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Review

Ginkgo biloba extract for essential hypertension: A systemic review

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ABSTRACT

Background: Ginkgo biloba extract (GBE), a traditional natural herbal product, is often used in the treatment of essential hypertension (EH) as complementary therapy in China and European countries.
Aim: To critically assess the current clinical evidence of efficacy and safety of GBE for EH.
Methods: 7 electronic databases (Cochrane Library, PubMed, EMBASE, VIP, CBM, Wanfang data, and CNKI) were searched to identify randomized controlled trials (RCTs) of GBE for EH. Methodological quality was assessed independently using the *Cochrane Handbook for Systematic Reviews of Interventions*.
Results: A total of 9 RCTs with 1012 hypertensive patients were identified and reviewed. Most RCTs were of high risk of bias with flawed study design and poor methodological quality. 6 trials demonstrated potential positive effect of GBE as complementary therapy on BP reduction when compared with antihypertensive drug therapy; however, it was not associated with a statistically significant effect on both SBP and DBP reduction in 3 other trials. Despite the positive findings, there were so many methodological limitations and significant clinical heterogeneity. Most of the trials did not report adverse effects, and the safety of GBE is still uncertain.
Conclusion: No confirmative conclusions on the efficacy and safety of GBE for EH could be drawn. More rigorous trials are warranted to support their clinical use.

Contents

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Introduction

Hypertension is an important worldwide public-health challenge, which can lead to severe complications and target organ damage (Karen et al. 2011). Oral antihypertensive drugs, lifestyle modification including exercise and dietary modification are milestones for hypertension therapy (Chobanian et al. 2003). However, the control rate of hypertension has not reached the expected requirements (Redwood 2007). Thus, a certain proportion of hypertensive patients has turned to traditional medicine (TM) (Ernst 2005), including traditional Chinese medicine (TCM) (Wang and Xiong 2012a), for better clinical efficiency in lowing blood pressure (BP) smoothly and improving uncontrolled hypertension-related symptoms (including headache, dizziness, fatigue, etc.) with little adverse effects (Mansoor 2001). Over the past 30 years, study on Chinese herbal medicine (CHM) for hypertension is the most active area of research within TCM and integrative medicine in China (Xiong et al. 2013). Currently, more and more randomized controlled trials (RCTs) and systematic reviews (SRs) have been conducted, which have paved the evidenced-based way in making recommendation for TCM physicians, hypertensive patients and policy makers (Wang and Xiong 2012b). It is demonstrated that CHM as complementary therapy appears to be more effective in reducing BP and relieving signs and symptoms in hypertensive patients (Wang and Xiong 2013).

Ginkgo biloba extract (GBE), made from the dried leaves of the Ginkgo tree, is one of the top sellers within the growing market for herbal remedies in many European countries as well as in the USA (Kressmann et al. 2002b). The chemical composition of GBE is complex and several of its constituents (e.g. flavone glycosides and terpenoids) have been proposed as being responsible for the cardiovascular protective effects and cerebrovascular-related disorders (Gaby 1996). In European countries, GBE shows promise in treating dementia and aging-associated cognitive impairment, vertigo, tinnitus, and peripheral arterial disease (Diamond et al. 2000). In China, the therapeutic indications of GBE described in *Pharmacopeia of People's Republic of China* (*2010 edition*) include chest impediment, heart pain, stroke, hemiplegia and dysphasia due to blockage of meridians by stagnated blood; angina pectoris of the stable type in coronary heart disease and cerebral infarction with above symptoms (National Pharmacopoeia Committee 2010). Although it is not used to treat hypertension in Western countries and China regularly, several studies did suggest antihypertensive effect both *in vitro* and *in vivo*, providing a possible alternative mechanism for cardiovascular disease prevention (Kudolo 2000). In hypertensive rats models, treatment with GBE attenuated the rise in BP (Sasaki et al. 2002), the mechanism of which may be related to inhibiting angiotensin converting enzyme activity, preserving vascular reactivity toward endothelium-dependent and -independent vasodilators, inhibit responses to vasoconstrictors, etc. (Mansour et al. 2011; Kubota et al. 2006). However, it is worth noting that differences in quality and composition may affect the bioavailability and therefore the biological effects of the active molecules in an extract (Kressmann et al. 2002a; Itil and Martorano 1995). 1 trial in 3069 elderly subjects did not find any difference between Ginkgo leaf extract EGb 761® and placebo with respect to changes in BP, neither in the normotensive nor in hypertensive participants (Brinkley et al. 2010). Therefore, whether GBE can be recommended for routine use based on the current evidence is still uncertain.

