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The Efficiency and Safety of Ginkgo Preparations for Attention Deficit Hyperactivity Disorder: A Systematic Review Protocol

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The Efficiency and Safety of Ginkgo Preparations for Attention Deficit Hyperactivity Disorder: A Systematic Review Protocol

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Abstract

Introduction Attention Deficit Hyperactivity Disorder (ADHD) is one of the most commonly diagnosed and treated childhood psychiatric disorders. Ginkgo preparations have been used in treating ADHD. The study aims to assess the efficiency and safety of Ginkgo preparations as treatment for ADHD through current published evidence.

Materials and methods We will conduct the comprehensive search for the randomised controlled trials to evaluate the effectiveness and tolerance of ginkgo preparations. The following databases will be searched from their inception until October 2017: Medline, Embase, the Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science (science and social science citation index),China Biology Medicine Disc (CBMdisc),China National Knowledge Infrastructure Database (CNKI), Wanfang Database and Chinese Scientific Journals Database (VIP). Selection of studies, data extraction and assessment of risk of bias will be conducted independently by two authors.

Ethics and dissemination This systematic review does not require ethics approval. It will be published in a peer-reviewed journal.

PROSPERO registration number CRD42017077190

Strengths and limitations of this study

This systematic review will evaluate the efficacy and tolerance of all types of ginkgo preparations in treating ADHD and aims to provide appropriate clinical evidence for clinicians, patients and parents.

This review will collect data by unbiased search of various databases without language restrictions.

Clinical heterogeneity maybe exists regarding of changes in different types of ginkgo preparations, dosage, duration and the treatment combined.

Introduction

Description of the condition of ADHD treatment

The prevalence of Attention deficit hyperactivity disorder (ADHD) in children and adolescents is as high as 3.4% in the general population[1]; and it is considered as one of the most commonly diagnosed and treated childhood psychiatric disorders[2]. It rises to 6.26% in China[3]. ADHD is a childhood-onset neurodevelopmental disorder, which can persist into adolescence and adulthood, appearing with a high societal burden. The main symptoms consist of inattention and hyperactivity/impulsivity, often accompanied by other neurodevelopment disorders such as autism spectrum disorder[4]and intellectual disability[5]. A large proportion of adolescents and adults with ADHD perform antisocial behavior and criminal activities, including conduct disorder, oppositional defiant disorder[6], risk of crashing[7], sexual offenses[8] and arson[9], especially among arrested, convicted and imprisoned adolescents and adults, which, has been increasingly considered as a severe social issue.

Stimulants such as methylphenidate used for the first-line treatments will lead to substance use disorders (SUDs), one among the most common comorbid psychiatric disorders in adolescent or adult patients[10-11]. Related adverse side-effects include cardiovascular events, insomnia, appetite loss, hypoevolutism, gastrointestinal symptoms, and tics[12]. The side effects, nonresponse, abuse and misuse of conventional pharmacological treatments call for complementary or alternative medical treatments for ADHD with mild side-effect, such as plant-based medications, acupuncture[13] and music therapy[14].

Description of the intervention

Ginkgo preparations are made of compounds abstracted from ginkgo leaves, including tablets, capsules, granules, oral solution, aerosol and injection. Ginkgo preparations are one of the best-sale botanical dietary supplements all over the world. Evidence indicated that Ginkgo preparations can alleviate cognitive disorders[15], cerebrovascular insufficiency, peripheral vascular disturbances, degenerative dementia, and various neuropsychiatric symptoms such as autism[16], depression[17] and anxiety[18]. It's reported ginkgo preparations affected ADHD patients on both behaviors and cognitive aspects. The predominant behavioral effects were calming and improved frustration tolerance; while for cognition, ginkgo biloba induced willful cognition, discriminant attention and decreased irritability[19].

How the intervention might work

Components isolated from ginkgo biloba contain terpene trilactones, flavonol glycosides, isoflavonoids, biflavones, proanthocyanidins, alkylphenols, carboxylic acids, 4-O-Methylpyridoxine and polyprenols[20-22]. Preclinical evidence indicates that ginkgo flavonol glycosides are predominantly responsible for antioxidant activity[23]. The antioxidant activity of ginkgo flavonol glycosides can reduce the reactive oxygen species (ROS) induced oxidative stress, which contributes to neurodevelopmental disorders by causing membrane damage, changes in proteins' structure and function, lipid denaturation and DNA damage[24]. The terpene trilactones associated with neuroprotective properties[25]. Investigations showed that terpene trilactones attenuated the decrease of brain-derived neurotropic factor (BDNF), norepinephrine transporter (NET) and dopamine transporter (DAT) [26], which were reported to be negatively related to the pathogenesis of ADHD [27-29].

