d*[28] by firstly subtracting the differences between the results on the assessment scale of the intervention and placebo, then dividing this by the pooled standard deviation at baseline.

Purpose-designed questionnaire:

1. Was the study described as randomised?
2. Was the randomisation protocol detailed and appropriate?
3. Was the study described as double-blind?
4. Was the blinding process detailed and appropriate?
5. Did the study have a control group?
6. Was the control detailed and appropriate?
7. Was there an adequate exclusion criterion?
8. Was the intervention used at a therapeutic dose?
9. Was there a description of withdrawals and dropouts?
10. Were the data clearly and adequately reported?

Yes = 1 point; no = 0 points; total/10.

Results

Overview of results

Out of 2354 located potential studies in the area of CAMs and ADHD, 233 were found to be RCTs. Two hundred and seventeen of these were eliminated, commonly due to irrelevance, methodological weakness (e.g. small sample, not controlled, or randomised), or the study not having a primary focus on attentional, behavioural or hyperactivity outcomes. This left 16 clinical trials for inclusion. Results were coded under ''Nutritional Medicines'' and ''Herbal Medicines''. Five nutritional interventions met criteria for inclusion: zinc, iron, omega-3, vitamin C, and acetyl-L-carnitine, while four herbal medicines were included: *Ginkgo biloba* (ginkgo), *Hypericum perforatum* (St. John's wort), *Pinus marinus* (French maritime pine bark), and Ningdong Granule (traditional Chinese herbal formula).

Natural products

Nutritional medicines

Eleven studies using nutrients met criteria for inclusion. These had an overall quality rating of 7.6 (range 7—9), with six revealing a quality rating of nine out of ten (see Table 1). The average sample size and duration of the studies were 92 (range 23—400), and 18.5 weeks (range 6—52), respectively. The intervention with the most research was found to be omega-3 (fish oil, DHA, or flaxseed oil). In our systematic review of the literature, four omega-3 RCTs were located that met inclusion criteria, with only one producing significant positive results on the main primary ADHD outcome measures. Two of the omega-3 studies, Stevens et al.[29] (480 mg/day DHA; 80 mg/day EPA) and Raz et al.[30] (240 mg/day linoleic acid: LA, omega-6 and 60 mg/day alpha-linolenic acid: ALA, omega-3) had some

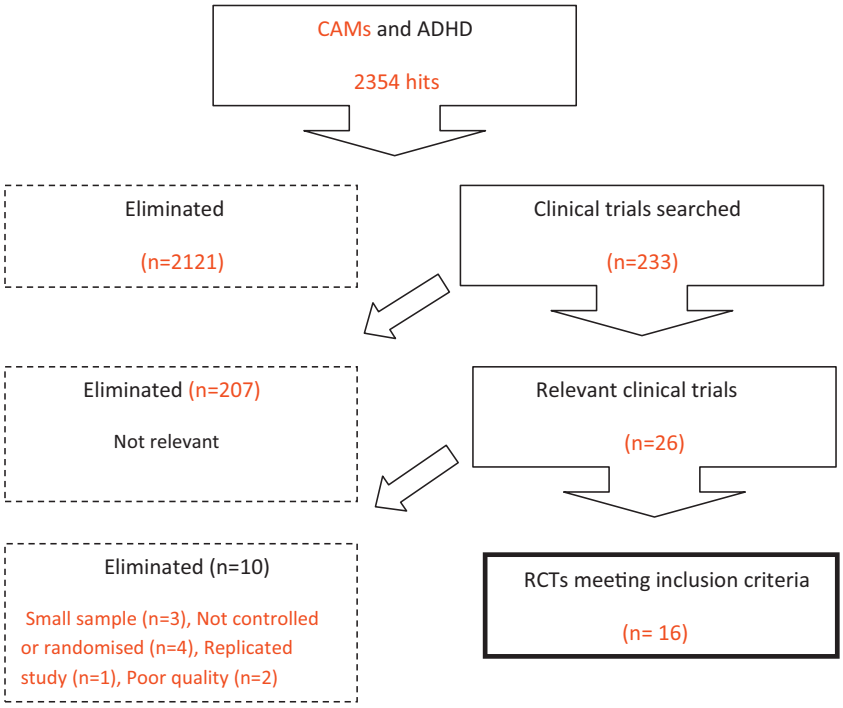

Figure 1 Systematic review flowchart.

