P.O. Box 144345 Austin, TX 78714-4345 ▪ 512.926.4900 ▪ Fax: 512.926.2345 ▪ www.herbalgram.org

HerbClip™

File: ■ Ginkgo (*Ginkgo biloba*, Ginkgoaceae)
■ Alzheimer's Disease
■ Cholinesterase Inhibitors

HC 051552-532

Date: November 13, 2015

RE: Adjunct Ginkgo Leaf Extract EGb 761® May Improve Cognition for Patients with Alzheimer's Disease Who Are Using Cholinesterase Inhibitors

Canevelli M, Adali N, Kelaiditi E, et al. Effects of *Gingko* [*sic*] *biloba* supplementation in Alzheimer's disease patients receiving cholinesterase inhibitors: Data from the ICTUS study. *Phytomedicine*. 2014;21(6):888-892.

There are many published studies evaluating the effect of ginkgo (*Ginkgo biloba*, Ginkgoaceae) leaf on memory and learning. While its efficacy in the prevention of dementia and Alzheimer's disease (AD) is still under debate, there is now evidence of efficacy in the treatment of manifest dementia. However, according to the authors, few studies evaluate the effect of adding ginkgo to an anti-dementia treatment regimen that includes cholinesterase inhibitors (ChEIs). The prospective, multicenter Impact of Cholinergic Treatment USe (ICTUS) study was a cohort study evaluating the clinical course, treatment outcomes, and socioeconomic impact of AD in Europe. The authors analyzed ICTUS data to evaluate the cognitive and/or functional benefits of adding ginkgo to ChEI treatment in patients with mild to moderate AD.

The ICTUS study included 29 centers from 12 European countries. The inclusion criteria were as follows: diagnosis of probable AD according to the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria, Mini-Mental State Examination (MMSE) score ranging from 10 to 26, living with a well-identified informal caregiver, and having no conditions that would reduce life expectancy to < 2 years. Excluded from the analyses were patients not taking ChEIs and patients who changed treatments during the 12-month follow-up period.

After baseline assessments, conducted between February 2003 and July 2005, patients were followed for 2 years with mid-term evaluations every 6 months. At every visit, concomitant pharmacological treatments were recorded.

This analysis included data from 828 patients (mean age, 75.8 years). Patients were divided into 2 groups depending on whether they were receiving only ChEIs or ChEIs plus ginkgo leaf extract (EGb 761®; Dr. Willmar Schwabe GmbH & Co. KG; Karlsruhe,

Germany). A total of 56% of the patients received 120 mg/day ginkgo. The assignment of treatment group was done prior to this study, was not described, and does not appear to have been randomized. The authors do not report the dose range and do not mention why the commonly used dose of 240 mg/day was apparently not used at all. At baseline and 12 months, cognition was analyzed with the MMSE and Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog), and functional ability was measured with the Activities of Daily Living (ADL) questionnaire.

At baseline, 799 (96.5%) patients were taking ChEIs alone, and 29 (3.5%) patients were taking ChEIs plus EGb 761. There were no significant differences between the 2 groups except that patients in the combined treatment group were significantly more educated ($P = 0.01$) and were less cognitively impaired ($P < 0.01$) compared with the ChEIs-only group.

There were no significant differences between groups at 6 months on any test, although there was a trend towards significance in MMSE scores for the combination group. At 12 months, the combination group showed a significant cognitive benefit on the MMSE compared with the ChEIs-only group ($P = 0.006$). Surprisingly, this finding was confirmed after re-analyzing the data to control for potential confounding variables, such as education and level of impairment, which are known to affect MMSE scores ($P = 0.005$). There were no significant differences between groups in the gold-standard measures, the ADAS-Cog score or the ADL score.

The authors conclude that ginkgo "might provide some added cognitive benefits" in patients with moderate AD who are already taking ChEIs. The authors point out a number of limitations of this type of observational cohort study, including (1) causality cannot be determined, (2) potential selection bias (patients who benefited from the combination treatment remained in the study while patients who did not benefit may have dropped out; the number of patients who stopped taking ginkgo during the 12-month study period was not reported), (3) doses were not steady throughout the study, (4) concomitant use of other drugs may have interacted with the tested treatments, (5) there could have been residual effects of ginkgo usage prior to the baseline assessment, and (6) the small percentage of patients taking ChEIs and ginkgo (3.5%). There might also be another limitation not mentioned by the authors as the majority of patients took ginkgo in a dose of 120 mg/day which is just the minimum effective dose. Usually a dose of 240 mg/day would have been considered more appropriate if this were a prospective study. The findings do not permit a definitive conclusion, and larger, controlled studies are needed to evaluate the additive effects of ginkgo and their clinical relevance in this population. The ICTUS study was partially supported from an unrestricted equal grant from each of Eisai, Jansen, Lundbeck, and Novartis pharmaceutical companies and partially supported by a grant from the European Commission within the Fifth Framework Program.

—Heather S. Oliff, PhD

The American Botanical Council has chosen not to include the original article.