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ORIGINAL RESEARCH

Efficacy and safety of *Ginkgo biloba* standardized extract in the treatment of vascular cognitive impairment: a randomized, double-blind, placebo-controlled clinical trial

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Objectives: The aim of this randomized, double-blind, placebo-controlled trial was to determine the efficacy and safety of *Ginkgo biloba* extract in patients diagnosed with vascular cognitive impairment (VCI).

Methods: A total of 90 patients (aged 67.1±8.0 years; 59 women) were randomly allocated (1:1:1) to receive *G. biloba* 120 mg, *G. biloba* 60 mg, or placebo during a 6-month period. Assessment was made for efficacy indicators, including neuropsychological tests scores (Sandoz Clinical Assessment Geriatric Scale, Folstein Mini-Mental State Examination, Mattis Dementia Rating Scale, and Clinical Global Impression) and transcranial Doppler ultrasound findings. Safety indicators included laboratory findings, reported adverse reactions, and clinical examination.

Results: At the end of 6-month study period, *G. biloba* 120 and 60 mg showed a statistically significant positive effect in comparison with placebo only on the Clinical Global Impression score (2.6±0.8 vs 3.1±0.7 vs 2.8±0.7, respectively; P=0.038). The Clinical Global Impression score showed a significant deterioration from the baseline values in the placebo group (−0.3±0.5; P=0.021) as opposed to *G. biloba* groups. No significant differences were found in the transcranial Doppler ultrasound findings. Adverse reactions were significantly more common and serious in the placebo group (16 subjects) than in either of the two *G. biloba* extract groups (eight and nine subjects, respectively), whereas laboratory findings and clinical examinations revealed no differences between the groups receiving *G. biloba* extract and placebo.

Conclusion: According to our results, *G. biloba* seemed to slow down the cognitive deterioration in patients with VCI, but the effect was shown in only one of the four neuropsychological tests administered. However, because of this mild effect in combination with a few adverse reactions, we cannot say that it is ineffective or unsafe either. Further studies are still needed to provide unambiguous evidence on the efficacy and safety of *G. biloba* extract.

Keywords: *Ginkgo biloba*, vascular cognitive impairment, dementia

Introduction

Ginkgo biloba leaf extracts have been used in medicine for centuries. The active ingredients responsible for its beneficial effect are flavonol glycosides and terpenoids.[1] *G. biloba* is suggested for use in Alzheimer's dementia, vascular cognitive impairment (VCI), vertigo, and tinnitus.[2–8] In symptomatic treatment of Alzheimer's dementia, *G. biloba* extract shows effect over a limited period of time in some patients and has fewer adverse reactions than donepezil, galantamine, or rivastigmine.[2] Clinical studies with *G. biloba* (EGb 761) in

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patients with dementia indicate that it stabilizes or slows down the decline in mental function, particularly in patients with neuropsychiatric symptoms.[9–12] Cieza et al[13] showed a favorable effect of *G. biloba* on mental health and quality of life in healthy volunteers aged >50 years.

Mechanisms of the action of *G. biloba* are complex, and its pharmacological effects include antioxidant activity as a free radical-scavenger, capillary fragility reduction,[14,15] antagonization of the platelet activating factor,[16] and modification of energy metabolism, particularly during hypoxia.[17] Moreover, *G. biloba* enhances cerebral and vestibular blood flow and protects neurons from oxidative damage.[18] A recent preclinical study showed the effect of *G. biloba* extract on the structure of the cornu ammonis in aged rats, thus providing a neuroanatomical basis for memory improvement.[19]

VCI is a broad spectrum of syndromes ranging from mild cognitive impairment to dementia, which are influenced by risk factors for cerebrovascular disease.[20] Cerebrovascular aging can lead to the loss of the integrity of the blood–brain barrier, eventually resulting in cognitive and sensorimotor decline. Two major types of cognitive dysfunction due to chronic cerebral hypoperfusion are VCI and dementia.[21] Also, the term VCI has sometimes been used in literature to denote a mild cognitive impairment due to cerebrovascular insufficiently severe to be diagnosed as dementia.[22]

The aim of our study was to determine the efficacy and safety of *G. biloba* in comparison with placebo in patients with VCI.

