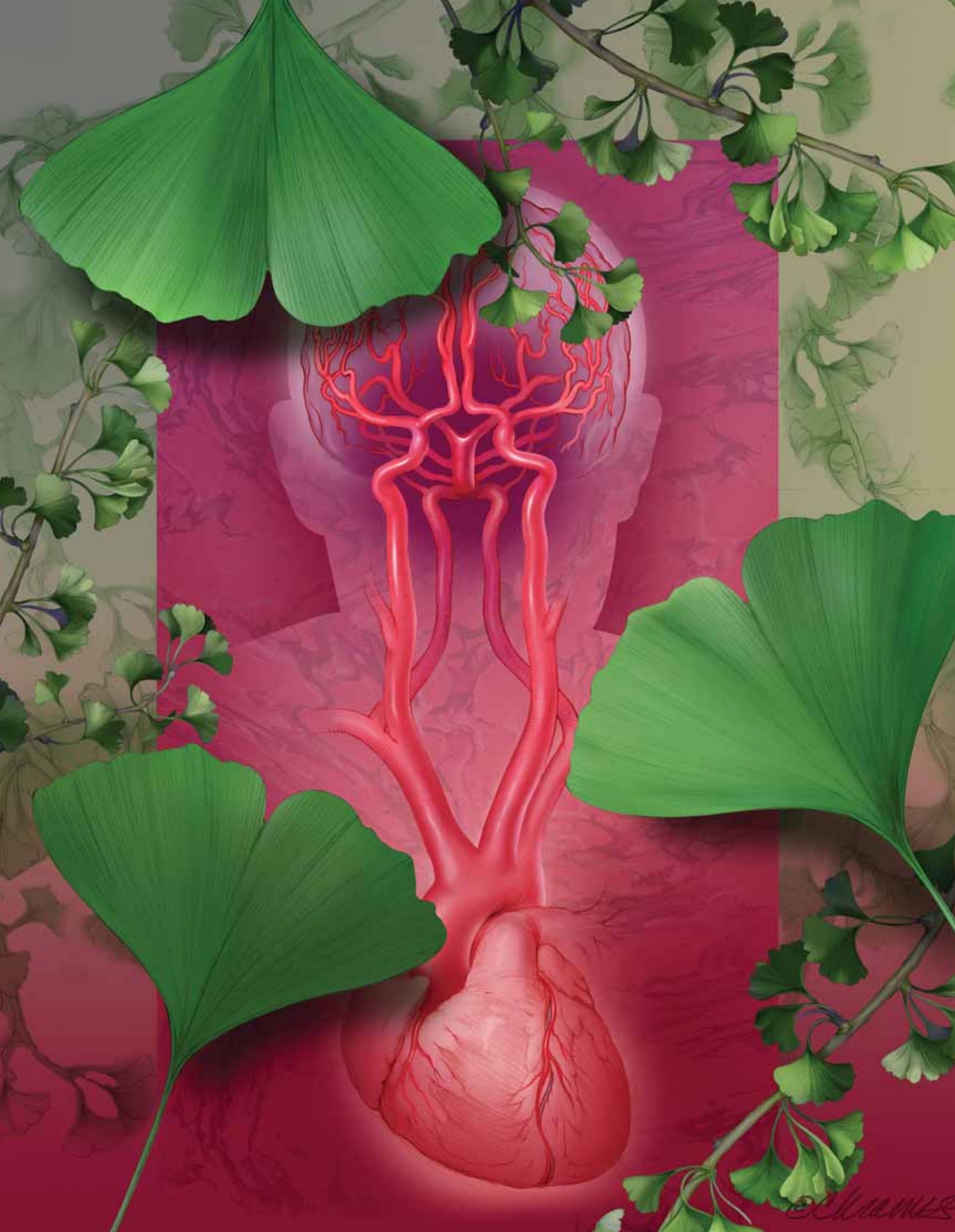

The Neuropsychological Efficacy of Ginkgo Preparations in Healthy and Cognitively Intact Adults

A Comprehensive Review

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Introduction

In recent years, there has been increased interest in the utilization of ginkgo (*Ginkgo biloba* L., Ginkgoaceae) leaf standardized extract (GBE) for the treatment of dementia and cognitive impairment. Much of this interest has undoubtedly been related to the growing number of research studies and clinical trials that have demonstrated the potential efficacy of GBE in the treatment of such disorders. While a detailed, systemic review of these studies is beyond the scope of this paper, a recent Cochran Review[1] of 33 randomized, double-blind, controlled trials that examined the effects of GBE on individuals with acquired cognitive impairment (including dementias) concluded that GBE was associated with "promising evidence of improvement in cognition and function."

Similarly, there is also a growing body of published research that has focused on the potential efficacy of GBE in enhancing the neuropsychological processes of "healthy" adults and those who are not experiencing (or without evidence of) notable cognitive difficulties (i.e., cognitively intact individuals). Canter and Ernst[2] authored a review of the controlled trials involving GBE's potential effects on cognitive functioning in healthy persons in 2002; however, there appears to be an absence of more recent reviews that have focused solely on such published studies of GBE. Thus, the purpose of this paper is to provide a comprehensive review of the published scientific literature (through September 2004) that has examined the efficacy of GBE (and unspecified preparations of ginkgo in one study) in healthy and cognitively intact persons.

The studies reviewed in this paper are divided into 2 categories: acute studies and short- to long-term studies. Acute studies were defined as the administration of GBE to healthy/cognitively intact adults for 2 days or less. Short- to long-term studies were defined as the administration of GBE to healthy/cognitively intact adults for a minimum of 5 days and up to 2 or more years. This review contains the following sections: Methods, Acute Studies, Summary of Acute Studies, Short- to Long-Term Studies, Summary of Short- to Long-Term Studies, and Conclusions and Directions for Future Research.

Method

Using the key words *Ginkgo biloba* and Cognitive (or Cognition), *Ginkgo biloba* and Memory, *Ginkgo biloba* and Healthy, *Ginkgo biloba* and Cognitively Intact, the authors of this paper conducted comprehensive literature searches in September 2004 of the following databases: PubMed (entire database through September 2004) and PsycINFO (entire database through September 2004). All articles obtained via these searches were also reviewed for additional, related articles that addressed the efficacy of ginkgo in healthy and cognitively intact persons. Published studies were selected for inclusion in this review if they utilized only "healthy" and/or "cognitively intact" adult participants, and if they employed one or more outcome measures that assessed the efficacy of ginkgo on some aspect(s) of neuropsychological functioning. It should be noted, however, that trials which involved the administration of GBE in combination with other agents, such as Asian ginseng (*Panax ginseng* C. A. Meyer, Araliaceae) root

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extract,[3-5] or bacopa (*Bacopa monnieri* [L.] Pennell, Scrophulariaceae)[6] were not included in this review due to the inability to separate the specific effects of GBE from the other phytomedicinal preparations.

The purpose of this paper is to provide a comprehensive review of the published scientific literature that has examined the neuropsychological efficacy of GBE in healthy and cognitively intact persons.

Acute Studies

A total of 7 published studies were found which have examined the acute neuropsychological effects of GBE in healthy individuals. (Acute studies were defined as the administration of GBE to healthy/cognitively intact adults for 2 days or less.) Table 1 on page 54 provides an overview of these studies, which are listed in chronological order. Table 2 provides summaries of the proprietary GBE preparations and Table 3 provides outcome measures utilized in the investigations (see pages 56 and 57, respectively).

Subhan and Hindmarch[7] were among the first to investigate the acute effects of GBE in healthy volunteers. In particular, 8 healthy female participants received 3 different doses (i.e., 120, 240, and 600 mg) of GBE [Tanakan®/Tebonin®, Dr. Willmar Schwabe Pharmaceuticals GmbH & Co., Karlsruhe, Germany] or a matching placebo via a randomized, double-blind, crossover design. A battery of psychological tests was administered one hour after each treatment (see Table 1 for a listing of the specific tests utilized). Among the extract doses and 4 outcome measures utilized in the study, participants exhibited significant improvement in their memory scanning abilities (a decrease in response latency on the Sternberg technique) following ingestion of 600 mg of GBE, as compared to placebo. The authors indicated that these results were suggestive of an effect of GBE on the serial comparison stage of the reaction process on the Sternberg task.

Ginkgo *Ginkgo biloba*. Photo © 2005 stevenfoster.com

Similarly, Hindmarch[8] reported in a French journal the results of an investigation involving 8 healthy female volunteers that appears strikingly similar, if not identical, to the one previously co-authored by Subhan and Hindmarch.[7] As noted in Table 1, the sample characteristics (i.e., size, gender-makeup, mean age and age range), study design, duration of treatments/assessments, GBE composition and doses, and outcome measures utilized appeared identical in both studies. Furthermore, the results across the 2 studies appeared identical, as the Hindmarch[8] study also indicated significant improvements in aspects of participants' short-term memory processes, as assessed via the Sternberg technique, 1 hour after ingestion of 600 mg of the GBE (Tanakan®), versus placebo. Similar to the Subhan and Hindmarch[7] study, no significant effects were found for any of the other extract doses or assessment measures.

In another investigation published in a French journal, Warot and colleagues[9] evaluated the acute efficacy of 600 mg of 2 GBE preparations (Ginkgo® and Tanakan®), versus a placebo, on the psychomotor and memory performances of 12 healthy female participants via a double-blind, placebo-controlled design (see Table 1 for a listing of the specific tests utilized). Psychological testing was completed before and 1 hour after the ingestion of each dose. Although no significant improvements were noted for the GBE treatments on any of the tests and measures utilized, as compared to baseline, participants' scores for image recall (picture recall) remained relatively unchanged during the Tanakan® trial, but decreased under the placebo and Ginkgo® conditions.