Considering that there hasn't been any updated and comprehensive quantitative review of ginkgo preparations to treat ADHD, it's important to investigate current evidence related to the effectiveness and tolerance of ginkgo preparations therapy for ADHD.

Materials and methods

Registration information

This systematic review protocol adhered to preferred reporting items for systematic review and meta analysis protocols (PRISMA-P) 2015[30]. The protocol was registered on PROSPERO and the registration number is CRD42017077190.

Eligibility criteria

Types of study

All prospective randomised controlled trials (RCTs) will be included in this systematic review, but trials without detailed data will be excluded. Abstracts with sufficient outcome data will be included. Cross-over trials will be included with the first phase of the data.

Type of participants

Children and adolescents between 6-14 years old with ADHD, or hyperkinetic disorder, diagnosed based on American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders 4th edition (DSM-IV), the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition2(DSM-5), and Chinese Classification and Diagnosis of Mental Diseases-3rd edition (CMDD) will be included. There will be no limitations of sex.

Type of interventions and controls

Randomised studies of the Ginkgo preparations, either as the sole treatment or as an adjunct to other treatments which were applied in both groups (intervention and control groups) in the same manner, will be included. Ginkgo preparations include ginkgo biloba, ginkgolides, bilobalides, ginkgo biloba leaves dispersible tablet, Ginkgo Leaf Capsule, Ginkgo Leaves Soft gel Capsule, Ginkgo damole Injection, Yinxing damo, 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, Yinxing Guttate Dropping Pills, Egb 761, Ginaton®, Tebonin forte, Rokan®, Tanakan®, Ginkobil®, GBE50, Kaveri® and Shuxuening Zhusheye. The control groups will include psychostimulants drug use, placebo use, psychotherapy and no treatment.

Outcomes measures

Primary outcomes:

The ADHD rating Scale-IV (ADHD-RS-IV).

Conner's Hyperactivity Index.

Secondary outcomes:

Quality of life.

Adverse effects/events.

Data sources

We will search the following electronic bibliographic databases: Medline, Embase, the Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science (science and social science citation index), China Biology Medicine Disc (CBMdisc), China National Knowledge Infrastructure Database (CNKI), Wanfang Database and Chinese Scientific Journals Database (VIP). The search strategy will include terms relating to or describing the patients and intervention. The terms will be combined with the Cochrane MEDLINE filter for controlled trials of interventions.

Search strategies

The search of Medline will be conducted using the following terms: (ginkgo biloba OR ginkgolides OR bilobalides OR ginkgo biloba leaves dispersible tablet OR Ginkgo Leaf Capsule OR Ginkgo Leaves Soft gel Capsule OR Ginkgo damole Injection OR Yinxing damo OR Ginkgo biloba granule OR Yinxing Guttate Dropping Pill OR Ginkgo biloba extract injection OR ginkgo distillate OR Diterpene Ginkgolides Meglumine Injection OR Ginkgolide Injection OR Ginkgo Biloba Leaves Extract Oral Solution OR Ginkgo Leaf Extract OR Armillariella Mellea Powders Oral Solution OR Yinxing Guttate Dropping Pills OR Egb 761 OR Egb761 OR Ginaton® OR Tebonin forte OR Tanakan® OR Rökan® OR Ginkobil® OR GBE50 OR Kaveri® OR Shuxuening Zhusheye) AND (attention deficit hyperactivity disorder OR ADHD OR hyperkinetic disorders). The strategies will be modified for Embase, Cochrane, Web of Science, CBM, CNKI, Wanfang and VIP.

The search terms will be adapted for use with above bibliographic databases in combination with database-specific filters for controlled trials, where these are available. There will be no language restrictions. Studies published with no limitations will be sought. The date the searches conducted will be recorded.

Data collection and analysis

Selection of studies

Two authors (SF He and M WANG) will select studies by assessing the titles and abstracts after duplication removal. Full-text will be further reviewed for eligibility. Randomized controlled trials that investigated the efficacy and safety of meditation therapy in children or adolescents diagnosed with ADHD will be selected. Study selection will be documented and summarised in a PRISMA-compliant flow chart (Figure 1)(http://www. prisma-statement. org).

