PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	The Efficiency and Safety of Ginkgo Preparations for Attention Deficit Hyperactivity Disorder: A Systematic Review Protocol
AUTHORS	He, Sufei Wang, Miao Si, Jinhua Zhang, Tianyi Cui, Hong Gao, Xiumei

VERSION 1 – REVIEW

REVIEWER	Cory Harris and Hajra Mazhar University of Ottawa, Canada
REVIEW RETURNED	17-Nov-2017

GENERAL COMMENTS	Please note: for this submission, many of the Review Checklist criteria fall somewhere between "yes" and "no". We feel unqualified to comment on the statistical approach but feel more detail could be provided. 1) The Protocol contains numerous spelling and grammatical errors that complicate understanding and interpretation of objectives and study design. - e.g. what is meant by "efficiency" in the title and objective? Efficacy, effectiveness, or efficiency (Braggio 2010)? - e.g. in the objectives statement, what is meant by "all types of Ginkgo preparations" - limited to those mentioned or listed as search terms? will there be any measure of product quality or authentication? 2) Published reviews about clinical use of Ginkgo for ADHD reveal only a few studies (in English) of variable quality. The inclusion criteria in terms of study quality states how quality will be assessed but not the protocol's threshold for inclusion in meta-analysis. The inclusion of non-English studies is a strength that will likely uncover additional studies. However, are the two identified researchers qualified to translate these studies consistently across languages? Note that, based on the identified search strategy, identified articles will be almost exclusively in English and Mandarin/Cantonese (e.g. no french or spanish terms) 3) Why did you limit the pediatric age range in your study to 6-14? pediatric trials, in general, in hard to find. Excluding adolescents and related rationale should be addressed within the protocol.

	4) Why do the authors propose including hyperkinetic disorder? While the symptoms overlap with sub-types of ADHD, hyperkinetic disorder is not in the DSM IV-V and is not discussed in the Introduction or design sections of the protocol - only in the "Types of participants". If the authors wish to include trials targeting hyperkinetic disorder, they need to provide a rationale and explination. 5) Primary outcomes: For the Connors 3 index, the authors need to specify which versions will be considered, self, parent, or teacher. The tools should be referenced by their currently accepted names (e.g. Connor hyperactivity index is not a current standard of measurement). Secondary outcome: how will wuality of life be measured (and if different tools or scales are applied, how will the data be integrated for meta-analysis? 6) Exclusion criteria in text only refer to bias and not blinding. How will blinding be considered in the review? If Figure 1, the listed exclusion criteria are limited in details not necessarily explained in the text (e.g. randomization not mentioned before or after). 7) Lines 149-151: Is the inclusion of meditation studies intended? These trials are far outside the scope of the protocol (unless Ginkgo treatment was included in one or more treatment arms). 8) The introduction is not balanced. Millions of children with ADHD safely manage their symptoms safely using stimulants. Whereas risk of substance abuse may increase among this patient population, the text states that stimulants "will lead" to addiction... This is inaccurate. Similarly, while plant-based medicines offer a potential alternative, the data are incomplete or lacking and the risk of side effects can still be substantial. You also list autism (line 66), as well as depression, as a symptom rather than a condition characterized by a set of symptoms.

REVIEWER	Prof Jerome Sarris NICM, Western Sydney University, Australia.
REVIEW RETURNED	27-Nov-2017

GENERAL COMMENTS	A general proof to tightened up the grammar would be of benefit e.g. "Efficiency" in the introduction of abstract- should this be "efficacy"? 1) I would have thought more detail on the inclusion and exclusion criteria in the abstract would be suitable for a systematic review protocol 2) More precision advised when discussing the evidence to do with the background evidence of Ginkgo and cognitive decline and dementia (to my knowledge the evidence is equivocal- esp re dementia) 3) As a comment, I am not sure there has been any specialised systematic review on Ginkgo and ADHD so not sure why mentioning there are no 'updated' reviews. If a previous one exists then reference it and state how your one will improve this or demonstrate the need of an update. 4) Not sure why only the first phase of cross-over data will be used (for inclusion of cross-over studies). If there is sufficient washout and return to baseline then combined data from both phases should be acceptable.

