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### 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<sup>1</sup> 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<sup>2</sup> authored a review of the controlled trials involving GBE’s potential

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

## 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 [[download Table 1, pdf file](#)] on page 54 provides an overview of these studies, which are listed in chronological order. Table 2 [[download Table 2, pdf file](#)] provides summaries of the proprietary GBE preparations and Table 3 [[download Table 3, pdf file](#)] provides outcome measures utilized in the investigations (see pages 56 and 57, respectively).

Subhan and Hindmarch<sup>7</sup> 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<sup>A8</sup>/Tebonin<sup>A8</sup>, 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.

Similarly, Hindmarch<sup>8</sup> 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.<sup>7</sup> 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<sup>8</sup> 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<sup>A8</sup>), versus placebo. Similar to the Subhan and Hindmarch<sup>7</sup> 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<sup>9</sup> evaluated the acute efficacy of 600 mg of 2 GBE preparations (Ginkgo<sup>A8</sup> and Tanakan<sup>A8</sup>), 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<sup>A8</sup> trial, but decreased under the placebo and Ginkgo<sup>A8</sup> conditions.

Rigney, Kimber, and Hindmarch<sup>10</sup> 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<sup>10</sup> indicated that their results were very similar to those of Subhan and Hindmarch<sup>7</sup> 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<sup>7</sup> study, the Rigney and associates<sup>10</sup> 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<sup>11</sup> via a double-blind, placebo-controlled, multi-dose, 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 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<sup>12</sup> 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<sup>A8</sup>, 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,<sup>13</sup> 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 [GinkgoforteAA; 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<sup>7</sup> and Kennedy and colleagues,<sup>11</sup> which also demonstrated no acute effects of GBE on memory at a dose of 120 mg.

## 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<sup>7</sup> and one in French<sup>8</sup>), 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<sup>7,8</sup> to a high of 36<sup>10</sup> participants. All but one<sup>10</sup> of these reports examined more females than males, including 3 studies<sup>7,8,10</sup> that involved only females. With the exception of 2 studies where the mean age of

participants was 43.6<sup>10</sup> and 58.46<sup>13</sup> 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 assess levels of cognitive intactness.

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

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

Five of the acute studies<sup>7,8,10,11,12</sup> evaluated multiple doses of GBE formulas, while 2 investigations<sup>9,13</sup> 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<sup>7</sup> and Hindmarch<sup>8</sup> 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.<sup>11</sup> 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.<sup>11</sup> A significant decrease in an accuracy of attention factor was also noted for a 240 mg dose of

GBE 1 hour after administration.<sup>11</sup> 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.<sup>12</sup> 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<sup>12</sup> noted that the results appeared broadly consistent with an improved “speed of attention” factor following GBE administration that was found in their previous study.<sup>11</sup>

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.<sup>7,8</sup> 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.<sup>10</sup> 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.<sup>7,8</sup>

Two other acute studies, which administered either a 120 mg<sup>13</sup> or 600 mg<sup>9</sup> dose of a GBE, failed to find significant positive effects on the neuropsychological processes of healthy adults. In one of these studies,<sup>9</sup> 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 remained relatively unchanged during a trial of Tanakan<sup>A8</sup>, but decreased under the placebo and Ginkgo<sup>A8</sup> 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<sup>9</sup> study to the one conducted by Subhan and Hindmarch<sup>7</sup> (and Hindmarch<sup>8</sup>), which also administered a 600 mg dose of a GBE, the mean age of participants in the Warot trial<sup>9</sup> was almost a decade younger than the mean age of participants in the Subhan and Hindmarch study.<sup>7</sup> 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<sup>14</sup>) may have negatively impacted the results of Warot’s<sup>9</sup> study. Furthermore, Nathan and colleagues<sup>13</sup> 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.

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<sup>7</sup> and Hindmarch<sup>8</sup> 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 [[download Table 4, pdf file](#)] 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<sup>15</sup> 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<sup>A8</sup>) 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<sup>A8</sup>) 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.