Rigney, Kimber, and Hindmarch[10] appeared to be among the first to include healthy males in an examination of the efficacy of acute doses of a GBE [Ginkgo Special Extract LI 1370; Lichtwer Pharma, Berlin, Germany] on memory and psychomotor performances. Specifically, their study compared 4 doses of GBE (i.e., total doses of 120, 150, 240, and 300 mg/day), versus placebo, for 2 days via a randomized, double-blind, placebo-controlled, 5-way cross-over design in a sample of 36 asymptomatic/healthy volunteers (i.e., 22 males, 14 females). Psychometric test batteries were administered across the 2 days of each treatment prior to GBE ingestion and then hourly until 11 hours post-dosing (see Table 1 for a listing of the specific tests utilized). Findings indicated that on the Sternberg short-term memory scanning task, participants exhibited significantly faster reaction times for both 120 mg and 300 mg of GBE, as compared to placebo, on each of the 2 days of the study. Participants receiving 240 mg of GBE, versus placebo, displayed significantly faster performances on the second day of the trial. It was noted that this enhancing effect was most evident for those taking the 120 mg dose of GBE and most pronounced for the oldest age group (i.e., 50 to 59 years). Although no significant treatment effects were observed on immediate and delayed word recall tasks, both 120 mg and 240 mg increased the overall number of words recalled during the immediate recall task, with a more pronounced increase noted for the 120 mg dose. On the Critical Flicker Fusion (CFF) task, although an overall treatment effect was significant, none of the GBE doses produced effects that differed significantly from placebo. Participants who received 120 mg of GBE, however, exhibited higher CFF thresholds, as

compared to all other treatments and placebo, and their performances were significantly higher than those who ingested 240 mg of the extract. No other significant treatment effects were observed for any of the remaining outcome measures. Overall, Rigney and associates[10] indicated that their results were very similar to those of Subhan and Hindmarch[7] which also found improved performances on the Sternberg memory scanning task, but no significant results on the CFF, choice reaction time, or subject ratings of arousal measures. It was noted, however, that as compared to the Subhan and Hindmarch[7] study, the Rigney and associates[10] findings suggested that (1) a much lower dose of GBE (i.e., 120 mg versus 600 mg) resulted in the most cognitive enhancement (e.g., working memory), (2) the effects of GBE may be dose dependent, but not necessarily in a linear dose-related fashion, and (3) such enhancing effects were more likely to be displayed by individuals 50 to 59 years old.

The dose-dependent cognitive effects of acute GBE administration in 20 healthy young adults were also examined by Kennedy and colleagues[11] via a double-blind, placebo-controlled, multidose, balanced, crossover design. Participants were administered 3 different doses (i.e., 120, 240, and 360 mg) of a standardized GBE [GK501; Pharmaton, SA, Lugano, Switzerland] or a matching placebo. The cognitive performances of the participants were evaluated via a tailored version of the Cognitive Drug Research (CDR) computerized assessment battery immediately prior to, and again at 1, 2.5, 4, and 6 hours after, each dose. Four cognitive performance factors, derived via factor analysis of the CDR battery's subtests (i.e., speed of attention, accuracy of attention, quality of memory, and speed of memory factors), were utilized as the primary outcome measures. The findings indicated significant improvements on the speed of attention factor for the 2 highest GBE doses (i.e., 240 and 360 mg) at time points 2.5, 4, and 6 hours post-dose. For the quality of memory factor, significantly enhanced performances were exhibited by participants after ingestion of 120 mg of GBE at both 1 and 4 hours post-dosing, as compared to placebo. A similar positive trend was also noted for the 240 mg dose of GBE for the same post-dosing time points. For the speed of memory factor, significantly enhanced speed was demonstrated on memory tasks after the administration of 360 mg of GBE at 2.5 hours post-dose, with positive trends also noted for the 120 mg and 360 mg at 6 hours post-dosing. Alternatively, a significant reduction in speed of memory was noted for the 240 mg dose of GBE, versus placebo, at 4 hours post-dosing and this dose was noted to "under-perform" the other doses on the speed of memory factor at all post-dose time points. Similarly, on the accuracy of attention factor, a significant decrease in accuracy was noted for the 240 mg dose of GBE at 1 hour post-dose. No significant treatment effects were found on 3 mood factors (i.e., alertness, contentedness, or calmness) derived from the Bond-Lader visual analogue scales. Taken together, the authors noted that (1) cognitive enhancement following administration of GBE was most evident in participants' increased speed of performance on tasks assessing attention and (2) such effects appeared both dose and time dependent (i.e., significant improvement seen only at

Ginkgo *Ginkgo biloba*. Photo © 2005 stevenfoster.com

the 2 highest doses and at the 3 later time points). A different pattern of effects was also noted on the quality of memory factor with significant enhancement observed for the lowest dose (i.e., 120 mg) at 1 and 4 hours post-dose, with similar trends apparent for 240 mg at the same time points.

Similarly, Scholey and Kennedy[12] documented the findings of 3 studies that examined the acute, dose-dependent cognitive effects of GBE [GK501; Pharmaton, SA, Lugano, Switzerland], Ginseng extract [G115; aka Ginsana®, Pharmaton, SA, Lugano, Switzerland], and a combination of the 2 extracts via double-blind, placebo-controlled, balanced, crossover designs. For the purposes of this paper, only the study involving doses of GBE will be reviewed. The GBE study involved a total of 20 healthy young volunteers who were each administered 3 different doses (120, 240, and 360 mg) of GBE or a placebo on separate days. The participants completed 2 computerized serial subtraction tasks (i.e., Serial Threes and Serial Sevens) at each pretreatment baseline and again after 1, 2.5, 4, and 6 hours post-dose. Findings indicated that all 3 doses of the GBE, as compared to placebo, resulted in significant increases in the number of Serial Threes subtractions at the 4-hour post-dosing testing session. A significant increase in Serial Threes subtractions was also observed 6 hours after ingestion of the 240 mg dose of GBE. In contrast, 4 hours after the administration of 120 mg of the GBE, significantly more subtraction errors were noted on the Serial Threes task. For the Serial Sevens task, while no significant differences were noted in the total number of subtractions for any of the doses of GBE, all doses resulted in significantly fewer errors at 2.5 hours post-dose, as compared to placebo.

When literature searches were conducted for the present paper, the most recent study of the acute cognitive effects of GBE was conducted by Nathan and associates,[13] which involved an examination of the phytomedicinal product on the memory functioning of 11 healthy "older" adults. In particular, participants were administered 120 mg of GBE [Ginkgoforte™; Blackmore's Ltd., Balgowlah, NSW, Australia] or a placebo during separate sessions via a repeated measures, double-blind, placebo-controlled design. During each treatment condition, participants were administered a series of memory tests from the Cognitive Drug Research computerized assessment system and the Rey Auditory Verbal Learning test at pretreatment baseline and again at 90 minutes post-dose. No significant acute effects of 120 mg of GBE were found for any of the memory tests utilized in the study. The authors indicated that these findings were consistent with those of Subhan and Hindmarch[7] and Kennedy and colleagues,[11] which also demonstrated no acute effects of GBE on memory at a dose of 120 mg.

The majority of studies that have examined the acute effects of GBE administration in healthy adults have found the herbal compound to be efficacious in enhancing certain aspects of participants' neuropsychological functioning, particularly performances on tasks assessing attention, memory, and speed of processing.

Summary of Acute Studies

As of September 2004, there have been a total of 7 published studies that have examined the acute neuropsychological effects of GBE in healthy adults. (Acute studies were defined as the administration of GBE to healthy/cognitively intact adults for 2 days or less.) Two of these studies (one published in English[7] and one in French[8]), however, appeared very similar, if not identical, particularly in terms of such features as their sample characteristics, methodology/design, treatments/doses, and results.

The sample sizes used in the acute studies were relatively small and ranged from a low of 8[7,8] to a high of 36[10] participants. All but one[10] of these reports examined more females than males, including 3 studies[7,8,10] that involved only females. With the exception of 2 studies where the mean age of participants was 43.6[10] and 58.46[13] years, the remaining acute studies of GBE utilized participants whose mean ages fell between 19.9 and 32 years. While the majority of the acute studies involved younger, versus older, participants who reportedly were "healthy," only one of these investigations appeared to include any objective measures to access levels of cognitive intactness.

All of the acute studies indicated that they employed double-blind, placebo-controlled, crossover/repeated measures designs with the duration of their GBE treatments/assessments ranging from 1 hour per dose[7,8,9] to 2 days.[10] In addition to a placebo, treatments involved the administration of various GBE preparations that were identified as follows:

- Tanakan®/Tebonin®,
- EGb 761,
- Ginkgo®,
- Ginkgo Special Extract LI 1370,
- Ginkgo biloba extract GK501, and
- Ginkgoforte™.

Five of the acute studies[7,8,10,11,12] evaluated multiple doses of GBE formulas, while 2 investigations[9,13] utilized only a single dose. The doses of GBE used in these studies ranged from a low of 120 mg to a high of 600 mg.

A diversity of outcome measures, assessing a wide range of neuropsychological processes, were administered across the acute studies ranging from measures of reaction time and line analogue rating scales, to computerized assessment batteries from which factor-derived scores were obtained. Among the most common measures that were administered in these studies were the Critical Flicker Fusion, Choice Reaction Time, Line/Visual Analogue Rating Scales, and Sternberg Memory tasks, as well as tests from the Cognitive Drug Research computerized assessment battery.

