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COMPARISON OF THE DESIGN DIFFERENCES BETWEEN THE GINKGO EVALUATION OF MEMORY STUDY AND THE GUIDAGE STUDY

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Abstract: The epidemic of late life dementia, prominence of use of alternative medications and supplements, and initiation of efforts to determine how to prevent dementia have led to efforts to conduct studies aimed at prevention of dementia. The GEM (Ginkgo Evaluation of Memory) and GuidAge studies are ongoing randomized double-blind, placebo-controlled trials of Ginkgo biloba, administered in a dose of 120 mg twice per day as EGb761, to test whether Ginkgo biloba is effective in the prevention of dementia (and especially Alzheimer's disease) in normal elderly or those early cognitive impairment. Both GEM and GuidAge will also add substantial knowledge to the growing need for expertise in designing and implementing clinical trials to test the efficacy of putative disease-modifying agents for the dementias. While there are many similarities between GEM and Guidage, there are also significant differences. We present here the first comparative design and baseline data fromGEM and Guidage, two of the largest dementia primary prevention trials to date.

Introduction

Life expectancy for persons reaching age 50 has dramatically risen over the past century, making the maintenance of independence and prevention of disability a major clinical and public health priority.(1) Cognitive impairment in late life is a prevalent condition which significantly impacts independent function and disability. It also leads frequently to dementias such as Alzheimer's disease (AD) and vascular dementia (VaD), leading causes of long-term care placement.(1-4) Improved understanding of development of the basic pathophysiology of AD and the other major late-life dementias has led to interventions aimed at delaying or reducing the incidence of Alzheimer's and other dementias in older people.

Ginkgo biloba is derived from the fan-shaped, bi-lobed ("biloba") leaves of the Ginkgo tree, one of the planet's most ancient trees. Ginkgo biloba's popularity is such that Ginkgo leaf extract was the most commonly prescribed monotherapy in Germany during the 1990's and its use in the United States increased substantially following enactment of the United States Dietary Supplement Health and Education Act in 1994, legislation which enabled manufacturers to make structure and function claims for substances now labeled "dietary supplements" (plant products, amino acids, vitamins, minerals, etc.). This legislation also exempted Ginkgo and other supplements from the stringent requirements for demonstration of safety and efficacy required of prescription drugs prior to marketing.

Ginkgo biloba may act to reduce the rate of cognitive decline and dementia incidence in several ways. Probably the most documented effects of Ginkgo biloba are its antioxidant and free-radical scavenging activities. (5-10) Reduction of oxidative stress, which may accelerate the cascade of AD pathological changes leading to dementia and cerebrovascular disease is a major mechanism by which Ginkgo biloba is proposed to exert its effect. (11, 12) In addition, in vitro studies indicate that Ginkgo extract has an anti-amyloid aggregation effect, (13) suggesting another mechanism whereby Gingko biloba may be effective in preventing or delaying the development of AD. Ginkgo biloba extract has also been reported to modulate gene expression. (14) For example, it has been shown to increase transthyretin RNA levels in mouse hippocampus; transthyretin is part of the mechanism for A-beta transport and stimulation of this mechanism may also protect against amyloid deposition in brain. (15) Finally recent evidence suggests a fourth possible mechanism, a modulation of the role of Gingko on alpha secretase, the enzyme that cuts the amyloid precursor protein and prevents amyloidogenic fragments from being produced (16, 17).

Other evidence also suggests that Ginkgo biloba may be useful in preventing and treating cardiovascular and peripheral vascular disease, particularly ischemic heart disease and intermittent claudication, respectively. Given that free radicals play a significant destructive role in cardiac ischemic reperfusion, as with its cognitive effects, the most likely pathway for an effect on cardiovascular disease is through Ginkgo biloba's antioxidant and free-radical scavenging activities. In particular, the purported cardioprotective effects (18) of Ginkgo may be mediated through its nitric oxide scavenging ability and suppression of production of nitric oxide in a dose-dependent manner. (10, 19) These scavenger activities also appear to be the mechanism by which Ginkgo biloba reduces the post ischemic contractile dysfunction in an animal model of regional ischemia. (20) Other in vitro and in

