

A double-blind, placebo-controlled, randomized trial of *Ginkgo biloba* extract EGb 761[®] in a sample of cognitively intact older adults: neuropsychological findings

Joseph A. Mix^{1*} and W. David Crews, Jr.^{2,3}

¹Liberty University, Lynchburg, Virginia, USA

²Virginia Neuropsychology Associates, Inc., Lynchburg, Virginia, USA

³Virginia Polytechnic Institute and State University, Blacksburg, Virginia, USA

There appears to be an absence of large-scaled clinical trials that have examined the efficacy of *Ginkgo biloba* extract on the neuropsychological functioning of cognitively intact older adults. The importance of such clinical research appears paramount in light of the plethora of products containing *Ginkgo biloba* that are currently being widely marketed to predominantly cognitively intact adults with claims of enhanced cognitive performances. The purpose of this research was to conduct the first known, large-scaled clinical trial of the efficacy of *Ginkgo biloba* extract (EGb 761[®]) on the neuropsychological functioning of cognitively intact older adults. Two hundred and sixty-two community-dwelling volunteers (both male and female) 60 years of age and older, who reported no history of dementia or significant neurocognitive impairments and obtained Mini-Mental State Examination total scores of at least 26, were examined via a 6-week, randomized, double-blind, fixed-dose, placebo-controlled, parallel-group, clinical trial. Participants were randomly assigned to receive either *Ginkgo biloba* extract EGb 761[®] ($n = 131$; 180 mg/day) or placebo ($n = 131$) for 6 weeks. Efficacy measures consisted of participants' raw change in performance scores from pretreatment baseline to those obtained just prior to termination of treatment on the following standardized neuropsychological measures: Selective Reminding Test (SRT), Wechsler Adult Intelligence Scale-III Block Design (WAIS-III BD) and Digit Symbol-Coding (WAIS-III DS) subtests, and the Wechsler Memory Scale-III Faces I (WMS-III FI) and Faces II (WMS-III FII) subtests. A subjective Follow-up Self-report Questionnaire was also administered to participants just prior to termination of the treatment phase. Analyses of covariance indicated that cognitively intact participants who received 180 mg of EGb 761[®] daily for 6 weeks exhibited significantly more improvement on SRT tasks involving delayed (30 min) free recall ($p < 0.04$) and recognition ($p < 0.01$) of noncontextual, auditory-verbal material, compared with the placebo controls. The EGb 761[®] group also demonstrated significantly greater improvement on the WMS-III FII subtest assessing delayed (30 min) recognition ($p < 0.025$) of visual material (i.e. human faces), compared with the placebo group. However, based on the significant difference ($p < 0.03$) found between the two groups' pretreatment baseline scores on the WMS-III FII, this result should be interpreted with caution. An examination of the participants' subjective ratings of their overall abilities to remember by treatment end on the Follow-up Self-report Questionnaire also revealed that significantly more ($p = 0.05$) older adults in the EGb 761[®] group rated their overall abilities to remember by treatment end as 'improved' compared with the placebo controls. Overall, the results from both objective, standardized, neuropsychological tests and a subjective, follow-up self-report questionnaire provided complementary evidence of the potential efficacy of *Ginkgo biloba* EGb 761[®] in enhancing certain neuropsychological/memory processes of cognitively intact older adults, 60 years of age and over. Copyright © 2002 John Wiley & Sons, Ltd.

KEY WORDS — *Ginkgo biloba* extract; neuropsychological; cognitive; memory; elderly; clinical trial

*Correspondence to: Professor J. A. Mix, Department of Health Sciences, Liberty University, 1971 University Boulevard, Lynchburg, Virginia 24502, USA.

Contract/grant sponsor: Dr Willmar Schwabe GmbH & Co., Karlsruhe, Germany.

Contract/grant sponsor: Nature's Way Products, Inc., Springville, Utah, USA.

INTRODUCTION

In recent years, the utilization of *Ginkgo biloba* extract for the treatment of dementia and 'cerebral insufficiency' has increased significantly. In fact, the results from a number of clinical trials that have demonstrated the efficacy of *Ginkgo biloba* extract

in cognitively impaired persons have led to its approval as a treatment for dementia in Germany (Itil and Martorano, 1995).

The majority of past studies that have evaluated the efficacy of *Ginkgo biloba* extract in the treatment of cognitive dysfunction (e.g. dementia, age-related memory impairment) have been conducted in Europe (Allain *et al.*, 1993; Drabaek *et al.*, 1996; Graessel, 1992; Haase *et al.*, 1996; Hoeffberth, 1989, 1994; Hoepfenmuller, 1994; Kanowski *et al.*, 1996; Rai *et al.*, 1991; Semlitsch *et al.*, 1995; Wesnes *et al.*, 1987). Patients who received the extract in these studies have been noted to exhibit improvements in such cognitive functions as memory (e.g. short-term, verbal memory) (Graessel, 1992; Hoeffberth, 1994; Semlitsch *et al.*, 1995), learning rate (Graessel, 1992), speed of information processing (Allain *et al.*, 1993), speed of responses (Rai *et al.*, 1991) and attention (Hoeffberth, 1994), compared with placebo controls. Furthermore, a meta-analysis of 11 controlled trials of *Ginkgo biloba* extract LI 1370 in patients suffering from 'cerebral insufficiency' confirmed the effectiveness of the extract (compared with controls) in seven studies, while in one study, the findings were inconclusive (Hoepfenmuller, 1994). Three additional studies were excluded from this analysis due to 'methodological' or 'objective' reasons.

Similarly, in a large clinical trial that was conducted in the United States, LeBars and his colleagues (1997) assessed the efficacy of *Ginkgo biloba* extract (120 mg/day) in mildly to severely demented outpatients over a 52-week period via a double-blind, placebo-controlled, randomized design. The findings from this trial indicated that the *Ginkgo biloba* extract group exhibited 'modest' improvements on the Alzheimer's Disease Assessment Scale-Cognitive subscale and the Geriatric Evaluation by Relatives Rating Instrument (a measure of daily living and social behaviors) compared with the placebo controls.