methodological flaws that may have contributed to the negative results, including the use of olive oil[29] or vitamin C[30] as a placebo. This may have potentially contributed to the better outcomes on the placebo groups. One study using a DHA-predominant blend (510 mg/day; 100 mg/day EPA) as a predominantly adjunctive intervention to psychostimulants, found no differential benefit of the supplement compared to controls.[31] The ratio of DHA to EPA in this study might suggest as a possible reason for the lack of significant findings with some recent literature indicating that EPA may be more beneficial in ameliorating ADHD symptoms.[32] Only one placebo-controlled trial using omega-3 with positive results was located. The Sinn and Bryan reporting more improvement on hyperactivity and inattention subscales using long-chain polyunsaturated fatty acids (PUFAs) (558 mg/day EPA; 174 mg/day DHA) compared to palm oil placebo in a sample of 132 children.[33] No significant effect however occurred on Conners Teacher Rating Scales. Strict exclusion criteria ensured no participants in the study were on stimulant medication or any additional omega-3 supplements within the previous 3 months.

Findings of studies using zinc in ADHD on various outcomes are mainly positive. In a large RCT ($n = 400$), children and adolescents randomised to a high dose of zinc (150 mg/day) experienced significant improvements over placebo in hyperactivity and impulsivity (but not inattention).[34] A high drop-out rate found in the study may however place limits on the significance of the findings. This was due mainly to protocol violations (zinc: 25.7%; placebo: 28.7%) rather than adverse reactions to the treatment (zinc: 12.3%; placebo: 8.5%). Another study adding zinc (55 mg/day) to psychostimulants (1 mg/kg/day) in 44 children resulted in a greater improvement in symptoms than use of the psychostimulant alone.[35] A recent study by Arnold et al.[36] did not however confirm the results of the previous zinc studies. Zinc glycinate was randomly assigned to 52 children with ADHD for 13 weeks (8 weeks monotherapy and then 5 weeks with added D-amphetamine). Results revealed on ADHD outcome scales that no significant improvements occurred with zinc supplementation in either dose group (15 mg/day or 30 mg/day) over placebo or beyond D-amphetamine.

In an RCT involving 23 children (with a small placebo group ($n = 5$)), non-anaemic ADHD children with abnormally low serum ferritin levels were randomised to oral iron (ferrous sulphate 80 mg/day) and showed progressive improvements in ADHD symptoms over placebo.[37] In a multisite study of 112 ADHD children randomised to placebo vs. acetyl-L carnitine (ALC: 1000 mg/day to 3000 mg/day depending on weight of child), results revealed that children with predominantly inattentive type ADHD experienced greater improvement over placebo (but there was no differential benefit on primary outcomes in children with combined type ADHD).[38] In complex and poorly reported study, L-carnitine (100 mg/kg/day) and placebo was given to 24 Dutch boys over three crossover control periods was found to have some effects on various outcome measures, excepting the primary outcome.[39] A novel study using ALC in 51 children with ADHD and a genetic disorder (Fragile-X syndrome), found that after one year of prescribed ALC, greater benefit on ADHD symptoms was found over placebo.[40]

Herbal medicines

Five studies using herbal medicines met criteria for inclusion. These had an overall average quality rating of 8

Table 1 CAM evidence in ADHD (nutrients).