Significant, positive neuropsychological effects of a GBE were found in 5 out of 7 acute studies (4 of 6 if the Subhan and Hindmarch[7] and Hindmarch[8] studies represent the same investigation). In particular, higher doses (i.e., 240 and 360 mg) of an extract

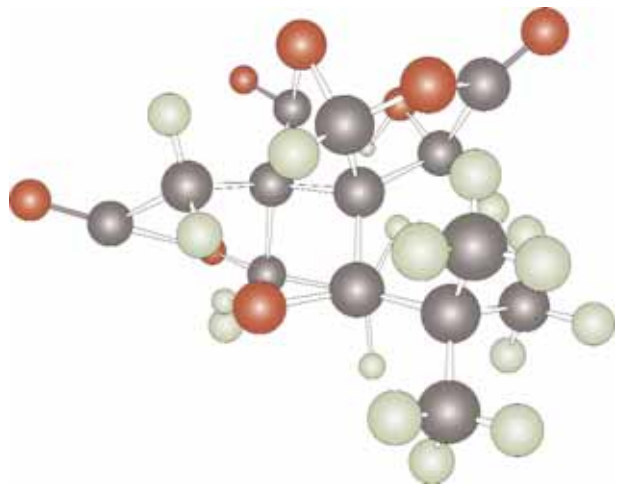
were shown to result in improvements on a factor-derived, speed of attention factor at 2.5, 4, and 6 hours post-dose and to significantly enhance a quality of memory factor after the ingestion of 120 mg of the product at 1 and 4 hours post-dose.[11] Furthermore, while significant enhancement was found for 360 mg of the GBE at 2.5 hours post-dose for a speed of memory factor, a significant reduction in this factor was observed for the 240 mg dose 4 hours after ingestion.[11] A significant decrease in an accuracy of attention factor was also noted for a 240 mg dose of GBE 1 hour after administration.[11] The authors acknowledged that these contrasting findings were not readily interpretable.

Additional dose and time-dependent effects were found for a GBE in a study that utilized 2 computerized serial subtraction tasks.[12] Specifically, single doses of 120, 240, and 360 mg of GBE were noted to significantly increase the number of Serial Threes subtractions (described as an attentional/concentration task with a procedural learning element) 4 hours post dose, while a 240 mg dose increased subtractions 6 hours after ingestion. In contrast, significantly more errors were made on the Serial Threes task following 120 mg of the extract at 4 hours post dose. While no significant differences were observed in the number of subtractions for any dose on a Serial Sevens task (reportedly involved in central executive resources), significantly fewer errors were noted after 2.5 hours for all doses. Although the precise interpretation of these observed effects remain somewhat difficult, the authors[12] noted that the results appeared broadly consistent with an improved "speed of attention" factor following GBE administration that was found in their previous study.[11]

The acute, positive effects of a GBE were also demonstrated in aspects of participants' high speed scanning and retrieval from short-term memory processes (as assessed via the Sternberg Memory Scanning task) after a single dose of 600 mg.[7,8] Similar, positive Sternberg results were exhibited across a 2-day period for 120 and 300 mg/day doses of a GBE and for a 240 mg/day dose of the extract on day 2.[10] In contrast, no significant effects were found on the Sternberg task 1 hour after the ingestion of single 120 and 240 mg doses of GBE.[7,8]

Two other acute studies, which administered either a 120 mg[13] or 600 mg[9] dose of a GBE, failed to find significant positive effects on the neuropsychological processes of healthy adults. In one of these studies,[9] however, while no significant improvements were found for the GBE treatment on any of the tests and measures utilized, as compared to baseline, participants' image free recall scores remain relatively unchanged during a trial of Tanakan®, but decreased under the placebo and Ginkgo® conditions.

A diversity of factors may have contributed to the general absence of positive results in these 2 investigations. Specifically, upon comparison of the Warot et al[9] study to the one conducted by Subhan and Hindmarch[7] (and Hindmarch[8]), which also administered a 600 mg dose of a GBE, the mean age of participants in the Warot trial[9] was almost a decade younger than the mean age of participants in the Subhan and Hindmarch study.[7] This factor, combined with the limited sample size and assessment duration (i.e., 1 hour, which is shorter than the extract's reported peak activity level(s) of 1.5 to 4 hours; see American Herbal Pharmacopoeia, 2003[14]) may have negatively impacted the results of Warot's[9] study. Furthermore, Nathan and colleagues[13] utilized a small sample of participants whose mean age (x = 58.46 years) was the highest of all the acute studies. They also limited their assessment duration to 90 minutes and administered a lower (i.e., 120 mg), versus higher, dose of a GBE which, when these factors were combined, may have interacted synergistically to contribute to the study's null findings.



Chemical structure of bilobalide. Image ©2005 ChromaDex

Taken together, the majority of studies that have examined the acute effects of GBE administration in healthy adults have found the herbal compound to be efficacious in enhancing certain aspects of participants' neuropsychological functioning, particularly performances on tasks assessing attention, memory, and speed of processing. While some of these studies have found the effects to be dose and time-dependent, though not necessarily in a linear fashion, inconsistencies remain among the acute studies that have been conducted to date. There appears to be a trend, however, among the limited number of acute studies that have included different doses of GBE for positive neuropsychological effects to be more closely associated with higher doses of GBE (i.e., $\geq$ 240 mg) and/or longer treatment/assessment durations (i.e., $\geq$ 2.5 hours). (The limited number of acute studies that included different doses of GBE is n = 4; i.e., if the Subhan & Hindmarch[7] and Hindmarch[8] studies represent the same data set.)

Short- to Long-Term Studies

A total of 9 published studies were found which have examined the short- to long-term neuropsychological effects of GBE/ginkgo in healthy/cognitively intact individuals. (Short- to long-term studies were defined as the administration of GBE to healthy/cognitively intact adults for a minimum of 5 days and up to 2 or more years.) Table 4 on page 59 provides an overview of these studies, which are listed in chronological order. Table 2 provides summaries of the proprietary GBE preparations and Table 3 provides outcome measures utilized in the investigations (see pages 56 and 57, respectively).

Mix & Crews[15] conducted the first known double-blind, fixed-dose, placebo-controlled, parallel-group design study that examined the short-term (6 weeks) efficacy of GBE (EGb 761®) on the neuropsychological functioning of 48 generally healthy, cognitively intact, older adults (i.e., 55 to 86 years of age). Participants in this study were randomly assigned to receive 180 mg/day of

GBE or a matching placebo, and they completed a series of neuropsychological tests and measures both at pretreatment baseline and again after 6 weeks of treatment (i.e., just prior to the termination of the regimen. (See Table 4 for a listing of the specific tests utilized.) The findings from this trial revealed that participants who received 180 mg/day of GBE (EGb 761®) 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, as compared to placebo controls. Nonsignificant trends favoring improved performances in the GBE group were also demonstrated on 3 of the 4 remaining tasks that involved a timed, speed of processing component. Furthermore, no significant differences were found between the GBE and placebo groups' change in performance scores on any of the verbal or nonverbal/visual memory measures included in the study. However, a nonsignificant trend, favoring the GBE group, was evident by treatment end on the Wechsler Memory Scale-Revised Visual Reproduction I subtest. Additionally, significantly more participants in the GBE group rated (via a self-report questionnaire) their overall abilities to remember by treatment end as "improved," as compared to placebo controls.

Ginkgo *Ginkgo biloba*. Photo © 2005 stevenfoster.com

Similarly, Stough and associates[16] investigated the neuropsychological changes in 50 healthy participants over a 30-day trial of 120 mg/day of GBE [Blackmore's Ginkgo Biloba Forte, Blackmore's Ltd., Balgowlah, NSW, Australia] via a randomized, double-blind, placebo-controlled design. Participants were administered batteries of neuropsychological tests designed to assess a diversity of cognitive variables both at pretreatment baseline and again following the 30-day treatment phase (see Table 4 on page 59 for a listing of the specific tests utilized). The results indicated that the group receiving the GBE exhibited significant improvements in speed of information processing (i.e., Working Memory Speed), working memory (i.e., Digit Span Backwards), and memory consolidation (i.e., over the 30-minute delay between presentations of the Rey Auditory Verbal Learning Test word list trials). Furthermore, participants who were classified in a "low," versus "high," cognitive ability group (via the Wechsler Adult Intelligence Scale-III Vocabulary subtest scores) exhibited significantly improved scores on the Trail Making Test (Part A), which the authors attributed to the GBE. A significant number of positive subjective effects were also reported by the GBE, versus the placebo, group; namely, subjective feelings of cognitive clarity and self-reported improvements in memory and attention. Conversely, no significant differences were found for negative side effects such as headaches and nausea.

In another study, Moulton and her colleagues[17] examined the effects of 120 mg/day of *Ginkgo biloba* [BioGinkgo 27/7, donated by Pharmanex, Inc., a division of NuSkin International, Provo, Utah] on the memory processes of 60 healthy, young male volunteers over 5 consecutive days via a double-blind, placebo-controlled, between-subjects design. On the fifth day of the study, after obtaining the GBE or placebo treatment, a series of cognitive tests were administered to participants (see Table 4 for a listing of the specific tests utilized). Results indicated that the group receiving the GBE, as compared to placebo controls, failed to demonstrate significantly improved performances on any of the memory measures. However, the Wechsler Adult Intelligence Scale-Revised Digit Span subtest results approached significance, with a higher mean score observed in the GBE, versus placebo, group. The authors acknowledged that factors such as the following may have contributed to the absence of significant findings: utilization of young healthy participants, limited dosage (120 mg/day) and treatment regimen (5 days), and the fact that baseline assessments were not administered to participants to which their performances at the end of treatment could have been compared.

In an effort to expand upon their previous study[15] of GBE (EGb 761®), Mix and Crews[18] published the first known, large-scale clinical trial of the short-term efficacy of GBE on the neuropsychological functioning of cognitively intact older adults (as assessed by the Mini Mental State Examination; MMSE). Two-hundred and sixty-two community dwelling adults, 60 years of age and older, who reported no history of dementia or significant neurocognitive impairments and obtained MMSE scores of at least 26, were examined via a 6-week, randomized, double-blind, fixed-dose, placebo-controlled, parallel-group design. Participants were randomly assigned to receive either 180 mg/day of EGb 761® or a matching placebo for 6 weeks and were administered a series of neuropsychological tests and measures at pretreatment baseline and again after 6 weeks of treatment (i.e., just prior to the cessation of the regimen). (See Table 4 for a listing of the specific tests utilized.)

