Ginkgo Biloba for Prevention of Dementia: A Systematic Review and Meta-Analysis

Thammanard Charernboon MD, MSc, FRCPsychT*,**,
Kankamol Jaisin MD, FRCPsychT*

** Department of Psychiatry, Faculty of Medicine, Thammasat University, Pathumthani, Thailand*
*** Stroke and Neurodegenerative Diseases Research Unit, Thammasat University, Pathumthani, Thailand*

Objective: *To determine the efficacy of Ginkgo biloba for the prevention of dementia in individuals without dementia.*
Material and Method: *English databases including Medline, Embase, Cochrane Library and PsycINFO, were searched, and randomized double-blind controlled studies comparing Ginkgo biloba with placebo in prevention of dementia were considered. Two trials met inclusion criteria. Methodological quality was assessed using the Jadad criteria.*
Results: *Meta-analysis of the two trials involving 5,889 participants indicated no significant difference in dementia rate between Ginkgo biloba and the placebo (347/2,951 vs. 330/2,938, odds ratio = 1.05, 95% CI 0.89-1.23) and there was no considerable heterogeneity between the trials. The two studies revealed no statistically significant differences in the rate of serious adverse effect between Ginko biloba and the placebo.*
Conclusion: *There is no convincing evidence from this review that demonstrated Ginkgo biloba in late-life can prevent the development of dementia. Using it for this indication is not suggested at present.*

Keywords: *Alzheimer disease, Dementia, Ginkgo biloba, Meta-analysis, Prevention*

J Med Assoc Thai 2015; 98 (5): 508-13
Full text. e-Journal: *http://www.jmatonline.com*

Dementia is one of the most important health problems of an aging population. About 5-10% individuals over the age of 65 will develop dementia. In 2010, it was approximated that there were 35.6 million dementia patients around the world and this number might increase to an estimated 65.7 million in 2030[1]. Therefore, potential prevention or delay of the onset of dementia is a critical challenge for all societies. Ginkgo biloba is one supplement that is commonly used in many countries for a range of conditions including memory loss and dementia prevention[2]. A number of reviews of the efficacy of Ginkgo biloba in treatment of dementia have been published; however, there is still no review of the efficacy of Ginkgo biloba for prevention of dementia in people without dementia. The aim of this study is to assess the efficacy and safety of Ginkgo biloba for prevention of dementia in a people without dementia.

Material and Method

Search strategy and study selection

Medline (1946-2013), Embase (1980-2013), Cochrane Library (2006-2013) and PsycINFO (2002-2013) were searched in all years up to September 2013. Search terms used consisted of two components: intervention [Ginkgo or Ginkgo$ or EGb761 or EGb?761 or Tanakan] and outcome [prevention or prevent$ or prophylaxis or dementia or Alzheimer$ or cognit$] with the limits: ["human(s)", "English language" and "clinical trial"]. Abstracts of the articles retrieved from search were read by the authors in order to exclude articles that are not eligible for inclusion criteria.

Correspondence to:
Charernboon T, Department of Psychiatry, Faculty of Medicine, Thammasat University (Rangsit Campus), Pathumthani 12120, Thailand.
Phone: +66-2-9269999
E-mail: dr.thammanard@gmail.com

Eligibility criteria

The authors included published studies with the following characteristics:

- Randomized double-blind controlled studies (RCT).
- Follow-up period of at least twelve months to ensure proper assessment of the protective effect.
- Investigation of population without dementia.
- Study outcome comparing Ginkgo biloba and placebo as prevention for dementia.

Data extraction and methodological quality assessment

Titles and abstracts of the articles were read independently by the authors (Charernboon T, Jaisin K) in order to exclude ineligible articles. Then, full-text articles of potentially relevant trials were obtained. The methodology quality of included trials was assessed

independently by Charernboon T, Jaisin K using the Jadad criteria[3]. Disagreements were resolved by author consensus.

Protocol and registration

This review was registered with the PROSPERO Centre for Reviews and Dissemination (the registration number is CRD42013006049).

Data analysis

The analyses were conducted on an intention-to-treat basis. The primary outcome was combined in a fixed-effect meta-analysis using the Mantel-Haenszel method. Statistical heterogeneity was assessed using the Chi^2 and I^2 statistics. All analyses were performed using RevMan 5.1 software (The Cochrane Collaboration).