	5) Suggest re age inclusion, that if 6-14 then the review be titled to include 'childhood and adolescent' ADHD as ADHD can persist into adulthood (although usually with less hyperactivity, but sustained inattention) and your review omits people >14 years old. 6) Re DSM-5 "Edition2", not sure if this is a typo or your mean section II 7) I would avoid including Yinxing Guttate Dropping Pill and Shuxuening Zhusheye, unless this is a Ginkgo only preparation. Otherwise need to include all Ginkgo combination studies. 8) I appreciate the Connors and ADHD Scale are the gold-standard rating, however I wouldn't restrict to just these scales unless absolutely important (i.e. other valid scales may have been used and ideally you don't want to omit this data). 8) More specificity is needed in the Types of Study section re inclusion criteria regarding doses, duration of study, minimum sample size etc. 9) Assessment of the quality of the types of studies via PRISMA grading or JADAD is required to perform a rigorous systematic review to assess the quality of design and reporting.

VERSION 1 – AUTHOR RESPONSE

Dear editor and reviewers,
Thank you for arranging a timely review for our manuscript. We have carefully revised our manuscript according to valuable comments and those of yours.
Here are the revisions and responses we made.

Reply to editor:
1) - The Strengths and Limitations section should be formatted into bullet points.
Reply:
This study will evaluate the safety of ginkgo preparations as a sole or adjunct agent for ADHD treatment.
Our review will be useful to clinicians, patients and parents who use ginkgo preparations for ADHD treatment.
Clinical heterogeneity may exist for different dosage forms of ginkgo preparations, doses, durations and combined treatments.
There may be a language bias with the limitation of English and Chinese studies.
2) - Please include the dates of the search in the methods section.
Reply: The databases will be searched from their inception until Jan 2018. It's included in the search strategies.
3) - Will you perform any quality assessment? Please detail this in your methods section.
Reply: We will perform quality assessment using the Grading of Recommendations Assessment, Development and Evaluation classification system (GRADE), which will be judged by limitations in the design and implementation, imprecision, inconsistency, indirectness and reporting bias. Evidence quality will be classified into four levels: high, moderate, low or very low. We will assess the risk of bias of the included studies using a risk of bias assessment tool according to the guidelines of the Cochrane Handbook.
4) - Please end the paper with an Ethics and Dissemination section, as per guidelines.
Reply: We added the Ethics and Dissemination section in the end.
Ethics and dissemination This systematic review does not require ethics approval. It will be published in a peer-reviewed journal.

Reply to reviewers
Reviewer: 1
Reviewer Name: Cory Harris and Hajra Mazhar
Institution and Country: University of Ottawa, Canada
Please state any competing interests or state 'None declared': none to declare

1) The Protocol contains numerous spelling and grammatical errors that complicate understanding and interpretation of objectives and study design.
- e.g. what is meant by "efficiency" in the title and objective? Efficacy, effectiveness, or efficiency (Braggio 2010)?
- e.g. in the objectives statement, what is meant by "all types of Ginkgo preparations" - limited to those mentioned or listed as search terms? will there be any measure of product quality or authentication?
Reply: Thank you very much for pointing out the shortcomings. We have made language editing and got the certificate by American Journal Experts (AJE). We are sorry that it's an error to use "efficiency" in the title and objective. We have replaced it with "efficacy".
Secondly, by saying all types of ginkgo preparations, we meant all dosage forms.
All dosage forms of ginkgo preparations contain tablets, granules, pills, injection distillates, oral solutions, extracts, dropping pills of Ginkgo biloba that have been approved for commercial marketing. Egb 761®, Ginaton®, Tebonin®, Rokan®, Tanakan®, Ginkobil®, GBE50®, Kaveri® are approved to market in USA, Europe, et al. Ginkgo Biloba Leaves Dispersible Tablet, Ginkgo Leaf Capsule, Ginkgo Leaves Soft Gel Capsule, Ginkgo Damole Injection, YinxingDamo, Ginkgo Biloba Granule, Yinxing Guttate Dropping Pill, Ginkgo Biloba Extract Injection, Ginkgo Distillate, Diterpene Ginkgolides Meglumine Injection, Ginkgolide Injection, Ginkgo Biloba Leaves Extract Oral Solution, Ginkgo Leaf Extract, Armillariella Mellea Powders Oral Solution, YinxingGuttate Dropping Pills, ShuxueningZhusheye are approved by China Food and Drug Administration(CFDA). Therefore, the product quality is assured.

2) Published reviews about clinical use of Ginkgo for ADHD reveal only a few studies (in English) of variable quality. The inclusion criteria in terms of study quality states how quality will be assessed but not the protocol's threshold for inclusion in meta-analysis.
The inclusion of non-English studies is a strength that will likely uncover additional studies. However, are the two identified researchers qualified to translate these studies consistently across languages? Note that, based on the identified search strategy, identified articles will be almost exclusively in English and Mandarin/Cantonese (e.g. no French or Spanish terms)
Reply: 1.We have strict inclusion criteria for the studies, listed from line 123 to line 163. For example, we limit the type of study, type of participants and types of interventions and controls.
2.We're sorry that it's really incorrect to state that this study is without language limitation. We attempted to include Korean databases because one of our team member Dr. Cui is familiar with Korean, but we found that we couldn't get the access to the databases. We will limit the studies to those published in English and Chinese.