Patients and methods

Study design

This was a 6-month, randomized, double-blind, placebo-controlled, parallel-group clinical trial conducted in a single center in Zagreb, Croatia. The study protocol was approved by the Local Ethics Committee of Sestre Milosrdnice University Hospital, and the study was registered with ClinicalTrials.gov (NCT00446485) before the start of patient enrollment.

Patients

The study included 90 patients presenting with VCI symptoms at the Outpatient Clinic of the Department of Neurology of "Sestre Milosrdnice" University Hospital from May 2007 to April 2010. The inclusion criteria were as follows: age ≥50 years; fulfilled VCI criteria based on cerebrovascular insufficiency and Folstein Mini-Mental State Examination (MMSE) score of >20 and ≤28; completed initial screening; for women, postmenopause or use of contraception; and signed written informed consent was received from all participants before participation.

The exclusion criteria included symptoms caused by psychiatric, metabolic, endocrine, nutritional, or heart disease; epilepsy, liver or kidney failure, uncontrolled diabetes mellitus, or hypertension; malignancy; history of myocardial infarction in the previous 6 months; alcohol or drug abuse; use of the following drugs: ticlopidine, clopidogrel, pentoxifylline, acetylsalicylic acid, dihydroergotamine, warfarin, and/or etibiskumacetate; and a positive pregnancy test in women.

The subjects were withdrawn from the study if they developed newly diagnosed psychiatric disease, acute myocardial infarction, resistant hypertension or diabetes mellitus, liver or kidney failure, alcohol or drug abuse, or serious adverse reaction during the course of the study. They could also be withdrawn at their own request or at the investigator's or sponsor's request (eg, noncompliance, lost to follow-up, consent withdrawal, and so on).

Screening

At the beginning of the study, the subjects underwent an initial screening assessment. The physician recorded patient demographic data, the presence or absence of inclusion/exclusion criteria, blood pressure, heart rate, respiratory rate, body temperature, weight and height, smoking habit, physical examination findings and concomitant diseases, symptoms and signs, and concomitant medications. The subjects also underwent a brain computed tomography scan, routine laboratory testing (erythrocyte sedimentation rate [ESR], complete blood cell count [CBC], blood glucose, urea, creatinine, transaminases, bilirubin, sodium, potassium, chlorides, high-density lipoproteins [HDL], low-density lipoproteins [LDL] triglycerides, activated partial thromboplastin time [APTT]), and prothrombin time, electrocardiogram (ECG), carotid and vertebral arteries ultrasound (CAVA), transcranial duplex ultrasound (TCD), and a neuropsychological test battery consisting of Sandoz Clinical Assessment Geriatric Scale (SCAG), MMSE, Mattis Dementia Rating Scale (MDRS), and Clinical Global Impression Scale (CGI).

Intervention

The study drug was a *G. biloba* extract in the form of a tablet containing 60 mg of dry extract of *G. biloba* leaf (*G. biloba L, folium*), that is, a standardized *G. biloba* extract EGb 761 that contains 24% flavonol glycosides and 6% terpens.

The subjects were randomly assigned to receive either two *G. biloba* tablets daily (a total of 120 mg of *G. biloba* extract), one placebo tablet and one *G. biloba* tablet daily (a total of 60 mg of *G. biloba* extract), or two placebo tablets daily for 6 months. The placebo tablet was identical to the

active tablet in size, color, and shape (white and round tablet). The odor and taste of tablets were masked. Patients were instructed to swallow the tablets whole, without breaking them, after a meal every day.

