

GINKGO BILOBA EFFECTIVENESS DISPUTED

In a new report in the *Journal of the American Medical Association*, 2009;302[24]:2663-2670, for December 23/30, 3,069 participants at six academic medical centers in the United States between 2000 and 2008 were tested in the Ginkgo Evaluation of Memory (GEM) study. These participants were 72 to 96 years of age. 1,545 received two doses of 120 mg per day of *Ginkgo biloba* extract and 1,524 received an identical looking placebo. This is the largest randomized and controlled study of *Ginkgo biloba* so far.

At the University of Pittsburgh, Beth E. Snitz, Ph.D. and colleagues analyzed outcomes. The aim was to see if the rate of mild cognitive impairment (MCI) decline was slowed. There was a median (midpoint) follow-up of 6.1 years.

The researchers found no evidence for an effect of *G. biloba* on global cognitive change and no evidence of effect on specific cognitive domains of memory, language, attention, visuospatial abilities and executive functions. They also found no evidence for differences in treatment effects by age, sex, race, education or baseline cognitive status (MCI vs. normal cognition).

NML Emailed lead researcher, Steven T. DeKosky, M.D. and asked him to describe the source of the *G. biloba* extract or to explain how it was made. His publications coordinator did not have the information and responded with a copy of the embargoed article that would be published in *JAMA*.

On the issue of what preparation was used, the article states, "Participants were randomized to twice-daily doses of *G. biloba* extract, 120 mg (EGb 761; Schwabe Pharmaceuticals, Karlsruhe, Germany), or an identical-appearing placebo, in a blister-pack format. Selection of the *G. biloba* preparation for the study was made via an independent procurement procedure by the National Center for Complementary and Alternative Medicine (NCCAM) and required specific standards of exact chemical content and consistency. The formulation EGb 761 is an extract standardized in its major constituents, approximately 24% ginkgo-specific flavone glycosides and 6% terpene lactones. The 120-mg twice daily doses of

EGb 761 was chosen based on information from prior clinical studies suggesting a dose-response relationship up to 240 mg." (footnotes omitted.)

In the Comment section of the report, it is mentioned that the "results are consistent with smaller trials. One trial by Solomon, *et al* used a 120-mg daily dose for six weeks in 219 older adults. A feasibility trial by Dodge, *et al* used a 240-mg per day in 118 older adults with 3.5 years of follow-up. *NML* finds this curious in that the original GEM study had enough patients involved to have more than one dose level for comparison. When smaller studies with the 120-mg to 240-mg daily dosing found no effect, would not there be some reason to increase the dose for a part of the 3069 participants to see if a larger dose produced different results?

GEM study authors mention some limitations of the study included the fact that for the first several years of treatment were not captured by detailed cognitive evaluations. This was addressed by conducting secondary analyses which reset the baseline to the time in the study when regular annual assessments for all participants began. "These secondary analyses were consistent with those of the primary analyses using all available assessments. We also assessed the 3MSE [Modified Mini-Mental State Examination] and ADAS-Cog [Alzheimer Disease Assessment Scale] outcomes throughout the study and found no significant difference by treatment group. Another point of consideration is the observed baseline differences in 3 neuropsychological tests favoring the placebo group; however, the magnitude of these differences were small and clinically nonsignificant, and analyses were adjusted for baseline scores with regard to treatment comparisons. Finally, we note constraints on the generalizability of the present results due to under representation in the cohort of individuals with divergent ethnic/cultural backgrounds and relatively few participants with lower education levels."

Other researchers involved in this study were: Ellen S. O'Meara, Ph.D.; Michelle C. Carson, Ph.D.; Alice M. Arnold, Ph.D.; Diane G. Ives, MPH; Stephen R. Rapp, Ph.D.; Judith Saxton, Ph.D.; Oscar L. Lopez, M.D.; Leslie O. Dunn, MPH; and Kaycee M. Sink,

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M.D. There were many other participants at the multiple locations.

Footnotes indicate that Schwabe was offered an opportunity to review the report before publication, but there was no requirement that any comments or suggestions had to be included in the final manuscript.

NML observed on December 29, 2009 that the Schwabe web site at: www.schwabepharma.com/international/media-relations/press-releases/items/2009_12_08_Kaschel.php contains the following statement issued December 8, 2009:

Ginkgo biloba extract is effective for cognitive decline

KARLSRUHE, Germany, 8 December 2009. "Ginkgo biloba not only improves declining memory but offers specific benefits for other cognitive functions as well" that's how Dr. Reiner Kaschel, Clinical Neuro-psychologist at the University of Osnabrueck, Germany, sum-marizes the results of a comprehensive new scientific publication.

Internet shopping, online-banking, non-stop heavy traffic, unfamiliar and complicated ticketing machines, PINs for mobile phones and credit cards - our everyday professional and private lives are varied and complex and demand a permanently high degree of mental performance. Because certain cognitive features such as information processing, speed and flexibility of thinking, as well as ability to concentrate tend to decline with age, more and more people feel there is a gap between demands and performance. This is leading to greater interest in possible ways to combat cognitive decline.