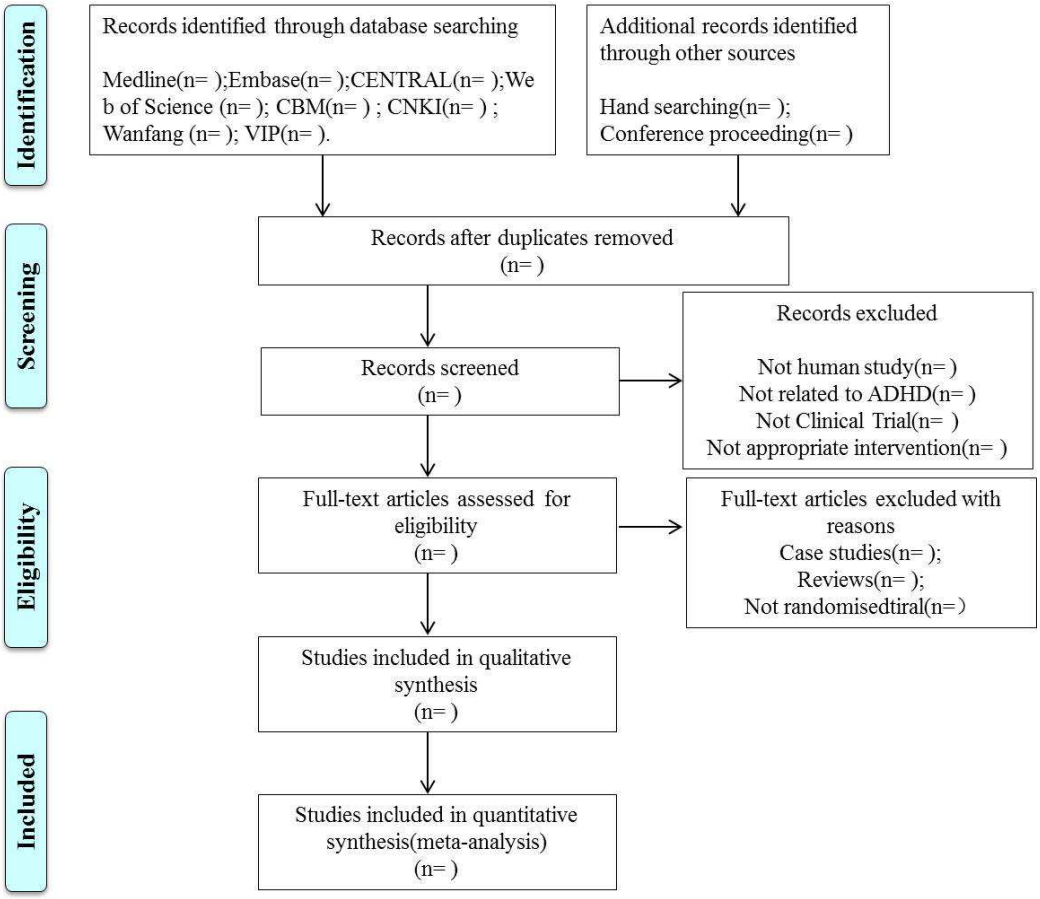

Figure 1 PRISMA flow diagram of searching and screening studies.

Data extraction

Two authors (SF He and M Wang) will independently conduct the data extraction and risk of bias assessment using a predefined data extraction form. Information will be collected with first author, publication year, study design, intervention, dosage, diagnostic criteria, disease duration, number of participants allocation, dropout, duration, outcome, outcome results(e.g., ADHD-RS-IV, Conner's Hyperactivity Index, quality of life and adverse effects/events), follow-up periods, adverse effects/events. We will conduct GRADEpro software to make a summary of findings table.

Any disagreement between two authors will be resolved by discussion, finally judged by XM Gao. When the data are insufficient, TY Zhang will contact the author for additional information by mail.

Assessment of risk of bias in included studies

We will assess risk of bias of included studies by risk of bias assessment tool according to the guidelines of the Cochrane Handbook[31]. Risk of bias in included studies will be classified as low, unclear and high 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.