There appear to be relatively few studies that have examined the effectiveness of *Ginkgo biloba* extract in persons with no history of neurocognitive dysfunction. We (Mix and Crews, 2000) recently examined the short-term (i.e. 6 weeks) efficacy of *Ginkgo biloba* extract EGb 761[®] on the neuropsychological functioning of cognitively intact persons over 55 years of age via a double-blind, fixed-dose, placebo-controlled, parallel-group experimental design. The findings from this investigation revealed that participants who received 180 mg of *Ginkgo biloba* extract EGb 761[®] daily for 6 weeks exhibited significantly more improvement on a task assessing speed of processing abilities (i.e. Stroop Color and Word Test

color-naming task) by the end of treatment compared with the participants who received placebo. Non-significant trends favoring improved performances in the *Ginkgo biloba* group were also exhibited on three of the four remaining tasks that involved a timed, speed of processing component. Furthermore, significantly more participants in the *Ginkgo biloba* extract group rated their overall abilities to remember by the end of the treatment as 'improved', compared with the placebo group. Taken together, these neuropsychological findings suggested that relatively short-term utilization of *Ginkgo biloba* extract EGb 761[®] may prove efficacious in enhancing certain neurocognitive processes of cognitively intact older adults.

Since publication of our study, two additional small-scaled studies have appeared in the literature that provide data supporting the acute/short-term efficacy of *Ginkgo biloba* extract on the cognitive processes of 'healthy, young' volunteers. Kennedy *et al.* (2000) investigated the effects of acute administration of three doses (120 mg, 240 mg and 360 mg) of a standardized extract of *Ginkgo biloba* on the cognitive abilities of 20 undergraduate volunteers (19–24 years of age) via a placebo-controlled, multi-dose, double-blind, balanced, crossover design. The results indicated dose-dependent improvements of a 'speed of attention' factor that was derived by factor analysis of a computerized assessment battery of subtests. This effect was noted at 2.5 h following the administration of 240 mg and 360 mg of *Ginkgo biloba* extract and continued to be present at 6 h post-dosing.

Stough *et al.* (2001) also examined the short-term effects of *Ginkgo biloba* extract (120 mg/day) on the cognitive processes of 61 young, healthy adults (18–40 years of age) via a 30-day, randomized, double-blind, placebo-controlled, clinical trial. Findings from this study indicated significant *Ginkgo biloba* extract-related improvements in working memory (and working memory speed) and memory consolidation following the 30-day treatment regimen.

With the exception of our (Mix and Crews, 2000) previous small-scaled study, there appears to be an absence of clinical trials that have examined the efficacy of *Ginkgo biloba* extract on the neuropsychological processes of cognitively intact older adults. Thus, the purpose of this research was to expand upon our previous study by conducting the first known, large-scaled, clinical trial of the efficacy of *Ginkgo biloba* extract (EGb 761[®]) on the neuropsychological functioning of cognitively intact older adults. The importance of such clinical research appears paramount in the light of the plethora of products containing *Ginkgo biloba* that are currently being widely

marketed to predominantly cognitively intact adults with claims of enhanced cognitive/memory performances.

METHOD

Participants

Two hundred and sixty-two, volunteer, participants, both male and female, 60 years of age and older, who reported no history of dementia or significant neurocognitive impairment were initially enrolled and randomized in this study. To be included in this trial, and considered as cognitively intact, all participants were required to obtain a total score greater than, or equal to, 26 on the Mini-Mental State Examination (MMSE; Folstein *et al.*, 1975). Participants' histories were unremarkable for active, or clinically significant, cardiovascular, neurological, pulmonary, endocrine, renal, hepatic, gastrointestinal, hematological, or oncological diseases/disorders, uncontrolled hypertension, learning disabilities, or psychiatric or substance abuse disorders. Individuals who had histories of bleeding disorders or hemorrhagic stroke, or who were being treated with anticoagulant or psychotropic medications, were also excluded from this study. Persons who were utilizing any form of *Ginkgo biloba* prior to their enrollment in the study were requested to terminate such therapy at least 28 days prior to their initial, pretreatment baseline neuropsychological assessments. The utilization of medications for other pre-existing conditions was not discontinued, although changes or additions to participants' medication regimens during the study were not permitted. Furthermore, participants' histories were unremarkable for uncorrected vision, hearing, language, or motor difficulties that could have possibly precluded their participation in, and/or compliance with, all of the neuropsychological procedures.

This project was approved by the Institutional Review Board and Human Subjects Committee at Liberty University. Prior to the initiation of this study, the nature and purpose of the research was explained to each participant and written, informed consent obtained.

Experimental design and procedures

The study utilized a 6-week, randomized, double-blind, fixed-dose, placebo-controlled, parallel-group experimental design. Individuals meeting inclusion criteria were randomly assigned to either the *Ginkgo biloba* extract EGb 761[®] ($n = 131$) or the placebo

group ($n = 131$). The EGb 761[®] (standardized to contain 24% flavone glycosides, 6% terpene lactones and less than 5 ppm ginkgolic acids) and placebo tablets, as well as the pharmaceutical preparation procedures (e.g. blister packaging) for both compounds, were furnished by the manufacturer, Dr Willmar Schwabe GmbH & Co., Karlsruhe, Germany. Computerized randomization was conducted via a random generator and in balanced blocks of size four by the manufacturer to assign numbers to boxes of blister pack cards (seven cards of 21 tablets each per box) containing either EGb 761[®] or placebo. The boxes of blister pack cards (and their corresponding numbers) were subsequently issued to participants in an ascending/sequential order as they entered the study (i.e. at the time of their pre-treatment baseline neuropsychological assessments). The EGb 761[®] (60 mg/dose) or placebo was to be taken orally by participants three times daily (i.e. 180 mg/day) in the form of film-coated tablets that did not differ as regards appearance (e.g. color, size), smell or taste. All of the EGb 761[®] that was utilized in this project originated from the same batch/lot number of the product.

Prior to the initiation of drug therapy, participants were requested to complete an initial medical history questionnaire. Individuals with unremarkable histories of active, or clinically significant, medical and psychiatric disorders/conditions (as defined in the 'Participants' section) were subsequently administered the MMSE (Folstein *et al.*, 1975). To be considered cognitively intact, participants were required to obtain a total score greater than, or equal to, 26. Those individuals who met the MMSE inclusion criteria were scheduled for a physical examination by a licensed physician that consisted of a comprehensive review of their medical and psychiatric histories, assessment of vital signs and laboratory screening tests (i.e. complete blood count, clinical chemistry screen, liver enzymes, thyroid function, urinalysis and electrocardiogram). Persons with abnormal vital signs or laboratory findings, and those individuals who were deemed by a physician to not meet inclusion medical criteria (e.g. absence of active or clinically significant, medical/psychiatric disorders) were debriefed and excused from participation in the project.

Participants meeting the preliminary cognitive and medical inclusion criteria were subsequently administered a series of neuropsychological tests immediately prior to the initiation of EGb 761[®]/placebo therapy (i.e. pretreatment baseline evaluation), and again, after 6 weeks of treatment and just prior to the termination of this regimen. All neuropsychological testing sessions were conducted by trained research assistants

under the supervision of a licensed clinical neuropsychologist.

