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Herbal medicines in children with attention deficit hyperactivity disorder (ADHD): A systematic review

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ABSTRACT

Objective: The purpose of this review is to identify evidence in herbal therapy in the treatment of ADHD concerning effectiveness and drug tolerability.
Method: For this Medline/PubMed, Scopus and the Cochrane Central Register of Controlled Trials (Central) were searched from their inception to 15 July 2016. Only randomized controlled trails (RCT) with children (0–18 years) suffering from ADHD were included in this review.
Results: Nine RCTs with 464 patients comparing herbal pharmaceuticals to placebo or active control were included. Seven different herbs were tested in the treatment of ADHD symptoms. Low evidence could be found for *Melissa officinalis*, *Valeriana officinalis* and *Passiflora incarnata*. Limited evidence could be found for pine bark extract and Gingko biloba. The other herbal preparations showed no efficacy in the treatment of ADHD symptoms.
Conclusion: While there is still a lack of sufficient numbers of RCTs no concrete recommendations for use can be made so far.

Contents

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1. Introduction

The attention deficit hyperactivity disorder (ADHD) is one of the most common behavioral disorders in childhood with increasing incidence rates.[1] The prevalence of ADHD in children in Germany is about 4–5% while another 4–5% are suspected to be cases of ADHD.[2,3] Worldwide, the estimated prevalence ranges between 6% and 8%[4] with boys being more likely than girls to develop ADHD.[5,6] According to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) of the American Psychiatric Association (APA),[7] ADHD is characterized by inattention, impulsivity and hyperactivity. In its criteria of diagnosis the DSM-V further identifies three subtypes of ADHD:

1. inattentive type
2. hyperactive-impulsive type
3. combined type

Besides psychotherapy, medication therapy plays an important role in the treatment of ADHD.[8,9] Nevertheless, up to 30% of children treated with pharmaceuticals do not respond to medication or suffer from adverse effects such as nausea, insomnia or weight loss.[10–14] Accordingly there is a growing considerable interest of parents with children suffering from ADHD in complementary and alternative medicine (CAM).[15–17] In Europe about 52% of all children are using some kind of CAM, often without knowledge of the attending pediatrician.[18–22] Besides non-pharmacological therapies like relaxation techniques or neurofeedback, herbal medicines are among those complementary therapies most frequently demanded by parents.[23–25] Most parents consider herbal pharmaceuticals less harmful than conventional drug therapy.[26,27] Therefore herbal medicines are particularly regarded as an alternative or complement to conventional pharmaceuticals in the treatment of ADHD symptoms by parents.[28] However, there is still a lack of sufficient research investigating efficacy and drug tolerance of herbal medicines in the field of ADHD.[17] Therefore the purpose of this review is to identify evidence for herbal therapy in the treatment of ADHD concerning effectiveness and safety.

2. Methods

The review was planned and conducted in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines[29] and the recommendations of the Cochrane Collaboration.[30]

2.1. Eligibility criteria

2.1.1. Types of studies

Only randomized controlled trials (RCTs) were included in this review. Studies were eligible only if they were published as full papers, and only publications in English or German language were considered eligible.

2.1.2. Types of participants

Only studies conducted on children and adolescents (age 0–18 years) who are suffering from ADHD were eligible. No limitations were made regarding the diagnosis of ADHD.

2.1.3. Types of intervention

Studies that compared herbal therapy with no treatment, placebo or any pharmaceutical medication were eligible. Studies were excluded if the herbal preparation was applied in homeopathic potency or if the herb was solely used in traditional Chinese medicine. No other dosage restrictions were made.

2.1.4. Types of outcomes

Only studies that assessed ADHD symptoms (inattention, impulsivity or hyperactivity as defined by the Diagnostic and Statistical Manual of Mental Disorders or the International Statistical Classification of Diseases and Related Health Problems) as a primary or secondary outcome were considered eligible.

2.2. Search methods

Medline/PubMed, Scopus and the Cochrane Central Register of Controlled Trials (Central) were searched from their inception to 15 July 2016. Embase was not searched separately since it is already covered by Scopus. The literature search was constructed around search terms for 'children' and search terms for 'herbal therapy'. The complete search strategy for PubMed/Medline is given as Supplementary material. The search strategy was adapted for each database as necessary. Abstracts identified during literature search were screened and potentially eligible articles were read in full text independently by three review authors (DA, HC, RL) to determine whether they met eligibility criteria. After identifying the literature in the field of interest, only articles with ADHD patients were taken into account. This review is part of a larger project to identify evidence in herbal therapy for children.

2.3. Data extraction and management

Data on participants (age, gender), medication, control/placebo groups, outcomes, and results were extracted independently by two review authors (DA and RL) using an a-priori-developed data extraction form. Discrepancies were discussed with a third review author (HC) until consensus was reached.

2.4. Risk of bias in individual studies

The risk of bias was assessed by two authors (DA, HC) independently using the risk of bias tool proposed by the Cochrane Collaboration.[30] This tool assesses the risk of selection bias, performance bias, attrition bias, reporting bias, detection bias and other bias using seven criteria (ratings: low, unclear or high risk of bias). Differences of opinion were discussed with a third review author[31] until a consensus was reached.