Data synthesis and analysis

A meta-analysis will be conducted with either random-effect model or fixed-effect model when studies are identified. We will use Review Manager 5.3.5 software (RevMan 5.3.5) to combine

data from trials. Mean differences (MD) or standardized mean differences (SMD) for continuous outcomes and risk ratio (RR) for dichotomous outcomes with 95% confidence intervals (95% CIs) will be pooled by RevMan 5.3.5. A systematic narrative synthesis will be done to summarise the relationship of the included studies if quantitative synthesis is not appropriate.

Dealing with missing data

We will attempt to collect data from original study investigators if possible for missing data or incomplete data. If failed to get data, we will consider estimating it.

Assessment of reporting biases

We will detect reporting biases by funnel plots if more than 10 studies are included. Asymmetry test will be conducted by Egger's method[32].

Assessment of heterogeneity

Heterogeneity will be tested with chi-squared ($\chi 2$, or Chi2) test for P value. I^2 will be calculated. We consider that the I^2 value >50% indicates substantial heterogeneity[33]. We will either perform subgroup analysis or narrative descriptions according to different situations(e.g., lack of included trials).

Subgroup analysis and investigation of heterogeneity

Subgroup analysis will be performed to explore the source of heterogeneity by the type of ginkgo preparations, the dose, follow-up period and type of control.

Sensitivity analysis

Low quality trials will be excluded by conducting sensitivity analysis according to different effect models. Reporting of sensitivity analysis will be done by producing a summary table.

Discussion

The purpose of our systematic review is to give a detailed summary of effectiveness and tolerance assessment of ginkgo preparations treatment for ADHD. Even though ginkgo preparations have been used in ADHD, no systematic reviews on the effects and safety have been published. We will identify subtypes that are particularly useful for specific subgroups according to different types of ginkgo preparations. We hope that our study will provide reference for physicians, patients and parents in ADHD clinical practice.

Contributors The protocol was drafted by SF He, M Wang, XM Gao. The search strategy was developed and will be run by SF He and JH Si. Selection of the studies will be carried out by SF He and M Wang. Extraction of data from studies will conducted by SF He and Hong Cui. Analysis will be performed by SF He and TY Zhang. All authors have read and approved the final protocol. This review will be updated by SF He and M Wang.

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Competing interests None.

Provenance and peer review Not commissioned; externally peer reviewed.

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PRISMA-P 2015 Checklist

This checklist has been adapted for use with protocol submissions to *Systematic Reviews* from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 **4**:1

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	☒	☐	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	☐	☒	
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	☒	☐	28
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	☒	☐	4-12
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	☒	☐	205-209
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	☐	☒	
Support					
Sources	5a	Indicate sources of financial or other support for the review	☒	☐	210-211
Sponsor	5b	Provide name for the review funder and/or sponsor	☒	☐	210-211
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	☒	☐	210-211
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	☒	☐	14-27

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	☒	☐	16-17
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	☒	☐	90-112
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	☒	☐	120-127
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	☒	☐	128-143
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	☒	☐	151
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	☒	☐	154-155
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	☒	☐	154-155
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	☒	☐	156-159
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	☒	☐	113-119
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	☒	☐	163-168
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	☒	☐	169-174
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2, Kendall's tau)	☒	☐	169-185
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-	☒	☐	186-191

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
		regression)			
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	☒	☐	174-175
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	☒	☐	179-181
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	☒	☐	159

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Primary Subject Heading:	Complementary medicine
Secondary Subject Heading:	Paediatrics, Complementary medicine
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Efficacy and Safety of Ginkgo Preparations for Attention Deficit Hyperactivity Disorder: A Systematic Review Protocol

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Abstract

Introduction Attention Deficit Hyperactivity Disorder (ADHD) is one of the most commonly diagnosed and treated childhood psychiatric disorders. The analogous diagnosis adopted in Europe is hyperkinetic disorder, which is defined in the World Health Organization's (WHO's) International Classification of Diseases (10th edition; ICD-10). Hyperkinetic disorder includes more severe conditions. Ginkgo preparations are used in the treatment of ADHD. The present study will assess the efficacy and safety of ginkgo preparations in the treatment of ADHD in the currently published literature.

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), 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 evaluated by 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.

Ethics and dissemination This systematic review does not require ethics approval. It will be published in a peer-reviewed journal.

PROSPERO registration number CRD42017077190

Strengths and limitations of this study

- 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.