Randomization, blinding, and study protocol

The block randomization was used to randomize subjects into three groups with equal sample sizes. Each box carried a unique drug number (code) that was generated and assigned to the active drug and placebo. The randomization codes were stored in a locked compartment at the sponsors' office. The sealed envelopes were also given to the principal investigator and were inaccessible to other staff involved in the trial. The block length was not disclosed to the investigators or clinical staff. This procedure ensured both double-blinding and concealment of allocation sequence. The principal investigator was instructed to open the sealed envelope only in case of a serious adverse event. In that case, the principal investigator was required to complete a special case report form. The envelopes were returned to the sponsor at the end of the study.

The subjects were invited to attend a total of seven study visits in 30-day intervals during the 6-month study period. Laboratory testing, TCD, and neuropsychological tests (MDRS, CGI, SCAG, and MMSE) were repeated every 90 days (visits 1, 4, and 7). ECG and CAVA were performed at the first and final visits, that is, 180 days apart. The duration of the treatment period was 180 days.

The primary outcome measure was a change in MDRS, CGI, SCAG, and MMSE scores from the baseline values. The secondary outcome measures were changes in the results of the laboratory tests, TCD, and CAVA from the baseline values. Reported adverse reactions, physical and neurological examination findings, blood pressure, pulse, respiration rate, body temperature, and changes in concomitant therapy were recorded at each study visit, visits 2–7. Adverse reactions were reported to the study clinical monitor and study steering committee. Treatment adherence was checked for all subjects by inquiry and by counting the returned tablets on visits 3, 5, and 7.

Statistical analysis

Data for categorical variables were presented as frequencies and proportion (%), and data for continuous variables were expressed as mean and standard deviation (mean ± SD). The comparison between the groups that finished the study per protocol and the ones that discontinued the study prematurely was done using either chi-square test or Fisher's exact test for categorical variables and Student's *t*-test or Mann–Whitney *U* test (depending on the type of distribution) for continuous variables. The difference between the treatment groups and placebo group in the primary and secondary outcome measures was evaluated using a repeated-measures analysis of variance (ANOVA) and, for categorical variables, using Friedman ANOVA. For multiple comparisons, Bonferroni correction was used. The treatment success rate was evaluated as a favorable therapeutic outcome defined as a global improvement on a 0–7 scale and efficiency index on a 1–16 scale. The incidences of adverse reactions, concomitant diseases, and medications were shown as frequencies. Data were analyzed using the software package Statistica for Windows, version 6.0 (StatSoft Inc., Tulsa, OK, USA). All tests were two-sided with $P<0.05$ considered as statistically significant.

Results

Subject characteristics

The study was completed according to the protocol by 58 of a total of 90 subjects included in the study (Figure 1).

A total of 32 patients discontinued the study before the end of the treatment period, with equal representation among groups ($P=0.953$). Adverse reactions as a reason for withdrawal were most frequent in the placebo group ($P=0.009$). Nine patients were lost to follow-up. Ten patients withdrew their consent. Seven subjects were excluded from the study because of inadequate compliance ($P=0.015$ for all reasons among groups).

There was no statistically significant difference for any baseline parameter in subjects who discontinued the study regarding their random distribution across groups and basic demographic parameters ($P>0.05$ for all). A statistically significant difference between the subjects who completed and those who discontinued the study was found only in the red blood cell count ($P=0.032$), platelet count ($P=0.049$), TCD of the left anterior cerebral artery ($P=0.003$), and TCD of the basilar artery ($P=0.04$) (Table 1).

Efficacy evaluation

No statistically significant difference between the *G. biloba* and placebo groups was found in MDRS, SCAG, and MMSE scores (Table 2). However, there was a statistically significant difference between the *G. biloba* and placebo groups in CGI scores ($P=0.038$).