The primary findings of the trial indicated that, compared to placebo controls, participants who received 180 mg/day of EGb 761® for 6 weeks exhibited significantly more improvement on (1) tasks (i.e., Selective Reminding Test) involving delayed (30 minutes) free recall and recognition of noncontextual, auditory-verbal material, and (2) a task (i.e., Wechsler Memory Scale-III, Faces II subtest) assessing delayed (30 minutes) recognition of visual material/human faces. It should be noted, however, that based on the significant difference found between the 2 groups pretreatment baseline scores on this particular visual/facial memory task, this result should be interpreted with caution. Additionally, of the 13 total neuropsychological outcome/efficacy variables included in this study, the GBE group exhibited more improvement by treatment end on 11 of these measures (includes both significant and nonsignificant results), as compared to the placebo group. Supporting data for these objective, standardized, neuropsychological findings were found via a subjective, Follow-up Self-report Questionnaire, in which participants rated changes in their overall abilities to remember from pretreatment baseline to 6 weeks after treatment. Specifically, significantly more older adults in the GBE group rated their overall abilities to remember by treatment end as "improved," as compared to placebo controls, which was a consistent finding with the investigators' previous smaller-scaled GBE study.[15] Taken together, the results from both the objective, standardized neuropsychological tests and the subjective, Follow-up Self-report Questionnaire utilized in this large-scale trial[18] provided complementary evidence of the potential efficacy of relatively short-term (6 weeks) utilization of GBE (EGb 761®) in enhancing certain neuropsychological/memory functions of cognitively intact older adults, 60 years of age and over.

Approximately 6 weeks after the online publication of the Mix and Crews large-scale clinical trial,[18] the results of a clinical trial conducted by Solomon and his colleagues[19] were published. This trial reportedly involved a 6-week, randomized, double-blind, placebo-controlled, parallel-group design using 120 mg/day of *Ginkgo biloba* extract [Ginkoba®, Pharmaton, Division of Boehringer Ingelheim, Ridgefield, CT.]. In this trial, 230 generally healthy and cognitively intact (as assessed by the MMSE) community-dwelling adults between 60 and 82 years of age were randomized in the study. Participants were administered a series of neuropsychological tests and measures one day prior to beginning the GBE or placebo treatment, and again, within 3 days of the end of the trial (see Table 4 on page 59 for a listing of the specific tests utilized). Analysis of both the modified intent-to-treat sample (n = 219) and the fully evaluable sample, which complied with the treatment regimen and returned for testing (n = 203), indicated no significant differences between treatment groups for any of the outcome measures. Furthermore, no significant differences were found between participants in the GBE and placebo groups on a subjective, self-report measure of memory functioning or on a global rating scale by spouses, relatives, and friends. It should be noted, however, that this study has not been free from controversy. In particular, a diversity of questions/concerns and potentially problematic issues have been raised about the study. These issues include the following: the reported utilization of both placebo capsules and GBE tablets (that were likely not similar in appearance and which may have compromised/not maintained blinding), questions concerning the appropriateness of the lead investigator (versus an independent party) performing the randomization of participants, and the apparent baseline differences among several outcome measures that were not accounted for in their analyses (see Arnold[20] and Cott[21] for detailed reviews). Such concerns raise questions about the validity of the study's overall findings and conclusions. [Despite these potentially confounding methodological questions, the reported negative outcomes of this trial received more media attention in the United States than probably any previous clinical trial on ginkgo. The general message was that "ginkgo does not work." The media apparently failed to provide any qualification that this trial was performed on healthy adults, which distinguished it from most of the trials previously conducted on cognitively impaired subjects, most of which reported positive findings. —Editor's note]

Ginkgo *Ginkgo biloba* grows in the gardens of the headquarters of the American Botanical Council in Austin, Texas. Photo © 2005 ABC.

In another study, Hartley and his colleagues[22] examined the effects of GBE [Ginkyo One-A-Day tablets, (LI 1370), Lichtwer Pharma UK, Mere Park, Marlow, Bucks, UK] on cognition and mood in 34 healthy, post-menopausal women via a randomized, double-blind, placebo-controlled design. The women were administered a battery of cognitive tests and measures of mood and menopausal symptoms at baseline and again following 7 days of treatment (see Table 4 for a listing of the specific tests utilized). The results of the investigation revealed that the group treated with the GBE, as compared to placebo controls, performed significantly better on a matching-to-sample test of short-term nonverbal memory, as well as on a frontal lobe task involving mental flexibility/rule shifting (i.e., IDED test), and on a test requiring sustained attention and frontal lobe functioning (i.e., PASAT). Alternatively, no group effects were found for the women's ratings of their menopausal and bodily symptoms, sleepiness, aggression, or mood. The authors noted that these results suggested that the observed cognitive benefits demonstrated by the women in the GBE group were unlikely due to any of the assessed menopausal/bodily symptoms, major mood changes, or sleepiness.

Cieza and associates[23] also investigated the short-term (i.e., 28 days) efficacy of 240 mg/day GBE (EGb 761®) on the "mental functioning" of 66 healthy volunteers, without age-associated cognitive impairment, via a randomized, double-blind, fixed-dose, placebo-controlled, parallel-group, monocentric design. Participants completed a series of subjective measures concerning their mental and general health and quality of life, as well as a diversity of tasks that were based on a neurobiologically based classification of functioning (see Table 4 on page 59 for a listing of the specific tests utilized), both at baseline and at the end of treatment (i.e., 28 days later). The results of the study indicated that GBE had significant, positive effects on participants' self-estimated mental health and quality of life. The GBE, versus placebo, group also demonstrated significantly better action and reaction motor performances (i.e., Finger Tapping Test) and judged their subjective mood states more positively during the entire treatment phase, especially (and significantly more) after 2 weeks of therapy.

Santos and colleagues[24] appeared to have reported the results of the first long-term (i.e., 8 months) study of the efficacy of GBE in 48 non-demented, elderly men. Specifically, the investigation utilized a double-blind, placebo-controlled, independent group design where participants consumed either 80 mg/day of a GBE [produced by Maze Produtos Quimicos e Farmaceuticos Ltda.] or matching placebo for 8 months. The men were evaluated at baseline and post-treatment via Single Photon Emission Computed Tomography (SPECT) scans, measures of blood viscosity, and a diversity of neuropsychological tests (see Table 4 for a listing of the specific tests utilized). By the end of treatment, the GBE group exhibited increased cerebral perfusion in several areas corresponding to bilateral frontal, bilateral parietal, right frontal-parietal, left temporal, and right occipital brain regions, as well as reduced blood viscosity. In contrast, the placebo group displayed areas of reduced cerebral perfusion and higher blood viscosity. Furthermore, the GBE, versus placebo, group exhibited improvements on the following: tests of general intelligence (e.g., WAIS-R Vocabulary, Comprehension, and Similarities subtests), visuospatial abilities (e.g., WAIS-R Block Design and Object Assembly subtests, Corsi Blocks), attentional processes (e.g., WAIS-R Digit Symbol, Toulouse-Pieron Concentrated Attention), information processing speed (assessed via timed tasks), enhanced verbal memory (e.g., WMS-R unrelated Verbal Paired Associates), delayed retrieval of visual material (e.g., Rey-Osterrieth Complex Figure Test), fewer non-perseveration errors per category on the Wisconsin Card Sorting Test, and fewer word intrusion, perseveration, and repetition errors on a verbal free recall task.

Persson and associates[25] also examined the utilization of unspecified formulas of ginkgo and ginseng in healthy volunteers, as compared to age and education-matched control groups that used either no nutritional supplements or nutritional supplements other than ginkgo or ginseng. For the purposes of this paper, the data

involving participants who utilized only ginkgo, as compared to controls, will be reviewed. Participants, who were free from organic disease (such as dementia) and scored 24 or greater on the MMSE, were selected from the Betula Prospective Cohort Study: Memory, Health, and Aging database (n = 3500) in Sweden. Among the 40 individuals who indicated current usage of ginkgo at the time of the study, 19 had been utilizing the phytomedicinal compound for 2 or more years, while the mean ginkgo intake time for the remaining 21 individuals was 5.3 months. Participants were evaluated at only one time point on a diversity of episodic and semantic memory tests and via questionnaires concerning individuals' life style factors and subjective memory ratings (see Table 4 on page 59 for a listing of the specific tests utilized). The performances of the individuals utilizing ginkgo were then compared to those obtained by the 2 control groups. With the exception of significantly better performances by Control Group 2 (see Table 2 on page 56 for inclusion criteria), versus the ginkgo group, on a cued recall task involving nouns from sentences encoded by verbal rehearsal, no significant group differences were found for any of the memory measures. As noted by the authors, however, this study lacked direct control of the dosage and specificity of ginkgo formulas utilized and, thus, did not report on the dosages or types of ginkgo that were used by participants, nor their overall levels of compliance over time. Furthermore, participants were evaluated at only one time point. Such concerns raise questions about the validity of the study's overall findings and conclusions.

A wide array of outcome measures were administered in the short- to long-term studies. These ranged from standardized and objective neuropsychological tests that are frequently utilized in clinical practice, to author-generated, subjective, self-report questionnaires and surveys of caregiver's impressions of global change.

Summary of Short- to Long-Term Studies

A total of 9 published studies were found in the literature that have evaluated the short- to long-term neuropsychological effects of GBE (and unspecified preparations of ginkgo in one study[25]) in healthy/cognitively intact adults. (Short- to long-term studies were defined as the administration of GBE to healthy/cognitively intact adults for a minimum of 5 days and up to 2 or more years.)

The number of participants enrolled in these studies ranged from a low of 34[22] to a high of 262.[18] Three investigations[15,16,23] utilized relatively similar numbers of male and female participants, while 3 other studies[18,19,25] included notably more (i.e., n > 20) females than males. Two additional trials[17, 24] included only males, while 1 study[22] assessed only females. With the exception of 2 investigations[16,17] where the mean age of participants fell below 31 years, the remaining short- to long-term studies of ginkgo involved participants whose mean ages were greater than 55 years. In contrast to the acute studies, 5 of the short- to long-term trials[15,18,19,24,25] included an objective measure to assess participants' levels of cognitive intactness (and specified inclusion

Ginkgo *Ginkgo biloba*. Photo © 2005 stevenfoster.com

criteria scores), while 1 study denoted that participants were without "age-associated cognitive impairment" (as judged by Cognitive Minimal Screening).[23] The remaining 3 studies[16,17,22] indicated only that they included "healthy" participants.