Introduction

Description of the condition of ADHD treatment

The prevalence of attention deficit hyperactivity disorder (ADHD) in children and adolescents is as high as 3.4% in the general population[1], and it is one of the most commonly diagnosed and treated childhood psychiatric disorders[2]. The diagnosis rate rises to 6.26% in China[3]. The analogous diagnosis adopted in Europe is hyperkinetic disorder, which is defined in the ICD-10. Hyperkinetic disorder includes more severe conditions.[4] ADHD is a childhood-onset neurodevelopmental disorder that may persist into adolescence and adulthood, and it has a high societal burden. The primary symptoms consist of inattention and hyperactivity/impulsivity that are often accompanied by other neurodevelopment disorders, such as autism spectrum disorder[5] and intellectual disability[6]. A large proportion of adolescents and adults with ADHD exhibit antisocial behaviour and criminal activities, including conduct disorder, oppositional defiant disorder[7], risk of crashing[8], sexual offenses[9] and arson[10], especially among arrested, convicted and imprisoned adolescents and adults. Therefore, ADHD has been increasingly considered a severe social issue.

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.

Description of the intervention

Ginkgo biloba preparations, including tablets, granules, pills, injection distillates, oral solutions, extracts, and dropping pills, are approved for commercial marketing. Egb 761®, Ginaton®, Tebonin®, Rokan®, Tanakan®, Ginkobil®, GBE50®, and Kaveri® are approved in the USA and Europe. Ginkgo Biloba Leaves Dispersible Tablet, Ginkgo Leaf Capsule, Ginkgo Leaves Soft Gel Capsule, Ginkgo Damole Injection, YinxingDamo, Ginkgo Biloba Granule, YinxingGuttate 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, and Shuxuening Zhusheye are approved by the China Food and Drug Administration (CFDA). 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].

How the intervention might work

Components isolated from ginkgo biloba contain terpene trilactones, flavonol glycosides, isoflavonoids, biflavones, proanthocyanidins, alkylphenols, carboxylic acids, 4-O-Methylpyridoxine and polyprenols[22-24]. Preclinical evidence indicates that ginkgo flavonol glycosides are predominantly responsible for the antioxidant activity[25]. The antioxidant activity of ginkgo flavonol glycosides reduce reactive oxygen species (ROS)-induced oxidative stress, which contributes to neurodevelopmental disorders by causing membrane damage, changes in protein structure and function, lipid denaturation and DNA damage[26]. Terpene trilactones are associated with neuroprotective properties[27]. Investigations have demonstrated that terpene trilactones attenuate the decrease in brain-derived neurotropic factor (BDNF), norepinephrine transporter (NET) and dopamine transporter (DAT) [28], which are negatively related to ADHD pathogenesis [29-31].

No comprehensive quantitative reviews of treatments of ADHD with ginkgo preparations have been performed. Therefore, it is important to investigate the current evidence of the efficacy and tolerance of ginkgo preparations therapy for ADHD.

Materials and methods

Registration information

This systematic review protocol adheres to the preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015[32]. The protocol was registered on PROSPERO, and the registration number is CRD42017077190.

Inclusion criteria

Types of study

All prospective randomized controlled trials (RCTs) will be included in this systematic review, but trials without detailed data will be excluded. Abstracts with sufficient outcome data will be included. Cross-over trials will be included with the two phases of data if there is sufficient washout and return to baseline.

Type of participants

Patients with ADHD or hyperkinetic disorder who were diagnosed based on 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. There will be no limitations on age or sex.

Types of interventions and controls

Randomized studies of the ginkgo preparations, as the sole treatment or as an adjunct to other treatments, that were used in the intervention and control groups in the same manner will be included. Ginkgo preparations include Egb 761®, Ginaton®, Tebonin®, Rokan®, Tanakan®, Ginkobil®, GBE50®, and Kaveri® , Ginkgo Biloba Leaves Dispersible Tablet, Ginkgo Leaf Capsule, Ginkgo Leaves Soft Gel Capsule, Ginkgo Damole Injection, YinxingDamo, Ginkgo Biloba Granule, YinxingGuttate 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, and Shuxuening Zhusheye. The control groups will include psychostimulant drug use, placebo use, psychotherapy and no treatment.

Outcomes measures

Primary outcomes:

The ADHD rating Scale-IV (ADHD-RS-IV).

The Revised Conners' Parent Rating Scale (CPRS-R).[33]

Secondary outcomes:

Quality of life on the KINDL scale.[34]

Adverse effects/events.