The differences between the *G. biloba* and placebo groups in TCD measurements were not statistically significant for any of the left- or right-side arteries ($P>0.10$ for all). The baseline CAVA measurements showed a wide range of

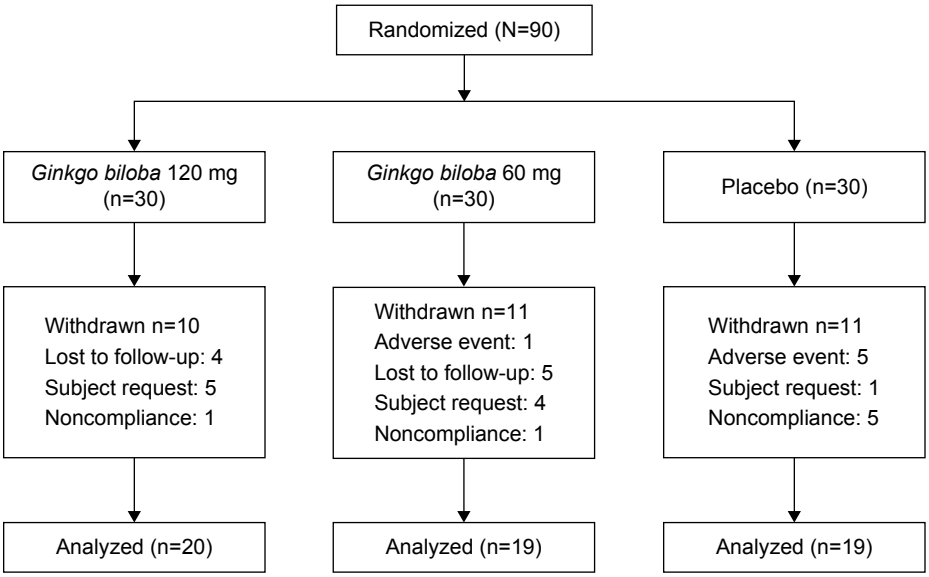

Figure 1 Study flow chart.

different values in the carotid arteries, ranging from normal (unremarkable) findings to bilateral carotid artery stenosis. The statistical significance of the observed internal carotid artery differences was not evaluated because of a wide range of recorded differences and no further categorization predicted.

Satisfactory compliance regarding the medication use (>80% of the dose taken) was determined in all subjects who completed the study in all the three groups at every visit.

Safety evaluation

At the end of the study, no statistically significant difference was found between the *G. biloba* and placebo groups in the secondary outcome indicators (ESR, CBC, glucose, urea, creatinine, transaminases, bilirubin, sodium, potassium, chlorides, HDL, LDL, triglycerides, APTT, and PV; $P>0.05$ for all). No statistically significant difference was found between the *G. biloba* and placebo groups in physical and neurological findings ($P>0.05$ for all). Also, there was no statistically significant difference between the *G. biloba* and placebo groups in compliance and premature withdrawal from the study. As for concomitant therapy, medications for cardiovascular conditions, neurological conditions, and nonsteroidal anti-inflammatory drugs (except acetylsalicylic acid) were most frequently used among the subjects.

Adverse reactions

A total of 33 adverse reactions was reported, 12 of which were serious (Table 3). The greatest number of adverse reactions was reported in the placebo group (nine serious), followed by the *G. biloba* 60 mg group (three serious) and the *G. biloba* 120 mg group (no serious adverse reactions; $\chi^2=7{,}342$; $df=2$; $P=0.026$). The most commonly reported adverse reaction was nausea, followed by vomiting and vertigo. These adverse reactions were most commonly reported in the placebo group. Six subjects terminated the study prematurely because of adverse reactions. For one subject in the placebo group, the randomization code had to be revealed because of a serious adverse reaction.

Discussion

Our study results for *G. biloba* efficacy in the treatment of patients with VCI showed a statistically significant positive effect of *G. biloba* extract only on the CGI as the primary outcome indicator.