Upon arrival for the pretreatment baseline neuropsychological assessment, a brief, rapport-building session was conducted with participants during which time the purpose of this phase of the study was explained and their questions answered. Neuropsychological testing was then initiated. All participants were administered the following neuropsychological tests while adhering to each measure's standardized administration and scoring procedures: Selective Reminding Test (SRT; Buschke and Fuld, 1974), the Wechsler Adult Intelligence Scale-III Block Design (WAIS-III, BD) and Digit Symbol-Coding (WAIS-III DS) subtests (Wechsler, 1997a), and the Wechsler Memory Scale-III Faces I (WMS-III FI) and Faces II (WMS-III FII) subtests (Wechsler, 1997b). Following testing, participants were assigned the next ascending participant number and provided with a supply of randomly assigned, film-coated, tablets containing either EGb 761[®] or placebo.

After 6 weeks of EGb 761[®] or placebo treatment, and immediately prior to the termination of the regimen, identical neuropsychological procedures were conducted with each participant with two exceptions. Since the MMSE was utilized as an inclusion/exclusion criterion measure, this measure was administered only during the pretreatment baseline assessment. Furthermore, a Follow-up Self-report Questionnaire was administered only during the second neuropsychological assessment session to subjectively assess participants' perceptions of changes in the following variables from pretreatment baseline to the end of the treatment phase (i.e. after 6 weeks): overall abilities to remember, mood changes, energy levels and overall health.

Compliance with the treatment regimen was assessed via pill counts conducted at the end point of the project (i.e. after 6 weeks of treatment) with a deviation of more than 20% from the optimum study treatment regimen being operationally defined as non-compliant.

Neuropsychological outcome/efficacy measures

Follow-up Self-report Questionnaire. This is an author-generated, self-report questionnaire designed to subjectively assess participants' perceptions of changes in the following variables from pretreatment baseline to the end of the treatment phase (i.e. after 6 weeks): overall abilities to remember, mood changes, energy levels and overall health. The specific questions that were posed to participants included the

following: 1. Based on what your memory was like before the study, how would you rate your overall ability to remember things now?; 2. Based on what your overall mood was like before the study, how would you rate your mood now?; 3. Based on what your energy level was like before the study, how would you rate your energy level now?; 4. Based on your overall health before the study, how would you rate your overall health now? Participants were requested to circle the one category from the following that most accurately reflected their perceptions with regard to each question: much worse, somewhat worse, no change, somewhat improved, much improved.

Mini-Mental State Examination. This measure (MMSE; Folstein *et al.*, 1975) provides a brief screen of the following cognitive domains: orientation, registration, attention and calculation, recall and language. Scores can range from 0 to 30 (maximum/perfect score). Scores of 23 or less have been suggested to denote cognitive impairment in individuals with greater than 8 years of education (Cockrell and Folstein, 1988). The MMSE was utilized as an inclusionary/exclusionary criterion measure where all participants were required to score between 26 and 30 to be considered cognitively intact and included in this study.

Selective Reminding Test. This standardized test (SRT; Buschke and Fuld, 1974) assesses a diversity of auditory-verbal memory components including retention, storage and retrieval (Lezak, 1995). The test consists of 12 unrelated words that are presented over 12 trials or until the entire list is recalled correctly on three consecutive trials (Spren and Strauss, 1998). Once trial one is completed, each subsequent learning trial involves the presentation of only those words that were not recalled during the preceding trial. After trial 12, or after all 12 words are recalled correctly on three consecutive trials, a cued-recall trial is administered. Thirty minutes later, a delayed free recall trial and a four-choice multiple choice recognition trial are conducted. In addition to the immediate and delayed free recall, cued-recall, and multiple-choice recognition variables, this test allows calculation of the following scores: long-term storage, short-term recall, long-term retrieval, consistent long-term retrieval, and random long-term retrieval.

Wechsler Adult Intelligence Scale-III Block Design. This test (WAIS-III BD; Wechsler, 1997a) is a standardized subtest of the WAIS-III that requires

participants to replicate three dimensional models or pictures of two-color (i.e. red and white), two-dimensional, geometric patterns with blocks that have two solid red sides, two solid white sides, and two half-red and half-white sides. The 14 geometric designs progress from simple two-block figures to relatively complex nine-block designs. Time limits are imposed for each design trial, although participants may obtain time-bonus points for quick, successful completion of designs 7–14 prior to the time limits. This task has been suggested to assess visuospatial organization and constructional abilities (Lezak, 1995; Kaufman and Lichtenberger, 1999).

Wechsler Adult Intelligence Scale-III Digit Symbol-Coding. This test (WAIS-III DS; Wechsler, 1997a) is a standardized subtest of the WAIS-III that involves a series of numbers (i.e. 1–9), each of which is paired with its own unique, hieroglyphic-like, symbol in a key at the top of the test booklet page (Wechsler, 1997a). Below this key are 140 blank squares (arranged in seven rows of 20) which are paired (above each blank) with randomly assigned numbers from 1 to 9. After a practice trial on the first seven squares, participants are required to fill in each blank square with the symbol that corresponds to its paired number (that appears above the blanks) as quickly as possible for a total of 120 s. This task has been suggested to assess sustained attention/focused con-

centration, response speed and visuo-motor persistence/coordination (Lezak, 1995; Kaufman and Lichtenberger, 1999).

Wechsler Memory Scale-III Faces I and II. These tasks (WMS-III FI and WMS-III FII; Wechsler, 1997b) are standardized subtests that are parts of the WMS-III. Faces I is composed of 24 stimulus photographs of human faces that are individually presented to participants at a rate of one face every 2 s. Immediately after presentation of the 24 faces, participants are presented a second series of 48 photographs of human faces, one at a time, and requested to say 'yes' if it is one that they remember having seen, and 'no' if it is one that they do not recognize. After 30 min, Faces II is administered. During this task, participants are presented 48 additional photographs of human faces, one at a time, and requested to denote whether or not each face is one that they were initially asked to remember. The WMS-III Faces I and II subtests have been suggested to assess immediate and delayed visual memory for human faces (Wechsler, 1997b, 1997c).