3) Why did you limit the pediatric age range in your study to 6-14? pediatric trials, in general, in hard to find. Excluding adolescents and related rationale should be addressed within the protocol.
Reply: Thank you very much for this comment. We included adolescents and adults in the first edition of manuscript before we submitted it, concerning that ADHD can persist into adulthood. We then excluded adolescents and adults concerning that the main symptoms such as hyperactivity were relieved to some extent. However, it's more proper to include adolescents and adults without limitation of age because our main objective is to evaluate the efficacy and safety of ginkgo preparations for ADHD. It's better to find more evidence. Thank you very much.

4) Why do the authors propose including hyperkinetic disorder? While the symptoms overlap with sub-types of ADHD, hyperkinetic disorder is not in the DSM IV-V and is not discussed in the Introduction or design sections of the protocol - only in the "Types of participants". If the authors wish to include trials targeting hyperkinetic disorder, they need to provide a rationale and explanation.
Reply: We included hyperkinetic disorder to get more evidence, concerning that the broadly equivalent diagnosis of ADHD used predominantly in Europe is hyperkinetic disorder, which is defined in ICD-10. (Ford T, Goodman R, Meltzer H. The British Child and Adolescent Mental Health Survey 1999: the prevalence of DSM-IV disorders. J Am Acad Child Adolesc Psychiatry 2003; 42: 1203–11.) The ICD-10 diagnosis of hyperkinetic disorder is the narrower category, and it appears that nearly all cases of hyperkinetic disorder should be included within ADHD.(Eric T, Manfred D, Joseph S, et al. European clinical guidelines for hyperkinetic disorder – first upgrade 2004;13: i7–i30.)
Thank you very much for the advice. We have added a rationale and explanation in the introduction and design section.

5) Primary outcomes: For the Connors 3 index, the authors need to specify which versions will be considered, self, parent, or teacher. The tools should be referenced by their currently accepted names (e.g. Connor hyperactivity index is not a current standard of measurement).
Secondary outcome: how will quality of life be measured (and if different tools or scales are applied, how will the data be integrated for meta-analysis?
Reply: 1. Thank you very much. We changed “Conner’s Hyperactivity Index” to “The Revised Conners' Parent Rating Scale (CPRS-R)”.
(C. Keith Conners, Gill Sitarenios, James D. A. Parker, Jeffery N. Epstein. The revised Conners" Parent Rating Scale (CPRS-R): factor structure, reliability, and criterion validity[J].Journal of Abnormal Child Psychology.1998, 26(4):257-268.)
2. In the section of "quality of life", we plan to collect those trials, which assess the quality of life with the outcome of the KINDL scale, a German generic quality of life instrument for children. The German KINDL is a reliable, valid and practical instrument to assess the health-related quality of life of children. However, it’s not commonly used in China. We added this instrument for more data if possible.
(Ravens-Sieberer, U., & Bullinger, M. Assessing health related quality of life in chronically ill children with the German KINDL: First psychometric and content analytical results. Quality of Life Research, 1998,7, 399–407.)

6) Exclusion criteria in text only refer to bias and not blinding. How will blinding be considered in the review? If Figure 1, the listed exclusion criteria are limited in details not necessarily explained in the text (e.g. randomization not mentioned before or after).
Reply: Blinding will be evaluated by risk of bias assessment tool according to the guidelines of the Cochrane Handbook, as designed in the text. Risk of bias in included studies will be classified as low risk, unclear risk and high risk. Blinding of participants and personnel, blinding of outcome assessment will be assessed. Furthermore, we will exclude the low quality evidence when sensitivity analysis is conducted.
I'm sorry that we spelt "radomisation" in the text, which was mentioned in "types of study" and "type of interventions and controls". We have replaced it for "randomization" according to Cochrane Handbook. Thanks a lot.

7) Lines 149-151: Is the inclusion of meditation studies intended? These trials are far outside the scope of the protocol (unless Ginkgo treatment was included in one or more treatment arms).
Reply: It's really an error of spelling mistake of medication studies. We have revised it in the text.

