Term Paper:

Ginkgo Biloba’s Influence on Memory and Cognition
Introduction

The aging process is inevitable. Over time our bodies and the functions they provide start to decline in many aspects. Cognitive function and memory are tools used on a daily basis, so when they start to slip away it is noticeable when these processes become a struggle. *Ginkgo biloba* is a herbal remedy that has been utilized for thousands of years in China and elsewhere. It is obtained from the leaves and seeds of a plant that is commonly known as the maiden hair tree, believed to be the oldest living species of tree. *Ginkgo biloba* is being marketed as a neuroprotective nutritional supplement that is used for the treatment of pathophysiological brain aging. Many studies have been performed looking to find the possible effects of this supplement on cognitive performance.

Through our research we found two studies that looked into the effects of *Ginkgo biloba* on the aging process and cognitive decline in subjects that are at risk for Alzheimer’s disease, dementia, or cognitive dysfunction syndrome. In the first study, results showed that consuming *Ginkgo biloba* after the age of 75 (having normal and mild cognitive impairment) did not have any effect on reducing the risk and severity of dementia and Alzheimer’s disease. In the second study, results showed that consuming a mixed supplement that included *Ginkgo biloba*, showed beneficial results on short-term memory and cognitive tests. The study showing *Ginkgo biloba* having no effects on cognitive decline has much stronger results due to the study design and subject pool.

Discussion

The study *Ginkgo Biloba for Prevention of Dementia: A Randomized Controlled Trial* is a randomized double blind placebo-controlled clinical trial study published in 2008. The objective of the study was to obtain the effectiveness of *Ginkgo biloba* in
prevention of dementia or Alzheimer’s disease in elderly individuals who had normal cognitive function and mild cognitive impairment (MCI). The study was established in five different academic medical centers in the United States over the period of 6.1 years with a total of 3,069 volunteers aged 75 years or older with a mean of 79 years. Out of the 3,069 volunteers, 2,587 had normal cognition and 482 had a mild cognitive impairment, and were followed up every 6 months for possibility of developing all cause dementia or dementia of the Alzheimer type.

The subjects were given doses of 120-mg extract of *Ginkgo biloba* or placebo twice daily. The team involved in the study tested the participants on a range of tasks such as language, visual and special construction, memory and attention. The rate of dementia did not differ for the group of 1,545 subjects who were given Ginkgo biloba and the 1,524 subjects who received the placebo. Towards the end of the study, out of the 523 individuals that did develop dementia, 277 had taken the *Ginkgo biloba* extract and 246 took the placebo. The overall dementia rate was 3.3 per 100 person/year for *Ginkgo biloba* extract and 2.9 for the placebo participants. The results demonstrate that there is no significant association between *Ginkgo biloba* and its rate of progression to dementia in participants with MCI (95% CI, 0.85-1.50; P=.39), for all cause dementia (95% CI, 0.94-1.33; P=.21) and for Alzheimer’s disease (95% CI, 0.97-1.39; P=.11).

Log-rank test was used as the statistical analysis to compare the time of dementia between the placebo and controlled group. The authors concluded that “the results from the Ginkgo Evaluation of Memory (GEM) study did not show that *Ginkgo biloba* is effective in preventing or delaying the onset of all cause dementia in participants older than 75 years” (DeKosky, 8). Therefore, based on the results of the study *Ginkgo Biloba*
is not recommended for preventing or delaying the onset of dementia and Alzheimer’s disease.

According to the author “the GEM study is by far the longest prevention trial conducted with this intervention” (Dekosky, 9). Having a large sample size and the random assignment of participants are essentials factors that contribute to the strength of the study. Moreover, randomization provides a very powerful tool for increasing the external validity and controlling the confounding factors even if they may be difficult to measure. The double blind portion of the study minimizes the experimenter bias so that there isn’t any indirect influence on the subjects to behave accordingly to the experimenter’s expectations. In addition, the controlled setting allows drawing conclusions on cause and effect relationship because all the extraneous variables are controlled in preventing the effects of the results. Randomization was done separately using a computer-generated list and all the participants were blinded for their assigned treatment during the entire period of the study. All of the individuals involved in the study were unaware of the subjects’ information. Only the pharmacist who disturbed the medication to the participants and the two personnel responsible for monitoring the adverse events were aware of the active and placebo medications.

Factors such as consuming different medications that would effect the outcome of the study, history of Parkinson’s disease, daily use of vitamin E and B12, abnormal thyroid tests, allergy to G biloba, disease-related life expectancy of less than 5 years and etc. were some of the confounding factors that were excluded prior to the study. The authors believe that “the extract [they] tested is among the best characterized and is the one for which the most efficacy data are available” (DeKosky, 9). Hence, the results can
be appropriate for using other *Ginkgo biloba* extracts. Using the Cox model regressions for adjusting sex, age, race/ethnicity, APOE genotype and history of certain cardiovascular disease plays a very crucial role in strengthening the study. Randomizing those with ApoE4 carries is important since ApoE4 is a major risk factor for Alzheimer’s disease.