Intervention	First author	Methodology	Duration (weeks)	Result	Effect size	Quality/10	Comment
Zinc	Arnold (2011)	DB, RAN, PC Zinc group 1 ($n=20$; 15 mg/day) or zinc group 2 ($n=8$; 30 mg/day) vs. Placebo ($n=24$) 52 children Aged 6—14	13 (8 controlled + 5 MPH add-on)	At conclusion of the controlled phase, no significant difference was found on primary outcomes between zinc and placebo. Addition of MPH to zinc did not alter result	**CPRS**: high-dose group (30 mg/day) *Inatt*: −0.54[b] *Hyp*: −0.27[b]	9	Adequate baseline zinc serum level may have limited results. Use of glycinate zinc chelation may be less effective than sulphate chelation
	Bilici (2004)	DB, RAN, PC Zinc ($n=202$) vs. placebo ($n=198$) 400 children and adolescents Aged 6—14	12	Zinc was superior to placebo in reducing both hyperactive/impulsive and impaired socialisation symptoms. Did not reduce inattention	**ADHDS** *Hyp*: 0.26[a,**] *Impul*: 0.18[a,*]	9	Results of this large high quality study encourages use of zinc, especially in deficient populations
	Akhondzadeh (2004)	DB, RAN, PC adjuvant study MPH + zinc ($n=22$) vs. MPH + placebo ($n=22$) 44 children Aged 5—11	6	Significant result over placebo after week 2 and at completion of study with a strong effect size. Both Parent and Teacher ratings improved as the study progressed	**ADHD-P-RS** 1.46[a,*]	9	Augmentation of MPH with zinc may be advised. No participants had received stimulant medication prior to the commencement of the study
Iron	Konofal (2008)	DB, RAN, PC Iron ($n=18$) vs. placebo ($n=5$) 23 children Aged between 5 and 8 with low ferritin levels	12	Progressive significant decrease on ADHD-RS over placebo with a strong effect size; iron also improved ADHD symptoms on CGI-I	**ADHD-RS** *Inatt*: 0.92[**] *Hyp*: 0.63[**]	9	Very specific population group. Young population. Small placebo group relative to zinc group
EFA supplement	Stevens (2003)	DB, RAN, PC LC-PUFAs ($n=25$) vs. placebo ($n=25$) 50 children Aged 6—13 ADHD with thirst/dry skin Controls with few thirst/dry skin symptoms	16	Clear benefit from LC-PUFAs was not observed on major parent or teacher rating scales	**ASQ-P** 0.12[b] **DBD** *Hyp*: −0.09[b] *Inatt*: −0.10[b]	8	Specific classification involving thirst/dry skin signs may not be generalisable to broad ADHD population. Olive oil as a placebo may have confounded effects

	Raz (2009)	DB, RAN, PC EFAs ($n = 39$) vs. placebo ($n = 39$) 78 children Aged 7—13	7	No significant differences were found between the groups	**DSM-P** *Inatt*: −0.37[b] *Hyp*: 0.15[b]	8	Placebo used contained 1000 mg of vitamin C which cannot be viewed as an inert control; vitamin C has been shown to improve the outcome of ADHD
	Sinn (2007)	3-Arm, DB, RAN, PC, CO EFA ($n = 36$) vs. EFA + MV ($n = 41$) vs. placebo ($n = 27$) 132 children (104 completers) Aged 7—12	30	Significant results on many subscales compared to placebo. No effects found with addition of micronutrients	**CPRS** *Hyp*: 0.26[*] *Inatt*: 0.48[**] (at week 15)	7	Significant results on CPRS at week 15. Single crossover (placebo to EFA) in weeks 16—30 reiterated these results. High drop-out rate from study mainly due to non-compliance or protocol violation
	Voigt (2001)	DB, RAN, PC, ADJ DHA ($n = 27$) vs. placebo ($n = 27$) 54 children Aged 6—12	16	No statistical significant improvement in any objective or subjective measure of ADHD when DHA was given with pre-existing stable psychostimulant medication	**CPRS** Non-significant data not provided	9	High quality design with strict inclusion criteria unable to find significance with DHA-only supplement. Supplement contained no EPA
Acetyl-L-carnitine	Arnold (007)	DB, RAN, PC ALC ($n = 53$) vs. placebo ($n = 59$) 112 children Aged 5—12	16	No effect on overall ADHD rating outcomes. Superiority of ALC over placebo in the inattentive subsample	**CTRS** *Inatt*: −0.18[b]	8	High quality study with non-significant results. Results of sample varied according to geography of recruitment
	Torrioli (2008)	DB, RAN, PC ALC ($n = 24$) vs. placebo ($n = 27$) 51 children (ADHD and Fragile-X syndrome) Aged 6—13	52	ALC decreased ADHD symptoms on CGI significantly over placebo at completion after 52 weeks. This results was not seen on CGI teacher's rating	**CGI-P** 0.46[*]	9	Well conducted complex study. Specific group of ADHD combined with Fragile-X-syndrome is difficult to generalise to normal ADHD population