3. Results

3.1. Literature search

A total of 10.083 non-duplicate records were retrieved by literature search of which 9.824 were excluded after screening title and abstract. 259 full texts were assessed for eligibility, excluding further 173 articles because they were no RCTs, did not include participants below 18 years of age, the investigated herbal medicines were solely used in traditional Chinese medicine or the herbal drug was applied in homeopathic potency. Eighty-six studies were included for general review. Among these, eleven studies were identified investigating children and adolescents suffering from ADHD. Two of these studies had to be excluded because ADHD symptoms were no primary or secondary outcome criteria.[32,33]

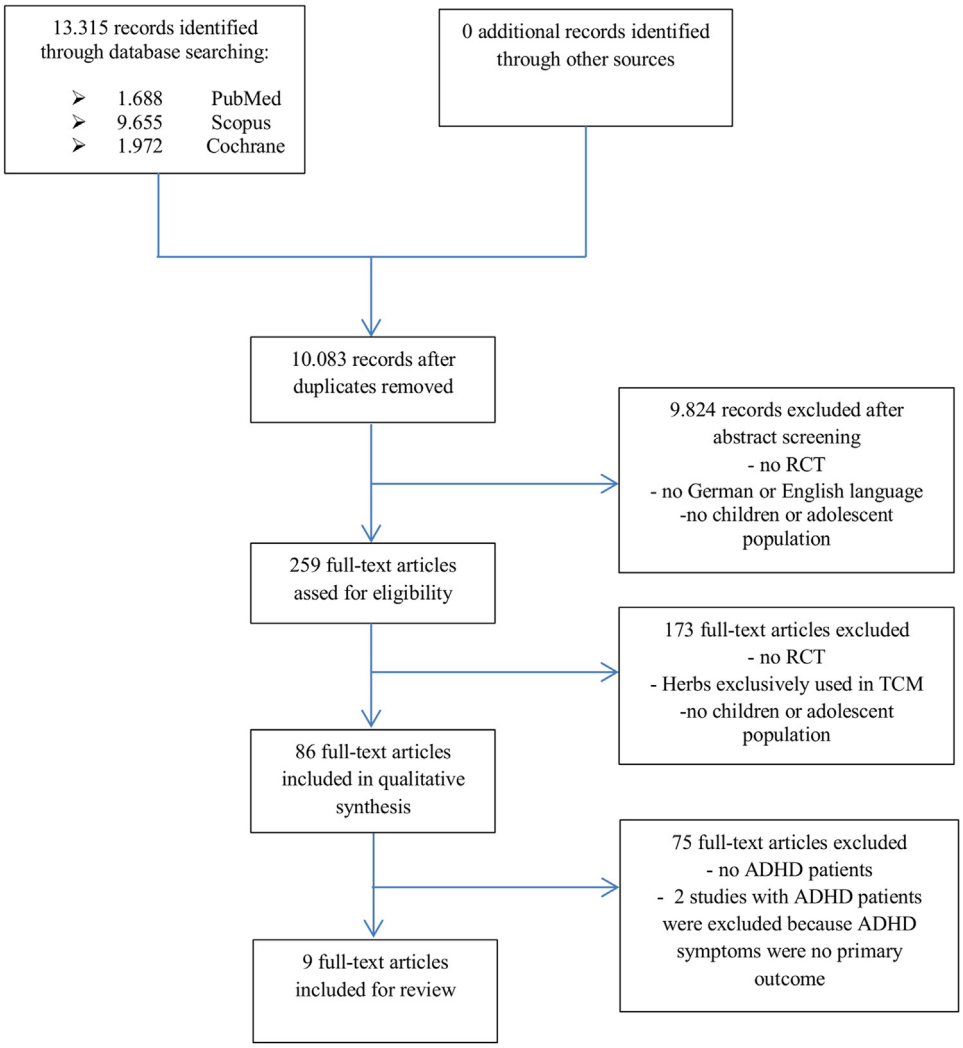

Fig. 1. Flow-chart of literature search.

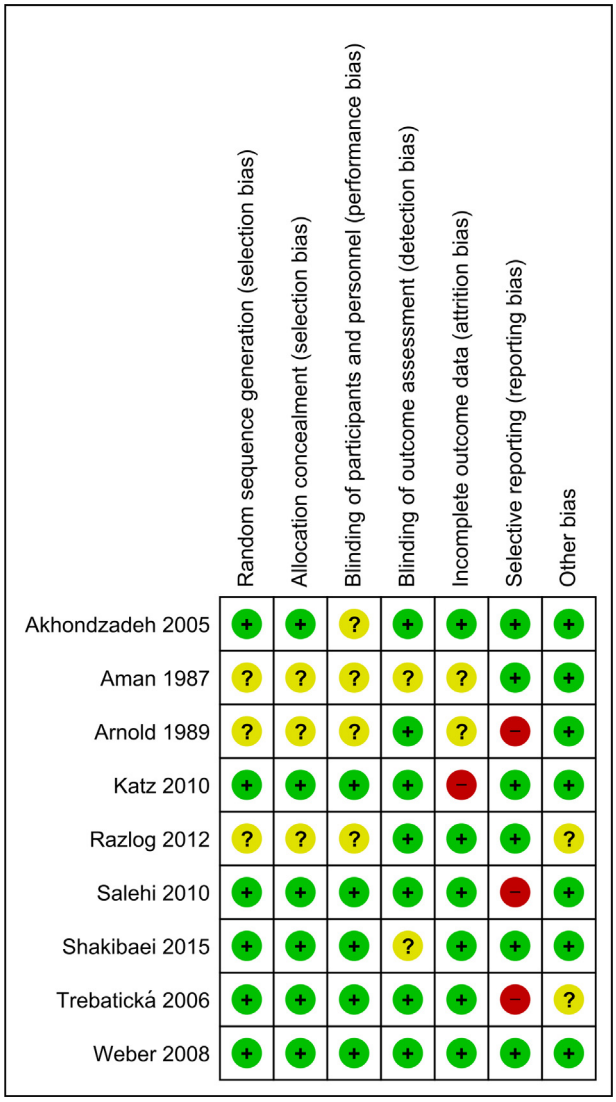

Fig. 2. Risk of bias assessment: using the Cochrane risk of bias tool and generated with Review Manager 5 software (version 5.2; The Nordic Cochrane Centre, Copenhagen, Denmark).