Several studies about the effect of *G. biloba* on cognition have been published, majority reporting a positive effect.[23] However, a randomized placebo-controlled trial by Vellas et al[24] showed that the long-term use of standardized *G. biloba* extract did not reduce the risk of progression to Alzheimer's disease compared with placebo. Two recently conducted large randomized trials, the GEM (*Ginkgo* Evaluation of Memory) study and the GuidAge study, showed no benefit of *G. biloba* for age-related cognitive decline.[25,26] However, a meta-analysis by Weinmann et al[27] showed *G. biloba* to be more effective than placebo in the treatment of dementia, although with a moderate effect. Meta-analyses by Tan et al[11] and Wang et al[28] suggest that *G. biloba* is able to slow down or stabilize cognitive decline in patients with dementia. A recent study by Amieva et al[29] showed that *G. biloba*

Table 1 Characteristics of subjects receiving either *Ginkgo biloba* extract or placebo who completed the study and discontinued the study

Characteristics	Subjects who (N=90)		*P*-value*
	Completed the study (n=58)	Discontinued the study (n=32)	
Gender (women), n (%)	37 (63.8)	22 (68.8)	0.636
Age (years), mean ± SD	66.7±7.7	68.0±8.6	0.343
Height (cm), mean ± SD	167.0±8.6	168.0±7.8	0.566
Weight (kg), mean ± SD	76.8±14.9	71.6±11.0	0.095
Smoking, n (%)	6 (10.3)	2 (6.5)	0.541
Arterial hypertension, n (%)	45 (77.6)	24 (75.0)	0.781
Diabetes mellitus, n (%)	10 (17.2)	8 (25.0)	0.378
Previous stroke, n (%)	6 (10.9)	4 (12.5)	0.824
Previous transient ischemic attack, n (%)	12 (20.7)	5 (15.6)	0.557
Previous myocardial infarction, n (%)	1 (1.7)	0 (0)	0.356
Mood disorder, n (%)	3 (5.2)	4 (12.5)	0.241
Parkinson's disease, n (%)	1 (1.7)	0 (0)	0.356
Chronic obstructive pulmonary disease, n (%)	3 (5.2)	2 (6.3)	0.652
Tinitus, n (%)	25 (43.19)	13 (40.6)	0.820
Headache, n (%)	21 (36.8)	13 (40.6)	0.725
Laboratory findings, mean ± SD			
Sedimentation rate (mm/h)	14.6±13.1	15.5±19.7	0.794
White blood cell count ($\times 10^9$/L)	7.2±0.4	6.7±0.5	0.391
Red blood cell count ($\times 10^{12}$/L)	4.5±2.5	4.3±2.0	**0.032**
Platelet count ($\times 10^9$/L)	248.4±51.4	229.5±36.4	**0.050**
Hemoglobin (g/L)	138.8±10.2	139.6±13.1	0.752
Hematocrit (L/L)	0.4±0.03	0.4±0.04	0.306
Glucose (mmol/L)	6.2±1.9	6.7±3.5	0.850
Total bilirubin (μmol/L)	17.1±13.3	14.7±7.7	0.412
Aspartate transaminase (IU/L)	21.0±10.7	21.5±7.0	0.805
Alanine transaminase (IU/L)	21.1±8.0	20.4±12.4	0.801
Urea (mmol/L)	6.3±1.7	6.9±3.7	0.567
Creatinine (μmol/L)	84.8±23.8	82.9±18.2	0.701
Potassium (mmol/L)	4.3±0.4	4.3±0.4	0.958
Sodium (mmol/L)	140.2±4.3	138.5±4.7	0.089
Chlorides (mmol/L)	106.7±6.7	105.7±4.4	0.481
Cholesterol – high-density lipoprotein (mmol/L)	1.6±0.7	1.6±0.4	0.981
Cholesterol – low-density lipoprotein (mmol/L)	3.6±1.0	3.4±1.2	0.267
Triglycerides (mmol/L)	1.8±0.8	1.5±0.5	0.076
Prothrombin time (s)	1.2±0.1	1.29±0.1	0.570
Activated partial thromboplastin time (s)	30.5±11.2	27.8±6.4	0.260
Transcranial doppler – mean (±SD) flow velocity (cm/s)			
Left carotid siphon	50.9±11.7	49.9±15.4	0.780
Right carotid siphon	50.3±9.9	52.4±14.1	0.533
Left middle cerebral artery	52.1±12.4	52.1±15.1	0.992
Right middle cerebral artery	51.9±10.8	54.4±13.6	0.482
Left anterior cerebral artery	–47.8±9.6	–33.9±35.8	**0.003**
Right anterior cerebral artery	–43.5±18.2	–35.3±36.9	0.622
Left posterior cerebral artery	28.1±14.6	33.5±18.7	0.252
Right posterior cerebral artery	28.3±12.6	33.9±18.9	0.216
Left vertebral artery	–27.6±11.5	–21.5±19.5	0.089
Right vertebral artery	–27.0±11.4	–22.3±17.1	0.158
Basilar artery	–30.3±13.8	–14.0±27.0	**0.004**
Neuropsychological assessment, mean ± SD			
Sandoz Clinical Assessment Geriatric Scale	45.7±10.6	45.2±11.1	0.889
Folstein Mini-Mental State Examination	25.8±2.4	25.5±2.2	0.478
Mattis Dementia Rating Scale	126.8±13.4	124.1±12.4	0.354
Clinical Global Impression	2.86±0.8	2.9±0.7	0.255