Table 1 (*Continued*)

Intervention	First author	Methodology	Duration (weeks)	Result	Effect size	Quality/10	Comment
L-Carnitine	Van Ouheusden (2002)	DB, RAN, PC, CO L-Carnitine ($n = 13$) vs. placebo ($n = 13$) 26 children (boys) Aged 6—13	24 (3×8 week cross-over treatment periods)	No significant effects were detailed on ADHD rating scales after week 8 (first control period). 50% were classed as responders on CTRS vs. 17% on placebo	**CTRS and CBCL** Non-significant data not provided	8	The data provided did not clearly indicate effects of the treatment vs. placebo (due to multiple cross-overs). Only measured behaviour of small sample of ADHD males

DB: double-blind; RAN: randomised; PC: placebo-controlled; POS-C: positive control; ADJ: adjunctive study; Att/Prob: attention problems; Hyp: hyperactivity; Inatt: inattention; Impul: impulsivity; ADHDS: Attention Deficit Hyperactivity Disorder Scale; ADHD-P-RS: Attention Deficit Hyperactivity Disorder Rating Scale — Parent; ADHD-RS: Attention Deficit Hyperactivity Disorder-Rating Scale; PTRS: Parent/Teacher Rating Scales; CPRS: Connors Parent Rating Scale; DSM-P: Parent Rating of DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition) Symptom Criteria; CGI: Clinical Global Impression; CGI-P: Connor's Global Index —Parent; ASQ-P: Connor's Abbreviated Symptom Questionnaires —Parent; CPRS: Connor's Parent Rating Scale; CTRS: Connor's Teacher Rating Scale; CBCL: Child Behaviour Checklist; MPH: methylphenidate; MV: multivitamin; LC-PUFAs: long-chain polyunsaturated fatty acids; EFA: essential fatty acids; ACL: acetyl-L-arnitine.

[a] Effect size calculated as Cohen's *d* via Pearson's *r* calculation.

[b] Effect size conducted on non-significant primary outcomes.

* Significant at $p < 0.05$.