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vivo effects of Ginkgo biloba that may impact on vascular disease include the ability to: 1) decrease platelet aggregation and thrombi formation (21, 22); 2) dilate blood vessels and improveme blood flow; (23-25) 3) reduce blood pressure; (26) and 4) prevent hypoxic damage (25, 27). Evidence suggests that both the terpnoid and flavonoid components of Ginkgo biloba are necessary to achieve maximum cardioprotection (28). Several clinical trials investigating Ginkgo biloba's effect on intermittent claudication along with a meta-analysis of these trials suggested that oral Ginkgo biloba may be efficacious for symptomatic treatment of intermittent claudication but the authors concluded that a large, definitive trial is necessary (29). These same mechanisms may also act to reduce cognitive decline and dementia related to vascular disease.

Despite these purported pharmacological effects and a large meta-analysis of treatment trials (30) suggesting the possible effectiveness of Ginkgo biloba in reducing cognitive decline and dementia in older people, there have been no adequately powered clinical trials demonstrating Ginkgo biloba's ability to reduce the incidence of cognitive decline, dementia, or heart disease.

Trials to determine the effectiveness of interventions to prevent dementia are expensive, and of long duration. Clinical trial experience in recruitment, treatment adherence, subject retention, and thorough cognitive outcome assessment is sparse. Most studies addressing primary prevention of dementia have been added on to larger clinical trials as secondary outcomes. Recent examples include the Women's Health Initiative (WHI) Memory Study (WHIMS) (31) and the Action to Control Cardiovascular Risk in Diabetes-Memory in Diabetes trial (32). Currently there are only a handful of prevention trials underway, two of which are the current Ginkgo Evaluation of Memory (GEM) Study in the United States and the GuidAge study in France. Both are randomized, double-blind trials, and each has successfully completed recruitment of their target cohort (GEMS n = 3,072, GuidAge n = 2,854). This paper compares the designs of the GEM and GuidAge studies, characteristics of the recruited cohorts and the primary and secondary outcomes of the trials.

Design

Subject Recruitment In Gem And Guidage

In GEM, volunteers age 75 years or older were recruited from 4 communities affiliated with academic medical centers in the United States: Hagerstown, Maryland (Johns Hopkins); Pittsburgh, Pennsylvania (University of Pittsburgh); Sacramento, California (University of California, Davis); Winston-Salem, North Carolina (Wake Forest University). In GuidAge participants age 70 years and older with a memory complaint were recruited from multiple communities in France through a private practice/hospital network of general practitioners and hospital practitioners specializing in memory disorders. In both trials, volunteer participants provided informed consent prior to a medical and cognitive assessment screen. Persons with prevalent dementia were excluded from each trial. The inclusion and exclusion criteria for each trial (Table 1) have been described elsewhere. (33-35), as are the specific design and recruitment of the trials.

Table 1
Inclusion and exclusion criteria for the GEM

Criteria	Description	GEM	GuidAge
Inclusion	Non-demented or mild cognitive impairment	X	
	Must have spontaneous memory complaint		X
	≥ 75 years of age	X	
	≥ 70 years of age		X
	Identify a person who will serve as a proxy	X	X
Exclusion	Meets DSM-IV criteria for dementia	X	X
	CDR score > 0.5	X	X
	Currently taking the anti-coagulant warfarin (Coumadin)	X	
	Taking donepezil (or similar agents) for cognitive problems or dementia	X	X
	Unwilling to discontinue taking over-the-counter (OTC) Ginkgo biloba, beginning at screening visit and for the duration of the study	X	X
	Currently being treated with tricyclic antidepressants, antipsychotics or other medications with significant psychotropic effects	X	X
	Use of greater than 400 IU vitamin E/day	X	
	History of bleeding disorders	X	
	Hospitalized for depression within the last year or ECT within last 10 years	X	X
	COVI Anxiety Scale ≥ 6		X
	History of Parkinson's disease or taking antiparkinson's medications	X	X
	Any cancer or diagnosed disease with live expectancy < 5 years	X	X
	Congestive heart failure with disability	X	
	Baseline abnormal thyroid studies, blood creatinine: > 2.0 mg/dL;gamma gGT, ALT and AST U/L (2 × ULN = 90 IU)	X	
	Baseline B12 levels ≤< 210 pg/mL, hematocrit < 30%, white blood count < 3000 or > 15,000/cmm		
	Platelet count < 100,000 or > 600,000 K/cmm	X	
	Allergy to Ginkgo biloba	X	X