STATISTICS AND RESULTS

A trial flow diagram for this study is provided in Figure 1. Since the trial design involved neuropsychological assessments only at pretreatment baseline and

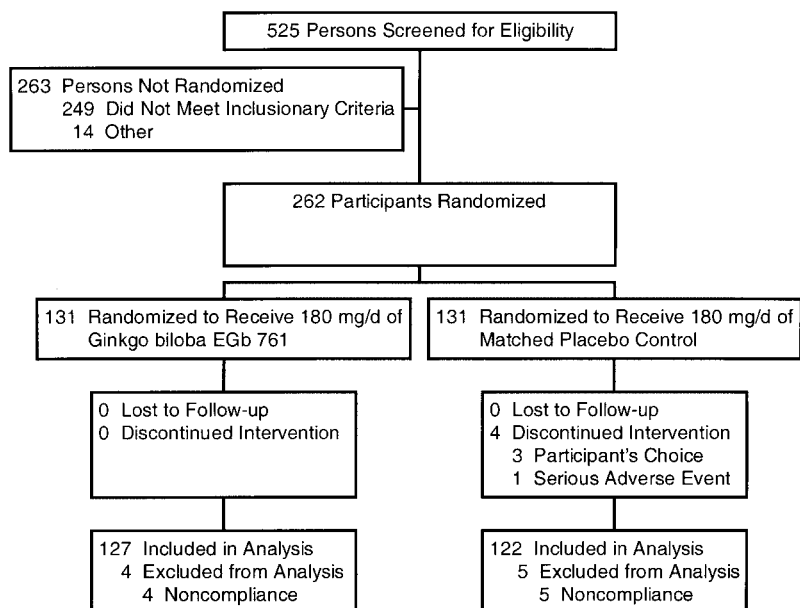


Figure 1. Trial flow diagram

again just prior to termination of treatment, the per protocol data set was utilized in the statistical analyses. From the 262 participants who were initially randomized/enrolled in this study, 249 participants completed the trial's protocol and were available for the efficacy analyses. Among the 13 participants who were excluded, four from the placebo group withdrew prematurely secondary to the following adverse events: hemorrhagic stroke ($n = 1$), allergies ($n = 1$), headache ($n = 1$) and elective bladder repair surgery ($n = 1$). Five additional participants from the placebo group and four from the EGb 761[®] group were excluded due to protocol violations (e.g. noncompliance with the treatment regimen).

To examine any differences that may have existed between the participants in the EGb 761[®] and placebo groups who were available for the efficacy analyses, separate analyses of variance (ANOVA) were conducted on the following descriptive and criterion measures: age in years, educational level in years, MMSE total scores and treatment regimen compliance defined as the percentage of maximum compliance. The only significant difference found between the groups was for age. Table 1 provides an overview of the groups' mean and standard deviations for each variable. A test for significance of difference between two proportions was also conducted on the nominal variable of sex. No significant difference was observed between the number of males ($n = 102$) and females ($n = 147$) who were available for the efficacy analyses.

To examine changes in performance on the neuropsychological measures over time between the EGb 761[®] and placebo control groups, participants' raw change in performance scores from the pretreatment baseline to those obtained just prior to the termination of treatment (i.e. end of treatment scores minus pretreatment baseline scores) were utilized as the dependent variables in the efficacy analyses. Based on the relative absence of previous clinical trials that have examined the efficacy of EGb 761[®] on the neuropsych-

Table 1. Group means and standard deviations for the descriptive and criterion measures

Variable	Ginkgo		Placebo	
	Mean	SD	Mean	SD
Age (years)	66.97	6.12	68.60	6.96 ^a
Education level (years)	14.30	2.74	14.18	2.66
Mini-Mental State Examination (total scores)	28.97	1.05	28.89	1.14
Treatment regimen compliance (%)	97.76	4.17	97.89	3.12

^a $p < 0.05$.

chological test performances of cognitively intact older adults, primary and secondary endpoints were not predefined. Rather, a series of endpoints was chosen that could be more rigorously defined and tested in future trials. To control for the significant difference found between the ages of the EGb 761[®] and placebo groups, separate, two-tailed, analyses of covariance (ANCOVA) were performed on the neuropsychological test change in performance scores. Table 2 provides a summary of the groups' change in performance score means and standard deviations for each neuropsychological test variable.

For the Selective Reminding Test delayed free recall task, a significant difference, $F(1, 217) = 4.36$, $p < 0.04$, was found between the EGb 761[®] and placebo groups' change in performance scores. Specifically, the EGb 761[®] group exhibited significantly greater improvement on the delayed recall task from baseline to after 6 weeks of treatment compared with the placebo control group.

A significant difference, $F(1, 217) = 6.79$, $p < 0.01$, was also noted between the EGb 761[®] and placebo groups' change in performance scores for the Selective Reminding Test delayed recognition task. In particular, the EGb 761[®] group, versus placebo controls, displayed significantly more improvement on the delayed recognition task from baseline to after 6 weeks of treatment.

Table 2. Neuropsychological test change in performance scores: means and standard deviations

Test/variable	Ginkgo		Placebo	
	Mean	SD	Mean	SD
Selective Reminding Test				
(raw scores)				
Immediate free recall	15.27	12.11	14.18	12.26
Long-term storage	19.97	19.51	18.44	18.97
Short-term recall	-6.73	9.16	-6.07	8.71
Long-term retrieval	22.00	19.22	20.25	18.87
Consistent long-term retrieval	24.82	26.40	24.26	27.15
Random long-term retrieval	-2.81	17.83	-4.01	18.38
Cued recall	1.04	1.67	1.32	1.64
Delayed free recall	1.69	1.79	1.13	1.95 ^a
Delayed recognition	0.43	0.88	0.16	0.77 ^a
Wechsler Adult Intelligence Scale-III				
(raw scores)				
Block design	2.29	5.61	1.88	5.19
Digit symbol	4.53	7.36	3.52	5.61
Wechsler Memory Scale-III				
(raw scores)				
Faces I	3.72	4.08	3.61	3.96
Faces II	3.48	4.19	2.25	3.82 ^a

^a $p < 0.05$.

Additionally, a significant difference, $F(1, 245) = 5.18$, $p < 0.025$, was also found between the two groups on the WMS-III Faces II subtest. Specifically, the EGb 761[®] group demonstrated significantly greater improvement on the delayed recognition task from baseline to after 6 weeks of treatment compared with the placebo control group. No significant differences were found between the two groups' change in performance scores on any of the other neuropsychological test variables.

To assess any significant differences between the EGb 761[®] and placebo control groups' pretreatment baseline neuropsychological test scores, while controlling for the significant difference observed between the ages of the two groups, separate two-tailed analyses of covariance (ANCOVA) were performed. The results from these analyses revealed only one significant difference between the two groups. Specifically, on the WMS-III Faces II subtest, the placebo group recognized significantly, $F(1, 245) = 4.67$, $p < 0.03$, more human faces ($n = 0.79$ faces) that had been presented to them 30 min earlier compared with the EGb 761[®] group.