Conners' Teacher Rating Scale (CTRS).[35]

Strengths and Weaknesses of ADHD Symptoms and Normal Behaviour (SWAN) Scale.[36]

Fremdbeurteilungsbogen für Hyperkinetische Störungen (FBB-HKS).[37]

Exclusion criteria

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.

Data sources

We will search the following electronic bibliographic databases: Medline, Embase, the Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science (science and social science citation index), China Biology Medicine Disc (CBMdisc), China National Knowledge Infrastructure Database (CNKI), Wanfang Database and the Chinese Scientific Journals Database (VIP). The search strategy will include terms relating to or describing the patients and intervention. The terms will be combined with the Cochrane MEDLINE filter for controlled trials of interventions.

Search strategies

A search of Medline will be performed using the following terms: (ginkgo biloba OR ginkgolides OR bilobalides OR ginkgo biloba leaves dispersible tablet OR Ginkgo Leaf Capsule OR Ginkgo Leaves Soft gel Capsule OR Ginkgo damole Injection OR Yinxing damo OR Ginkgo biloba granule OR Yinxing Guttate Dropping Pill OR Ginkgo biloba extract injection OR ginkgo distillate OR Diterpene Ginkgolides Meglumine Injection OR Ginkgolide Injection OR Ginkgo Biloba Leaves Extract Oral Solution OR Ginkgo Leaf Extract OR Armillariella Mellea Powders Oral Solution OR Yinxing Guttate Dropping Pills OR Egb 761 OR Egb761 OR Ginaton® OR Tebonin forte OR Tanakan® OR Rökan® OR Ginkobil® OR GBE50 OR Kaveri® OR Shuxuening Zhusheye) AND (attention deficit hyperactivity disorder OR ADHD OR hyperkinetic

disorders). The strategies will be modified for Embase, Cochrane, Web of Science, CBM, CNKI, Wanfang and VIP.

The search terms will be adapted for use with the above bibliographic databases in combination with database-specific filters for controlled trials, when available. Language is limited with English and Chinese. The databases will be searched from their inception until Jan 2018.

Data collection and analysis

Selection of studies

Two authors (SF He and M WANG) will select studies by assessing the titles and abstracts after duplication removal. The full text will be further reviewed for inclusion. Randomized controlled trials that investigated the efficacy and safety of meditation therapy in patients diagnosed with ADHD will be selected. Study selection will be documented and summarized in a PRISMA-compliant flow chart (Figure 1)(http://www.prisma-statement.org).

Data extraction

Two authors (SF He and H Cui) will independently perform data extraction and risk of bias assessments using a predefined data extraction form. The first author, publication year, study design, intervention, dosage, diagnostic criteria, disease duration, number of participants allocation, dropout, duration, outcome, outcome results (e.g., ADHD-RS-IV, CPRS-R, quality of life on the KINDL scale and adverse effects/events, et al) and follow-up periods will be collected. We will use GRADEpro software to create a summary of findings table.

Any disagreement between the two authors will be resolved by discussion, and XM Gao will make the final decision. TY Zhang will contact the authors for additional information by mail when the data are insufficient.

Assessment of study quality and risk of bias

The quality of the studies for each outcome will be assessed 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[38]. SF He and M Wang will classify the risk of bias in the included studies as low risk, unclear risk and high risk. The following factors 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.

Data synthesis and analysis

A meta-analysis will be performed using a random-effect model or fixed-effect model for the identified studies. We will use Review Manager 5.3.5 software (RevMan 5.3.5) to combine the data from the trials. The mean differences (MD) or standardized mean differences (SMD) for continuous outcomes and risk ratio (RR) for dichotomous outcomes with 95% confidence intervals (95% CIs) will be pooled in RevMan 5.3.5. A systematic narrative synthesis will be performed to summarize the relationship of the included studies when quantitative synthesis is not appropriate.

Dealing with missing data

We will attempt to collect data from original study investigators if possible for missing or

incomplete data. We will consider estimating data if we cannot obtain the original source.

Assessment of reporting biases

We will detect reporting biases using funnel plots if more than 10 studies are included. An asymmetry test will be performed using Egger's method[39].

Assessment of heterogeneity

Heterogeneity will be tested using the chi-squared ($\chi 2$, or Chi2) test for the P value. I^2 will be calculated. An I^2 value >50% will indicate substantial heterogeneity[40]. We will perform subgroup analyses or narrative descriptions based on the situation (e.g., lack of included trials).