Table 2
Neuropsychological Domain Analysis

DOMAIN	GEMS	GUIDAGE
Estimated verbal IQ	National Adult Reading Test—American Version Raven's Coloured Progressive Matrices	Determination of sociocultural level
Memory (subjective complaint)	NA	Mac Nair Scale Visual analogue scale
Memory (Testing)	California Verbal Learning Test	Free and Cued Selective Reminding Test (Grober and Buschke test)
	Delayed Recall Rey-Osterrieth Modified Figure WAIS-R	
Working Memory	WAIS-R Digit Span Backwards	NA
Construction	Block Design (Modified) Rey-Osterrieth Modified Figure	NA
Language	Boston Naming Test (30-item Version) Word Generation (Verbal Fluency)	Verbal fluency
Attention / Psychomotor speed	Trail Making Part A WAIS-R Digit Span Forwards	TMT-part A
Executive functions	Trail Making Part B Stroop Color/Word Test	TMT-part B
Global cognitive function	3MSE and ADAS	MMSE
Global Rating	CDR	CDR
Other Scales		
Proxy assessment	PQCODE	
Depression	CES-D	GDS
Anxiety	N/A	Covi scale (anxiety)

Specific ginkgo biloba preparation used

In both clinical trials, enrolled participants were randomized to either 120 mg Ginkgo biloba extract (EGb761; Schwabe Pharmaceuticals, Karlsruhe, Germany) or an identical appearing placebo, twice per day. The 240 mg dose of EGb 761 was chosen because of the availability of the results of clinical studies using this dose in dementias (36, 37)

Cognitive assessment procedures and batteries

GEM

The components of the assessment batteries for each trial are shown in Table 2. In GEM, participants receive cognitive and medical assessments every 6 months with an additional phone contact at 3 months between each in person 6-month assessment. Adherence and compliance assessments were done at every visit. Decline on a cognitive screening battery leads to a more extensive evaluation including more detailed neuropsychological testing, neurological consultation, MRI scan, and other diagnostic studies. These results are used to confirm a diagnosis of dementia (study end point reached) and subsequently consensus diagnosis of a specific dementia type. Beginning in Year 4 in GEM, all subjects received the detailed neuropsychological battery once annually, regardless of performance on the screening battery.

GuidAge

In GuidAge, participants are scheduled every 3 months with their primary care physician to assess physical condition, diseases and corresponding treatments, adherence to and tolerance of treatment, and to deliver the medication. In addition, visits are scheduled every 12 months to the hospital memory center for administration of a battery of cognitive function tests and assessment for incident dementia.

Study Outcomes

GEM

The primary outcome of the study is the incidence rate of all-cause dementia, which was predicted to decrease following G. biloba administration. The incidence of AD was also predicted to decrease.

At follow-up visits, participants are all administered a battery composed of the Modified Mini-Mental State Examination) 3MSE, the Clinical Dementia Rating Scale (CDR)(38) or the cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS) (39). Participants who declined a certain number of points from their study entry scores on two of three tests are required to undergo complete administration of the full NPB. Participants are then considered to have possibly reached dementia endpoint according to the GEM Neuropsychological Battery (NPB) if any of the following apply:

1. Incident abnormal scores on five or more tests with at least one of the abnormal scores being on a memory test.
2. Incident abnormal scores on four tests, at least one of the abnormal scores is on a memory test, and the participant failed to complete one or more of the other neuropsychological tests.
3. Incident abnormality in two or more cognitive domains (subject scored below cutoff for age- and education-adjusted norms in both tests of that domain) and one of those domains is memory.