Results

The electronic search identified 882 potentially relevant titles. Of these, 874 were excluded on the ground of irrelevance (Fig. 1). Eight trial reports were retrieved in full-text for further assessment. Then, six further articles were excluded (Table 1). There were two studies included in the study.

Description of included studies

In total, two studies were included in this review with the characteristics described in Table 2. All of them compared Ginkgo biloba extract to placebo in a multicenter, double-blind, parallel, randomized controlled trial with full inclusion and exclusion criteria given. The study durations were six years in DeKosky et al (2008)[10] (median = 6.1 years), and five years in Vellas et al (2012)[11] (median = 5.0). Both studies used the same treatment dose, Ginkgo biloba extract (EGb761) 240 mg/day, which is the recommended dosage based on the prior clinical studies.

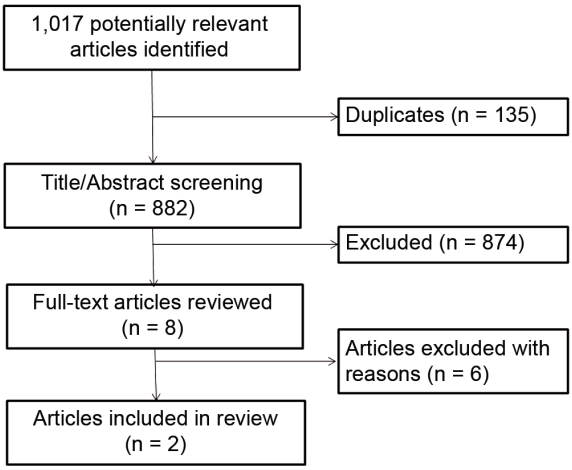

Fig. 1 Flow chart of study selection.

In DeKosky et al (2008)[10], participants were recruited from four US communities using voter registration records and mailing lists. In Vellas et al (2012)[11], participants were recruited throughout France by 712 primary care providers (PCPs) or by staff members at one of the 25 memory centers participating in the study. The mean age of participants was 79.1 years (SD 3.3) in DeKosky et al (2008)[10], and 76.3 (SD 4.4) in Vellas et al (2012)[11].

In both studies, information on cognitive function was available at the start of the study. The two studies either included normal cognitive function participants and mild cognitive impairment. In Dekosky et al (2008)[10], the percentage of participants who had mild cognitive impairment was lower than Vellas et al (2012)[11] (DeKosky et al (2008)[10]: 16.6% in Ginkgo biloba group, 14.8% in placebo group; Vellas et al (2012)[11]: 54% in Ginkgo biloba group, 53% in placebo group).

The primary efficacy end point in Dekosky et al (2008)[10] was the diagnosis of dementia by DSM-IV criteria as determined by an expert panel.

Table 1. Studies that were excluded from the analysis

Study	Reason for exclusion
Andrieu et al., 2003[4]	Case-control study
van Dongen et al., 2003[5]	Participants included dementia patients and age-associated memory impairment
Dodge et al., 2008[6]	Outcome was progression from CDR = 0 to CDR = 0.5
Baurle et al., 2009[7]	Outcomes limited to cognitive function only
Snitz et al., 2009[8]	Outcomes limited to cognitive function only
Amieva et al., 2013[9]	Cohort study

* CDR = the Clinical Dementia Rating

The primary outcome in Vella et al (2012)[11] was incidence of probable Alzheimer's disease according to DSM-IV and NINCDS-ADRDA criteria.

Assessment of risk of bias in included studies

The risk of bias was assessed in each included study. Both studies indicated a high-quality randomized controlled trial with a low risk of bias (see Table 3 for Jadad scores[3] of included studies). There were adequate generation of the randomization sequence, blinding technique and outcome reporting in two trials. Nevertheless, the loss to follow-up rate was low in DeKosky et al (2008)[10] (6.3%), but higher in Vellas et al (2012)[11] (25.8%).

Included studies funding

Vellas et al (2012)[11] was sponsored by Ipsen, Boulogne, France, which markets the Ginkgo biloba extract. DeKosky et al (2008)[10] was supported by grants from the National Center for Complementary and Alternative Medicine (NCCAM), the Office of Dietary Supplements and National Institute on Aging, National Heart, Lung, and Blood Institute, University of Pittsburgh Alzheimer's Disease Research Center, Wake Forest University School of Medicine, and National Institute of Neurological Disorders and Stroke. Schwabe Pharmaceuticals, Germany, donated the Ginkgo biloba tablets and placebos for the DeKosky et al[10] study.

