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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

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