Table 3
Pre-specified Outcomes

	GEMS	GUIDAGE
PRIMARY	Dementia: All cause and Alzheimer's type	Dementia: all cause and Alzheimer's type
SECONDARY	Rate of Cognitive Decline Rate of Functional Decline Incident Cardiovascular Disease Incident Stroke Mortality	Rate of Cognitive Decline Rate of Functional Decline Falls , one leg balance Age-related Macular Degeneration Sarcopenia Mortality

In addition to algorithmic failure of the preliminary battery, participants were also readministered the full NPB if the participant or family reported the onset of a new memory or other cognitive problem, or if in the intervening six months there was a diagnosis of dementia by a private physician, or the participant initiated a medication for a memory or cognitive problem such as donepezil (Aricept), rivastigmine (Exelon), galantamine (Reminyl/Razadyne) or memantine (Namenda). Additionally, in instances where the participant's scores on the NPB have declined noticeably from baseline but have not fully reached the change criteria that would trigger an NPB evaluation, as above, the Cognitive Diagnostic Center (CDC) neuropsychologist will review the chart for determination of whether the battery should be administered anyway. The CDC neuropsychologist may refer the participant's case to the CDC for adjudication if:

1. The participant has abnormal scores on three tests, one is in memory and two or more tests are missing or incomplete and these tests were successfully completed at baseline.
2. The participant has abnormal scores on five or more tests, none are in memory and there are a higher number of impaired tests than at baseline.

For some participants with decline on NPB scores, continued follow-up, instead of classification to dementia endpoint, may be recommended by the CDC neuropsychologist or the adjudication committee. Reasons for continuation include performance worsened due to temporary illness producing missing values on parts of the test battery, macular degeneration impairing the ability to complete visual tests, or incident, untreated depression. In these cases, continued follow-up is maintained until there is clear evidence of decline on a broad range of tests not limited to sensory impairment or to worsened medical illness.

Because lack of awareness of one's own cognitive deficits (anosoagnosia) is common in subjects with dementia, (40) GEM required that each participant identify a proxy (informant) and consent to assessment of the subject's cognitive and functional status throughout the study. At screening, the Dementia Questionnaire DQ (41) was used. The Informant Questionnaire for Cognitive Decline in the Elderly (IQCode) (42) was given to the proxy at each 6-month visit. The CDR also has a component that includes assessment of the participant's functional and cognitive capacity by the proxy. If a proxy is no longer willing or able to continue that role, a new proxy is designated by the participant for subsequent visits. Proxies had requirements for minimal hours of contact with the subject to assure their ability to adequately assess the subjects' cognition and function, as well as any changes over time.

GuidAge

The primary outcome in Guidage is conversion to dementia. GuidAge assesses cognitive function in both the general practice (from where participants were originally recruited) and the hospital memory clinic setting. If, in the context of general medical care, the participant's general practitioner notes initial signs of cognitive decline, the subject is referred to the memory clinic. Additionally, the GuidAge memory clinics investigate cognitive function at annual study visits using a battery of neuropsychological tests including the Grober and Buschke test, the Mini Mental State Examination (MMSE), the Clinical Dementia Rating (CDR) scale, the Inventory of Activities of Daily Living (IADL), verbal fluency, and the Trail Making Test (TMT). (38, 43-47)

Once a Guidage Memory Clinic confirms a high suspicion of conversion to dementia, the participant undergoes an additional standard evaluation to establish the diagnosis according to the recommendations of ANAES (French Agency for Medical Evaluation and Recommendations, French Ministry of Health) and as defined by the Diagnostic and Statistical Manuel of Mental Disorders fourth edition (DSM-IV), the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer Disease and Related Disorders Association (NINCDS-ADRDA), and the National Institute for Neurological Disorders and Stroke with the Association Internationale pour la Recherche et l'enseignement en Neurosciences (NINDS-AIREN). The full component of clinical and test results are then referred to an independent adjudication committee, composed of four clinicians not connected with the study, which confirms the conversion to dementia and makes a final diagnosis of the specific type of dementia. In the event of disagreement, the committee may request further information from the neurologist or the memory specialist. or, as in GEM, the participant may be seen again 6