All but one investigation[25] utilized double-blind, placebo-controlled designs. The duration of the short- to long-term studies' GBE/ginkgo treatments ranged from 5 days[17] to 2-plus years.[25] In addition to a placebo, treatments involved the administration of various GBEs/ginkgo treatments that were identified as follows:

- Ginkgo biloba extract EGb 761®,
- Blackmore's Ginkgo Biloba Forte,
- BioGinkgo 27/7,
- Ginkoba®, Ginkyo One-A-Day (LI 1370),
- A GBE that was only cited as having been produced by Maze Produtos Quimicos e Farmaceuticos Ltda. and prepared by Magister Medicamentos, Ltda., and
- Unspecified preparations of ginkgo in one study.[25]

The daily doses of GBE in these trials ranged from a low of 80 mg[24] to a high of 240 mg.[23] It should be noted that in one additional study,[25] the formula(s) and dose(s) of ginkgo were unspecified and participants' levels of compliance with the treatment regimen(s) were not monitored.

A wide array of outcome measures, assessing a diversity of neuropsychological processes, were administered in the short- to long-term studies. These ranged from standardized and objective neuropsychological tests that are frequently utilized in clinical practice, to author-generated, subjective, self-report questionnaires and surveys of caregiver's impressions of global change.

Significant, positive effects of GBE/ginkgo were found in 6 out of 9 short- to long-term studies. Specifically, a dose of 80 mg/day of a GBE administered for 8 months was shown to increase cerebral perfusion in various brain regions and result in a significant reduction in blood viscosity, as compared to placebo.[24] Participants who received this GBE treatment also performed significantly better than controls on several verbal and performance subtests of the WAIS-R, on 2 subtests from the WMS-R, and on 3 additional retrieval tasks. In addition, the GBE group exhibited fewer non-perseverative errors per category on the WCST and significantly more cancellations and fewer errors on a test assessing concentrated attention, as well as fewer word intrusion, perseveration, and repetition errors on a verbal free recall task, as compared to placebo controls.

Doses of 120 mg/day of GBE were utilized in 4 of the short- to long-term studies.[16, 17, 19, 22] In one trial,[22] after 7 days of 120 mg/day of a GBE, the treatment group, versus placebo controls, displayed significantly better short-term verbal memory on the Digit Matching-to-Sample Test and enhanced performances on tasks involving rule shifting (i.e., IDED task) and sustained attention (i.e., PASAT). Stough and associates[16] also found significant neurocognitive improvements in participants who received 120 mg/day of a GBE for 30 days, as compared to placebo controls, on a backwards digit span task, in working memory speed, and on an auditory verbal learning delayed recall task. Improved perform-

ances on a task involving sequencing and psychomotor speed (i.e., TMT, Part A) were also noted in a low, versus high, cognitive ability group that received the extract. Furthermore, the GBE, versus placebo, group self-reported significantly more feelings of clarity and improvements in memory and attention.

The Mix and Crews research group has conducted 2 clinical trials[15,18] that examined the neuropsychological efficacy of 180 mg/day of a GBE for 6 weeks. Results of these studies revealed that older, cognitively intact participants who received the phytomedicinal extract for 6 weeks exhibited significantly more improvement on standardized neuropsychological tests assessing speed of processing abilities,[15] delayed free recall and recognition of auditory-verbal material,[18] and delayed recognition of visual material,[18] as compared to placebo controls. Furthermore, in both studies significantly more older adults who received the GBE, versus a placebo, rated their overall abilities to remember by treatment end as "improved."

Another short- to long-term study examined the effectiveness of 240 mg/day of a GBE administered for 28 days.[23] Participants in the GBE group exhibited superior performances on a motor task (i.e., Finger Tapping Test) measuring both action and reaction functions, and they self-rated their levels of mental health and quality of life higher and judged their mood states more positively during the treatment phase, as compared to the controls.

In contrast, 3 short- to long-term studies[17,19,25] failed to find significant positive results for formulas of GBE or unspecified ginkgo preparations. As noted earlier, in at least 2 of these investigations, which utilized either 120 mg/day dose of a GBE for 6 weeks[19] or unspecified formulas and doses of ginkgo products for up to 2-plus years,[25] questions/concerns have been raised about the soundness of their methodologies and validity of their findings. Furthermore, the third investigation[17] with null results utilized the youngest sample of participants (i.e., $x < 21.0$ years), the shortest treatment/assessment duration (i.e., 5 days) of any of the short- to long-term studies, and did not conduct baseline cognitive/memory assessments, which may have contributed to the reported negative findings in this study.

Overall, the majority of investigations that have examined the short- to long-term effects of GBE/ginkgo in healthy/cognitively intact persons have found the herbal product to improve certain neuropsychological processes, especially performances on tasks assessing aspects of memory, attention, and speed of processing abilities. Four of the short-term studies also bolstered their objective neurocognitive test findings with self-report data, as compared to placebo controls. In 2 of these studies,[15,18] significantly more participants who received GBE rated their overall abilities to remember by treatment end as improved. In the third study,[16] participants reported significantly more feelings of clarity and improvements in memory and attention. In the forth study, [23] participants rated their levels of mental health and quality of life significantly higher, and they judged their mood states more positively during treatment.

Conclusions and Directions for Future Research

Taken together, a total of 16 published studies were found in the scientific literature (through September 2004) which have examined the acute or short- to long-term neuropsychological efficacy of GBE (and unspecified preparations of ginkgo in one study[25]) in healthy and cognitively intact adults. Significant positive results for formulas of GBE were found in 11 out of 16 studies (10 of 15 studies if the Subhan & Hindmarch[7] and Hindmarch[8] studies represent the same investigation). Although inconsistencies exist in

Ginkgo *Ginkgo biloba*. Photo © 2005 stevenfoster.com

Table 1. Summary of studies examining the acute effects of GBE in healthy/cognitively intact individuals* (page 1 of 2)

Study & Year	Sample Size	Mean Age of Participants	Design	Duration of Treatments/ Assessments	Ginkgo Product	Dose(s)	Outcome Measures	Findings
Subhan & Hindmarch (1984)[7]	F = 8	x = 32 Range: 25 to 40	R, DB, PC, CO design	1 hour per dose	Tanakan/ Tebonin (EGb 761®)	- 120 mg - 240 mg - 600 mg - placebo	1. Critical flicker fusion (CFF) 2. Choice reaction time (CRT) 3. Sternberg Memory Scanning Test 4. Line analogue rating scale (LARS)	- Memory scanning processes assessed via the Sternberg technique improved significantly ($P < 0.0001$) following 600 mg of GBE, as compared to placebo. - No significant effects for the other 3 outcome measures.
Hindmarch (1986)[8]	F = 8	x = 32 Range: 25 to 40	R, DB, PC, CO design	1 hour per dose	Tanakan (EGb 761®)	- 120 mg - 240 mg - 600 mg - placebo	1. Critical flicker fusion (CFF) 2. Choice reaction time (CRT) 3. Sternberg Memory Scanning Test 4. Line analogue rating scale (LARS)	- Memory scanning processes assessed via the Sternberg technique improved significantly ($P < 0.0001$) following 600 mg of GBE as compared to placebo. - No significant effects for the other 3 outcome measures.
Vitro et al. (1991)[9]	F = 12	x = 22.33 Range: 19 to 30	DB, PC design	1 hour per dose	Ginkgo® Tanakan®	- 600 mg - placebo	1. Critical flicker frequency (CFF) 2. Choice reaction time (CRT) 3. Picture recognition 4. Sternberg Scanning Test (SCT) 5. Self-rating evaluation (visual analogue scales)	- Significant effect ($P < 0.05$) for Tanakan® on the image free recall test. Compared to baseline, free recall scores remained unchanged with Tanakan®; but decreased under placebo and Ginkgo.® - No significant treatment changes, compared to placebo on the CFF, CRT, Picture recognition, SCT, or a subjective rating of drug effects.
Rigney et al. (1999)[10]	M = 22 F = 14	x = 43.6 Range: 30 to 59	R, DB, PC, 5-way CO design	2 days per daily dose	Ginkgo Special Extract LI 1370	- 120 mg mane - 150 mg (50 mg t.d.s.) - 240 mg mane - 300 mg (100 mg t.d.s.) - placebo	1. Critical flicker fusion (CFF) 2. Sternberg's Short-term Memory task (STM) 3. Line Analogue Rating Scale for Sedation (LARS) 4. Choice reaction time (CRT) 5. Leeds Sleep Evaluation Questionnaire 6. Immediate & delayed recall of supraspan word lists 7. Digit Symbol Substitution Task 8. Stroop task 9. Wristactigmphy	- Significantly faster ($P < 0.05$) reaction times on the STM scanning task for 120 mg and 300 mg of GBE over both days, while participants receiving 240 mg of GBE exhibited significantly faster ($P < 0.05$) performances on day 2. - No significant treatment effects noted on the immediate and delayed word recall tasks; however, 120 mg and 240 mg of GBE increased the overall number of words recalled on the immediate recall task, with a more pronounced increase for the 120 mg dose. - Overall significant treatment effect ($P = 0.043$) on the CFF threshold, although none of the GBE doses differed significantly from placebo. 120 mg of GBE associated with higher thresholds than all other treatments and placebo and was significantly higher than the 240 mg dose. - No significant effects of GBE reported for any of the remaining outcome measures.
Kennedy et al. (2000)[11]	M = 2 F = 18	x = 19.9 Range: 19 to 24	DB, PC, multi-dose, balanced, CO design	6 hours per dose	Standardized extract of Ginkgo (GK501)	- 120 mg - 240 mg - 360 mg - placebo	1. Four factors derived via factor analysis of the Cognitive Drug Research Computerized Assessment Battery subtests 2. Three derived mood factors from the Bond-Lader Visual Analogue Scales	- Significant improvements ($P < 0.04$) on the speed of attention factor for the two highest doses (i.e., 240 and 360 mg) of GBE at time points 2.5, 4, and 6 hours post-dose. - Significantly enhanced ($P < 0.033$) quality of memory performances for 120 mg of GBE at 1 and 4 hours post-dose. Positive trends were also noted for 240 mg at the same time points. - For the speed of memory factor, significant enhancement ($P = 0.04$) was found for 360 mg of GBE at 2.5 hours post-dose, with non-significant trends noted at both 120 mg and 360 mg at 6 hours post-dose. Alternatively, a significant reduction ($P = 0.03$) was observed for the 240 mg dose at 4 hours post-dose, as compared to placebo, and this dose underperformed the other doses at all time points. - A single, significant decrease ($P = 0.045$) in accuracy of attention was noted for 240 mg of GBE at 1 hour post-dose. -No significant effects noted for any of the 3 visual analogue scale factors.