Data and analysis

Effects of interventions

Table 4 shows the summary of events and dementia incidence rates of the two studies. In DeKosky et al (2008)[10], by 6 years, the overall incidence rate of dementia in participants assigned to Ginkgo biloba group was 3.3 per 100 person-years, and 2.9 per 100 person-years in the placebo group. The hazard ratio (HR) for Ginkgo biloba group compared with placebo group was 1.12 (95% CI 0.94-1.33, p = 0.21). Of the total dementia cases, 92% were classified as Alzheimer's disease or Alzheimer with vascular dementia (mixed dementia). The rate of Alzheimer-type and mixed dementia also did not differ between the two treatment groups (Ginkgo biloba: 3.0/100 person-years vs. placebo: 2.6/100 person-years; HR, 1.16; 95% CI, 0.97-1.39; p = 0.11). In subgroup analysis of participants with baseline normal cognition (n = 2,587), the rate of total dementia did not differ between Ginkgo biloba and placebo groups (2.16/100 and 2.25/100 person-years; HR 1.05 (0.84-1.30), p = 0.67).

Table 2. Characteristics of included studies (ordered by year)

Study	Study design	Duration	Participants	Intervention	Outcome
DeKosky et al., 2008[10]	Randomized double-blind	6 years	3,090 non-demented participants, age ≥75	1. Placebo 2. Ginkgo biloba extract, 240 mg/day	1. Incidence rate of all-cause dementia 2. Serious adverse events
Vellas et al., 2012[11]	Randomized double-blind	5 years	2,854 non-demented participants, age ≥70	1. Placebo 2. Ginkgo biloba extract, 240 mg/day	1. Incidence rate of Alzheimer's disease 2. Serious adverse events

Table 3. Quality assessment: Jadad scores

Study	Jadad scores			Total score
	Randomization	Double blinding	Withdrawals/drop-outs	
DeKosky et al., 2008[10]	2	2	1	5
Vellas et al., 2012[11]	2	2	1	5

Table 4. Summary of events and incidence rates comparing Ginkgo biloba with placebo

Study	Number of dementias/participants		Hazard ratio (95% CI)	p-value	Incidence rate (100 person-years)	
	Placebo	Ginko biloba			Placebo	Ginko biloba
DeKosky et al., 2008[10]	246/1,524*	277/1,545*	1.12 (0.94-1.33)	0.21	2.9	3.3
Vellas et al., 2012[11]	73/1,414**	61/1,406**	0.84 (0.60-1.18)	0.31	1.4	1.2

* All cause dementia, ** Alzheimer's disease

In Vellas et al (2012)[11], for the primary outcome, the Alzheimer-type dementia rate was 1.2 and 1.4 per 100 person-years in the Ginkgo biloba and placebo groups, respectively. The HR for Ginkgo biloba group compared with placebo group was 0.84 (95% CI 0.60-1.18, p = 0.31). Seventy participants receiving Ginkgo biloba were diagnosed with Alzheimer's disease or mixed dementia (1.4 per 100 person-years) compared with 84 participants receiving placebo (1.6 per 100 person-year). The between-group difference was also not significant (p = 0.267).

Meta-analysis

In order to estimate the efficacy of Ginkgo biloba for prevention of dementia, we used all cause dementia as events in DeKosky et al (2008)[10], and Alzheimer's disease or Alzheimer's with vascular dementia in Vellas et al (2012)[11].

The combined result of the two trials involving 5,889 participants indicated no significant difference in dementia rate between Ginkgo biloba and placebo (347/2,951 vs. 330/2,938, odds ratio = 1.05, 95% CI 0.89-1.23, p = 0.565; Fig. 2). There was no evidence of heterogeneity between the trials (Chi^2 = 2.66, df = 1, p = 0.10; I^2 = 62%).

Safety of Ginkgo biloba

The secondary outcome of this study included an examination of reported serious adverse effects. The combined result of the two studies showed no statistically significant differences in the rate of serious adverse effect. The mortality rate was similar in Ginkgo biloba and placebo groups (273/2,951 vs. 270/2,938, odds ratio = 1.0, 95% CI 0.84-1.20, p = 0.971, I^2 = 0%). There were also no differences in the incidence of total strokes (145/2,951 vs. 131/2,938, odds ratio = 1.11, 95% CI 0.87-1.41, p = 0.412, I^2 = 0%), cardiac disorders (552/2,951 vs. 558/2,938, odds ratio = 0.99, 95% CI 0.86-1.12, p = 0.817, I^2 = 0%) and total bleeding (286/2,951 vs. 304/2,938, odds ratio = 0.93, 95% CI 0.79-1.10, p = 0.409, I^2 = 0%).