A new approach to assessing the scientific evidence for Ginkgo biloba, Kaschel analyzed the scientific evidence for Ginkgo from a total of 29 published clinical trials to clarify whether Ginkgo extracts may be recommended to improve declining mental performance. Central to Kaschel's publication were the following questions not yet fully explored in the scientific literature:

- Does Ginkgo biloba improve mental performance in general or are there specific areas of cognitive functions where the extract shows a particular benefit?
- Which specific aspects of memory are strengthened?
- Does Ginkgo biloba also offers benefits for selective attention, executive functioning or intelligence?

The review covered all placebo-controlled, double-blind, random-ized studies between 1980 and 2007, in which function-specific tests for cognitive decline were applied. The study findings were then analyzed for separate areas of mental performance: Memory, attention, executive functions, and intelligence.

Efficacy shown in all areas of cognitive function 29 studies with a total of 2,414 participants being either healthy old adults or patients showing first signs of cognitive decline provided the database for the review. In total 209 Ginkgo - placebo comparisons were analyzed with the result that in all cognitive functional areas examined, Ginkgo extract showed significant positive effects compared to placebo. Drug effects could thus be proven in areas including but not limited to short- and long-term memory, concentration, attention and executive functions with a probability 4-8-fold higher than expected purely by chance. Author's Conclusion: "There is consistent evidence that chronic administration (of Ginkgo extract) improves selective attention, some executive processes and long-term memory for verbal and non-verbal material."

EGb 761® is a patented Ginkgo biloba extract developed and manufactured by Dr. Willmar Schwabe GmbH & Co. KG, Karlsruhe, Germany. It is widely recognized as the best researched phytomedicine world-wide and is available in more than 80 countries.

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[1] Kaschel R. Ginkgo biloba: specificity of neuropsychological improvement-a selective review in search of differential effects. *Hum Psychopharmacol.* 2009 Jul;24(5):345-70.

NML Emailed Schwabe to see if the company would supply the doses of *G. biloba* used in the 29 studies cited by the Kaschel study. Schwabe has issued earlier statements saying that the results from a large French study should be waited on before drawing any conclusions about the effectiveness of *G. biloba*. See www.npicenter.com/anm/templates/newsATemp.aspx?articleid=22705&zoneid=2 posted on November 18, 2009.

On January 4, 2009, a reply was received from Dr. Jochen Muehlhoff indicating that "[i]n 26 of the 29

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RCTs *Ginkgo biloba* was administered in daily doses between 120 mg and 240 mg per day. Only in three of the trials the dosage was below this: 2 studies with 80 mg / day, one trial with 1.93 mg ginkgolides per day.”

The Kaschel study indicates “significant positive effects,” while the GEM study found no effects in some of the same outcome measurements. This does not help clinicians make objective determinations about using *G. biloba*. It appears to *NML* that a larger study, utilizing a 360 mg per day dose or larger could show some different results.

On December 30, 2009 the American Herbal Products Association issued a release commenting on the *JAMA* report saying, “This week’s publication involved a review of the data generated in the original GEM study to see if ginkgo slowed the rate of cognitive decline in the study participants. ‘The data review conducted for this article suffers from the same limitations as the original GEM study with an additional challenge due to the testing schedule not being ideally suited for this new endpoint,’ said American Herbal Products Association (AHPA) Chief Science Officer, Steven Dentali, Ph.D.”

“Furthermore, as with the primary findings of the GEM study, the findings of the secondary analysis in no way undermines what has already been observed with regard to the usefulness of ginkgo extract, and EGb 761 in particular, in providing symptomatic relief in persons who already suffer from dementia or Alzheimer’s disease. Also what has not yet been published, but is clear from a review of the study data, is that the common supposition of increased risk of bleeding from EGb 761 ingestion turns out not to be true.’ said Dentali [footnote omitted].”

The Natural Products Association also issued a comment on December 30, 2009:

“As we stated in our comments regarding the 2008 GEM [Ginkgo Evaluation of Memory] study last year, the boat has left the dock and this study isn’t on it,” said Daniel Fabricant, Ph.D., vice president for scientific and regulatory affairs at the Natural Products Association. “When one considers that age-related cognitive decline may initiate in healthy adults as early

as their 30s, it would seem that if the authors were indeed serious about investigating prevention as a secondary outcome, they would have selected a population that was situated closer to the onset of cognitive decline instead of one where its effects most likely have already taken hold.” See www.npicenter.com. Search :ginkgo.

Some of the combativeness of the comments can be understood as market positioning, but there does appear to be some effectiveness in Ginkgo for people with dementia and cognitive difficulties. But that could be dangers in larger doses of Ginkgo if we are not careful.