*Table includes only data for the studies that examined GBE.

Key: GBE = Ginkgo biloba extract, M = males, F = females, x = mean, SD = standard deviation, R = randomized, DB = double-blind, PC = placebo-controlled, CO = crossover

Table 1. Summary of studies examining the acute effects of GBE in healthy/cognitively intact individuals[a] (page 2 of 2)

Study & Year	Sample Size	Mean Age of Participants	Design	Duration of Treatments/ Assessments	Ginkgo Product	Dose(s)	Outcome Measures	Findings
Scholey & Kennedy (2002)[16]	M = 2 F = 18	N = 19.9 SD = 1.47	3 Studies[b] examining Ginkgo, Ginseng, and a Ginkgo/Ginseng combination; All DB, PC, balanced, CO designs	6 hours per dose	Ginkgo biloba extract (GK501)	~120 mg ~240 mg ~360 mg placebo	1. Computerized versions of two serial subtraction tests (i.e., Serial Threes [ST] and Serial Sevens [SS])	- For the ST task, all 3 doses of GBE, as compared to placebo, resulted in significant increases ($P < 0.05$) in the number of subtractions at 4 hours post-dose. - A significant increase ($P < 0.05$) in ST subtractions was also noted for the 240 mg dose of GBE after 6 hours. - Alternatively, significantly more ($P < 0.01$) errors were made on the ST task following 120 mg of GBE at 4 hours post-dose. - For the SS task, while no significant differences were noted in the total number of subtractions for any dose, as compared to placebo, significantly fewer ($P < 0.05$) errors were noted at 2.5 hrs for all doses, as compared to placebo controls.
Nathan et al. (2002)[18]	M = 5 F = 6	N = 58.46 SD = 10.92 Range: 50 to 70	Repeated measures, DB, PC design	90 minutes per dose	Ginkgo-forte™	~120 mg placebo	1. Cognitive Drug Research Computerized Assessment System memory test 2. Rey Auditory Verbal Learning Test	- No significant effects reported for any of the memory tasks administered.

[a] Table includes only data for the studies that examined GBE

Key: GBE = Ginkgo biloba extract; M = males; F = females; x = mean; SD = standard deviation; R = randomized; DB = double-blind; PC = placebo-controlled; CO = crossover

this limited body of research, some of the most common positive neuropsychological effects found for GBE across the acute and short- to long-term studies involving healthy/cognitively intact participants have been enhanced performances on tasks assessing aspects of memory, attention, and speed of processing abilities. Furthermore, as cited earlier, complementary subjective/self-report evidence to support the findings from the objective neurocognitive tests has been provided in four of the short- to long-term studies that included such measures.

However, this review of the scientific literature on acute and short- to long-term studies has also revealed a diversity of findings. These findings include an array of ginkgo product formulations, doses, treatments/assessment durations, and outcome measures utilized, as well as the methodological limitations of some of the investigations (e.g., limited sample sizes, young ages of participants). Because of these diverse findings, future well-designed trials are required to precisely identify the optimum dose(s), type(s)/formula(s) of ginkgo product(s), and treatment regimen(s). These kinds of trials will maximize the likelihood of obtaining certain neurocognitive/neuropsychological benefits in particular groups of healthy/cognitively intact adults (e.g., of varying ages and genders). Specifically, large-scale investigations (both acute and short-term) are needed, especially with healthy/cognitively intact middle-aged and older adults who often complain of (age-related) memory/cognitive difficulties, that compare and contrast different formulas, dosage regimens, and treatment/assessment durations of GBE in healthy/cognitively intact males and females from various age groups. These clinical trials should utilize rigorous methodology/designs, and precisely define and assess their medical and neuropsychological inclusionary/exclusionary criteria (e.g., via objective measures of cognitive intactness). Outcome measures should be carefully selected to ensure that they have been documented to be reliable, valid, and sensitive measures of particular neuropsychological processes, and that they decrease the possibility of familiarity/practice effects over successive administrations (e.g., alternate forms). Furthermore, methodologically sound, longitudinal, clinical trials are also needed that examine the neuropsychological efficacy of GBE(s) over periods of several months to years to ascertain if additional neuropsychological benefits/effects become evident and/or if the phytomedicinal compound demonstrates long-term neuroprotective properties.

Authors' Biographical Sketches

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Table 2-Listing of proprietary ginkgo extract preparations: compositions, manufacturers, and studies examining the products.*

Brand	Reported Composition	Manufacturer	Study/Studies Examining the Products
BioGinkgo 27/7	50:1 extract; 27% flavonols, 7% terpenes	Pharmaneye Inc., Division of NuSkin International, Provo, Utah	Moulton et al. (2001)[77]
Blackmore's Ginkgo Biloba Forte	50:1 extract; 24% flavonal glycosides, 6% terpenes	Blackmores Ltd., Balgowlah, NSW, Australia	Stough et al. (2001)[47]
EGb 761®	50:1 extract; 24% flavone glycosides, 6% terpene lactones	Dr. Willmar Schwabe Pharmaceuticals GmbH & Co., Karlsruhe, Germany	Mix & Crews (2000[54], 2002[53]), Ciera et al. (2003)[46]
GK501	50:1 extract; 24% flavone glycosides, 6% terpene lactones	Pharmaton, SA, Lugano, Switzerland	Kennedy et al. (2000)[78], Scholey & Kennedy (2002)[79]
Ginkgo	Unknown/Unspecified	Unspecified	Warot (1991)[80]
Ginkgo biloba extract	Extract ratio unknown; 24% flavonoids, 6.1% terpenoids	Produced by Maze Produtos Quimicos e Farmaceuticos, Ltda. Prepared by Magister Medicamentos Ltda.	Santos et al. (2003)[81]
Ginkgoforte™	50:1 extract; 10.7 mg ginkgo flavonglycosides, 2.7 mg ginkgolides and bilobalides	Blackmore's Ltd., Balgowlah, NSW, Australia	Nathan et al. (2002)[82]
Ginkoba®(EGb 761®)	50:1 extract; 24% flavonols, 6% terpenes	Pharmaton Natural Health Products, Boehringer Ingelheim Pharmaceuticals, Ridgefield, CT	Solomon et al. (2002)[83]
Ginkyo One-A-Day (LI 1370)	50:1 extract; 24% flavonoids, 6% terpenoids	Lichtwer Pharma UK, Mere Park, Marlow, Bucks, UK	Hartley et al. (2003)[84]
LI 1370	50:1 extract; 24% flavonols, 6% terpenes	Lichtwer Pharma, Berlin, Germany	Rigney et al. (1999)[85]
Tanakan®(Trademark in France)	See EGb 761® above	Ipsen Boufour, France, Dr. Willmar Schwabe Pharmaceuticals GmbH & Co., Karlsruhe, Germany	Subhan & Hindmarch (1984)[7], Hindmarch (1986)[8], Warot (1991)[9]
Tebonin®(Trademark in Germany)	See EGb 761® above	Dr. Willmar Schwabe Pharmaceuticals GmbH & Co., Karlsruhe, Germany	Subhan & Hindmarch (1984)[7]

*Information obtained/compiled from the specific studies that utilized the preparation and from written correspondence with Mark Blumenthal (e-mail, January 11, 2005).

Table 8-Outcome measures utilized in the ginkgo studies and the purported domains assessed (page 1 of 2)	
Outcome Measure	**Purported Domains Assessed**
Auditory Choice Reaction Time Test	Time necessary for decision-making and stimulus discrimination
Auditory Order Threshold Test	Information processing time
Blood Viscosity	Viscosity of blood
Border-Lader Visual Analogue Scales	Subjective mood measures of alertness, calmness, and contentedness, bodily symptoms, and aggression
Boston Naming Test	Object/picture naming
California Verbal Learning Test	Verbal learning, recall and recognition of verbal information
Caregiver Global Impression of Change Rating Scale	Global ratings of changes in memory
Choice Reaction Time	Motor movement and processing/reaction time, ability to attend and respond to stimuli
Cognitive Drug Research Computerized Assessment Battery of Memory Tasks	Spatial and numeric working memory, picture recognition, reaction time
Cognitive Drug Research Computerized Assessment Battery, Primary Cognitive Factors	Four factor analysis-derived, global factors assessing speed of attention, accuracy of attention, quality of memory and speed of memory
Cognometer Battery of Tests (2 tests)	Simple reaction time, working memory
Color Word Test	Activation, attention
Controlled Category Fluency Test	Verbal fluency for categories of items
Corsi Block-Tapping Test	Immediate recall of sequential block tapping
Critical Flicker Fusion	Integrative CNS activity, ability to distinguish sensory information
Cued Recall of Sentences Encoded by Enactment	Cued verbal memory/recall
Cued Recall of Words/Nouns Encoded by Verbal Rehearsal	Cued verbal memory/recall
Delayed Matching-to-Sample Test	Short-term nonverbal memory
Digit Connection Test-G	Speed of information processing
Digit Span	Immediate rote memory for digits, attention/concentration, working memory
Digit Symbol Substitution Task	Information processing, psychomotor performance, sustained attention, visuomotor coordination
Epworth Sleepiness Scale	Subjective assessment of sleepiness
Finger Tapping Test	Action, reaction, volition, and decision
Follow-up Self-report Questionnaire	Subjective self-report of treatment-related changes in the following variables: overall ability to remember, mood, energy level, sexual responsiveness, overall health
Free Recall of Sentences Encoded by Enactment	Verbal memory, free recall
Free Recall of Sentences Encoded by Verbal Rehearsal	Verbal memory, free recall
Greene Climacteric Scale	Subjective, self-report of menopausal symptoms
Hospital Anxiety and Depression Scale	Subjective, self-report of anxiety and depressive symptomatology
IDED Test	Rule learning, reversal and shifting/mental flexibility
Incidental Learning Test	Latent/incidental learning, information processing, attention and retrieval processes
Increment Threshold for Visual Stimuli	Stimulus perception, sensitivity for visual stimuli
Immediate and Delayed Recall of Supraspan Word Lists	Immediate and delayed (30 min.) free recall/memory of words
Inspection Time	Inspection time/speed of processing
Leeds Sleep Evaluation Questionnaire	Subjective, self-ratings of the effects of psychoactive compounds on sleep and early morning behavior
Line Analogue Rating Scales	Subjective, self-ratings of drug effects, indexes of mood and sedation
Mini-Mental State Examination	Brief screening of the following cognitive domains: orientation, registration, attention, calculation, recall, and language
Memory Questionnaire	Subjective, self-ratings of the frequency of certain memory lapses
Paced Auditory Serial Addition Test	Sustained attention, information processing
Picture Memory Task/Picture Recognition	Recall/recognition of pictures/images
Picture Recall	Long-term episodic memory, recall of pictures
Profile of Mood States	Assessment of emotional well-being and mood
Prose Memory Test	Immediate recall of stories
(Note: Not all of the studies reviewed were true clinical trials)	