** Significant at $p < 0.01$

(range 7—9), with two revealing a maximum quality rating of nine out of ten (see Table 2). Average sample size and duration were 52 (range 24—61) and 7 weeks (range 4—9), respectively. A recent study by Salehi et al. (2009) found that a ginkgo preparation (80—120 mg/day) had no comparable benefit to methylphenidate in a sample of fifty children.[41] The time involved in this study (6 weeks) may not have allowed for clinical effects of gingko to reach full potential. Pycnogenol® is a French maritime pine bark (FMPB) extract which has exhibited anti-oxidant and anti-inflammatory properties. A study containing 61 ADHD children aged 6—14 found that FMPB (1 mg/kg/day) was able to ameliorate the negative symptoms associated with ADHD including reduced hyperactivity, increased attention and increased visual-motor coordination.[42] Further investigation of FMPB by Dvořáková[43] found a significant effect on symptoms of hyperactivity from a re-analysis of the sample. However, a small crossover study on an adult population (mean age of 42 years) found no significant effects of FMPB (1 mg/0.5 kg/day) over 3 weeks administration compared to placebo.[44] It should be noted that neither the positive control methylphenidate nor FMPB outperformed placebo on any ADHD rating scales. Dosage in this study was also much higher than in previous studies. A rigorous study by Weber et al. investigated St. John's wort (900 mg/day) in the treatment of ADHD symptoms but was unable to find any positive results after an 8 week placebo-controlled intervention.[45] A recent study by Li et al.[46] evaluated the efficacy and safety of a traditional Chinese herbal medicine preparation (Ningdong: NDG) (5 mg/kg/day) vs. methylphenidate (1 mg/kg/day) in 72 children with ADHD. The 8-week, randomised, methylphenidate-controlled, doubled-blinded trial, found that NDG significantly reduced ADHD symptoms from baseline after an 8-week medication with fewer side effects compared to methylphenidate. The study also showed the herbal formula to be safe and tolerable for ADHD children as monitored by the blood, urine, and stool analysis and liver and renal function. Interestingly the serum level of homovanillic acid increased in the NDG group, although the content of dopamine was not significantly altered during the study.

Discussion

The findings of the systematic review revealed a mixture of positive and inconclusive evidence from CAM in the treatment of ADHD. The strength of this review is that a rigorous systematic search criteria and quality analysis was conducted. As discussed in the introduction, this is the first systematic review to our knowledge on natural products in the treatment of ADHD. A further strength is that effect sizes were calculated to determine the clinical strength of the result. We however acknowledge a couple of potential weaknesses with this review. Firstly, we only reviewed studies in English, thereby some non-English RCTs were excluded involving three Chinese papers (three herbal medicine studies)[47—49] and one Russian paper (magnesium plus B vitamin combination).[50] In all studies, the results favoured the CAM intervention. Secondly, while a systematic review of the literature is a gold standard methodological

Table 2 CAM evidence in ADHD (herbal medicines).

Intervention	First author	Methodology	Duration (weeks)	Results	Effect size	Quality/10	Comment
Ginkgo (*Ginkgo biloba*)	Salehi (2009)	DB, RAN, POS-C GB ($n=25$) vs. MPH ($n=25$) 50 children and adolescents Aged 6—14	6	GB has no comparable efficacy in comparison to MPH in treating ADHD. MPH was significantly more effective on all outcomes	**PRS** *Inatt*: 0.95* *Hyp*: 0.88** (in favour of MPH)	8	Results demonstrate the strong relative clinical effect of a psychostimulant vs. GB. All patients included were ADHD-combined type
St. John's wort (*Hypericum perforatum*)	Weber (2008)	DB, RAN, PC SJW ($n=27$) vs. placebo ($n=27$) 54 children Aged 6—17	8 (+1 week for placebo run-in)	No significant difference was found between groups	**ADHD-RS** *Hyp*: −0.32;[b] *Inatt*: −0.12;[b]	9	High quality design. Participants were allowed to continue using alternative supplements throughout study
Pycnogenol® French maritime bark (*Pinus marinus*)	Trebaticka (2006) and Dvorakova (2007)[a]	DB, RAN, PC Pycnogenol® ($n=44$) vs. Placebo ($n=17$) 61 Children Aged 6—14	4	Significant reduction in hyperactivity, improvements in attention and visual-motor coordination and concentration. Relapse of symptoms noted after cessation	**CAP** *Hyp*: 0.87** *Inatt:* 1.09**	8	High quality study design. Notable relapse in symptoms after cessation indicate a potential withdrawal effect
	Tenenbaum (2002)	DB, RAN, PC, CO, POS-C Pycnogenol® vs. placebo vs. MPH (*n* not detailed) 24 adults Aged 24—53	9 (3 × 3 week treatments with 1 week washout between)	Neither MPH nor Pycnogenol® outperformed placebo	**Barkley-ADHD** *Inatt*: −0.52[b] *Hyp*: −0.04[b]	7	The use of a cross-over design may have obscured the effect. Positive results of the Trebaticka (2006) study (children sample) not replicated in this adult sample study
TC herbal formula (Ningdong: NDG)	Li (2011)	DB, RAN, POS-C ND ($n=36$) vs. MPH ($n=36$) 72 children Aged 6—13	8	An equivocal effect was found between ND and MPH on Teacher and Parent ADHD rating scales at week 8	**TARS** 0.59*	9	While no inert control was used in this study, it appears that Ningdong Granule had efficacy, albeit with less side effects (excepting hypersomnia)