For the Follow-up Self-report Questionnaire, a proportional odds model (Agresti, 1989) was utilized to account for the ordinal structure of the four outcome questions. For analysis purposes, frequency data for each question were summarized into three categories, namely 'worse' ('much worse' and 'somewhat worse' categories), 'no change', and 'improved' ('somewhat improved' and 'much improved' categories). From the four questions included in the Follow-up Self-report Questionnaire, only a significant relationship ($\chi^2(1) = 3.83$, $p = 0.05$) was found between the type of treatment received (i.e. EGb 761[®] or placebo) and participants' ratings of their 'overall abilities to remember' by treatment end. Specifically, more ($n = 34$ [27%]) participants in the EGb 761[®] group rated their overall abilities to remember by treatment end as either 'somewhat improved' or 'much improved' compared with the placebo control group ($n = 21$ [17%]). Table 3 provides an overview of the

Table 3. Proportional odds model and chi square tests for the summarized Follow-up Self-report Questionnaire frequency data

Source	Model fit		Group difference	
	χ^2	p	χ^2	p
Memory	0.04	0.84	3.83	0.05 ^a
Mood	0.24	0.63	0.31	0.58
Energy	0.28	0.60	2.16	0.14
Health	0.45	0.50	0.33	0.57

^aSignificant.

Table 4. Number of adverse events categorized by body system among participants who were initially randomized

Body system/adverse event	Total ($n = 262$)	Ginkgo ($n = 131$)	Placebo ($n = 131$)
Nervous system	11	6	5
Gastrointestinal	8	3	5
Respiratory/allergic	5	2	3
Genitourinary	3	1	2
Cardiovascular	2	0	2
Dermatologic	1	0	1
Miscellaneous	2	0	2
Total	32	12	20

proportional odds model and chi square tests for the summarized Follow-up Self-report Questionnaire frequency data.

SAFETY

Data from the 262 participants who were initially randomized in this study were utilized in the safety analyses. Table 4 provides an overview of the reported adverse events classified by body system for the EGb 761[®] and placebo groups.

Only one serious adverse event was reported during the study. Specifically, one participant in the placebo group suffered an intracranial bleed which was found to be consistent with a hemorrhagic cerebrovascular accident. All of the remaining adverse events that were reported were rated as either mild or mild to moderate in intensity and no causal relationship was determined between the EGb 761[®] treatment and any adverse event.

Of the 11 adverse events categorized as related to the nervous system, nine were headaches (EGb 761[®] group, 5; placebo group, 4) and two were episodes of insomnia (EGb 761[®] group, 1; placebo group, 1). Gastrointestinal adverse events consisted of episodes of gastrointestinal upset, including bouts of nausea and/or vomiting of limited duration (EGb 761[®] group, 3; placebo group, 3), gastrointestinal pain (placebo group, 1), and a 'gallbladder attack' (placebo group, 1). Respiratory system/allergic adverse events included allergy symptoms involving nasal congestion, sensation of pressure in the ears and/or coughing (EGb 761[®] group, 1; placebo group, 3) and sinus infection (EGb 761[®] group, 1). Specific genitourinary adverse events consisted of increased urinary frequency (EGb 761[®] group, 1; placebo group, 1) and elective bladder repair surgery (placebo group, 1). As previously noted, one of the two adverse events classified as related to the cardiovascular

system was an intracranial hemorrhage (placebo group, 1), while the other event was a report of lower extremity edema (placebo group, 1). Only one dermatologic system event was reported during the study, namely a rash on the arms and nose (placebo, 1). Two adverse events occurring in the placebo group (i.e. weight gain and leg pain) could not be readily categorized into any particular body system.

Overall, more adverse events were reported by the placebo controls than by the EGb 761[®] group. Specifically, a total of 20 adverse events were reported by the placebo group compared with 12 events reported by the EGb 761[®] group.

DISCUSSION

To our knowledge, this is the first large-scaled, double-blind, placebo-controlled, randomized clinical trial to examine the short-term (i.e. 6 weeks) efficacy of *Ginkgo biloba* extract EGb 761[®] on the neuropsychological functioning of cognitively intact older adults.

The primary findings of this study indicated that participants who received 180 mg of EGb 761[®] daily for 6 weeks exhibited significantly more improvement on the Selective Reminding Test's delayed free recall and delayed recognition tasks by treatment end compared with individuals in the placebo-controlled group. These parallel results indicated that relatively short-term (i.e. 6 weeks) utilization of EGb 761[®] enhanced both delayed (i.e. 30 min) free recall and delayed (i.e. 30 min) recognition of noncontextual, auditory-verbal material.

The group receiving EGb 761[®] also demonstrated significantly greater improvement on the WMS-III Faces II subtest by treatment end compared with the placebo group. Although this finding was suggestive of enhanced delayed (i.e. 30 min) recognition of visual material (i.e. human faces) in the EGb 761[®] group, based on the significant difference found between the two groups' pretreatment baseline subtest scores on this measure (where the placebo group recognized slightly more ($n = 0.79$) faces), the result should be interpreted with caution. Taken together, however, the significant SRT and WMS-III FII delayed free recall and recognition findings suggested that relatively short-term (i.e. 6 weeks) utilization of EGb 761[®] proved efficacious in enhancing certain aspects of declarative episodic memory, particularly as regards the efficiency of retrieval, and possibly the consolidation/storage, of recently (30 min earlier) learned material.

It should also be noted that the EGb 761[®] group demonstrated more improvement, albeit nonsignifi-

cant, on five out of seven of the remaining Selective Reminding Test variables by treatment end compared with the placebo controls. The EGb 761[®] group, versus placebo controls, also exhibited more non-significant improvement by treatment end on the two WAIS-III subtests (i.e. Block Design and Digit Symbol) and the WMS-III Faces I subtest that were included in this study. Overall, of the 13 total neuropsychological outcome/efficacy variables that were utilized in this study, the EGb 761[®] group exhibited more improvement by treatment end on 11 of these measures (includes both significant and nonsignificant results) compared with the placebo group.