Table 4
Selected baseline characteristics of GEM and GuidAge study participants

	GEMS	GuidAge
Characteristic	N or mean (% or S.D.)	N or mean (% or S.D.)
Number of participants	3072	2854
Women (%)	46.2	66.7%
Self-perceived general health		N/A
Age	78.62 (SD 3.3)	76.8 (4.4)
75–79 years	2031 (66.1)	
80–84 years	850 (27.7)	
85 and older	191 (6.2)	
Race		
White	2933 (95.5)	N/A
Non-White	139 (4.5)	N/A
Excellent	292 (9.5)	N/A
Very good	1238 (40.3)	N/A
Good	1316 (42.9)	N/A
Fair	203 (6.6)	N/A
Poor	7 (0.2)	N/A
History of "heart attack"	300 (9.8)	
Hypertension	1305 (42.9)	
Diabetes	278 (9.1)	
Difficulty with any ADLs	544 (17.7)	792 (27.8%)
Blood pressure (mm Hg)		
Systolic	133.0 (18.4)	134.8 (11.4)
Diastolic	68.9 (9.9)	77.1 (7.2)
Smoking status		
Never	1225 (40.2)	2097 (73.7%)
Former	1642 (53.9)	657 (23.1%)
MMSE Score (0-30)	N/A	27.8 (1.7)
3MSE score (0–100)	93.3 (4.7)	N/A

months later by the GuidAge Memory Clinic neurologist and the memory specialist. Data on a final diagnosis of dementia are entered for analysis only after validation by the committee.

Additional outcome measures

Primary and secondary endpoints for both GEM and GuidAge are shown in Table 3. Both studies assess additional cognition-related outcomes. In addition, GuidAge is examining the possible effect of EGB 761 on macular degeneration and on number of falls, while GEM secondary outcomes include functional decline and the incidence of cardiovascular and cerebrovascular events. Both studies will track total mortality by group.

Results

Baseline characteristics of participants in each study

Selected baseline characteristics for each clinical trial including age, gender and race, are provided in Table 4. Study participants in GEM were predominantly white, 54% male and 65–70% of the participants were between 75 and 79 years of age. Self-reported health and selected co-morbid conditions as well as results of clinical characteristics at baseline in each study cohort are also presented in Table 4. For GEM, almost 80% of the cohort described their health as 'good' or 'very good'. Hypertension was present in 43% of the cohort; almost 18% described a difficulty with at least one ADL. Only 4.5% of the cohort described themselves as active smokers, although over 50% described themselves as former smokers. The mean 3MS score for the GEM cohort was 93.3 (SD 4.7) .

Discussion

The GEM and GuidAge trials are the only adequately powered trials to date that address the question of Ginkgo biloba's efficacy in preserving cognitive function and preventing dementia. GEM will end in 2008 and Guidage in 2010 and, while these trials have many similarities, there are some significant differences. These differences are primarily due to eligibility criteria and recruitment strategies. Because of higher age cutoffs, GEM participants are slightly older. GuidAge targeted for recruitment persons from within multiple primary care practices throughout France, a significantly different approach from GEM's recruitment focus on volunteers from four US communities. Probably as a result of recruiting older adults from the health care practice setting versus the community, the Guidage cohort reported more functional impairment at baseline as measured by Activities of Daily Living. Although the cognitive profiles of two cohorts appear to be similar, what will be of particular interest in the future is whether the rates of cognitive change and dementia incidence differ between the two populations. The GEM Study follow-up

period was extended previously due to a lower than precicted dementia incidence but it may be that the GuidAge cohort's poorer baseline functional status may be associated with an increased likelihood of cognitive decline.

While both trials include similar prespecified cognitive decline, functional decline and dementia outcomes, there are major differences in the prespecified secondary outcomes. Cardiovascular disease, stroke, peripheral vascular disease are prespecified in GEM but falls, balance, macular degeneration and sarcopenia are prespecified secondary outcomes in GuidAge. The two trials will also be able to assess for a spectrum of possible Ginkgo biloba side effects as well as address the widely held but unproven hypothesis that Ginkgo biloba causes increased bleeding. Although both studies included persons on aspirin, only GuidAge included persons on other anticoagulants which will allow for testing for any interactions between Ginkgo and anticoagulants such as warfarin that may increase bleeding risk.