DB: double blind; RAN: randomised; PC: placebo controlled; POS-C: positive control (e.g. psychostimulant); CO: cross-over; CAP: child attention problems (teacher rated); Hyp: hyperactivity; Inatt: inattention; Impul: impulsivity; PRS: Parent Rating Scale; Barkley-ADHD: Barkley's ADHD Rating Scale; TARS: Teacher ADHD Rating Scale; MPH: methylphenidate; SJW: St. John's wort; GB: *Ginkgo biloba*; TC: traditional Chinese; NDG: Ningdong Granule; NA: not applicable.

[a] An additional analysis conducted and published.

[b] Refers to Effect size conducted on non-significant primary outcomes.

* Significant at $p < 0.05$.

** Significant at $p < 0.01$.

technique, such an approach may neglect studies that alter the landscape of the conclusions.

Omega-3 studies reveal primarily unsupportive evidence, although one recent large study provided some positive results on parent-rated measures. Sinn and Bryan[33] were able to find significance with a large population of ADHD children using a common behavioural observational measure and utilised the same population age range as the other omega-3 studies did. The high drop-out rate from this study poses an issue when looking to validate such a design, but it should be noted that the drop-out rate was evenly spread between active and non-active groups and that the drop-out rate was more often due to non-compliance than to adverse events. Raz et al.[30] used a greater dosage of omega-6 (240 mg per capsule) over omega-3 (60 mg per capsule) in their study which may be why significance was not reached. As well as the issue of dosage, vitamin C was used for placebo which has significant antioxidant properties and may have also play a role in the lack of findings within the study. Stevens et al.[29] were unable to find significance when they used omega-3 (LC-PUFAs) supplementation in children with ADHD and skin/thirst problems. The specificity of the population may not be generalisable to a broad ADHD population, and so may have acted as a confounding variable in this case. The use of olive oil as a placebo may mask the beneficial clinical effects of essential fatty acids because an active constituent of olive oil is converted into oleamide which is known to affect brain function.[51] Additionally, the short durations and low doses of essential fatty acids used in some studies may not be adequate to result in long-term changes in neuronal membrane structure required for clinical improvement. The dosage issue has been explored by a small open-label study ($n = 9$) in which ADHD children were supplemented with high dose EPA/DHA concentrates (16.2 g/day) while continuing on stimulant medications.[51] Most children were rated by a blinded psychiatrist as having significant improvements in both inattention and hyperactivity that correlated with reductions in the AA:EPA ratio at the end of 8-week treatment period. Large prospective trials are needed to replicate these findings. Voigt et al.[31] used a supplement of DHA of 2415 mg per week in a strictly psychostimulant treated population. The oil used in this study had no traces of EPA in it at all, which may call into question the balance of DHA and EPA needed in ADHD treatment.[52] Current evidence does not support the use of EFA in ADHD as a stand-alone treatment, and future studies should focus on its use only in deficient samples.