Supporting data for this study's objective, standardized, neuropsychological findings were found in the participants' subjective Follow-up Self-report Questionnaire ratings of changes in their overall abilities to remember from pretreatment baseline to after 6 weeks of treatment. Specifically, significantly more ($n = 34$ [27%]) cognitively intact, older adults in the EGb 761[®] group rated their overall abilities to remember by treatment end as either 'somewhat improved' or 'much improved' compared with placebo controls ($n = 21$ [17%]). This finding suggested that EGb 761[®] not only enhanced aspects of participants' memory processes by treatment end that could be identified via objective, standardized, neuropsychological measures (i.e. Selective Reminding Test tasks), but that the memory improvements were also of the magnitude that could be perceived by participants who received a 6-week treatment regimen of EGb 761[®]. This subjective finding was also consistent with the results from our (Mix and Crews, 2000) previous small-scaled study where more participants who received EGb 761[®] for 6 weeks rated their abilities to remember by treatment end as 'improved,' compared with the placebo controls.

Taken together, the results from both the objective, standardized, neuropsychological tests and subjective Follow-up Self-report Questionnaire provided complementary evidence of the potential efficacy of relatively short-term (i.e. 6 weeks) utilization of EGb 761[®] in enhancing certain neurocognitive/memory functions of cognitively intact older adults, 60 years of age and over. The limited number and intensity of adverse events that were reported by the EGb 761[®] group, as well as the absence of identifiable causal relationships between the extract and these events, also suggested that the extract was well tolerated by those participants who received 180 mg of EGb 761[®] daily for 6 weeks.

The present study's findings appeared consistent with past studies that have demonstrated the efficacy

of *Ginkgo biloba* extract for the treatment of dementia and 'cerebral insufficiency' (Allain *et al.*, 1993; Drabaek *et al.*, 1996; Graessel, 1992; Hofferberth, 1994; Hoepfenmuller, 1994; Kanowski *et al.*, 1996; Rai *et al.*, 1991; Semlitsch *et al.*, 1995; LeBars *et al.*, 1997). The results also bolster those from the few previously published, small-scaled studies that have found improvements in cognitive functioning among older cognitively intact adults (Mix and Crews, 2000) and young, healthy volunteers (Kennedy *et al.*, 2000; Stough *et al.*, 2001).

A diversity of mechanisms has been proposed to account for the effects of *Ginkgo biloba* extract that have been reported in previous studies involving animals and humans. These include: increased cerebral blood flow (Cahn, 1985; Heiss and Zeiler, 1978; Tea *et al.*, 1987), protection against hypoxia/ischemic damage (Cahn, 1985; Heiss and Zeiler, 1978; Tea *et al.*, 1987; Karcher *et al.*, 1984; Spinnewyn *et al.*, 1986), platelet activating factor (PAF) antagonism (Borzeix, 1980; Braquet *et al.*, 1985; Chung *et al.*, 1987; Klein, 1988; Guinot *et al.*, 1989), reduction in relative erythrocyte viscosity (Anadere *et al.*, 1985; Költringer *et al.*, 1989; Artmann *et al.*, 1989, 1991; Költringer *et al.*, 1995), radical scavenging properties (Chatterjee and Gabard, 1981; Pincemail *et al.*, 1989; Barth *et al.*, 1991; Dorman *et al.*, 1992; Dumont *et al.*, 1992), protection against cerebral edema (Gabard and Chatterjee, 1980; Otani *et al.*, 1986; Sancesario and Kreutzberg, 1986; Borzeix, 1985; Attella *et al.*, 1989), a myelin protective effect (Chatterjee and Gabard, 1984), increased neurotransmitter uptake (Ramassamy *et al.*, 1992; Křištofiková *et al.*, 1992) and neurotransmitter receptor density (Taylor, 1985; Hugué *et al.*, 1994), decreased age-related cerebral changes (Barkats *et al.*, 1994) and increased alpha wave activity with concomitant reduction in theta wave frequencies as measured by electroencephalography (Hofferberth, 1989, 1991, 1994; Sitzer, 1987; Luthringer *et al.*, 1995; Itil *et al.*, 1996). Although the precise mechanisms responsible for the current findings remain speculative, it seems plausible that several of these factors may have interacted synergistically to promote the enhancement of the EGb 761[®] group's memory processes.

Future research is required to extend the present study's findings. Specifically, large-scaled clinical trials are needed to examine the efficacy of EGb 761[®] on the neuropsychological processes of younger, cognitively intact groups (e.g. middle-aged individuals). Longitudinal studies should also be conducted to investigate the efficacy of long-term (e.g. 6 months, plus) utilization of *Ginkgo biloba* extract on

the neuropsychological functioning of cognitively intact persons of varying age cohorts. Finally, additional research is required that examines the precise mechanisms that are responsible for EGb 761[®]'s observed beneficial neurocognitive effects.

ACKNOWLEDGMENTS

The authors are indebted to the following persons who provided administrative assistance and/or served as neuropsychological test technicians: Megan S. Burris, Gladys R. Crews, Nancy A. Davis, Megan N. Dinsmore, Julie M. Gabrielli, Michael A. Leger, Culvette L. Miller, Lynne Mix, Tanya K. Nolette and Cherad R. Woodyard. Special thanks are also extended to Jannie M. Teufel, BS, for her assistance in coordinating this research, to SoonBok Park, PhD, for her statistical support, to Richard Lane, MD, who served as Medical Director of this project, and the staff of Light Medical, Inc.

This research was supported by independent research grants from Dr Willmar Schwabe GmbH & Co., Karlsruhe, Germany and Nature's Way Products, Inc., Springville, Utah.

REFERENCES

- Agresti A. Tutorial on modeling ordered categorical response data. *Psychol Bull* 1989; **105**: 290–301.
- Allain H, Raoul P, Lieury A, LeCoz F, Gandon JM, d'Arbigny P. Effect of two doses of *Ginkgo biloba* extract (EGb 761[®]) on the dual-coding test in elderly subjects. *Clin Ther* 1993; **15**: 549–558.
- Anadere I, Chmiel H, Witte S. Hemorheological findings in patients with completed stroke and the influence of a *Ginkgo biloba* extract. *Clin Hemorheol* 1985; **5**: 411–420.
- Artmann G, Keller U, Schmid-Schönbein H. Changes in red cell micromechanics as *ex vivo* bioassay for drug effects. *Clin Hemorheol* 1991; **11**: 76, abstract F4.12.
- Artmann G, Michaelis P, Schmid-Schönbein H. Effect of *Ginkgo biloba* extract 761 on microheological parameters of red blood cells. *Clin Hemorheol* 1989; **9**: 444.
- Attella MJ, Hoffman SW, Stasio MJ, Stein DG. *Ginkgo biloba* extract facilitates recovery from penetrating brain injury in adult male rats. *Exp Neurol* 1989; **105**: 62–71.
- Barkats M, Venault P, Christen Y, Cohen-Salmon C. Effect of long-term treatment with EGb 761[®] on age-dependent structural changes in the hippocampi of three inbred mouse strains. *Life Sci* 1994; **56**: 213–222.
- Barth SA, Inselmann G, Engemann R, Heidemann HT. Influences of *Ginkgo biloba* on cyclosporin A induced lipid peroxidation in human liver microsomes in comparison to vitamin E, glutathione and *N*-acetylcysteine. *Biochem Pharmacol* 1991; **41**: 1521–1526.
- Borzeix MG. 1985. Effects of *Ginkgo biloba* extract on two types of cerebral edema. In *Effects of Ginkgo biloba Extract on Organic Cerebral Impairment*, Agnoli A, Rapin JR, Scapagnini V, Weitbrecht W-U (eds). John Libbey Eurotext Ltd: London, UK. 1985; 51–56.