Table 3-Outcome measures utilized in the ginkgo studies and the purported domains assessed (page 2 of 2)	
Outcome Measure	**Purported Domains Assessed**
Questionnaire Assessing Life Style Factors	Subjective, self-report of the following lifestyle factors: physical activities, cultural interests, organizational activities, traveling, social life
Reaction Time Control Test	Reaction time
Reading Span Test	Recall of words from sentences
Rey Auditory Verbal Learning Test	Verbal learning, immediate, short-term, and delayed free recall and recognition of verbal material/word lists
Rey-Osterrieth Complex Figure Test	Nonverbal/visual memory processes
Recognition of Faces	Visual memory, recognition of faces
Selective Reminding Test	Immediate and delayed free recall and recognition of auditory-verbal material, cued recall, long-term storage, short-term recall, long-term retrieval, consistent long-term retrieval, random long-term retrieval
Self-rating Depression Scale	Subjective, self-rating of depressive symptomatology
Sensorimotor Synchronization Test	Integration, sequential information
Serial Sevens (computerized)	Attention, concentration, procedural learning, working memory
Serial Threes (computerized)	Attention, concentration, procedural learning
Single Photon Emission Computed Tomography	Cerebral perfusion
Speed of Comprehension Test	Comprehension speed
Stanford Sleepiness Scale	Subjective assessment of sleepiness
Sternberg Memory Scanning Test	High speed scanning, retrieval from short-term memory
Stockings of Cambridge Test	Frontal lobe functioning
Stroop Test/Stroop Color-Word Test	Speed of processing, selective attention, concentration, response inhibition/effects of perceptual interference
Subjective Intensity Scale-Mood and Tiredness	Assessment of mood state and tiredness
Subjective Memory Rating	Subjective, self-report of memory performance
Symbol Digit Modalities Test	Complex scanning, visual tracking, response speed
Temporal Reproduction Test	Integration, sequential information
Toulouse-Pieron Concentrated Attention	Concentrated attention
Trail Making Test (Parts A & B)	Visuomotor scanning/tracking speed, sequencing, shift of perceptual sets/cognitive flexibility, concentration/vigilance
Verbal Fluency for Occupations	Verbal fluency for categories of items
Verbal Free Recall	Free recall of verbal material
Visual Analogue Scales	Subjective, self-ratings (e.g., mental health, general health &quality of life)
Wechsler Adult Intelligence Scale-Revised	Verbal, Performance, and Full Scale IQs
Wechsler Adult Intelligence Scale-Revised Digit Span subtest	Immediate rote memory for digits, attention/concentration, working memory
Wechsler Adult Intelligence Scale-Revised/III Digit Symbol-Coding subtest	Sustained attention/focused concentration, response speed, visuomotor persistence/coordination
Wechsler Adult Intelligence Scale-III Block Design subtest	Visuospatial organization, constructional abilities
Wechsler Adult Intelligence Scale-Revised/III Vocabulary subtest	Vocabulary and word knowledge skills, verbal conceptualization, estimate of Verbal IQ
Wechsler Memory Scale-Revised	Verbal, nonverbal/visual, and overall memory processes, orientation, attention/concentration
Wechsler Memory Scale-III Faces I &II subtests	Immediate and delayed recognition/visual memory for faces
Wechsler Memory Scale-Revised Digit Span subtest	Rote memory, attention/concentration, working memory
Wechsler Memory Scale-Revised Logical Memory I &II subtests (Paragraph Recall)	Immediate and delayed auditory-verbal memory for material occurring in a context/story format
Wechsler Memory Scale-Revised Mental Control subtest	Recital of number and letter series/strings
Wechsler Memory Scale-Revised Visual Reproduction I &II subtests	Immediate and delayed nonverbal/visual memory
Wisconsin Card Sorting Test	Abstract reasoning, shift of set abilities, frontal lobe functioning
Word Comprehension	Comprehension of words/synonyms
Word List Test	Short-term memory, verbal processing, long-term memory
(Note: Not all of the studies reviewed were true clinical trials)	

Table 4. Summary of studies examining the short- to long-term effects of GBE in healthy/cognitively intact individuals[a] (page 1 of 4)

Study & Year	Sample Size	Mean Age of Participants	Design	Duration of Treatment/ Assessments	Ginkgo Product	Dose(s)	Outcome Measures	Findings
Mix & Crews (2000)[16]	Enrolled: n = 48 Completed protocol: M = 21 F = 19	Range: 55 to 86 Ginkgo group: x = 67.50 SD = 9.23 Placebo group: x = 68.65 SD = 6.95	DB, FD, PC, PG design	6 weeks	Ginkgo biloba extract EGb 761®	- 180 mg/d -placebo	1.Stroop Color and Word Test (SCWT) 2.Trail Making Test Parts A and B 3.Wechsler Memory Scale-Revised (WMS-R) Logical Memory I (LM-I) and II (LM-II) and Visual Reproduction I (VR-I) and II (VR-II) subtests 4.Follow-up, self-report questionnaire (FSRQ)	- GBE, versus placebo, group exhibited significantly more ($P < 0.03$) improvement on the SCWT Color-naming task by treatment end. - Nonsignificant trends, favoring the GBE group, on 3 out of 4 of the remaining tasks involving a timed, speed of processing component - On the FSRQ, significantly more ($P < 0.03$) participants in the GBE, versus placebo, group rated their overall abilities to remember by treatment end as "improved." - No significant differences between groups on any of the memory measures, although a positive trend favoring the GBE group was noted on the WMS-R VR I subtest.
Stough et al. (2001)[17]	Enrolled: n = 61 Completed protocol: M = 24 F = 26	Range: 18 to 40 x = 30.4 SD = 5.7	R, DB, PC design	30 days	Bladamores Ginkgo Biloba Forte	- 120 mg/d -placebo	1.Wechsler Adult Intelligence Scale-III (WAIS-III) Vocabulary (V) subtest 2.Digit Symbol Substitution Test (DSST) 3.Speed of Comprehension Test (SCT) 4.Symbol Digit Modalities Test (SDMT) 5.Digit Span (DS) 6.Trail Making Test (TMT) 7.Rey Auditory Verbal Learning Test (AVLT) 8.Inspection Time (IT) 9.Two tests from the Cognometer Battery of Tests (measuring simple reaction time and working memory)	- GBE, versus placebo, group displayed significant improvements on the DS Backwards task ($P < 0.05$), working memory speed ($P < 0.05$), and the AVLT delayed list ($P < 0.01$). - A low, versus high, cognitive ability group who received GBE exhibited significantly ($P < 0.01$) improved TMT, Part A scores. - GBE, versus placebo, group self-reported significantly more ($P < 0.001$) feelings of clarity and improvements in memory and attention. - No significant differences between treatment groups for negative side effects (e.g., headaches, nausea).
Moulton et al. (2001)[18]	Enrolled: M = 60	Ginkgo group: x = 20.57 SD = 1.89 Placebo group x = 20.40 SD = 1.77	DB, PC, BS design	5 days	BioGinkgo 27/7	- 120 mg/d -placebo	1.Sternberg Memory Scanning Test (SMST) 2.Reaction time control test 3.Wechsler Adult Intelligence Scale-Revised (WAIS-R) Vocabulary (V) and Digit Span (DS) subtests 4.Reading span test 5.Prose memory task	- No significant effects of GBE on any of the memory measures, although the WAIS-R DS Backwards subtest results were in the predicted direction.
Mix & Crews (2002)[19]	Enrolled n = 262 Completed protocol: M = 102 F = 147	Ginkgo group: x = 66.97 SD = 6.12 Placebo group: x = 68.60 SD = 6.96	R, DB, FD, PC, PG, design	6 weeks	Ginkgo biloba extract EGb 761®	- 180 mg/d -placebo	1.Selective Reminding Test (SRT) 2.Wechsler Adult Intelligence Scale-III (WAIS-III) Block Design (BD) and Digit Symbol-Coding (DS-C) subtests 3.Wechsler Memory Scale-III (WMS-III) Faces I (FI) and Faces II (FII) subtests 4.Follow-up, Self-report, Questionnaire (FSRQ)	- GBE, versus placebo, group exhibited significantly more improvement on SRT delayed free recall ($P < 0.04$) and recognition ($P < 0.01$) tasks. - GBE, versus placebo, group displayed significantly greater ($P < 0.025$) improvement on the WMS-III, FII subtest (delayed recognition of faces). - GBE, versus placebo, group exhibited more improvement (both significant and nonsignificant results) on 11 out of 13 of the neuropsychological efficacy/outcome variables. - On the FSRQ, significantly more ($P = 0.05$) participants in the GBE, versus placebo, group rated their overall abilities to remember by treatment end as "improved."