The minerals studied (iron and zinc) displayed mainly positive evidence of effect on reducing ADHD symptoms. This beneficial effect could be potentially occurring due to addressing deficiency, as mineral deficiency is common is Western child and adolescent populations.[53] Results with L-acetyl carnitine were positive in two out of three studies, this being potentially due to its effect on the metabolism and transportation of fatty acids.[54]

While the herbal medicines St. John's wort and ginkgo monotherapies did not show positive results, other botanicals still may provide a beneficial effect. Future potential studies could involve kava (*Piper methysticum*) or brahmi (*Bacopa monniera*). Kava has demonstrated positive effects on cognition,[55] this activity theoretically due to reuptake inhibition of noradrenaline in the pre-frontal cortex and GABA-ergic effects.[55] Safety considerations regarding the use of kava in children and adolescents however would need to be strongly considered (especially regarding the potential effect on the liver).[56,57] Brahmi has emerging evidence as a cognitive enhancer which is beneficial in improving various outcomes of mental performance.[58,59] This may be achieved via cholinesterase inhibition and antioxidant effects. Antioxidant effects may potentially be beneficial in ADHD as evidence by the beneficial effects of pine bark, which due to the oligomeric proanthocynadin compounds provides a strong antioxidant activity.[42]

It is worth noting that five studies were found to use some form of Continuous Performance Test (CPT). A CPT is an objective neurophysiological measure of attention, impulsivity and inhibition that removes the subjectivity found in behavioural measures.[60] When used in this context CPT provides reaction times of ADHD children in response to stimuli and is interpreted as a measure of attention or activation processes.[61] All five studies using CPT found no significant effects of the tested CAM product over placebo. These results could indicate that CPTs are sensitive enough to only pick up strong effects, such as from psychostimulants.[61]

One potential application of technology to enhance research of CAMs in ADHD is via the use of neuroimaging technologies. These techniques are valuable to observe effects of substances on brain waves (electroencephalography: EEG), cerebral blood flow (fMRI), and activation of brain function (PET).[62] Future application of these techniques may reveal biological evidence of effects of CAMs, uncovering a physiological effect before it manifests as a psychological change on the attention or hyperactivity symptoms.

In respect to the results of our systematic review informing clinical practice, currently there is no clear picture about which, if any, CAMs can be recommended for use in treating ADHD. The CAM natural products reviewed provide a mixture of results, with the most promising concerning minerals zinc and iron, and the antioxidant botanical French maritime pine bark. Mineral status and deficiency should always be a clinical consideration when treating children and adolescents with ADHD, however beyond addressing deficiency, it may be unlikely that a greater effect will occur from supplementation in those with a good diet. While the current omega-3 data are not supportive of its use in ADHD, future studies using higher dose preparations may reveal better effects, and regardless, can still be advised in cases of deficiency. Herbal medicines while presently under-researched in this area may yet provide novel treatments of ADHD. Interventions involving combinations of herbal and nutritional medicines to address mineral deficiency, provide antioxidant and GABA-ergic effects, and those that modulate prefrontal cortex activity may be of benefit in this population.

Conflict of interest statement

None declared.

Appendix 1. Intervention search terms

Disorders	Major interventions	Specific interventions
ADHD	Nutritional medicine	*Ginkgo biloba*
ADD	Nutraceutical	*Bacopa monniera*
Attention Deficit Hyperactivity Disorder	Nootropic	Bacopa
Attention deficit disorder	Ayurvedic medicine	Ginkgo
Hyperkinetic syndrome	Herbal medicine	Vitamins
Oppositional defiance disorder	Botanical medicine	Minerals
Learning disorders	Natural medicine	Zinc
	Traditional Chinese medicine	Magnesium
	Complementary medicine	Iron
	CAM	Pycnogenol
		Omega-3
		Essential fatty acids
		Polyunsaturated essential fatty acids
		Panax ginseng
		Panax quinquefolium
		Ginseng

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