Notes: Bold figures represent as statistically significant different values. *Two-sided *P*-value of Student's *t*-test for continuous variables and chi-square test for categorical variables.
Abbreviation: SD, standard deviation.

Table 2 Neuropsychological test results of subjects receiving *Ginkgo biloba* extract and placebo during the 6-month study period

Scale/visit No	Study groups, mean ± SD			*F*	*P*-value
	G. biloba 120 mg (n=20)	*G. biloba* 60 mg (n=19)	Placebo (n=19)		
Sandoz Clinical Assessment Geriatric Scale				0.39454	0.676
V1	48.3±12.8	44.9±9.1	43.3±9.2		
V4	45.7±12.7	40.7±8.2	39.1±6.9		
V7	43.6±14.7	39.1±6.9	36.7±6.1		
Folstein Mini-Mental State Exam				0.26780	0.766
V1	26.0±2.6	25.1±2.3	26.4±2.3		
V4	27.4±2.1	26.9±2.4	27.8±2.3		
V7	27.9±2.5	26.7±2.9	28.1±2.8		
Mattis Dementia Rating Scale				0.29030	0.749
V1	128.8±10.0	123.9±14.4	127.6±15.6		
V4	126.2±14.1	125.1±14.7	125.9±12.7		
V7	128.4±13.7	124.9±16.5	127.2±12.4		
Clinical Global Impression				3.4714	**0.038**
V1	2.6±0.8	3.1±0.7	2.6±0.8		
V4	2.6±0.8	3.1±0.7	2.7±0.7		
V7	2.6±0.8	3.1±0.7	2.8±0.7		

Notes: *F* represents as a value calculated by ANOVA test to verify the statistical significance of difference between groups. Bold figure represents as statistically significant different value.
Abbreviations: V1, V4, V7, study visit number; ANOVA, analysis of variance.

Table 3 ARs reported by subjects taking *Ginkgo biloba* and placebo during the 6-month study period

AR	No of subjects (N=58)			Total
	G. biloba 120 mg (n=20)	*G. biloba* 60 mg (n=19)	Placebo (n=19)	
Rash	1	0	2	3
Arterial hypertension	1	0	0	1
Varicose veins on legs	2	0	0	2
Headache	2	1	0	3
Tinnitus	1	1	0	2
Abdominal pain	0	1	0	1
Retching	0	1	0	1
Vertigo	1	1	3	5
Nausea	0	2	4	6
Vomiting	0	2	3	5
Tachycardia	0	0	1	1
Concentration impairment	0	0	1	1
Insomnia	0	0	1	1
Feeling generally unwell	0	0	1	1
Total (severe AR)	8 (0)	9 (3)	16 (9)	33 (12)

Abbreviation: AR, adverse reaction.