[a]Table includes data for participants taking only GBE or placebo.

Key: GBE = Ginkgo biloba extract, M = males, F = females, x = mean, SD = standard deviation, R = randomized, DB = double-blind, PC = placebo-controlled, FD = fixed-dose, PG = parallel group, BS = between subjects

Table 4 Summary of studies examining the short- to long-term effects of GBE in healthy/cognitively intact individuals[a] (page 2 of 4)

Study & Year	Sample Size	Mean Age of Participants	Design	Duration of Treatment & Assessments	Ginkgo Product	Dose(s)	Outcome Measures	Findings
Solomon et al. (2002)*	Enrolled: n = 230 Completed protocol: n = 203 Returned for 6-week evaluation: M = 91 F = 128	Ginkgo group: x̄ = 68.7 SD = 4.7 Placebo group: x̄ = 69.9 SD = 5.4	R, DB, PC, PG design	6 weeks	Ginkoba®	-120 mg/d placebo	1. California Verbal Learning Test 2. Wechsler Memory Scale Digit Span, Logical Memory I & II, Visual Reproduction I & II, and Mental Control subtests 3. Wechsler Adult Intelligence Scale-R Digit Symbol subtest 4. Stroop Test 5. Controlled Category Fluency test 6. Boston Naming Test 7. Memory Questionnaire 8. Caregiver Global Impression of Change Rating Scale	- Analysis of both the modified intent-to-treat and fully evaluable samples indicated no significant differences between the GBE and placebo groups. - No significant differences between the GBE and placebo groups on the self-report measure of memory functioning or global rating scale.
Hartley et al. (2003)*	Enrolled: N = 34 Completed protocol: F = 31	Range 53 to 65 Ginkgo group: x̄ = 59.3 S.E.M. = +1.0 Placebo group: x̄ = 59.6 S.E.M. = +1.0	R, DB, PC design	7 days	Ginkgo One-A-Day (LI 1370)	-120 mg/d placebo	1. Hospital Anxiety and Depression Scale 2. Greene Climacteric Scale 3. Stanford Sleepiness Scale 4. Epworth Sleepiness Scale 5. Wechsler Memory Scale-Revised Paragraph Recall 6. Delayed Matching-to-Sample Test 7. Picture Recall 8. First six stages of the IDED test 9. Stockings of Cambridge test 10. Paced Auditory Serial Addition Test 11. Visual Analogue Rating Scales of mood, aggression, and bodily symptoms	- GBE, versus placebo, group displayed significantly better ($P < 0.05$) performances on the Matching-to-Sample test of short term nonverbal memory. - GBE, versus placebo, group exhibited significantly better performances on tasks involving rule shifting (IDED task; $P < 0.05$) and sustained attention (PASAT; $P = 0.05$). - No significant group differences on any of the other cognitive measures. - No significant group differences on ratings of menopausal or bodily symptoms, sleepiness, aggression, or mood.

*Table includes data for participants taking only GBE or placebo

Key: GBE = Ginkgo biloba extract, M = males, F = females, x̄ = mean, SD = standard deviation, R = randomized, DB = double-blind, PC = placebo-controlled, FD = fixed-dose, PG = parallel group, BS = between subjects

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Table 4. Summary of studies examining the short- to long-term effects of GBE in healthy/cognitively intact individuals[a] (page 3 of 4)

Study & Year	Sample Size	Mean Age of Participants	Design	Duration of Treatment/ Assessments	Ginkgo Product	Dose(s)	Outcome Measures	Findings
Ciem et al. (2003)[48]	Enrolled: n = 66 Completed protocol: M = 29 F = 37	Ginkgo group: Males: x = 55.1 SD = 3.7 Females: x = 56.5 SD = 3.8 Placebo group: Males: x = 57.3 SD = 2.9 Females: x = 56.3 SD = 3.8	R, DB, FD, PC, PG design	28 days	Ginkgo biloba extract EGb 761®	- 240 mg/d - placebo	Primary Measures: 1. Visual Analogue Scale ratings of mental health, general health, and quality of life Secondary Measures: 1. Increment Threshold for Visual Stimuli 2. Digit Connection Test-G 3. Word List Test 4. Profile of Mood States 5. Subjective Intensity Scale-Mood and Tiredness 6. Self-rating Depression Scale 7. Finger Tapping Test 8. Auditory Choice Reaction Time 9. Color-Word Test 10. Incidental Learning Test 11. Auditory Order Threshold Test 12. Temporal Reproduction Test 13. Sensorimotor Synchronization Test	- Significantly higher ($P < 0.05$) self-ratings of mental health and quality of life by GBE, versus placebo, group. - GBE, versus placebo, group exhibited superior performances ($P < 0.05$) on the Finger Tapping Test. - Participants receiving GBE, versus placebo, judged (via the Subjective Intensity Scale-mood measure) their mood states more positively during the entire treatment phase, particularly (and significantly more; $P < 0.05$) after two weeks of therapy.
Santos et al. (2003)[49]	Enrolled: n = 50 Completed protocol: M = 48	Range: 60 to 70	DB, PC, independent-group design	8 months	Ginkgo biloba extract (produced by: Maze Produtos Quimicos e Farmaceuticos Ltda.)	-80 mg/d -placebo	1. Single Photon Emission Computed Tomography (SPECT) 2. Measures of blood viscosity 3. Wechsler Adult Intelligence Scale-Revised (WAIS-R) 4. Wechsler Memory Scale-Revised (WMS-R) 5. Corsi Block-Tapping Test (CBT) 6. Rey-Osterrieth Complex Figure Test (R-OCF) 7. Wisconsin Card Sorting Test (WCST) 8. Toulouse-Pieron Concentrated Attention Test (T-PCA) 9. Verbal Free Recall (VFR)	- GBE group displayed increased ($P < 0.04$) cerebral perfusion in several areas corresponding to bilateral frontal, bilateral parietal, right frontal-parietal, left temporal, and right occipital brain regions, whereas the placebo group demonstrated the opposite (regions of reduced cerebral perfusion). - By treatment end, the GBE group exhibited a significant ($P < 0.0001$) reduction in blood viscosity, while the placebo group displayed a higher viscosity. - GBE, versus placebo, group performed significantly better ($P < 0.002$) on the following WAIS-R subtests: Vocabulary, Block Design, Arithmetic, Object Assembly, Comprehension, Digit Symbol, and Similarities. - GBE, versus placebo, group performed significantly better on the WMS-R Mental Control (i.e., time and error variables; $P < 0.001$) and Verbal Paired Associates-no semantic relationship ($P < 0.001$). - GBE, versus placebo, group exhibited significantly enhanced CBT performances for both forward ($P < 0.001$) and backward ($P < 0.001$) retrieval tasks. - GBE, versus placebo, group performed significantly better ($P = 0.003$) on the R-OCF Delayed Retrieval task. - GBE, versus placebo, group exhibited significantly fewer ($P < 0.001$) non-perseverative errors/category on the WCST. - On the T-PCA test, the GBE, versus placebo, group displayed significantly more ($P < 0.001$) cancellations and fewer errors. - On the VFR task, the GBE, versus placebo, group made fewer ($P < 0.001$) word intrusion, perseveration, and repetition errors.

[a]Table includes data for participants taking only GBE or placebo.

Key: GBE = Ginkgo biloba extract, M = males, F = females, x = mean, SD = standard deviation, R = randomized, DB = double-blind, PC = placebo-controlled, FD = fixed-dose, PG = parallel group, BS = between subjects

Table 4. Summary of studies examining the short- to long-term effects of GBE in healthy/cognitively intact individuals* (page 4 of 4)

Study & Year	Sample Size	Mean Age of Participants	Design	Duration of Treatment/ Assessments	Ginkgo Product	Dose(s)	Outcome Measures	Findings
Persson et al. (2004)[24]	M = 44 F = 76	Ginkgo group: x = 68.0 SD = 10.9 Control group 1 (no use of nutritional supplements): x = 68.8 SD = 11.6 Control group 2 (utilized nutritional supplements other than Ginkgo): x = 67.6 SD = 11.6	Participants selected from a prospective cohort study database (n = 3500) who were taking either Ginkgo or Ginseng or compared to two control groups matched by age and education at one time point	Participants utilizing Ginkgo for 2 or more years: n = 19 Mean Ginkgo intake time for remaining 21 participants in the Ginkgo group: x = 5.3 months	Unspecified formulas of Ginkgo biloba	Unspecified	1. Free recall of sentences encoded by enactment 2. Free recall of sentences encoded by verbal rehearsal 3. Verbal fluency for words beginning with the letter "S" 4. Verbal fluency for occupations beginning with the letter "S" 5. Word comprehension 6. Recognition of faces 7. Cued recall of sentences encoded by enactment 8. Cued recall of words/nouns encoded by verbal rehearsal 9. Questionnaire assessing life style factors (i.e., physical activities, cultural interests, organizational activities, traveling, and social life) 10. Subjective memory ratings	- Control group 2, as compared to the Ginkgo group, exhibited significantly better ($P < 0.01$) performances on the Cued recall of nouns from sentences encoded by verbal rehearsal task. - No significant differences between the Ginkgo and control groups (1 and 2) on any of the other memory measures or life style or subjective memory rating questionnaires.

*Table includes data for participants taking only GBE or placebo.

Key: GBE = Ginkgo biloba extract, M = males, F = females, x = mean, SD = standard deviation, R = randomized, DB = double-blind, PC = placebo-controlled, PG = parallel group, BS = between subjects

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