Finally, nine studies were included in this review. The flowchart of literature search is shown in Fig. 1, while the risk of bias assessment is shown in Figs. 2 and 3. In-depth information on the characteristics and results can be found in Table 1.

3.2. Evening primrose oil

3.2.1. Characteristics of the included studies

Two RCTs with a total of 49 participants who were treated with evening primrose oil were included.[34,35] In both studies ADHD symptoms were measured by teachers and parents using external assessment questionnaires. Aman et al.[34] additionally analyzed blood samples and conducted cognitive and psycho-motoric tests. Male participants were over-represented (87% and 100%) in both studies. Mean age was 8.89 years[34] and 9.0 years.[35] Ethnicity was not reported. Both RCTs compared a preparation of 500 mg evening primrose oil (efamol) with placebo treatment. While Aman et al.[34] used a two-arm study design, Arnold et al. performed a four-arm study design including a D-amphetamine preparation as an active control. In both studies, risk of bias was unclear for most domains, as the authors did not report any adequate form of randomization or blinding. Arnold et al. did not specify any kind of primary outcome, resulting in expectation of a high risk of reporting bias.

3.2.2. Outcomes

In terms of ADHD symptoms Aman et al.[34] reported that only two of six subscales of the questionnaires used showed significant improvements over time compared to placebo, but only if reported by parents. In addition only two of nine subtests of the psycho-motoric test battery showed significant improvements in symptoms. Furthermore an increase in dihomogammalinolenic acid serum concentration after efamol intake was observed by Aman et al.[34] In contrast to these results Arnold et al. reported that parent ratings showed no significant benefits of efamol compared to placebo and if assessed by teachers, only one subscale showed significant improvement in symptoms of ADHD.

One serious adverse event was only reported by Aman et al.[34] The authors described one participant in the Efamol® group who developed severe diarrhea. The authors reported that the patient was previously given a questionable diagnosis of pancreatic enzyme deficiency and has been excluded for further statistical analysis therefore.

3.3. Melissa officinalis

3.3.1. Characteristics of the included study

Katz et al. tested a compound herbal preparation (CHP) to treat ADHD symptoms in 120 children.[36] The main ingredient of this preparation was *Melissa officinalis*, however it also contained some

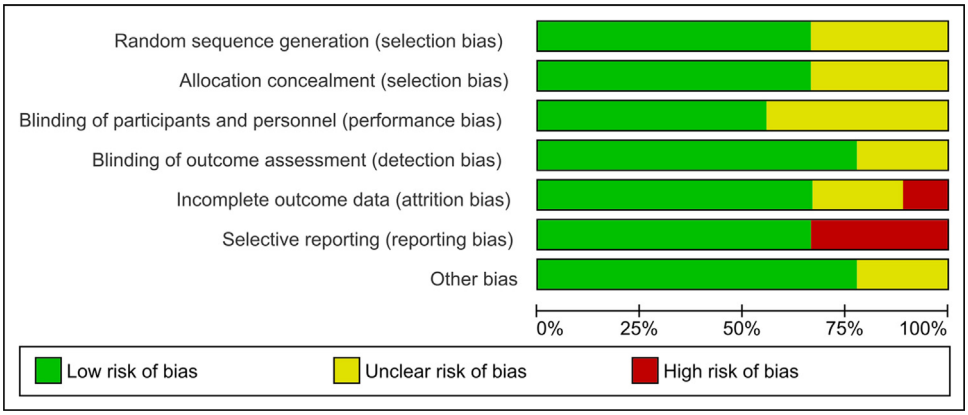

Fig. 3. Risk of bias graph: presented as percentages across all included studies and generated with Review Manager 5 software (version 5.2; The Nordic Cochrane Centre, Copenhagen, Denmark).

Table 1
In-depth information on the characteristics and results of the included studies.