In this review, only GBE, containing total flavonol glycosides 9.6 mg and terpene lactones 2.4 mg in each tablet, could be included for further analysis. As a pure extracts of Ginkgo biloba leaves, it has been approved by the China Food and Drug Administration (available in http://www.sda.gov.cn). It is also known as Ginkgo leaf tablet, a popular Chinese patent medicine (CPM) which have been subjected to a relatively strict drug evaluation process including active constitutes identification, compatibility mechanism study, efficiency and safety evaluation, and RCTs. This SR is aimed at critically evaluating the data from RCTs of GBE for EH to provide the best available evidence for clinical practice and further research planning on EH.

Methods

Database and search strategies

Literature searches were conducted in the following 7 electronic databases: Cochrane Library (November, 2013), PubMed (1959–2013), EMBASE (1980–2013), Chinese National Knowledge Infrastructure (CNKI, 1979–2013), Chinese Scientific Journal Database (VIP, 1989–2013), Chinese Biomedical Literature Database (CBM, 1978–2013) and Wanfang data (1998–2013). As GBE is used and researched in China, 4 main databases in Chinese language were searched to retrieve the maximum possible number of clinical trials. Literature searches were ended on 17 November, 2013. Ongoing registered trials were searched in the website of Chinese clinical trial registry (http://www.chictr.org/) and international clinical trial registry by U.S. National Institutes of Health (http://clinicaltrials.gov/). The following search terms were used individually or combined: 'Ginkgo biloba extract', 'Ginkgo biloba leaf extract', 'Ginkgo leaf extract', 'Ginkgo leaf tablet', 'yin xing ye tablet', 'yinxingye tablet', 'yin xing ye pill', 'yinxingye pill', 'yin xing ye pian', 'yinxingye pian', 'hypertension', 'essential hypertension', 'blood pressure', 'high blood pressure', 'clinical trial', and 'randomized controlled trial'. Reference lists of retrieved papers were searched as well.

Inclusion criteria

We included all parallel RCTs comparing GBE as monotherapy or adjunct therapy to conventional medicine with antihypertensive drugs for EH, which used BP reduction as the main outcome measure with no restrictions on population characteristics, language and publication type. Interventions in either experimental or control group including other CHM were excluded. Interventions in control group should include no treatment, placebo, and conventional medicine (antihypertensive drugs). Quasi randomized trials and animal experiments were also excluded as well. Duplicated publications reporting the same groups of participants were excluded. Participants with EH should meet the following diagnostic criteria: systolic blood pressure (SBP) $\geq$ 140 mmHg, and/or, diastolic blood pressure (DBP) $\geq$ 90 mmHg. There is no restriction on dosage including frequency, dose, and intensity. Duration of treatment courses should be more than 4 weeks.

Data extraction and quality assessment

Two authors independently conducted the literature searching (Xiong X, Yang X), study selection (Liu W, Feng B), and data extraction (Zhang Y, Li S). According to the predefined criteria, extracted data information included authors, title of study, year of publication, study size, age and sex of the participants, details of methodological information, treatment process, details of the control interventions, outcome measures, and adverse effects for each study. Disagreement was resolved by discussion and reached consensus through a third party (Li XK, Wang J).