Publication bias

There were insufficient data to investigate the presence of reporting bias using funnel plots.

Discussion

The objective of this meta-analysis was to determine the effect of Ginkgo biloba in preventing dementia. Two studies involving a total of 5,889 participants are included in this review. The analyses of the effect of Ginkgo biloba revealed no statistical difference in preventing dementia. Participants in both the control and intervention groups had similar incident rates of dementia. The results from the two studies confirm that Ginkgo biloba at dosage of 240 mg/day appears to be safe to use in an elderly population.

Three considerations that should be taken into account with respect to the generalizability, which are:

1) The trials included participants in very late life with mean ages of 76 and 79 years old which may not be applied to populations in middle age or early elderly.

2) The median follow-up times were 6.1 years in DeKosky et al (2008)[10] and 5.0 years in Vellas et al (2012)[11]. This gives rise to a concern about how long should humans need to take Ginkgo biloba in order for it to be effective for dementia prevention. In an animal study, for example, Augustin et al (2009)[12], Ginkgo biloba extract significantly lowered Amyloid precursor protein in mice, but with the duration of 16 months which is more than half of their life. Therefore, the question is whether an administration of Ginkgo biloba for a much longer period may increase its efficacy.

3) The two trials, especially Vellas et al (2012)[11], included many participants with mild cognitive impairment. Regarding the current knowledge of Alzheimer's disease, these participants are likely to have the pathology of Alzheimer's disease already but do not yet have full symptoms of dementia. This may lead to the ineffectiveness of the intervention. Despite DeKosky et al (2008)[10]'s subgroup analysis showing that Ginkgo biloba is also not effective for dementia

Fig. 2 Forest plot of comparison: incidence of dementia and number dementia cases.

prevention in pure participants with normal cognition, there is a concern that the sample size was only 2,587.

Conclusion

The findings of two high quality RCTs show that there is no benefit in preventing dementia from Ginkgo biloba in elderly people. Using it for this indication is not suggested at present. However, Ginkgo biloba at dosage of 240 mg/day appears to be safe to use in an elderly population.

Implications for research

Ginkgo biloba has not been shown to be effective in the prevention of dementia in randomized controlled trials. However, there were insufficient data in the existing trials to answer the following questions:

1) Whether the effect of Ginkgo biloba treatment in participants with normal cognition may differ from the previous studies.

2) Whether Ginkgo biloba treatment started in mid-life or in the early elderly may have an advantage over treatment started at the age of more than 70 years old.

3) Whether longer duration studies of Ginkgo biloba therapy may increase the ability to detect the possible benefits of Ginkgo biloba.

Limitation

Grey literatures and other unpublished resources were not searched for this article.

What is already known on this topic?

Ginkgo biloba is widely used for its potential effects on memory and cognition. To date, there is still no review of the efficacy of Ginkgo biloba for the prevention of dementia.

What this study adds?

There is no convincing evidence from this review that demonstrated Ginkgo biloba in late-life can prevent the development of dementia.

Acknowledgement

The present study received funding from a 2014 Grant from Faculty of Medicine, Thammasat University.

Contributors

Charernboon T designed the study, read and assessed the articles, analyzed the data, and wrote the manuscript. Jaisin K read and assessed the articles, and assisted with writing the manuscript. All authors have approved the final manuscript.

Potential conflicts of interest

None.