G. biloba also contains Ginkgotoxin and this ingredient can be trouble if not carefully monitored. In the *Journal of Natural Products*, December 30, 2009, Eckhard Leistner and Christel Drewke at the Institut für Pharmazeutische Biologie der Rheinischen Frederich Wilhelms-Universität Bonn in Bonn, Germany, wrote a review of *G. biloba*. They state the obvious that ginkgo has a variety of compounds in it. They point out that the German and European Pharmacopeias are limited to 5 ppm of the dried extract (EGb 761) because of the allergenic potential.

Ginkgotoxin structure was shown to be 4'-methoxy pyridoxol. The structure and biosynthesis is discussed and the authors conclude that “the evidence shows that ginkgotoxin is structurally and biosynthetically a derivative of pyridoxol formed by the deoxyxylulose-independent pathway.”

In Japan the authors say that “gin-nan,” the name of Ginkgo in Japan, was the cause of about 70 reports with 27% lethality known as “gin-an sitotoxism,” a food poisoning. Children were affected in 58% of these cases of intoxication. In August, the *G. biloba* seeds have their maximum ginkgotoxin of about 85 micrograms per seed. After this time period the amount declines.

Three plants of the family Fabaceae, *Albizzia tanganyicensis*, Bak, *Albizzia lucida* Benth., and *Albizzia julibrissin* Durazz., also contain ginkgotoxin.

The authors discuss the molecular basis of ginkgotoxin intoxication pointing out that 30mg

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(corresponding to 2 mg/Kg body weight) of pyridoxal 5'-phosphate administered to a child led to recovery and that poisoned sheep can be cured in a similar fashion.

Ginkgotoxin occurs in leaves and seeds, with 5 micrograms per leaf in August. This corresponds to about 7 micrograms/g fresh weight in leaves. Many allopathic *G. biloba* medications contain a range of 11.4 and 58.62 micrograms of ginkgotoxin in a recommended daily dose. Homeopathic medications have lesser amounts of 0.09 to 11.92 micrograms.

Eckhard and Drewke say that the presence of ginkgotoxin in *G. biloba* products raises the question of

whether this could cause undesirable health effects such as seizures.

Assuming that 58.62 micrograms of ginkgotoxin ends up in the blood serum from a daily dose of a *G. biloba* product, the authors calculate that concentration of 53 nM to 80 nM of ginkgotoxin found in 6 or 4 liters of blood, respectively, would result. They compare this to vitamin B6 levels in blood plasma, reported at 114 nM.

Eckhard and Drewke say that P. Gregory warned in 2001 about the seizures from *G. biloba* in *Ann. Int. Med.*, 134, 344. A list of other articles cited warn of potential adverse effects.

In 1996, these authors and others assumed there was more safety. *Planta Med*, 1996, 62, 548-551. The authors now say they are "convinced ... that *G. biloba* medications and other products can have a detrimental effect on a person's health condition."

This conclusion is supported, they say, by the presence of ginkgotoxin in medications and the now known effect of ginkgotoxin on the action of pyridoxal/pyridoxol/pxridoxamine kinase, a pivotal reaction responsible for the supply of the brain with pyridoxal 5'-phosphate, and the reports in which it was shown that *G. biloba* leaf extract exerts a proconvulsive effect on mammals including rabbits and mice.

There have been other reports of interactions of *G. biloba* with anticonvulsants and other medications.

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settlement with its terms, the stipulations, the preliminary approval papers, the proposed preliminary approval order and proposed final judgment with all state Attorney Generals and the Attorney General of the United States. In addition, the FTC has already "been given a lot of information about this settlement" and it could intervene if it feels it appropriate.

Garganta further advised the Court that a web site has been set up where consumers and lawyers all over the country can go and look at the terms, and objectors can and will appear, and they can be represented by counsel. "So the Court is not going to be looking at this thing in isolation...."

Michael Ungar chimed in that, "Court approve settlement every day of the week without adjudicating the merits. It is not different than any other one." Ungar then discussed the prior mediation before Judge Tevrisian. Judge Polster replied, "I'm not sure that I would have mediated a settlement that required me to some judicial primatur on the fairness – on the accuracy of claimed health benefits for a product. That's the concern I've got."

Blood interjected, "And Your Honor, that is absolutely not plaintiff's intent. It's just the opposite, in fact. Your comments have been exceedingly helpful." And the Court responded, "Well, you are saying it is not your intent, but that is what is happening here."

During the remaining discussions, the Court suggested counsel meet and confer on what to suggest and they determined to have another telephone status conference on October 21 at 3:00 P.M.

The next filing in the Court Docket is a December 31, 2009 Notice of Change of Firm Affiliation Effective January 1, 2010 by Timothy G. Blood, Esq., Leslie E. Hurst, Esq. and Thomas J.O'Reardon, II, Esq. counsel of record for plaintiff for service at the firm of Blood, Hurst & O'Reardon in San Diego.

These are the latest developments in this case, *James Gemelas, et al v. The Dannon Company, Inc.*, No. 1:08-cv-236, U.S. District Court, Northern District of Ohio, as of January 12, 2010.