To assess the methodological quality, the Cochrane Handbook for Systematic Review of Interventions, Version 5.1.0 was used (Higgins and Green 2011). The items included the following 7 aspects: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection

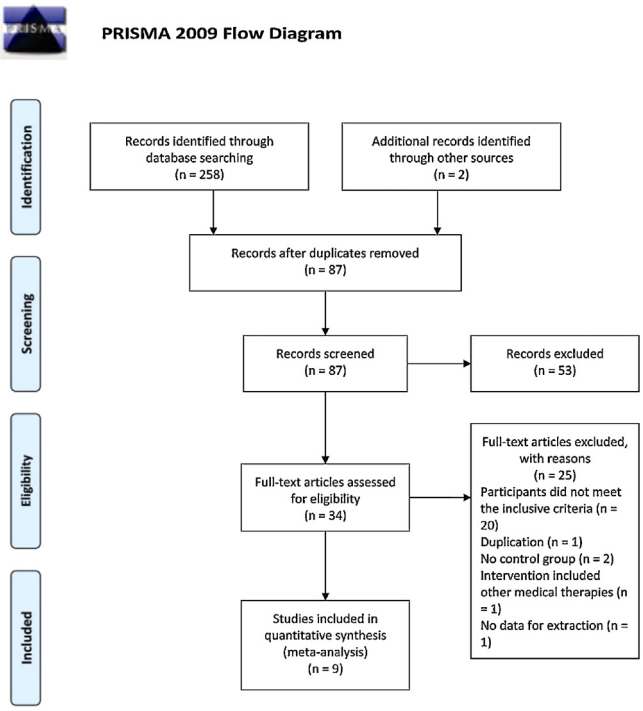

Fig. 1. PRISMA 2009 flow diagram.

bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and other bias. Methodological quality of all included trials was categorized to low/unclear/high risk of bias ("Yes" for a low of bias, "No" for a high risk of bias, "Unclear" otherwise). Then trials were categorized into three levels: low risk of bias (all the items were in low risk of bias), high risk of bias (at least one item was in high risk of bias), unclear risk of bias (at least one item was in unclear). Discrepancies were resolved through discussion between the authors.

Data synthesis

Two researchers (Xiong X, Yang X) used Review Manager 5.1, provided by the Cochrane corporative network, to analyze the data. Dichotomous data were presented as risk ratio (RR) and continuous outcomes as mean difference (MD), both with 95% confidence interval (CI). The chi-square test was used to test heterogeneity across studies with a significance level of 0.05. Heterogeneity was recognized significant when $I^2 \geq 50\%$. Fixed effects model was used if there is no significant heterogeneity of the data ($I^2 < 50\%$); random effects model was used if significant heterogeneity existed ($50\% < I^2 < 85\%$). Publication bias would be explored by funnel plot analysis if sufficient studies were found.

Results

Description of included trials

As shown in Fig. 1, a flow chart depicted the search process and study selection. Finally, 9 studies with 1012 hypertensive patients were included for analysis (Chen 2011; Ge and Pan 2008; Guo and Chen 2013; Liu et al. 2010; Tu and Zhou 2007; Wang et al. 2012; Xu et al. 2008; Yu 1999; Zhou et al. 2007). All studies were conducted in China and published in Chinese (1999–2013). The characteristics of 9 trials were listed in Table 1.

Among them, 4 diagnostic criteria of EH were specified. 2 trials (Tu and Zhou 2007; Zhou et al. 2007) used Chinese Guidelines for the Management of Hypertension-1999 (CGMH-1999), 2 trials (Liu et al. 2010; Wang et al. 2012) used Chinese Guidelines for the Management of Hypertension-2005 (CGMH-2005), 2 trials (Ge and Pan 2008; Guo and Chen 2013) used WHO-ISH guidelines for the management of hypertension-1999 (WHO-ISH GMH-1999), 1 trial used Practice of Internal Medicine (10th edition), and 2 trials (Chen 2011; Xu et al. 2008) only demonstrated patients with EH without detailed information.