First author	Population	Intervention	Control	Measurements	Outcomes	Results
Akhondzadeh et al.[42]	N = 34; age: mean = exp.grp.: 9.58 ± 2.09 y. contr.grp.: 9.05 ± 2.53 y. (6–13 y.) gender: exp.grp.: 11/6 contr.grp.: 12/5 (m/f)	*Passiflora incarnata* tablets 0.04 mg/kg/day (twice daily)	Methylphenidate 1 mg/kg/day (twice daily)	Baseline-measurement, then every 2 weeks of the 8 week treatment period; rating scales in external assessment (parents and teacher).	ADHD symptoms measured by parents and teacher with a standardized rating scale.	No significant differences between the groups in all measured parameters. For both groups a significant clinical benefit after treatment period was reported.
Aman et al.[34]	N = 31; age: mean = 8.86 ± 1.88 y. gender: 27/4 (m/f)	500 mg capsule Efamol® (Evening primrose oil) (6 capsule/day).	500 mg capsule with liquid paraffin oil in same dosage.	Pretest, 2nd & 4th week of treatment period, wash-out, then change from placebo to Efamol® treatment and vice-versa; rating scales in external assessment (parents and teacher); psychomotoric and cognitive tests; Blood samples.	ADHD symptoms measured by parents with RBPC and by teacher with CTRS; Measurement of serum concentration of essential fatty acids; psychomotoric testbatterie; cognitive tests.	Accuracy increased in psychomotoric test. Parents reported fewer problems with ADHD symptoms of their children. An increase of Omega-3-fatty acid concentration in serum was observed.
Arnold et al.[35]	N = 18; age: mean = 9 y. (6–12 y.) gender: 18/0 (m/f)	exp.grp.1: D-amphetamine + placebo exp.grp. 2: D-amphetamine + 500 mg capsule Efamol® (Evening primrose oil) exp.grp. 3: 500 mg capsule Efamol® (Evening primrose oil) + placebo (5 capsule in the morning & 4 in the evening).	Placebo in same dosage.	Measurements at baseline, then every 2 weeks of the 12 week treatment period; behaviormental measurements in external assessment (teacher).	ADHD symptoms measured by teacher with CTRS.	Efamol® showed no differences compared to placebo in relation to the CTRS.
Katz et al.[36]	N = 120; age: exp.grp.: 9.82 ± 1.56 y. contr.grp.[j]: 9.36 ± 1.97 y. (6–12 y.) gender: exp.grp.: 60/20 contr.grp.: 32/8 (m/f)	3 ml of a compound herbal preparation 3 times a day in 50–60 ml of water (*Melissa officinalis*, *Paeoniae alba*, *Withania somnifera*, *Centella asiatica*, *Spirulina platensis* & *Bacopa monieri*).	3 ml placebo 3 times a day in 50–60 ml of water.	TOVA at baseline and post-treatment.	TOVA scores.	Increase of TOVA scores within the exp.grp. The contr.grp showed no changes over treatment period. The differences between exp.grp. and placebo were statistically significant.
Razlog et al.[37]	N = 30; age: mean = 7.93 y. (5–11 y.) gender: 18/9 (m/f)	exp.grp. 1.: *Valeriana officinalis* (mother tincture) 10 drops/3 times per day exp.grp. 2: *Valeriana officinalis* (homeopathic 3× potency) 10 drops/3 times per day.	Placebo tincture in same dosage.	Self-assessment and external assessment (parents and teacher) at baseline, first and second week of treatment period and one week after treatment period.	ADHD symptoms measured by parents with CCT & PSQ and by teacher with Barkley and DuPaul teacher rating scale.	PSQ: nearly all subscales (except psychosomatic problem and conduct problems scale) showed a significant improvement of both treatment groups after two weeks of treatment but not one week after treatment compared to contr.grp. CCT: Total and speed score showed a significant improvement after two weeks of treatment and one week after treatment for the two experimental groups; there was no significant improvement for the placebo group, Barkley and DuPaul teacher rating scale: 9 of 14 questions showed a significant improvement in both experimental groups after two weeks of treatment; there was no statistical significant overall between the two treatment groups.

Salehi et al.[38]	N = 50; age: exp.grp.: 9.12 ± 1.61 y. contr.grp.: 9.61 ± 2.26 y. (6–14 y.) gender: exp.grp.: 19/6 contr.grp.: 20/5 (m/f)	Gingko biloba capsule 80–120 mg/day depending on weight.	Methylphenidate 20–30 mg/day depending on weight.	External assessment (parents and teacher) at baseline, at day 21 and day 42 of treatment period.	ADHD symptoms measured by parents and teacher with the ADHD-RS-IV.	Significant differences between the two groups; contr.grp with significant better scores than exp.grp.
Shakibaei et al.[39]	N = 66; age: exp.grp.: 7.83 ± 1.21 y. contr.grp.: 8.41 ± 1.40 y. (6–12 y.) gender: exp.grp.: 19/12 contr.grp.: 20/9 (m/f)	Gingko biloba enteric coated tablets 80 mg to 120 mg per day depending on weight + usual care (Methylphenidate 20 mg to 30 mg per day depending on weight)	Placebo tablets in same dosage + usual care (Methylphenidate 20 mg to 30 mg per day depending an bodyweight)	External assessment (parents and teacher) at baseline, week 2 and week 6 of treatment period; measurement of general psychosocial functioning by a child and adolescent psychiatrist at baseline, week 2 and week 6 of treatment period.	ADHD symptoms measured by parents and teacher with the ADHD-RS-IV; general psychosocial functioning measured with CGAS.	Significant interaction of time and treatment for inattention rated by parents and teacher, but non-significant main effect of treatment; significant interaction of time and treatment for ADHD-RS-IV total score rated by parents, but non-significant main effect of treatment.
Trebatická et al.[40]	N = 61; age: exp.grp.: mean = 9.5 y. (6–14 y.) contr.grp.: mean = 8.8 y. (6–12 y.) gender: 50/11 (m/f)	1 mg/kg bodyweight Pycnogenol® (pine bark extract) per day.	Placebo in same dosage.	Self- & external assessment (parents and teacher) and blood samples at baseline, after treatment and after wash-out period.	ADHD symptoms measured by parents with CAP and CPRS and by teacher with CTRS; self-assessment with PDW.	No changes between the groups over time in blood sample parameters; significant improvements in inattention and hyperactivity reported by teacher (CAP), over time and in comparison with placebo; no significant improvements in inattention or hyperactivity reported by teacher with CTRS; improvements of hyperactivity and inattention rated by parents (CPRS) do not reach significance; relapse of symptoms after termination of pine bark extract rated by teacher and parents; no improvements in the placebo group.
Weber et al.[41]	N = 54; age: exp.grp.: mean = 9.9 y. contr.grp.: mean = 9.7 y. (6–17 y.) gender: exp.grp.: 20/7 contr.grp.: 14/13 (m/f)	1 capsule (300 mg) 3 times a day of St. John's Wort.	Placebo in same dosage.	Self- and external assessment (parents) at baseline and at week 1,2,4,6 and 8 of treatment.	ADHD symptoms measured by parents with the ADHD-RS-IV; side-effect measurement with Monitoring of Side-effects system & CGI.	No significant differences between the groups in all measured parameters.