- Borzeix MG. Recherches sur l'action atigrégante de l'extrait de *Ginkgo biloba*. Activité au niveau des artères et des veines de la pie mère chez le lapin. *Extrait de La Semaine des Hôpitaux de Paris* 1980; **56**: 393–398.
- Braquet PG, Spinnewyn B, Braquet M, et al. BN 52021 and related compounds: a new series of highly specific PAF-acether receptor antagonists isolated from *Ginkgo biloba* L. *Blood Vessel* 1985; **16**: 559–572.
- Buschke H, Fuld PA. Evaluating storage, retention, and retrieval in disordered memory and learning. *Neurology* 1974; **11**: 1019–1025.
- Cahn J. Effects of *Ginkgo biloba* extract (GBE) on the acute phase of cerebral ischemia due to embolisms. In *Effects of Ginkgo biloba Extract on Organic Cerebral Impairment*, Agnoli A, Rapin JR, Scapagnini V, Weitbrecht W-U (eds). John Libbey Eurotext Ltd: London, UK, 1985; 43–49.
- Chatterjee SS, Gabard B. Protective effect of an extract of *Ginkgo biloba* and other hydroxyl radical scavengers against hypoxia. *Eighth International Congress of Pharmacology, Tokyo* 19–24 July, 1981; International Union of Pharmacology (IUPHAR), Tokyo, Japan. Abstr S483.
- Chatterjee SS, Gabard B. Effect of an extract of *Ginkgo biloba* on experimental neurotoxicities. *Naunyn Schmiedeberg's Arch Pharmacol* 1984; **325**: R82, Abstr 327.
- Chung KF, McCusker M, Page CP, Dent G, Guinot PH, Barnes PJ. Effect of a ginkgolide mixture (BN 52063) in antagonising skin and platelet responses to platelet activating factor in man. *Lancet* 1987; **1**: 248–250.
- Cockrell JR, Folstein MF. Mini-Mental State Examination (MMSE). *Psychopharmacol Bull* 1988; **24**: 689–692.
- Dorman DC, Côté LM, Buck WB. Effects of an extract of *Ginkgo biloba* on bromethalin induced lipid peroxidation and edema in rats. *Am J Vet Res* 1992; **53**: 138–143.
- Drabaek H, Petersen JR, Winberg N, Hansen KF, Mehlsen J. Effekten af *Ginkgo biloba*-ekstrakt hos patienter med claudicatio intermittens. *Ugeskr Laeger* 1996; **158**: 3928–3931.
- Dumont E, Petit E, Tarrade T, Nouvelot A. UV-C irradiation-induced peroxidative degradation of microsomal fatty acids and proteins: protection by an extract of *Ginkgo biloba* (EGb 761). *Free Rad Biol Med* 1992; **13**: 197–203.
- 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; **12**: 189–198.
- Gabard B, Chatterjee SS. Cerebral edema induced by triethyltin in the rat: effect of an extract of *Ginkgo biloba*. *Naunyn Schmiedeberg's Arch Pharmacol* 1980; **311**: R68, Abstr. 271.
- Graessel E. Einfluss von *Ginkgo biloba*-Extrakt auf die geistige Leistungsfähigkeit. Doppelblindstudie unter computerisierten Messbedingungen bei Patienten mit Zerebralsuffizienz. *Fortschr Med* 1992; **110**: 73–76.
- Guinot P, Caffrey E, Lambe R, Darragh A. Tanakan inhibits platelet-activating-factor-induced platelet aggregation in healthy male volunteers. *Haemostasis* 1989; **19**: 219–223.
- Haase J, Halama P, Hoerr R. Wirksamkeit kurzdauernder Infusionsbehandlungen mit *Ginkgo-biloba*-Spezialextrakt EGb 761 bei Demenz von vaskulären und Alzheimer-Typ. *Z Gerontol Geriatr* 1996; **29**: 302–309.
- Heiss WD, Zeiler K. Medikamentöse Beeinflussung der Hirndurchblutung. *Pharmakotherapie* 1978; **1**: 137–144.
- Hoefenmuller W. Nachweis der therapeutischen Wirksamkeit eines *Ginkgo biloba*-Spezialextraktes. Meta-Analyse von 11 klinischen Studien bei Patienten mit Hirnleistungsstörungen im Alter. *Arzneimittelforschung* 1994; **44**: 1005–1013.
- Hofferberth B. The effect of *Ginkgo biloba* extract on neurophysiological and psychometric measurement results in patients with psychotic organic brain syndrome: a double-blind study against placebo. *Arzneimittelforschung* 1989; **39**: 918–922.
- Hofferberth B. Simultanerfassung elektrophysiologischer, psychometrischer und rheologischer Parameter bei Patienten mit hirnrorganischem Psychosyndrom und erhöhtem Gefäßrisiko—Eine placebokontrollierte Doppelblindstudie mit *Ginkgo-biloba*-Extrakt EGb 761[®]. In *Mikrozirkulation in Gehirn und Sinnesorganen*, Stodtmeister R, Pillunat LE (eds). Enke: Stuttgart, 1991; 64–74.
- Hofferberth B. The efficacy of EGb 761[®] in patients with senile dementia of the Alzheimer type, a double-blind, placebo-controlled study on different levels of investigation. *Hum Psychopharmacol Clin Exp* 1994; **9**: 215–222.
- Huguet F, Drieu K, Piriou A. Decreased cerebral 5-HT_{1A} receptors during aging: reversal by *Ginkgo biloba* extract (EGb 761[®]). *J Pharm Pharmacol* 1994; **46**: 316–318.
- Itil TM, Eralp E, Tsambis E, Itil K, Stein U. Central nervous system effects of *Ginkgo biloba*, a plant extract. *Am J Ther* 1996; **3**: 63–73.
- Itil T, Martorano D. Natural substances in psychiatry (*Ginkgo biloba* in dementia). *Psychopharmacol Bull* 1995; **31**: 147–158.
- Kanowski S, Herrmann WM, Stephan K, Wierich W, Hoerr 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; **29**: 47–56.
- Karcher L, Zagermann P, Krieglstein J. Effects of an extract of *Ginkgo biloba* on rat brain energy metabolism in hypoxia. *Naunyn Schmiedeberg's Arch Pharmacol* 1984; **327**: 31–35.
- Kaufman AS, Lichtenberger EO (eds). *Essentials of WAIS-III Assessment*. John Wiley: New York, 1999.
- Kennedy DO, Scholey AB, Wesnes KA. The dose-dependent cognitive effects of acute administration of *Ginkgo biloba* to healthy young volunteers. *Psychopharmacology* 2000; **151**: 416–423.
- Klein P. Untersuchung über die Hemmwirkung von *Ginkgo-biloba*-Extrakt. PAF-induzierte Thrombozytenaggregation *in vitro* und *in vivo* und Spontanaggregation—Untersuchung mit Tebonin[®]. *Therapiewoche* 1988; **38**: 2379–2383.
- Költringer P, Eber O, Lind P, et al. Mikrozirkulation und Viskoelastizität des Vollblutes unter *Ginkgo-biloba*-Extrakt. Eine placebokontrollierte, randomisierte Doppelblind-Studie. *Perfusion* 1989; **1/89**: 28–30.
- Költringer P, Langsteiger W, Ober O. Dose-dependent hemorheological effects and microcirculatory modifications following intravenous administration of *Ginkgo biloba* special extract EGb 761[®]. *Clin Hemorheol* 1995; **15**: 649–656.
- Křištofiková Z, Benešová O, Tejkalová H. Changes of high-affinity choline uptake in the hippocampus of old rats after long-term administration of two nootropic drugs (tacrine and *Ginkgo biloba* extract). *Dementia* 1992; **3**: 304–307.
- LeBars PL, Katz MM, Berman N, Itil TM, Freedman AM, Schatzberg AF. A placebo-controlled, double-blind, randomized trial of an extract of *Ginkgo biloba* for dementia. *J Am Med Assoc* 1997; **278**: 1327–1332.
- Lezak MO. *Neuropsychological Assessment*, 3rd edn. Oxford University Press: New York, 1995; 502–505.
- Luthringer R, d'Arbigny P, Macher JP. *Ginkgo biloba* extract (EGb 761[®]), EEG and event-related potentials. In *Advances in Ginkgo biloba Extract Research*, Vol. 4. *Effects of Ginkgo biloba on Aging and Age-related Disorders*, Christen Y, Courtois Y, Droy-Lefaix MT (eds). Elsevier: Paris, 1995; 107–118.
- Mix JA, Crews WD, Jr. An examination of the efficacy of *Ginkgo biloba* extract EGb 761[®] on the neuropsychological functioning of cognitively intact older adults. *J Altern Complement Med* 2000; **6**: 219–229.