Interventions of all trials included GBE combined with antihypertensive drugs. Controls included antihypertensive drugs alone. Total treatment course duration ranged from 8 weeks to 6 months. All of them used BP as the outcome measure. Adverse effect was also described in details.

Methodological quality of included trials

Methodological quality of most trials was evaluated to be general low according to the predefined quality assessment criteria. All trials declared that hypertensive patients were randomly assigned to the experimental group and control group; however, only 1 trial has described method for random sequence generation (random number table) (Guo and Chen 2013). Allocation concealment and double-blind were not reported in all trials. Only 1 trial reported drop-out (Liu et al. 2010). No trial reported a pre-trial estimation of sample size.

Effect of the interventions

3 grades, which were authoritatively recommended by Guidelines of Clinical Research of New Drugs of Traditional Chinese Medicine (GCRNDTCM), were used to evaluate the therapeutic effects of GBE for EH in 6 trials (Chen 2011; Liu et al. 2010; Tu and Zhou 2007; Xu et al. 2008; Yu 1999; Zhou et al. 2007). Detailed information about 3 classifications were described as follows: "significant improvement" (DBP decreased by 10 mmHg reaching the normal range, or, DBP has not yet returned to normal, but has been reduced ≥20 mmHg), "improvement" (DBP decreased to less than 10 mmHg reaching the normal range, or, DBP decreased by 10–19 mmHg, but did not reach the normal range, or, SBP decreased ≥30 mmHg), and "no improvement" (not to meet the above standards) (Xiong et al. 2014). To permit at least some overall analysis, these outcomes were converted into dichotomous data. We grouped together both "significant improvement" and "improvement" as "effective", and "no improvement" as "ineffective". Meta-analysis showed that BP is significantly decreased in experimental group at the end of treatment (RR: 1.08 [1.02, 1.14]; $P = 0.01$) (Fig. 2).

3 trials (Ge and Pan 2008; Guo and Chen 2013; Wang et al. 2012) used BP values to assess the therapeutic effect of GBE for EH. When it comes to SBP, significant homogeneity in the trial was found, chi-square = 16.32 ($p = 0.0003$); $I^2 = 88\%$. Thus, random effects model was used for statistical analysis. Meta-analysis showed there is no significant difference between experimental and control group on SBP (MD: −4.37 [−11.20, 2.45]; $p = 0.21$) (Fig. 3). When it comes to DBP, there is also significant homogeneity, chi-square = 7.54 ($p = 0.02$); $I^2 = 73\%$. Therefore, random effects model was used for statistical analysis. No significant difference between experimental and control group on DBP (MD: −3.09 [−6.50, 0.33]; $p = 0.08$) was found (Fig. 4).

Publication bias

The number of included trials in this review was too small to conduct any sufficient additional analysis of publication bias.

Table 1
Characteristics of included trials.