8) The introduction is not balanced. Millions of children with ADHD safely manage their symptoms safely using stimulants. Whereas risk of substance abuse may increase among this patient population, the text states that stimulants "will lead" to addiction. This is inaccurate. Similarly, while

plant-based medicines offer a potential alternative, the data are incomplete or lacking and the risk of side effects can still be substantial. You also list autism (line 66), as well as depression, as a symptom rather than a condition characterized by a set of symptoms.
Reply: Thank you so much for the advice. The former statements in the protocol's introduction were imprecise. We have made a revision as below:
Stimulants are the first-line medications for ADHD treatment. Patients with ADHD manage their symptoms by using stimulants. However, the risk of substance abuse may increase in this patient population, and substance use disorder (SUD) is one of the most common comorbid psychiatric disorders in adolescent and adult patients [11-12]. The related adverse side-effects of stimulants include cardiovascular events, insomnia, appetite loss, hypoevolutism, gastrointestinal symptoms, and tics [13]. Complementary or alternative medical treatments for ADHD, such as plant-based medications, acupuncture [14] and music therapy [15], are considered because of the side effects, abuse and misuse of conventional pharmacological treatments. It is also important to evaluate the efficacy and safety of plant-based medications and acupuncture.
We also made a revision on "autism and depression" as below:
Ginkgo preparations alleviate the conditions such as autism [18], depression [19], and neuropsychiatric symptoms such as anxiety [20]. Ginkgo preparations may affect the behavioral and cognitive aspects of ADHD. The predominant behavioral effects are calming and improved frustration tolerance. Ginkgo biloba induces willful cognition, discriminant attention and decreases irritability [21].

Reviewer: 2
Reviewer Name: Prof Jerome Sarris
Institution and Country: NICM, Western Sydney University, Australia.
Please state any competing interests or state ‘None declared’: No major conflicts identified

Please leave your comments for the authors below
A general proof to tightened up the grammar would be of benefit e.g. "Efficiency" in the introduction of abstract- should this be "efficacy"?
Reply: I'm sorry it's an error to use "efficiency" in the title and objective. We have replaced it with "efficacy". We have submitted our manuscript to American Journal Experts (AJE) for language editing and get the certificate. We uploaded the certificate in the manuscript system.

1) I would have thought more detail on the inclusion and exclusion criteria in the abstract would be suitable for a systematic review protocol
Reply: Thank you very much for this comment. We have given more detail on the inclusion and exclusion criteria in the abstract of the revision as below:
Materials and methods All prospective randomized controlled trials (RCTs) will be included in this systematic review. Patients diagnosed with ADHD according to American Psychiatric Association’s Diagnostic and Statistical Manual of Mental Disorders 4th edition (DSM-IV), Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), WHO’s International Classification of Diseases (10th edition; ICD-10), or Chinese Classification and Diagnosis of Mental Diseases-3rd edition (CMDD) will be included. A comprehensive search for randomized controlled trials to evaluate the effectiveness and tolerance of ginkgo preparations will be performed. The primary outcomes are the ADHD rating Scale-IV (ADHD-RS-IV) and Revised Conners' Parent Rating Scale (CPRS-R). The secondary outcomes are quality of life using the KINDL scale, adverse effects/events, Conners’ Teacher Rating Scale (CTRS), Strengths and Weaknesses of ADHD Symptoms and Normal Behaviour (SWAN) Scale, and Fremdbeurteilungsbogen für Hyperkinetische Störungen (FBB-HKS). Exclusion criteria are the following: 1) Case reports; not randomized trial; non-comparative studies, 2) Patients who were not diagnosed based on DSM-IV, DSM-5, ICD-10) or CMDD. The following databases will be searched from their inception until Jan 2018: Medline, Embase, the Cochrane

Central Register of Controlled Trials, Web of Science, China Biology Medicine Disc, China National Knowledge Infrastructure Database, Wanfang Database and Chinese Scientific Journals Database. Two authors will independently perform the study selection, extract the data, and assess the study quality and risk of bias.

2) More precision advised when discussing the evidence to do with the background evidence of Ginkgo and cognitive decline and dementia (to my knowledge the evidence is equivocal- esp re dementia)
Reply: Thank you very much. We have made revision as below.
Ginkgo preparations are among the best-selling botanical dietary supplements worldwide. Clinical evidence indicates that Ginkgo biloba is safe and exhibits no excess side effects compared with placebo for cognitive impairment and dementia [16]. However, the evidence of efficacy is equivocal [17]. Ginkgo preparations alleviate the conditions such as autism[18], depression[19] , and neuropsychiatric symptoms such as anxiety[20]. Ginkgo preparations may affect the behavioral and cognitive aspects of ADHD. The predominant behavioral effects are calming and improved frustration tolerance. Ginkgo biloba induces willful cognition, discriminant attention and decreases irritability [21].