One of the weaknesses of the GEM study was the high drop out rate. Even though the study did focus extensively on the treatment adherence and participant retention, only 60.3% of active participants were taking their assigned study medication at the end of the trial. Some participants were consuming cholinesterase inhibitors or memantine during the study that resulted as a reason for discontinuing the study medication. There were 379 deaths from any cause and 195 were either lost to follow up with the study or withdrew from the experiment. Even though the length of this study seems to be long, use of *Ginkgo biloba* and its biological effects on the changes in human brain may take much longer to be evident than compared to the median of 6.1 years. Another limitation of the study could be that since the study only focused on people ages 75 and over, we are limited in knowing how the effects of *Ginkgo biloba* would have been altered if it had been taken at an earlier age. Therefore, “further analysis of brain function and pathology by group is planned using MRIs of a subset of participants”(DeKosky, 9).

Considering all the strengths and weaknesses of this study, we support the author’s conclusion that consuming 240 mg/daily of Ginkgo Biloba does not delay or prevent the onset of dementia or Alzheimer’s disease. This GEM study had a very large sample size and was well controlled with minimum confounding factors. The study showed that the participants who consumed *Ginkgo biloba* showed no notable differences
in attention, memory, and other cognitive measures compared to the participants who took the placebo.

The article Improvement of short-term memory performance in aged beagles by a nutraceutical supplement containing phosphatidylserine, *Ginkgo biloba*, vitamin E, and pyridoxine examined the cognitive decline associated with brain aging in dogs. As dogs age they can develop a neurodegenerative disease that has effects similar to Alzheimer’s disease. “Diagnosing cognitive dysfunction syndrome (CDS) in the dog is difficult, because it is primarily dependent on the pet owner reporting signs in specific categories, including disorientation, alterations in social interactions with owners or other pets, alterations in sleep-wake cycles, appearance of house soiling or changes in learned behaviors, and alterations in activity levels” (Araujo, 379).

The purpose of this study was “to examine if a commercially available nutraceutical supplement that may be neuroprotective and contains phosphatidylserine, *Ginkgo biloba*, vitamin E, and pyridoxine could improve cognitive function in aged beagles” (Araujo, 379). The researchers also “examined the effects of this nutraceutical formula on memory performance of aged dogs using the delayed-non-matching-to-position (DNMP) … with the overall purpose of determining if the combination could improve short-term memory and if neuropsychological test protocols in screening interventions that modify cognitive function were able to predict clinical outcomes” (Araujo, 380).

This research was performed using a blinded crossover study design. The subjects of the study were nine beagles with an age range of 7 to 12.7 years old (four male and five female). The study took place over a 145-day period that was broken up into two
phases with five days prior for baseline testing. The baseline period was used to have five DNMP test sessions with each subject. The subjects were then split up into two groups (one group of 4 and one group of 5). They were initially split using the baseline DNMP tests so one group was not at a higher performance level than another. Then they were split by age and gender as much as possible to keep the groups as even as possible. Each phase lasted 70-days with the first 60-days being the wash-in period and the last 5-days being the DNMP testing period. In the first phase (days 6 to 65), one group’s subjects received one meatball daily containing the supplement, while the other group received a plain meatball. Phase one DNMP testing then took place on days 66 through 75. In the second phase (days 76 to 135) the groups were switched, so the subjects receiving the supplement in phase one were then given the plain meatball and vice versa. Phase two DNMP testing then took place on days 136 through 145.

“(…) neuropsychological testing in the laboratory clearly reveals age differences in canine learning and memory. These tests provide quantitative and objective measures of cognitive function without relying on subjective owner evaluations. Neuropsychological test results indicate that learning and memory deficits in a test of short-term working memory, the delayed-non-matching-to-position (DNMP) task, can be identified in dogs as early as 6 years of age, thereby indicating that the DNMP is particularly sensitive to age” (Araujo, 380).