Study ID	Sample size (randomized/analyzed) M/F	Age (yrs)	Diagnosis standard	Intervention	Control	Course	Outcome measure
Xu et al. (2008)	220/220 T: 115 C: 105	60–82 (T/C: NR)	Hypertension diagnostic criteria (unclear)	GBE (1# tid) + control	Amlodipine (5 mg qd)	6 months	BP
Chen (2011)	120/120 T: 34/26 C: 33/27	T: 59.8 ± 5.2 C: 60.1 ± 4.8	Hypertension diagnostic criteria (unclear)	GBE (1# tid) + control	Antihypertensive drugs (no detailed information)	6 months	BP
Zhou et al. (2007)	116/116 T: 36/20 C: 40/20	T: 49.7 ± 3.2 C: 48.7 ± 3.0	CGMH-1999	GBE (2# tid) + control	Metoprolol (100 mg bid)	24 weeks	BP
Liu et al. (2010)	123/116 T: 36/20 C: 40/20	60–82 (T/C: NR)	CGMH-2005	GBE (2# tid) + control	Metoprolol (50 mg qd/bid)	24 weeks	BP
Yu (1999)	50/50 T: 30 C: 20	NR	Practice of Internal Medicine (10th edition)	GBE (1# tid) + control	Capoten (6.25–25 mg tid)	6 months	BP
Tu and Zhou (2007)	58/58 T: 18/10 C: 20/10	T: 49.7 ± 3.2 C: 48.7 ± 3.0	CGMH-1999	GBE (2# tid) + control	Metoprolol (100 mg bid)	24 weeks	BP
Wang et al. (2012)	152/152 T: 76 C: 76	60–75 (T/C: NR)	CGMH-2005	GBE (2# tid) + control	Valsartan (80–160 mg qd)	6 months	BP; adverse effect
Guo and Chen (2013)	84/84 T: 20/22 C: 21/21	T: 68.8 ± 7.7 C: 67.5 ± 7.4	WHO-ISH GMH-1999	GBE (19.6 mg tid) + control	Amlodipine besylate tablets (5 mg qd)	8 weeks	BP
Ge and Pan (2008)	96/96 T: 25/23 C: 26/22	52–82 (T/C: NR)	WHO-ISH GMH-1999	GBE (80 mg tid) + control	Amlodipine besylate tablets (2.5 mg qd)	6 months	BP; adverse effect

Abbreviations: T: treatment group; C: control group; NR: not reported; BP: blood pressure; CGMH: Chinese Guidelines for the Management of Hypertension; WHO-ISH GMH: WHO-ISH guidelines for the management of hypertension; #: tablet; GBE: a pure extracts of Ginkgo biloba leaves containing total flavonol glycosides 9.6 mg and terpene lactones 2.4 mg in each tablet.

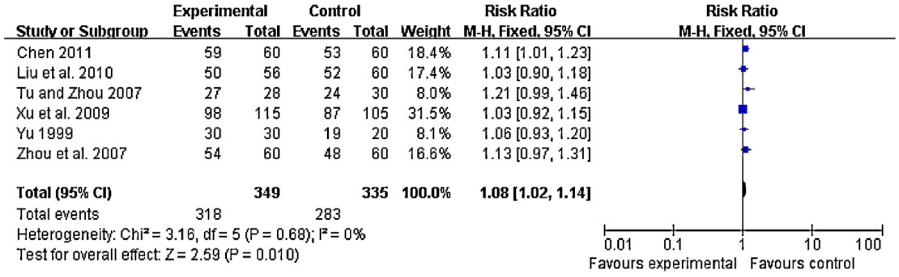

Fig. 2. Analyses of blood pressure on 6 trials. Ginkgo biloba extract plus antihypertensive drugs vs antihypertensive drugs.

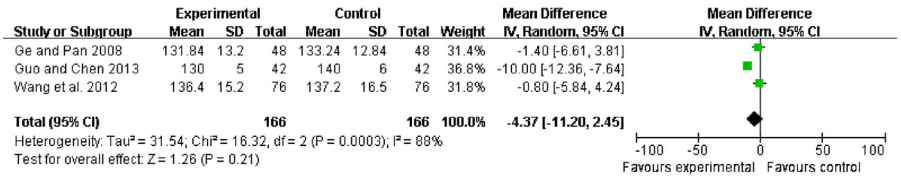

Fig. 3. Analyses of systolic blood pressure on 3 trials. Ginkgo biloba extract plus antihypertensive drugs vs antihypertensive drugs.

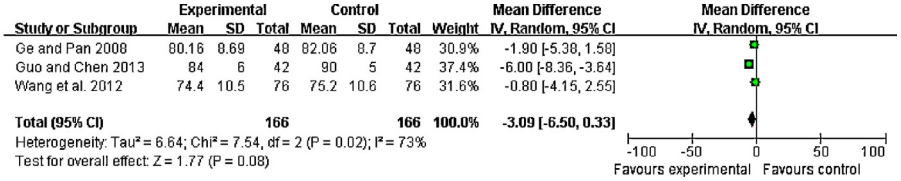

Fig. 4. Analyses of diastolic blood pressure on 3 trials. Ginkgo biloba extract plus antihypertensive drugs vs antihypertensive drugs.