Summary

Translation of basic research to help in the prevention of chronic diseases and conditions ultimately depends on clinical trials in humans who are at increased risk for experiencing the outcome(s) of interest. This has been the pathway to progress for all major public health efforts aimed at decreasing morbidity and mortality for infectious diseases, cancer, cardiovascular disease, hyperlipidemia, hypertension, stroke and other disorders. Only in the past several years has progress in the basic mechanisms of dementia research allowed for consideration of testing promising interventions that might prevent dementia. The serial assessment of cognitive status of the large GEM and GuidAge cohorts will enable us to determine the potential effects of G. biloba on the primary and secondary outcomes of this trial. In addition, the data from these trials will provide valuable insights into normal rates of cognitive decline in late life, the relationships between physical and cognitive function and the possible interactions between comorbidity and cognitive function. Of equal importance, the GuidAge and GEM clinical trials will also provide a wealth of other data related to the future design and conduct of dementia prevention trials and clinical trials in the very old that will be necessary for evaluating the next generation of experimental medications in this growing population.

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References

1. Guralnik JM, Leveille SG, Hirsch R, Ferrucci L, Fried LP. The impact of disability on older women. JAMWA 1997;52(3):113-120.
2. guero-Torres H, Fratiglioni L, Guo Z, Viitanen M, von SE, Winblad B. Dementia is the major cause of functional dependence in the elderly: 3-year follow-up data from a population-based study. Am J Public Health 1998 Oct;88(10):1452-1456.
3. Magsi H, Malloy T. Underrecognition of cognitive impairment in assisted living facilities. J Am Geriatr Soc 2005 Feb;53(2):295-298.
4. National Institute on Aging. Progress Report on Alzheimer's Disease. Bethesda, MD: U.S. Department of Health and Human Services, Public Health Service; 2000. Report No.: NIH Publication no. 00-4859.
5. Haines DD, Bak I, Ferdinandy P, et al. Cardioprotective effects of the calcineurin inhibitor FK506 and the PAF receptor antagonist and free radical scavenger, EGb 761, in isolated ischemic/reperfused rat hearts. J Cardiovasc Pharmacol 2000 Jan;35(1):37-44.
6. Pietri S, Maurelli E, Drieu K, Culcasi M. Cardioprotective and anti-oxidant effects of the terpenoid constituents of Ginkgo biloba extract (EGb 761). J Mol Cell Cardiol 1997 Feb;29(2):733-742.
7. Pietri S, Maurelli E, Drieu K, Culcasi M. Cardioprotective and anti-oxidant effects of the terpenoid constituents of Ginkgo biloba extract (EGb 761). J Mol Cell Cardiol 1997 Feb;29(2):733-742.
8. Robak J, Gryglewski RJ. Flavonoids are scavengers of superoxide anions. Biochem Pharmacol 1988 Mar 1;37(5):837-841.
9. Tosaki A, Engelman DT, Pali T, Engelman RM, Droy-Lefaix MT. Ginkgo biloba extract (EGb 761) improves postischemic function in isolated preconditioned working rat hearts. Coron Artery Dis 1994 May;5(5):443-450.
10. Varga E, Bodi A, Ferdinandy P, Droy-Lefaix MT, Blasig IE, Tosaki A. The protective effect of EGb 761 in isolated ischemic/reperfused rat hearts: a link between cardiac function and nitric oxide production. J Cardiovasc Pharmacol 1999 Nov;34(5):711-717.