List of abbreviations: ADHD = attention deficit hyperactivity disorder; ADHD-RS-IV = Attention Deficit Hyperactivity Disorder Rating Scale fourth edition; CAP = Child Attention Problems scale; CCT = Children's Checking Task; CGAS = Children's Global Assessment Scale; CGI = Clinical Global Impression Improvement Scale; contr.grp. = control group; CPRS = Conner's Parents Rating Scale; CTRS = Conner's Teacher Rating Scale; exp.grp. = experimental group; kg = kg; (m/f) = (male/female); mg = milligrams; ml = milliliter; N = number of participants; PDW = Prague Wechsler Intelligence Scale; PSQ = Conner's Parent Symptom Questionnaire; RBPC = Revised Behavior Problem Checklist; TOVA = Test of variables in attention; y = year.

Ayurvedic (Bacopa monieri) and other herbal extracts. Treatment dose was set to 3 ml in 50–60 ml of water. Mean age in the CHP group was 9.82 years and 9.36 years in the placebo group. Male participants were over-represented in this study (77%). Ethnicity differences were not reported. Primary outcome criterion was the score of the test of variables of attention (TOVA). Risk of bias in this study was overall low, although a high risk of incomplete outcome data could be noticed due to more than 50% withdrawals from the placebo group.

3.3.2. Outcomes

Katz et al.[36] reported significant improvement of TOVA-score for the CHP-group between baseline and post intervention measurement. These changes were observed in all subtests of the TOVA and their aggregation. No significant changes over time could be noted in the placebo group. Also the differences between CHP-group and placebo were statistically significant.

According to the safety analysis no serious adverse events occured. Minor side effects (such as insomnia, headache etc.) occurred within the CHP-group and the control group.

3.4. Valeriana officinalis

3.4.1. Characteristics of the included study

The aim of the pilot RCT from Razlog et al. was to investigate if *Valeriana officinalis* had an influence on ADHD symptoms.[37] The study compared two groups of which one received a mother tincture of *Valeriana officinalis* while the other group was given a homeopathic potency of this tincture. A placebo tincture served as control condition. For the purpose of this review, only the comparison of mother tincture and placebo was considered relevant. The mean age of the thirty participants was 7.93 years with boys being slightly over-represented (18 males). No ethnic differences were reported in this study. Evaluation of ADHD symptoms was done at baseline, at weeks one and two of intervention and two weeks after intervention. Self as well as external assessments were retrieved using children's checking task (CCT), Conner's parent symptom questionnaire (PSQ) and the Barkley and DuPaul teacher rating scale. No further measurements were collected. As for the risk of bias assessement Razlog et al. did not report any adequate form of randomization or blinding. Therefor the presence of selection, performance, detection bias and other bias remained unclear.

3.4.2. Outcomes

The PSQ showed a significant improvement for both treatment groups compared to placebo in nearly all subscales (except psychosomatic problems and conduct problems). These improvements appeared after two weeks of treatment but did not persist after one week follow-up. Total score and speed score of the CTT assessment showed a significant improvement in both experimental groups after two weeks of treatment and one week after treatment. Within the placebo group no significant improvement could be obtained. Nine of fourteen subscales of the Barkley and DuPaul teacher rating scale showed a significant improvement after two weeks of treatment in both groups receiving *Valeriana officinalis*. The placebo group only showed significant improvements for two of the fourteen questions. The differences between experimental group and control group were statistically significant. No serious adverse event or side effects were reported by the authors.

3.5. Ginkgo biloba

3.5.1. Characteristics of the included studies

The study of Salehi et al. compared an herbal preparation of Ginkgo biloba with methylphenidate in the treatment of ADHD,[38] whereas Shakibaei et al.[39] compared Ginkgo biloba and placebo as an add-on therapy to a methylphenidate treatment. Male participants were over-represented (65%[39] and 78%[38]) in both studies. The mean age in the experimental groups were 9.12 years[38] and 7.83 years.[39] For both studies the reported treatment dose was 80–120 mg per day for Ginkgo biloba and 20–30 mg per day for methylphenidate, depending on the participant's body weight respectively. Both studies assessed ADHD symptoms by parents and teachers using the ADHD Rating Scale IV. Salehi et al. performed measurements at baseline and at days 21 and 42 of treatment period, while Shakibaei et al. performed measurements at baseline and 2 and 6 weeks after a 6-week medication period. In both studies risk of bias was low in general. Salehi et al. collected serum and urine samples at the period of measurement but did not present any results. Therefore a high risk of selective reporting has to be expected.

3.5.2. Outcomes

For the Study of Salehi et al. a within-subject analysis showed no significant changes over time in the assessed ADHD symptoms for the Ginkgo biloba group neither if rated by parents, nor if rated by teachers. Whereas in the methylphenidate group changes over time appeared significant for both assessment conditions. Furthermore a between-group comparison showed significant differences in the improvement of ADHD symptoms. In children treated with methylphenidate significant improvements in symptoms were reported by parents and teachers after treatment period but not in children treated with ginkgo biloba. Shakibaei et al. showed significant improvements in inattention rated by parents and teachers if the children were treated with Ginkgo biloba in addition to methylphenidate compared to placebo.

A safety analysis in both studies showed only mild to moderate side effects. For the study by Salehi et al. the difference between the ginkgo biloba and methylphenidate group in the overall frequency of side effects was not significant, whereas headache, insomnia and decreased appetite were observed more frequently in the methylphenidate group, while Shakibaei reported no significant difference between Ginkgo biloba and placebo in overall frequency of side effects.