Adverse effect

2 out of 9 included trials mentioned the adverse effect (Ge and Pan 2008; Wang et al. 2012). 1 trial reported abdominal discomfort and loss of appetite in 6 cases (Wang et al. 2012). 1 trial reported flushing, dizziness and slight edema of the lower limbs in both experimental and control group (Ge and Pan 2008). All of the adverse events were not serious.

Discussion

This SR was initiated because GBE is often used by TCM physicians and patients for the treatment of EH. Yet there is uncertainty about its clinical recommendation. In this review, 9 RCTs with 1012 participants were included. Several trials demonstrated potential positive effect on BP reduction when compared with antihypertensive drug therapy; however, it was not associated with a statistically significant effect on both SBP and DBP reduction in other 3 trials. What is more, methodological issues, small sample size, and significant heterogeneity of included trials did limit the extent to which any conclusions can be drawn. Therefore, as an adjunctive treatment to antihypertensive drugs, the therapeutic effect of GBE for EH is still uncertain.

Inadequate reporting on adverse effects was also found in our review. It is widely accepted by part of patients and physicians that natural herbal products are relatively safe for long term use with fewer adverse effects as compared to antihypertensive drugs. However, in this review, only 2 studies with small simple size described mild adverse events of GBE with spontaneous remission. Due to the insufficient data, it is too early to evaluate the safety of GBE for EH patients at present. Therefore, detailed description of adverse events in future studies of GBE is needed to confirm the results.

The following limitations of this article should also be paid attention to. None of the included studies was assessed to be at low risk of bias. In our review, in fact, it was impossible to find well-designed trials to evaluate efficacy of GBE for the management of EH. All the included trials had risk of bias in terms of design, reporting, and methodology. Inadequate reporting of study design, allocation sequence, allocation concealment, blinding, intention to treat analysis and drop outs were provided in the most trials. The main reasons are as follows: randomization was mentioned in all the trials; however, only 1 trial has described the concrete methods for random sequence generation, which might lead to potential selection bias. Similar problem also exists in the trials of Chen (2011), Yu (1999), Tu and Zhou (2007), Guo and Chen (2013) and Ge and Pan (2008). 5 trials mentioned above only had one or two authors. It is so difficult to conduct a RCT properly in terms of randomization procedure, allocation concealment, and double-blind by them alone. Blinding is an essential method for preventing research outcomes from being influenced by either the placebo effect or the observer bias (Smyth et al. 2011). However, neither blinding of participants and personnel nor blinding of outcome assessment is mentioned in all trials. Due to both researchers and patients being aware of the therapeutic interventions for the subjective outcome measures, the potential performance bias and detection bias may be generated. The placebo effect is another noteworthy issue in TCM clinical studies (Kaptchuk 2002). Without a rigorous control for placebo effect, conclusions of these studies might be exaggerated because of nonspecific placebo effects (Brody and Miller 2011). However, no trial reported the application of placebo. Only 1 trial reported drop-out. Intention to treat analysis was not applied in the vast majority of clinical trials. Most trials were small sample size and single-center. No trial has reported a pre-trial estimation of sample size. Therefore, whether sample size meets the requirements of clinical research is still unknown. We are not sure if they could provide enough power to detect the difference between groups. What is more, due to the variations in methodological quality, participants, intervention, and control, significant clinical heterogeneity was found in our review, which might weaken the reliability of the data statistics. Thus, we expect that more RCTs of GBE will be appropriately designed, conducted, and reported according to CONSORT statement and CONSORT statement for herbal interventions.

Conclusion

There is no convincing evidence to support the routine use of GBE for EH. More randomized trials with well design and adequate sample size are warranted to generate high level of evidence thus to support or refute the result in future.

Conflict of interest

None.

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