The amount of supplement distributed to subject was dependent on his or her weight, 1 capsule for every 5kg. “Each capsule contained 25 mg of phosphatidylserine (from GM-free soya), 50 mg of Ginkgo biloba extract titrated in ginkgosides (24%), 20.5 mg of pyridoxine HCl (vitamin B6), and 33.5 mg of d-alpha-tocopherol (natural vitamin
The cognitive testing took place in a wooden chamber with a sliding tray that contained three bowls. “During the test trials, 1 or 2 wells were covered by objects; (...) yellow blocks. Displacement of any object was considered a response choice (...) Each trial consisted of 2 phases. The initial sample presentation consisted of placing a block in 1 of 3 spatial positions (left, middle, right). The subject was required to displace the block to obtain a hidden food reward. The tray was then removed from view and a delay (20 or 90 seconds) was initiated. After the delay, on the test phase, the tray was presented with 2 identical blocks covering 2 spatial positions, 1 of which was the position used during the sample phase. To obtain the food reward, the animal was required to remember the location used in the sample phase and displace the block at the other location” (Araujo, 381). Each testing day the subject was presented with 12 different trials.

This study showed significant effect of the supplemental treatment (P=0.039), while the subjects receiving the control did not show an improvement from their baseline tests. When the subjects receiving the control in phase I were switched to the treatment group in phase II they performed significantly better (P=0.022). In phase I, the group receiving treatment was the control group in phase II. During phase II these subjects were still performing at higher levels compared to their baseline due to the possible long-term effects of the supplement. Both groups performed at their highest levels when on the supplement. “The present results indicate that a nutraceutical supplement containing phosphatidylserine, Ginkgo biloba, vitamin E, and pyridoxine improved canine short-term memory performance when assessed by the DNMP (...) Further research is required to determine the mechanism of action of this long-term beneficial effect”
Gingko biloba within the supplement has the potential to improve cognitive function and promote short-term retention of spatial memory in animals and humans. The supplement given as the treatment was mixture of four different components, so “we can speculate that the treatment may have acted in a multimodal fashion by augmenting cholinergic transmission, increasing antioxidant defense, and possibly reducing amyloid lesions, all of which are known to be modified in canine aging and likely contribute to CDS” (Araujo, 383).

Strengths within this study included that researchers of this study based their research methods on data from many previous, proven studies for supplemental information. They used DNMP testing which is a strong, proven test method. The use of animal subjects makes the possibility of having noncompliance within a study. Having only 9 subjects made it easy to keep a close eye on their behavior and monitor any changes that may take place. The study’s findings were statistically significant making this a strong study.

Within this study there were more weaknesses than strengths. The sample size was very small with only 9 subjects, having a larger sample size makes findings more thorough. Studies with animal subjects do not always end in the same results when humans are given the same treatments. A mixed supplement was used instead of a pure supplement, so we are unable to know which of the four components had the most beneficial effect. The cross over study design did not have a real washout period for the group that was taking the supplement during phase I of the study. The subjects might have done better in the second phase trials due to the practice effect. The research period only lasted 145 days overall with each phase being 70 days, which is not enough time to
thoroughly test the supplement. This study did not look into the mechanism of the supplement itself, so we don’t know how the supplement was working within the subject’s bodies. Within the article it states that the age of the subjects in the study are younger than the animals usually brought into the CDS clinics because owners often do not see the difference in their pet’s behavior until they are older.

This study is difficult to support because there was a very small sample size and the crossover study design did not have a real washout period. Even though their findings were statistically significant the weakness within the study outweighed the strengths.

The results of the GEM study, a randomized placebo-controlled study, on *Ginkgo biloba* was not effective in preventing the onset of Alzheimer’s disease or mild cognitive impairment. This large study included multiple strengths and some minor weaknesses that led the study to be amongst the largest and strongest randomized clinical trials on *Ginkgo biloba* and its effects on dementia and Alzheimer’s disease. The second study focused on a mixed supplement that included *Ginkgo biloba* and its effects on the cognitive function in aged beagles. The results of this study were statistically significant that the certain nutraceutical supplement can improve memory in aged dogs. However we are unable to conclude that this was a strong study due its high number of limitations.

**Conclusion**

From the two studies, we are able to conclude that consuming *Ginkgo biloba* had no effect on the cognitive decline associated with dementia and Alzheimer’s disease in humans. However the consumption of a *Ginkgo biloba* mixed supplement had a positive effect on short-term memory and cognition in aging beagles. Overall, our view on *Ginkgo biloba* is that it does not affect cognition in a positive or negative way. The high number
of strengths in the first study and numerous weaknesses from the second study led us to our conclusion. If further studies are to be performed using this supplement, large sample sizes, long term follow up, and the study of the mechanism of *Ginkgo biloba* within the body would make for more significant conclusions.
Bibliography


Work Summary

Between the two of us, we worked together to find our topic and articles that supported and did not support the use of the supplement. Shirin focused on the first article, Ginkgo biloba for Prevention of Dementia: A randomized Controlled Trial and Tracie focused on the second article, Improvement of short-term memory performance in aged beagles by a nutraceutical supplement containing phosphatidylycerine, Ginkgo biloba, vitamin E and pyridoxine. We worked together on the Introduction and Conclusion of the paper.