3.6. Pine bark extract

3.6.1. Characteristics of the included study

Another study included tested the effects of a French maritime pine bark extract (Pycnogenol®) compared to a placebo.[40] For this 61 children between six and fourteen years were recruited. The mean age for children in the pine bark group was 9.5 years and 8.8 for those in the placebo group. Consisting of 50 male and 11 female participants, boys were over-represented in this study too. Treatment dose was 1 mg of pine bark extract per kg bodyweight per day. Symptoms were measured through self-assessment and external assessment by parents and teacher. Child Attention Problems scale (CAP), the Conner's Parents Rating Scale (CPRS) and the Conner's Teacher Rating Scale (CTRS) were used. Additionally five subscales of the Prague Wechsler Intelligence test (PDW) were utilized for self-assessment. Furthermore blood samples were taken at baseline, after treatment period and after a wash-out period. The risk of bias for this study was generally low. Only a high risk for selective reporting has to be given because of an unclear determination of primary and secondary outcome criteria. It has to be further mentioned that the study was funded by Horphag Research, the manufacturer and holder of the Pycnogenol® registered trademark. Due to this an unclear risk of other bias has to be expected.

3.6.2. Outcomes

Trebatická et al.[40] reported significant improvements in inattention and hyperactivity when assessed by teachers (CAP). These

improvements could be shown over time as well as in comparison with placebo. CTRS ratings showed no significant improvements in inattention or hyperactivity. However, the reported improvements of hyperactivity and inattention during the intervention period rated by parents (CPRS) did not reach significance. A relapse of symptoms was observed after the medication with pine bark extract was discontinued. The placebo group revealed no improvements over treatment period.

The authors reported no serious side effects. However a rise of slowness and a moderate gastric discomfort could be observed in two patients in the pine bark group.

3.7. St. John's wort

3.7.1. Characteristics of the included study

Weber et al. conducted a study to determine the safety and efficacy of a Hypericum perforatum (St. John's wort) preparation in the treatment of ADHD.[41] 54 children between six and seventeen years participated in the study. 27 children were randomly assigned either to receive 300 mg St. John's wort three times a day or a placebo at the same dose. The mean age of the experimental group was 9.9 years and of the placebo group 9.7 years. With 34 male participants, boys were slightly over-represented. The ADHD Rating Scale IV was used to assess symptoms rated by parents. Symptom severity was also assessed by physicians with the Clinical Global Impression Improvement Scale (CGI). For this study the risk of selection, performance, detection, attrition, reporting and other bias has to be considered as low.

3.7.2. Outcomes

Weber et al.[41] reported no significant differences between Hypericum perforatum and placebo group in all measured parameters after post-intervention measurement.

The analysis of adverse events and side effects both showed no statistical differences between the two groups.

3.8. Passiflora incarnata

3.8.1. Characteristics of the included study

The study by Akhondzadeh et al.[42] tested the effects of a *Passiflora incarnata* preparation compared to a standard methylphenidate therapy. 34 children between six and thirteen years were recruited. The mean age of the children in the *Passiflora incarnata* group was 9.58 years and 9.05 for those in the methylphenidate group. In this study boys were over-represented as well. Treatment dose was 0.04 mg of *Passiflora incarnata* per kg bodyweight per day, while a dose of 1 mg methylphenidate per kg bodyweight per day was used. Symptoms were measured by a standardized ADHD rating scale through self-assessment and external assessment by parents and teachers. The risk of bias for this study was generally low. Only the blinding of participants and personnel remained unclear.

3.8.2. Outcomes

The study by Akhondzadeh et al.[42] revealed no significant differences between *Passiflora incarnata* and methylphenidate on parent and teacher ratings over the investigated period. Both groups showed significant clinical benefits.

The authors reported no serious side effects. However anxiety and decreased appetite were significantly more reported within the methylphenidate group. There were no other significant group differences for reported side effects.

4. Discussion

4.1. Summary of evidence

This systematic review of nine RCTs on herbal therapy in children with ADHD found low evidence of efficacy only for specific herbal preparations. While the treatment with *Melissa officinalis* and *Valeriana officinalis* showed improvements in self assessed psychomotoric and cognitive tests, the results in external assessed questionnaires were ambiguous. *Melissa officinalis* was only administered as a compound herbal preparation and therefore the results have to be interpreted carefully. Moreover, Trebatická et al.[40] could show improvements in specific teacher-rated subscales, but not of parental-rated questionnaires for children treated with pine bark extract. Furthermore Akhondzadeh et al.[42] demonstrated no significant differences in ADHD symptoms if rated by parents and teachers for *Passiflora incarnata* in comparison to a usual methylphenidate therapy. No evidence of effectiveness was found for Evening primrose oil and St. John's wort for the treatment of ADHD, while the results for Gingko biloba were ambiguous. With the exception of one study[34] all other studies reported no serious adverse event or severe side effects.

4.2. Agreements with prior systematic reviews

The findings of this review are partly in line with a prior systematic review that investigated the evidence of herbal and nutritional products in the treatment of ADHD.[43] Three of the seven studies assessed in this review were also included in the review of Sarris et al. [38,40,41] Assessment of these studies by Sarris et al.[43] matched our findings in terms of inefficacy of Gingko biloba and St. John's wort and in terms of potential efficacy of pine bark extract in the therapy of ADHD. Another systematic review and meta-analysis could show that pine bark extract was used in the treatment of a wide range of chronic diseases.[44] Due to insufficient evidence the authors were not able to make any recommendations in favor of pine bark extract for any of the observed diseases. The other herbs included in this review were not reviewed in this comprehensiveness before.

4.3. Applicability of evidence

A disease specific over-representation of male participants was found in all of the included RCTs. Apart from this the population of these studies was mostly heterogeneous. With five to seventeen years children with a wide range of age were observed. Further it needs to be taken into consideration that the countries where the different studies have been conducted differ culturally. The results of this review therefore seem to be applicable although more research is needed before the general applicability of the findings can be conclusively judged.