EGb 761 significantly slowed down the cognitive decline in comparison to piracetam. The possible stabilizing effect on cognitive decline and clinical presentation measured with CGI was also shown in our study.

Unfortunately, we did not find any improvement in cognitive decline measured by MMSE, SCAG, and MDRS or blood flow velocity increase in the cerebral arteries. Recently, Zhang and Xue[4] showed that *G. biloba* with any platelet therapy increases blood flow velocities in the middle and anterior cerebral arteries in VCI patients with cognitive ability improvement measured by the Montreal Cognitive Assessment after 3 months.

Lower cognitive decline was reported in nondemented elderly subjects who used *G. biloba* extract.[29] Some studies showed the improvement of cognitive and neuropsychiatric symptoms and functional ability in dementia.[10,30] The results reported by Brondino et al[31] suggest improved cognitive function and activities of daily living in patients with dementia treated with *G. biloba*. A systematic review and meta-analysis by Yang et al[32] found that *G. biloba* is potentially beneficial for the improvement of cognitive function, activities of daily living, and global clinical assessment in patients with mild cognitive impairment or Alzheimer's disease. However, Mazza et al[33] reported no evidence of relevant differences in the efficacy of *G. biloba* and donepezil in the treatment of mild-to-moderate Alzheimer's dementia. Kruntoradova et al[34] results suggest that EGb 761® represents a cost-saving intervention with more quality-adjusted life years/life years gained, that is, dominant therapy compared to no pharmacotherapy in the treatment of mild dementia in a 10-year horizon, as EGb 761 showed very similar results (slightly cheaper and less effective) in comparison to iAchE (eg, donepezil). Still, due to limited sample sizes, and inconsistent findings and methodological quality of included trials, more research is warranted to confirm the effectiveness and safety of *G. biloba* in the treatment of mild cognitive impairment and Alzheimer's disease.[32]

Despite no statistically significant differences for safety outcomes regarding laboratory and clinical findings in our study, adverse reactions were significantly more common and serious in the placebo group. *G. biloba* seemed to be safe, with no serious adverse reactions compared to placebo. *G. biloba* extract is widely used in the treatment of acute ischemic stroke in the People's Republic of China.[35] A Cochrane Collaboration systematic review showed that high-quality, large-scale randomized trials are necessary to confirm the beneficial effect of *G. biloba* on recovery after acute stroke.[36] Recent studies on *G. biloba* extract have proven *G. biloba* to be beneficial and safe in the treatment of acute cerebral infarction, improving the outcome and showing neuroprotective effect.[37,38] However, previous investigations on *G. biloba* in prophylactic therapy for ischemic stroke did not show that daily intake was able to prevent stroke or other cardiovascular

or cerebrovascular events.[12,39–41] Although *G. biloba* has not been found effective in dementia prevention, clinical evidence for the use of *G. biloba* to slow its progression is promising and warrants further clinical investigation.[24]

Similar to other clinical trials, our study had several limitations. The CGI rating scale to measure symptoms severity, treatment response, and efficacy of treatment is considered to be somewhat subjective, and the follow-up period was relatively short, with a high dropout rate. One more limitation was that the patients were enrolled at only one study center.

Conclusion

According to our results, *G. biloba* seemed to slow down the cognitive deterioration in patients with VCI, but the effect was shown in only one of the four neuropsychologic tests administered. However, because of this mild effect in combination with a few adverse reactions, we cannot say that it is ineffective or unsafe either. Further studies are still needed to provide unambiguous evidence on the efficacy and safety of *G. biloba* extract.

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Author contributions

All authors were involved in either the design of the study or data analysis and interpretation. All authors contributed to the drafting of the manuscript or critical revision of the manuscript for important intellectual content.

Disclosure

The authors report no conflicts of interest in this work.

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