Similarly, Stough and associates<sup>16</sup> 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<sup>17</sup> 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<sup>15</sup> of GBE (EGb 761A8), Mix and Crews<sup>18</sup> 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 761A8 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 761A8 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 the initiation of 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.<sup>15</sup> 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<sup>18</sup> provided complementary evidence of the potential efficacy of relatively short-term (6 weeks) utilization of GBE (EGb 761A8) 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,<sup>18</sup> the results of a clinical trial conducted by Solomon and his colleagues<sup>19</sup> 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<sup>A8</sup>, 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<sup>20</sup> and Cott<sup>21</sup> 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]

In another study, Hartley and his colleagues<sup>22</sup> 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<sup>23</sup> also investigated the short-term (i.e., 28 days) efficacy of 240 mg/day GBE (EGb 761<sup>A8</sup>) 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<sup>24</sup> 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<sup>25</sup> 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 4 on page 62 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.

### **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<sup>25</sup>) 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<sup>22</sup> to a high of 262.<sup>18</sup> Three investigations<sup>15,16,23</sup> utilized relatively similar numbers of male and female participants, while 3 other studies<sup>18,19,25</sup> included notably more (i.e., n > 20) females than males. Two additional trials<sup>17, 24</sup> included only males, while 1 study<sup>22</sup> assessed only females. With the exception of 2 investigations<sup>16,17</sup> 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<sup>15,18,19,24,25</sup> included an objective measure to assess participants' levels of cognitive intactness (and specified inclusion criteria scores), while 1 study denoted that participants were without "age-associated cognitive impairment" (as judged by Cognitive Minimal Screening).<sup>23</sup> The remaining 3 studies<sup>16,17,22</sup> indicated only that they included "healthy"

participants.

All but one investigation<sup>25</sup> utilized double-blind, placebo-controlled designs. The duration of the short- to long-term studies' GBE/ginkgo treatments ranged from 5 days<sup>17</sup> to 2-plus years.<sup>25</sup> 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.<sup>25</sup>

The daily doses of GBE in these trials ranged from a low of 80 mg<sup>24</sup> to a high of 240 mg.<sup>23</sup> It should be noted that in one additional study,<sup>25</sup> 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.<sup>24</sup> 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.<sup>16, 17, 19, 22</sup> In one trial,<sup>22</sup> 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<sup>16</sup> 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 performances 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<sup>15,18</sup> 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,<sup>15</sup> delayed free recall and recognition of auditory-verbal material,<sup>18</sup> and delayed recognition of visual material,<sup>18</sup> 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.<sup>23</sup> 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<sup>17,19,25</sup> 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<sup>19</sup> or unspecified formulas and doses of ginkgo products for up to 2-plus years,<sup>25</sup> questions/concerns have been raised about the soundness of their methodologies and validity of their findings. Furthermore, the third investigation<sup>17</sup> 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,<sup>15,18</sup> significantly more participants who received GBE rated their overall abilities to remember by treatment end as improved. In the third study,<sup>16</sup> participants reported significantly more feelings of clarity and improvements in memory and attention. In the fourth study,<sup>23</sup> 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<sup>25</sup>) 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<sup>7</sup> and Hindmarch<sup>8</sup> studies represent the same investigation). Although inconsistencies exist in 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 across these investigations. Based on these findings and the 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), 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.

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## References

1. Birks J, Grimley-Evans J, Van Dongen M. *Ginkgo biloba* for cognitive impairment and dementia (Cochrane Review). *The Cochrane Library*, Issue 4, 2002. Oxford: Update Software.
2. Canter PH, Ernst E. A systematic review of controlled trials of the cognitive effects of *Ginkgo biloba* extracts in healthy people. *General Psychopharmacology*. 2002;36(3):108-123.
3. Kennedy DO, Scholey AB, Wesnes KA. Differential, dose-dependent changes in cognitive performance following acute administration of a *Ginkgo biloba*/*Panax ginseng* combination to healthy young volunteers. *Nutritional Neuroscience*. 2001;4:399-412.
4. Wesnes K A, Faleni RA, Hefting NR, et al. The cognitive, subjective, and physical effects of a *Ginkgo biloba*/*Panax ginseng* combination in healthy volunteers with neurasthenic complaints. *Psychopharmacology Bulletin*. 1997;33(4):677-683.
5. Wesnes KA, Ward T, McGinty A, Petrini O. The memory enhancing effects of a *Ginkgo biloba*/*Panax ginseng* combination in healthy middle-aged volunteers. *Psychopharmacology*. 2000;152:353-361.
6. Nathan PJ, Tanner S, Lloyd J, et al. Effects of a combined extract of *Ginkgo biloba* and *Bacopa monniera* on cognitive function in healthy humans. *Human Psychopharmacology*. 2004;19:91-96.
7. Subhan Z, Hindmarch I. The psychopharmacological effects of *Ginkgo biloba* extract in normal healthy volunteers. *International Journal of Clinical Pharmacological Research*. 1984;IV(2):89-93.
8. Hindmarch I. Activite de l'extrait de *Ginkgo biloba* sur la memoire a court terme. *La Presse Medicale*. 1986;15:1592-1594.
9. Warot D, Lacomblez L, Danjou P, Weiller E, Payan C, Puech AJ. Comparaison des effets d'extraits de *Ginkgo biloba* sur les performances psychomotrices et la memoire chez le sujet sain. *Therapie*. 1991;46:33-36.