Subgroup analysis and investigation of heterogeneity

Subgroup analysis will be performed to explore the source of heterogeneity by the different dosage forms of ginkgo preparations, dose, follow-up period and type of control.

Sensitivity analysis

Low-quality trials will be excluded from sensitivity analyses according to the different effect models. A summary table will report the results of the sensitivity analyses.

Discussion

Our systematic review will provide a detailed summary of the efficacy and tolerance of ginkgo preparations for the treatment of ADHD. Ginkgo preparations are used in ADHD treatment, but no systematic reviews on the efficacy or safety have been published. We will identify ginkgo preparation subtypes that are particularly useful in specific subgroups. We hope that our study will provide a reference for physicians, patients and parents in ADHD clinical practice.

Contributors SF He, M Wang, and XM Gao drafted the protocol. SF He and JH Si developed and will perform the search strategy. SF He and M Wang will select the studies. SF He and Hong Cui will extract data from selected studies. SF He and TY Zhang will perform the analyses. All of the authors read and approved the final protocol. SF He and M Wang will update this review.

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Competing interests None.

Provenance and peer review Not commissioned; externally peer reviewed.

Ethics and dissemination This systematic review does not require ethics approval. It will be published in a peer-reviewed journal.

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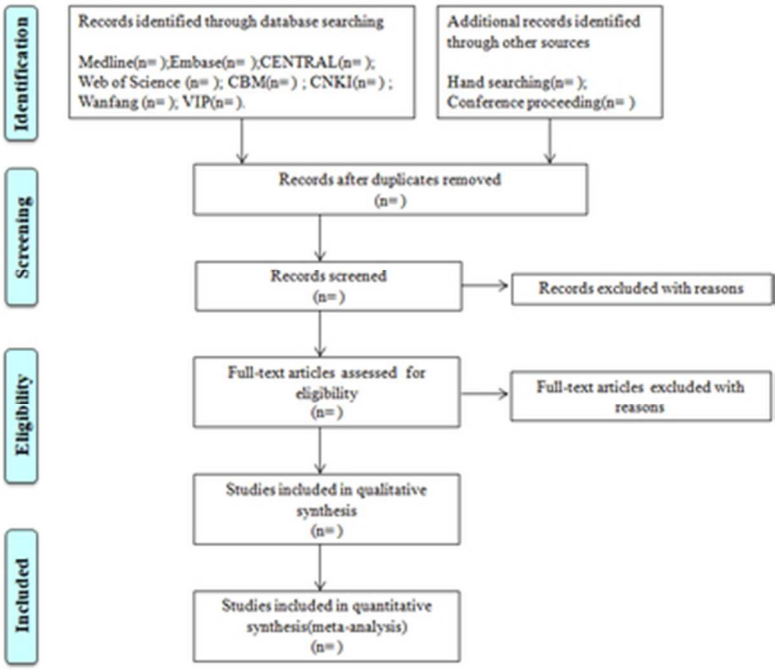
Figure 1 PRISMA flow diagram of the study searching and screening.



PRISMA flow diagram of the study searching and screening studies

16x14mm (600 x 600 DPI)

PRISMA-P 2015 Checklist

This checklist has been adapted for use with protocol submissions to *Systematic Reviews*from Table 3 in Moher D et al**:** Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews*2015 **4**:1

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	☒	☐	1-2
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	☐	☒	
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	☒	☐	43
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	☒	☐	3-14
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	☒	☐	239-242
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	☐	☒	
Support					
Sources	5a	Indicate sources of financial or other support for the review	☒	☐	243-244
Sponsor	5b	Provide name for the review funder and/or sponsor	☒	☐	243-244
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	☒	☐	243-244
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	☒	☐	55-108
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	☒	☐	23-33

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	☒	☐	118-151
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	☒	☐	155-162
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	☒	☐	163-177
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	☒	☐	185-230
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	☒	☐	179-184
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	☒	☐	185-194
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	☒	☐	187-190
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	☒	☐	142-151
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	☒	☐	195-206
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	☒	☐	207-210
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2, Kendall's tau)	☒	☐	210-214 221-224
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	☒	☐	225-230
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	☒	☐	212-214
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective	☒	☐	218-220

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
		reporting within studies)			
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	☒	☐	195-200