11. Christen Y. Oxidative stress and Alzheimer disease. Am J Clin Nutr 2000 Feb;71(2):621S-629S.
12. Simonian NA, Coyle JT. Oxidative stress in neurodegenerative diseases. Annu Rev Pharmacol Toxicol 1996;36:83-106.
13. Luo Y, Smith JV, Paramasivam V, et al. Inhibition of amyloid-beta aggregation and caspase-3 activation by the Ginkgo biloba extract EGb761. Proc Natl Acad Sci U S A 2002 Sep 17;99(19):12197-12202.
14. Rimbach G, Wolffram S, Watanabe C, Packer L, Gohil K. Effect of Ginkgo biloba (EGb 761) on differential gene expression. Pharmacopsychiatry 2003 Jun;36 Suppl 1:S95-S99.
15. Watanabe CM, Wolffram S, Ader P, et al. The in vivo neuromodulatory effects of the herbal medicine ginkgo biloba. Proc Natl Acad Sci U S A 2001 Jun 5;98(12):6577-6580.
16. Bastianetto S, Ramassamy C, Dore S, Christen Y, Poirier J, Quirion R. The Ginkgo biloba extract (EGb 761) protects hippocampal neurons against cell death induced by beta-amyloid. Eur J Neurosci 2000 Jun;12(6):1882-1890.
17. Brunetti L, Orlando G, Menghini L, Ferrante C, Chiavaroli A, Vacca M. Ginkgo biloba leaf extract reverses amyloid beta-peptide-induced isoprostane production in rat brain in vitro. Planta Med 2006 Nov;72(14):1296-1299.
18. Mahady GB. Ginkgo biloba for the prevention and treatment of cardiovascular disease: a review of the literature. J Cardiovasc Nurs 2002 Jul;16(4):21-32.
19. Marcocci L, Maguire JJ, Droy-Lefaix MT, Packer L. The nitric oxide-scavenging properties of Ginkgo biloba extract EGb 761. Biochem Biophys Res Commun 1994 Jun 15;201(2):748-755.
20. Rioufol G, Pietri S, Culcasi M, et al. Ginkgo biloba extract EGb 761 attenuates myocardial stunning in the pig heart. Basic Res Cardiol 2003 Feb;98(1):59-68.
21. Huang SY, Jeng C, Kao SC, Yu JJ, Liu DZ. Improved haemorrheological properties by Ginkgo biloba extract (Egb 761) in type 2 diabetes mellitus complicated with retinopathy. Clin Nutr 2004 Aug;23(4):615-621.
22. Koltringer P, Langsteger W, Klima G, Reisecker F, Eber O. [Hemorheologic effects of ginkgo biloba extract EGb 761. Dose-dependent effect of EGb 761 on microcirculation and viscoelasticity of blood]. Fortschr Med 1993 Apr 10;111(10):170-172.
23. Auguet M, DeFeudis FV, Clostre F. Effects of Ginkgo biloba on arterial smooth muscle responses to vasoactive stimuli. Gen Pharmacol 1982;13(2):169-171.
24. Chen X, Salwinski S, Lee TJ. Extracts of Ginkgo biloba and ginsenosides exert cerebral vasorelaxation via a nitric oxide pathway. Clin Exp Pharmacol Physiol 1997 Dec;24(12):958-959.
25. Haramaki N, Aggarwal S, Kawabata T, Droy-Lefaix MT, Packer L. Effects of natural antioxidant ginkgo biloba extract (EGB 761) on myocardial ischemia-reperfusion injury. Free Radic Biol Med 1994 Jun;16(6):789-794.
26. Sasaki Y, Noguchi T, Yamamoto E, et al. Effects of Ginkgo biloba extract (EGb 761) on cerebral thrombosis and blood pressure in stroke-prone spontaneously hypertensive rats. Clin Exp Pharmacol Physiol 2002 Nov;29(11):963-967.
27. Fitzl G, Welt K, Schaffranietz L. Myocardium-protective effects of Ginkgo biloba extract (EGb 761) in old rats against acute isobaric hypoxia. An electron microscopic morphometric study. I. Protection of cardiomyocytes. Exp Toxicol Pathol 1996