- Otani M, Chatterjee SS, Gabard B, Kreutzberg GW. Effects of an extract of *Ginkgo biloba* on triethyltin-induced cerebral edema. *Acta Neuropathol (Berl)* 1986; **69**: 54–65.
- Pincemail J, Dupuis M, Nasr C, *et al.* Superoxide anion scavenging effect and superoxide dismutase activity of *Ginkgo biloba* extract. *Experientia* 1989; **45**: 708–712.
- Rai GS, Shovlin C, Wesnes KA. A double-blind, placebo-controlled study of *Ginkgo biloba* extract ('tanakan') in elderly outpatients with mild to moderate memory impairment. *Curr Med Res Opin* 1991; **12**: 350–355.
- Ramassamy C, Christen Y, Clostre F, Costentin J. The *Ginkgo biloba* extract, EGb 761[®], increases synaptosomal uptake of 5-hydroxytryptamine: *in vitro* and *ex vivo* studies. *J Pharm Pharmacol* 1992; **44**: 943–945.
- Sancesario G, Kreutzberg GW. Stimulation of astrocytes affects cytotoxic brain edema. *Acta Neuropathol (Berl)* 1986; **72**: 3–14.
- Semlitsch HV, Anderer P, Saletu B, Binder GA, Decker KA. Cognitive psychophysiology in nootropic drug research: effects of *Ginkgo biloba* on event-related potentials (P300) in age-associated memory impairment. *Pharmacopsychiatry* 1995; **28**: 134–142.
- Sitzer G. Die zerebrovaskuläre Insuffizienz. EEG-Langzeitstudie zur Wirksamkeit von Tebonin[®] forte bei Patienten mit chronischer zerebrovaskulärer Insuffizienz. *Der Kassenarzt* 1987; **18**: 28–35.
- Spinnewyn B, Blavet N, Clostre F. Effets de l'extrait de *Ginkgo biloba* sur un modèle d'ischémie cérébrale chez la gerbille. *Presse Méd* 1986; **15**: 1511–1515.
- Spreen O, Strauss E. *A Compendium of Neuropsychological Tests*. Oxford University Press: New York, 1998; 282–295.
- Stough C, Clarke J, Lloyd J, Nathan PJ. Neuropsychological changes after 30-day *Ginkgo biloba* administration in healthy participants. *Int J Neuropsychopharmacol* 2001; **4**: 131–134.
- Taylor JE. The effects of chronic, oral *Ginkgo biloba* extract administration on neurotransmitter receptor binding in young and aged Fisher 344 rats. In *Effects of Ginkgo biloba Extract on Organic Cerebral Impairment*, Agnoli A, Rapin JR, Scapagnini V, Weitbrecht W-U (eds). John Libbey Eurotext Ltd: 1985; 31–34.
- Tea S, Celsis P, Clanet M, Marc-Vergnes J-P, Boeters U. Quantifizierte Parameter zum Nachweis von cerebraler Durchblutungs- und Stoffwechselsteigerung unter *Ginkgo-biloba*-Therapie. *Therapiewoche* 1987; **37**: 2655–2657.
- Wechsler D. *WAIS-III Administration and Scoring Manual*. The Psychological Corporation: San Antonio, TX. 1997a.
- Wechsler D. *WMS-III Administration and Scoring Manual*. The Psychological Corporation: San Antonio, TX. 1997b.
- Wechsler D. *WAIS-III, WMS-III Technical Manual*. The Psychological Corporation: San Antonio, TX. 1997c.
- Wesnes K, Simmons D, Rook M, Simpson PM. A double-blind placebo-controlled trial of Tanakan in the treatment of idiopathic cognitive impairment in the elderly. *Hum Psychopharmacol Clin Exp* 1987; **2**: 159–169.