4.4. Limitations

The main limitation of this review is the paucity of eligible trials. For most herbal medicines except for Evening primrose oil and Gingko biloba only one study each could be identified. Furthermore, small sample sizes of the studies have to be considered a limitation. Therefore no concrete recommendation in case of efficacy and safety can be made at this point.

4.5. Implications for further research

Despite of the acceptable methodological quality of most studies, the small sample size needs to be taken into consideration. To draw further conclusions from the results obtained more research

is needed. Especially for both of the studies conducted in the late 1980s which investigated the efficacy of evening primrose oil replication is needed due to poor methodological quality.[34,35] As mainly sedative plants have shown to be effective, randomized controlled studies investigating plants with similar properties such as lavender could be of interest.

5. Conclusions

In summary the studies assessed in this systematic review indicate modest efficacy of *Melissa officinalis* as part of a CHP, *Valeriana officinalis* and *Passiflora incarnata* in the treatment of ADHD symptoms. Based on the trials those herbal medicines appear to be relatively safe with only one serious adverse event and no severe side effects. Since there is still a lack of sufficient numbers of RCTs investigating herbal medicines for ADHD in general, no specific recommendations for use can be made at this point. Given its preliminarily positive benefit-risk-ratio, the use of *Melissa officinalis*, *Valeriana officinalis* and *Passiflora incarnata* might be considered on an individual basis.

Conflict of interest

The authors declare that they have no conflict of interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ctim.2016.11.004.

References

1. Polanczyk GV, Willcutt EG, Salum GA, Kieling C, Rohde LA. ADHD prevalence estimates across three decades: an updated systematic review and meta-regression analysis. *Int J Epidemiol*. 2014;43(2):434–442.
2. Schlack R, Holling H, Kurth BM, Huss M. The prevalence of attention-deficit/hyperactivity disorder (ADHD) among children and adolescents in Germany. Initial results from the German Health Interview and Examination Survey for Children and Adolescents (KiGGS). *Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz*. 2007;50(5–6):827–835.
3. Huss M, Holling H, Kurth BM, Schlack R. How often are German children and adolescents diagnosed with ADHD? Prevalence based on the judgment of health care professionals: results of the German health and examination survey (KiGGS). *Eur Child Adolesc Psychiatry*. 2008;17(Suppl. 1):52–58.
4. Thomas R, Sanders S, Doust J, Beller E, Glasziou P. Prevalence of attention-deficit/hyperactivity disorder: a systematic review and meta-analysis. *Pediatrics*. 2015;135(4):e994–1001.
5. Knopf H, Holling H, Huss M, Schlack R. Prevalence, determinants and spectrum of attention-deficit hyperactivity disorder (ADHD) medication of children and adolescents in Germany: results of the German Health Interview and Examination Survey (KiGGS). *BMJ Open*. 2012;2(6).
6. Willcutt EG. The prevalence of DSM-IV attention-deficit/hyperactivity disorder: a meta-analytic review. *Neurotherapeutics*. 2012;9(3):490–499.
7. American Psychiatric Association. *DSM-5 Task Force. Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. Arlington, VA: American Psychiatric Publishing; 2013.
8. Biederman J. Attention-deficit/hyperactivity disorder: a selective overview. *Biol Psychiatry*. 2005;57(11):1215–1220.
9. Tarver J, Daley D, Sayal K. Attention-deficit hyperactivity disorder (ADHD): an updated review of the essential facts. *Child Care Health Dev*. 2014;40(6):762–774.
10. Efron D, Jarman F, Barker M. Methylphenidate versus dexamphetamine in children with attention deficit hyperactivity disorder: a double-blind, crossover trial. *Pediatrics*. 1997;100(6):E6.
11. Efron D, Jarman F, Barker M. Side effects of methylphenidate and dexamphetamine in children with attention deficit hyperactivity disorder: a double-blind, crossover trial. *Pediatrics*. 1997;100(4):662–666.
12. Schachter HM, Pham B, King J, Langford S, Moher D. How efficacious and safe is short-acting methylphenidate for the treatment of attention-deficit disorder in children and adolescents? A meta-analysis. *CMAJ*. 2001;165(11):1475–1488.
13. Gardiner P, Adams D, Filippelli AC, et al. A systematic review of the reporting of adverse events associated with medical herb use among children. *Glob Adv Health Med*. 2013;2(2):46–55.
14. Sonuga-Barke EJ, Coghill D, Wigal T, DeBacker M, Swanson J. Adverse reactions to methylphenidate treatment for attention-deficit/hyperactivity disorder: structure and associations with clinical characteristics and symptom control. *J Child Adolesc Psychopharmacol*. 2009;19(6):683–690.
15. Stubberfield T, Parry T. Utilization of alternative therapies in attention-deficit hyperactivity disorder. *J Paediatr Child Health*. 1999;35(5):450–453.
16. Chan E. The role of complementary and alternative medicine in attention-deficit hyperactivity disorder. *J Dev Behav Pediatr*. 2002;23(Suppl. 1):S37–S45.
17. Searight HR, Robertson K, Smith T, Perkins S, Searight BK. Complementary and alternative therapies for pediatric attention deficit hyperactivity disorder: a descriptive review. *ISRN Psychiatry*. 2012;2012:804127.
18. Zuzak TJ, Zuzak-Siegrist I, Simoes-Wust AP, Rist L, Staubli G. Use of complementary and alternative medicine by patients presenting to a Paediatric Emergency Department. *Eur J Pediatr*. 2009;168(4):431–437.
19. Zuzak TJ, Bonkova J, Careddu D, et al. Use of complementary and alternative medicine by children in Europe: published data and expert perspectives. *Complement Ther Med*. 2013;21(Suppl 1):S34–S47.
20. Längler A, Zuzak TJ. Complementary and alternative medicine in paediatrics in daily practice?a European perspective. *Complement Ther Med*. 2013;21(Suppl 1):S26–S33.
21. Cala S, Crismon ML, Baumgartner J. A survey of herbal use in children with attention-deficit-hyperactivity disorder or depression. *Pharmacotherapy*. 2003;23(2):222–230.
22. Sinha D, Efron D. Complementary and alternative medicine use in children with attention deficit hyperactivity disorder. *J Paediatr Child Health*. 2005;41(1-2):23–26.
23. Kemper KJ, Vohra S, Walls R. American Academy of Pediatrics: the use of complementary and alternative medicine in pediatrics. *Pediatrics*. 2008;122(6):1374–1386.
24. Chan E, Rappaport LA, Kemper KJ. Complementary and alternative therapies in childhood attention and hyperactivity problems. *J Dev Behav Pediatr*. 2003;24(1):4–8.
25. Kemper KJ, Gardiner P, Birdee GS. Use of complementary and alternative medical therapies among youth with mental health concerns. *Acad Pediatr*. 2013;13(6):540–545.
26. Barnes PM, Bloom B, Nahin RL. Complementary and alternative medicine use among adults and children: united States. *Natl Health Stat Rep*. 2007;2008(12):1–23.
27. Zuzak TJ, Zuzak-Siegrist I, Rist L, Staubli G, Simoes-Wust AP. Medicinal systems of complementary and alternative medicine: a cross-sectional survey at a pediatric emergency department. *J Altern Complement Med*. 2010;16(4):473–479.
28. Bussing R, Zima BT, Gary FA, Garvan CW. Use of complementary and alternative medicine for symptoms of attention-deficit hyperactivity disorder. *Psychiatr Serv*. 2002;53(9):1096–1102.
29. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ Open*. 2009;339:b2535.
30. Higgins JPT, Green S. *Cochrane Handbook for Systematic Reviews of Interventions*. West Sussex: John Wiley & Sons Ltd.; 2008.
31. Ladas EJ, Kroll DJ, Oberlies NH, Cheng B, Ndao DH, Rheingold SR, et al. A randomized: controlled, double-blind, pilot study of milk thistle for the treatment of hepatotoxicity in childhood acute lymphoblastic leukemia (ALL). *Cancer*. 2010;116(2):506–513.
32. Dvorakova M, Sivonova M, Trebaticka J, et al. The effect of polyphenolic extract from pine bark: pycnogenol on the level of glutathione in children suffering from attention deficit hyperactivity disorder (ADHD). *Redox Rep*. 2006;11(4):163–172.
33. Dvorakova M, Jezova D, Blazicek P, et al. Urinary catecholamines in children with attention deficit hyperactivity disorder (ADHD): modulation by a polyphenolic extract from pine bark (pycnogenol). *Nutr Neurosci*. 2007;10(3–4):151–157.
34. Aman MG, Mitchell EA, Turbott SH. The effects of essential fatty acid supplementation by Efamol in hyperactive children. *J Abnorm Child Psychol*. 1987;15(1):75–90.
35. Arnold LE, Kleykamp D, Votolato NA, Taylor WA, Kontras SB, Tobin K. Gamma-linolenic acid for attention-deficit hyperactivity disorder: placebo-controlled comparison to D-amphetamine. *Biol Psychiatry*. 1989;25(2):222–228.
36. Katz M, Levine AA, Kol-Degani H, Kav-Venaki L. A compound herbal preparation (CHP) in the treatment of children with ADHD: a randomized controlled trial. *J Atten Disord*. 2010;14(3):281–291.