Jan;48(1):33-39.
28. Liebgott T, Miollan M, Berchadsky Y, Drieu K, Culcasi M, Pietri S. Complementary cardioprotective effects of flavonoid metabolites and terpenoid constituents of Ginkgo biloba extract (EGb 761) during ischemia and reperfusion. Basic Res Cardiol 2000 Oct;95(5):368-377.
29. Pittler MH, Ernst E. Ginkgo biloba extract for the treatment of intermittent claudication: a meta-analysis of randomized trials. Am J Med 2000 Mar;108(4):276-281.
30. Birks J, Grimley EV, Van DM. Ginkgo biloba for cognitive impairment and dementia. Cochrane Database Syst Rev 2002;(4):CD003120.
31. Shumaker SA, Legault C, Rapp SR, et al. Estrogen plus progestin and the incidence of dementia and mild cognitive impairment in postmenopausal women: the Women's Health Initiative Memory Study: a randomized controlled trial. JAMA 2003 May 28;289(20):2651-2662.
32. Williamson JD, Miller ME, Bryan RN, et al. The Action to Control Cardiovascular Risk in Diabetes Memory in Diabetes Study (ACCORD-MIND): rationale, design, and methods. Am J Cardiol 2007 Jun 18;99(12A):112i-122i.
33. Dekosky ST, Fitzpatrick A, Ives DG, et al. The Ginkgo Evaluation of Memory (GEM) study: design and baseline data of a randomized trial of Ginkgo biloba extract in prevention of dementia. Contemp Clin Trials 2006 Jun;27(3):238-253.
34. Fitzpatrick AL, Fried LP, Williamson J, et al. Recruitment of the elderly into a pharmacologic prevention trial: the Ginkgo Evaluation of Memory Study experience. Contemp Clin Trials 2006 Dec;27(6):541-553.
35. Vellas B, Andrieu S, Ousset PJ, Ouzid M, Mathiex-Fortunet H. The GuidAge study: methodological issues. A 5-year double-blind randomized trial of the efficacy of EGb 761 for prevention of Alzheimer disease in patients over 70 with a memory complaint. Neurology 2006 Nov 14;67(9 Suppl 3):S6-11.
36. Kanowski S, Herrmann WM, Stephan K, Wierich W, Horr R. Proof of efficacy of the ginkgo biloba special extract EGb 761 in outpatients suffering from mild to moderate primary degenerative dementia of the Alzheimer type or multi-infarct dementia. Pharmacopsychiatry 1996 Mar;29(2):47-56.
37. Maurer K, Ihl R, Dierks T, Frolich L. Clinical efficacy of Ginkgo biloba special extract EGb 761 in dementia of the Alzheimer type. J Psychiatr Res 1997 Nov;31(6):645-655.
38. Morris JC. The Clinical Dementia Rating (CDR): current version and scoring rules. Neurology 1993 Nov;43(11):2412-2414.
39. Rosen WG, Mohs RC, Davis KL. A new rating scale for Alzheimer's disease. Am J Psychiatry 1984 Nov;141(11):1356-1364.
40. Lopez OL, Becker JT, Somsak D, Dew MA, Dekosky ST. Awareness of cognitive deficits and anosognosia in probable Alzheimer's disease. Eur Neurol 1994;34(5):277-282.
41. Kawas C, Segal J, Stewart WF, Corrada M, Thal LJ. A validation study of the Dementia Questionnaire. Arch Neurol 1994 Sep;51(9):901-906.
42. Jorm AF, Korten AE. Assessment of cognitive decline in the elderly by informant interview. Br J Psychiatry 1988 Feb;152:209-213.
43. Cardebat D, Doyon B, Puel M, Goulet P, Joanette Y. [Formal and semantic lexical evocation in normal subjects. Performance and dynamics of production as a function of sex, age and educational level]. Acta Neurol Belg 1990;90(4):207-217.
44. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975 Nov;12(3):189-198.
45. Grober E, Buschke H, Crystal H, Bang S, Dresner R. Screening for dementia by memory testing. Neurology 1988 Jun;38(6):900-903.
46. Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental activities of daily living. Gerontologist 1969;9(3):179-186.
47. Reitan RM. The relation of the trail making test to organic brain damage. J Consult Psychol 1955 Oct;19(5):393-394.