References

1. Prince M, Jackson J. Alzheimer's disease international: world alzheimer report 2009. London: Alzheimer's Disease International; 2009.
2. Qato DM, Alexander GC, Conti RM, Johnson M, Schumm P, Lindau ST. Use of prescription and over-the-counter medications and dietary supplements among older adults in the United States. JAMA 2008; 300: 2867-78.
3. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials 1996; 17: 1-12.
4. Andrieu S, Gillette S, Amouyal K, Nourhashemi F, Reynish E, Ousset PJ, et al. Association of Alzheimer's disease onset with Ginkgo biloba and other symptomatic cognitive treatments in a population of women aged 75 years and older from the EPIDOS study. J Gerontol A Biol Sci Med Sci 2003; 58: 372-7.
5. van Dongen M, van Rossum E, Kessels A, Sielhorst H, Knipschild P. Ginkgo for elderly people with dementia and age-associated memory impairment: a randomized clinical trial. J Clin Epidemiol 2003; 56: 367-76.
6. Dodge HH, Zitzelberger T, Oken BS, Howieson D, Kaye J. A randomized placebo-controlled trial of Ginkgo biloba for the prevention of cognitive decline. Neurology 2008; 70: 1809-17.
7. Baurle P, Suter A, Wormstall H. Safety and effectiveness of a traditional ginkgo fresh plant extract-results from a clinical trial. Forsch Komplementmed 2009; 16: 156-61.
8. Snitz BE, O'Meara ES, Carlson MC, Arnold AM, Ives DG, Rapp SR, et al. Ginkgo biloba for preventing cognitive decline in older adults: a randomized trial. JAMA 2009; 302: 2663-70.
9. Amieva H, Meillon C, Helmer C, Barberger-Gateau P, Dartigues JF. Ginkgo biloba extract and long-term cognitive decline: a 20-year follow-up population-based study. PLoS One 2013; 8: e52755.
10. DeKosky ST, Williamson JD, Fitzpatrick AL, Kronmal RA, Ives DG, Saxton JA, et al. Ginkgo

biloba for prevention of dementia: a randomized controlled trial. JAMA 2008; 300: 2253-62.
11. Vellas B, Coley N, Ousset PJ, Berrut G, Dartigues JF, Dubois B, et al. Long-term use of standardised Ginkgo biloba extract for the prevention of Alzheimer's disease (GuidAge): a randomised placebo-controlled trial. Lancet Neurol 2012; 11: 851-9.
12. Augustin S, Rimbach G, Augustin K, Schliebs R, Wolffram S, Cermak R. Effect of a short- and long-term treatment with Ginkgo biloba extract on amyloid precursor protein levels in a transgenic mouse model relevant to Alzheimer's disease. Arch Biochem Biophys 2009; 481: 177-82.

***Ginkgo biloba* สำหรับการป้องกันโรคสมองเสื่อม: การทบทวนวรรณกรรมอย่างเป็นระบบและการวิเคราะห์อภิมาน**

ธรรมนาถ เจริญบุญ, กันต์กมล จัยสิน

วัตถุประสงค์: *เพื่อศึกษาถึงประสิทธิภาพของ Ginkgo biloba ต่อการป้องกันการเกิดโรคสมองเสื่อม*
วัสดุและวิธีการ: *ทำการสืบค้นฐานข้อมูลอิเล็กทรอนิกส์ ได้แก่ Medline, Embase, Cochrane Library และ PsycINFO โดยทำการเลือกการศึกษาที่เป็นการทดลองเชิงวิจัยแบบสุ่มที่เปรียบเทียบระหว่าง Ginkgo biloba กับยาหลอกในการป้องกันโรคสมองเสื่อม โดยพบว่ามีสองการศึกษาที่ตรงกับเกณฑ์การคัดเลือกคุณภาพของวิธีศึกษาถูกประเมินโดยใช้ Jadad criteria*
ผลการศึกษา: *การวิเคราะห์อภิมานของสองการศึกษาซึ่งมีกลุ่มตัวอย่างรวม 5,889 ราย แสดงให้เห็นว่าไม่มีความแตกต่างอย่างมีนัยสำคัญในอัตราการเกิดโรคสมองเสื่อมระหว่าง Ginkgo biloba และยาหลอก (347/2,951 และ 330/2,938, odds ratio = 1.05, 95% CI 0.89-1.23) โดยไม่พบ heterogeneity จากทั้งสองการศึกษานี้ไม่พบความแตกต่างอย่างมีนัยสำคัญในการเกิดผลข้างเคียงที่รุนแรงระหว่าง Ginkgo biloba และยาหลอก*
สรุป: *ไม่พบหลักฐานที่น่าเชื่อได้ว่าการใช้ Ginkgo biloba ในผู้สูงอายุสามารถป้องกันโรคสมองเสื่อมได้ ดังนั้นจึงยังไม่แนะนำให้ใช้ Ginkgo biloba ด้วยข้อบ่งชี้นี้*