37. Razlog R, Pellow J, White SJ. A pilot study on the efficacy of Valeriana officinalis mother tincture and Valeriana officinalis 3 x in the treatment of attention deficit hyperactivity disorder. *Health SA Gesondheid*. 2012;17(1).
38. Salehi B, Imani R, Mohammadi MR, et al. Ginkgo biloba for attention-deficit/hyperactivity disorder in children and adolescents: a double blind, randomized controlled trial. *Prog Neuropsychopharmacol Biol Psychiatry*. 2010;34(1):76–80.
39. Shakibaei F, Radmanesh M, Salari E, Mahaki B. Ginkgo biloba in the treatment of attention-deficit/hyperactivity disorder in children and adolescents. A randomized: placebo-controlled, trial. *Complement Ther Clin Pract*. 2015;21(2):61–67.
40. Trebaticka J, Kopasova S, Hradecna Z, et al. Treatment of ADHD with French maritime pine bark extract. Pycnogenol. *Eur Child Adolesc Psychiatry*. 2006;15(6):329–335.
41. Weber W, Vander Stoep A, McCarty RL, Weiss NS, Biederman J, McClellan J. Hypericum perforatum (St John's wort) for attention-deficit/hyperactivity disorder in children and adolescents: a randomized controlled trial. *JAMA*. 2008;299(22):2633–2641.
42. Akhondzadeh S, Mohammadi MR, Momeni F. Passiflora incarnata in the treatment of attention-deficit hyperactivity disorder in children and adolescents. *Therapy*. 2005;2(4):609–614.
43. Sarris J, Kean J, Schweitzer I, Lake J. Complementary medicines (herbal and nutritional products) in the treatment of Attention Deficit Hyperactivity Disorder (ADHD): a systematic review of the evidence. *Complement Ther Med*. 2011;19(4):216–227.
44. Schoonees A, Visser J, Musekiwa A, Volmink J. Pycnogenol(R) (extract of French maritime pine bark) for the treatment of chronic disorders. *Cochrane Database Syst Rev*. 2012;4:CD008294.