3) As a comment, I am not sure there has been any specialised systematic review on Ginkgo and ADHD so not sure why mentioning there are no 'updated' reviews. If a previous one exists then reference it and state how your one will improve this or demonstrate the need of an update.
Reply: Thank you very much. It's not appropriate to use "updated" in the text. We didn't find any specialized systematic review on Ginkgo and ADHD before. We have revised it.

4) Not sure why only the first phase of cross-over data will be used (for inclusion of cross-over studies). If there is sufficient washout and return to baseline then combined data from both phases should be acceptable.
Reply: Thanks a lot. We have revised it according to your advice, to use combined data from both phases if it's suitable.

5) Suggest re age inclusion, that if 6-14 then the review be titled to include 'childhood and adolescent' ADHD as ADHD can persist into adulthood (although usually with less hyperactivity, but sustained inattention) and your review omits people >14 years old.
Reply: We included adolescents and adults in the first edition of manuscript before we submitted it, concerning that ADHD can persist into adulthood. We then excluded adolescents and adults concerning that the main symptoms such as hyperactivity were relieved to some extent. It's more proper to include adolescents and adults without limitation of age because our main objective is to evaluate the efficacy and safety of Ginkgo preparations for ADHD. It's also better to find more evidence. Thank you very much. We have revised it in revision.

6) Re DSM-5 "Edition2", not sure if this is a typo or your mean section II
Reply: I'm sorry it's a typo. Revision has been made.

7) I would avoid including YinxingGuttate Dropping Pill and ShuxueningZhusheye, unless this is a Ginkgo only preparation. Otherwise need to include all Ginkgo combination studies.
Reply: Thank you very much for the advice. Both of these two preparations are Ginkgo only preparations that approved by China Food and Drug Administration (CFDA).
Details of these two drugs are as below:
YinxingGuttate Dropping Pill and Shuxuening Zhusheye are both extracted from Folium Ginkgo, as Ginkgo only preparations. Both drugs contain Ginkgo flavone and ginkgolide.
(①Li QIN, Ma Feng-xian, Cheng Tie-feng. Determination of terpenelactones in Yinxing Tongzhi Dripping Pills by HPLC-ELSD[J]. Chinese Traditional Patent Med icine,2007,(06):836-839.

②Chen Jing-jing, Zhou Yuan, Huang Xiao-lei, et al. Determination of content of Shuxuening Injection based on quantitative analysis of multi-components by single marker[J]. Chinese Traditional and herbal Drugs,2016,47(11):1890-1896.)
It may be suitable to include these two preparations. Thank you very much.

8) I appreciate the Connors and ADHD Scale are the gold-standard rating, however I wouldn't restrict to just these scales unless absolutely important (i.e. other valid scales may have been used and ideally you don't want to omit this data).
Reply: Thank you very much for your advice. It's appropriate to include other scales since the two scales are the gold-standard rating. We use them as primary outcomes. We have added several other scales as secondary outcomes, such as Conners' Teacher Rating Scale (CTRS), Strengths and Weaknesses of ADHD Symptoms and Normal Behaviour (SWAN) Scale, Schedule for Non-adaptive and Adaptive Personality (SNAP)- Teacher and Fremdbeurteilungsbogen für Hyperkinetische Störungen (FBB-HKS).

8) More specificity is needed in the Types of Study section re inclusion criteria regarding doses, duration of study, minimum sample size etc.
Reply: Thank you very much. Yes, we didn't strictly limit the doses, duration of study or minimum sample size etc, aiming to collect data as more as possible. We will conduct subgroup analysis and investigation of heterogeneity by the type of ginkgo preparations, the dose, follow-up period and type of control, as designed in the subgroup analysis and investigation of heterogeneity. And as study in small size has smaller weight in data analysis, so we didn't limit the minimum sample size.

9) Assessment of the quality of the types of studies via PRISMA grading or JADAD is required to perform a rigorous systematic review to assess the quality of design and reporting.
Reply: Thank you very much for this comment. Revision is as below:
Assessment of study quality and risk of bias Assessment
The quality of studies for each outcome will be assessed by the Grading of Recommendations Assessment, Development and Evaluation classification system(GRADE) , which will be judged by limitations in the design and implementation, imprecision, inconsistency, indirectness and reporting bias. Evidence quality will be classified into four levels of high, moderate, low or very low.
We will assess risk of bias of included studies by risk of bias assessment tool according to the guidelines of the Cochrane Handbook. Risk of bias in included studies will be classified as low risk, unclear and high risk by SF He and M Wang. The following will be assessed: random sequence generation, allocation sequence concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data and selective outcome reporting.