10. Rigney U, Kimber S, Hindmarch I. The effects of acute doses of standardized *Ginkgo biloba* extract on memory and psychomotor performance in volunteers. *Phytotherapy Research*. 1999;13: 408-415.
11. 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.
12. Scholey AB, Kennedy DO. Acute, dose-dependent cognitive effects of *Ginkgo biloba*, *Panax ginseng* and their combination in healthy young volunteers: differential interactions with cognitive demand. *Human Psychopharmacology*. 2002;17:35-44.
13. Nathan PJ, Ricketts E, Wesnes K, Mrazek L, Greville W, Stough C. The acute nootropic effects of *Ginkgo biloba* in healthy older subjects: a preliminary investigation. *Human Psychopharmacology*. 2002;17:45-49.
14. Upton R, ed. *American Herbal Pharmacopoeia and Therapeutic Compendium: Ginkgo Leaf, Ginkgo Leaf Dry Extract, Ginkgo biloba L.; Standards of Analysis, Quality Control, and Therapeutics*. Soquel, CA: American Herbal Pharmacopoeia. 2003:24.
15. Mix JA, Crews WD Jr. An examination of the efficacy of *Ginkgo biloba* extract EGb 761A8 on the neuropsychological functioning of cognitively intact older adults. *Journal of Alternative and Complementary Medicine*. 2000;6(3):219-229.
16. Stough C, Clarke J, Lloyd J, Nathan PJ. Neuropsychological changes after 30-day *Ginkgo biloba* administration in healthy participants. *International Journal of Neuropsychopharmacology*. 2001;4:131-134.
17. Moulton PL, Boyko LN, Fitzpatrick JL, Petros TV. The effect of *Ginkgo biloba* on memory in healthy male volunteers. *Physiology & Behavior*. 2001;73:659-665.
18. Mix JA, Crews WD Jr. A double-blind, placebo-controlled, randomized trial of *Ginkgo biloba* extract EGb 761 in a sample of cognitively intact older adults: Neuropsychological findings. *Human Psychopharmacology*. 2002;17:1-11.
19. Solomon PR, Adams F, Silver A, Zimmer J, DeVeaux R. Ginkgo for memory enhancement: A randomized controlled trial. *JAMA*. 2002;288(7):835-840.
20. Arnold KR. Ginkgo and memory: To the editor: *JAMA*. 2002;289(5):546.
21. Cott J. Comments on the paper by Paul R. Solomon et al published in *JAMA* August 21, 2002; 288:835-840. Ginkgo for Memory Enhancement. A randomized controlled trial. Available at: <http://www.jerrycott.com>. Accessed March 18, 2004.

22. Hartley DE, Heinze L, Elsabagh S, File SE. Effects on cognition and mood in postmenopausal women of 1-week treatment with *Ginkgo biloba*. *Pharmacology, Biochemistry and Behavior*. 2003;75:711-720
23. Cieza A, Maier P, Poppel E. Effects of *Ginkgo biloba* on mental functioning in healthy volunteers. *Archives of Medical Research*. 2003;34:373-381.
24. Santos RF, Galduroz JCF, Barbieri A, Castiglioni MLV, Ytaya LY, Bueno OFA. Cognitive performance, SPECT, and blood viscosity in elderly non-demented people using *Ginkgo biloba*. *Pharmacopsychiatry*. 2003;36:127-133.
25. Persson J, Bringlov E, Nilsson LG, Nyberg L. The memory-enhancing effects of ginseng and *Ginkgo biloba* in healthy volunteers. *Psychopharmacology*. 2004;172:430-434.

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