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

HerbClip™

▪ **Ginkgo (*Ginkgo biloba*)**
▪ **EGb 761®**
▪ **Metformin**
▪ **Type-2 Diabetes**

HC 090161-314

Date: October 13, 2006

RE: Effects of Ginkgo Use on Metformin Pharmacokinetics in Diabetic and Non-Diabetic Subjects

Kudolo GB, Wang W, Javors M, Blodgett J. The effect of the ingestion of *Ginkgo biloba* extract (EGb 761) on the pharmacokinetics of metformin in non-diabetic and type 2 diabetic subjects—a double blind placebo-controlled, crossover study. *Clin Nutr*. 2006;25:606–616.

One of the most popular herbal supplements is ginkgo (*Ginkgo biloba*) extract. Ginkgo is usually ingested for its beneficial cognitive effects to enhance mental acuity and to help enhance memory, and, secondarily, for its peripheral circulatory effects. However, the focus of this trial was to evaluate the effect of ginkgo ingestion on metformin in diabetic and non-diabetic patients.

In a previous study, the authors showed that the ingestion of a single dose (120 mg) of a generic ginkgo extract for 3 months resulted in an increase in pancreatic β-cell function and a decrease in collagen- and arachidonic acid–mediated platelet aggregation and thromboxane B_2 synthesis. [Twenty volunteers at the University of Texas Health Science Center in San Antonio took 120 mg of a 50:1 standardized ginkgo extract, with guaranteed chemical standardization of 24% ginkgo flavone glycosides and 6% terpenes (Walgreens Co., Deerfield, IL). The volunteers took ginkgo at bedtime each day for three months, and each served as his or her own control. See HC 010919-196] Type-2 diabetic patients usually have hyperactive platelets which lead to a high tendency to form blood clots (thrombi) in the tiny blood vessels. Thus diabetic subjects are prone to the development of heart attacks and stroke. Low-dose aspirin is now recommended for the prevention of platelet hyperactivity, which leads to inhibition of thromboxane B2 formation, makes the blood more fluid and free-flowing to prevent both first and secondary heart attacks. They also showed that ingestion of the ginkgo extract might improve platelet function in patients with type-2 diabetes mellitus (T2DM). Because of the increasing popularity of ginkgo and the increasing prevalence of T2DM, a strong possibility exists that ginkgo extracts and diabetes medications will be co-ingested. Thus, the objective of this study was to determine whether

the ingestion of a ginkgo extract [described as containing 24.7% flavone glycosides (12.6% quercetin, 10.1% kaempferol, and 2.0% isorhamnetin) and 6% terpenes (4.3% ginkgolide A, 3.3% ginkgolide B, 0.09% ginkgolide C, and 2.4% bilobalide)] in conjunction with metformin—a drug used to treat type-2 diabetes—would alter the pharmacokinetics and efficacy of metformin (Glucophage®, Merck, licensed in US to Bristol-Meyers Squibb).

Twenty subjects (*n* = 12 women and 8 men), 10 with normal glucose tolerance (NGT) and 10 with T2DM, were enrolled in this randomized, double-blind, placebo-controlled crossover study, which was conducted at the Frederic C. Bartter General Clinical Research Center of the South Texas Veterans Health Care System (San Antonio, TX). The subjects ingested either an alfalfa (*Medicago sativa*)-based placebo or a single dose (120 mg) of ginkgo extract daily for 3 months in each arm of the study. The subjects returned to the research center monthly to provide blood samples and to complete questionnaires. At the end of each 3-month treatment period, the subjects returned to the research center to undergo the pharmacokinetic studies. The subjects fasted overnight and then the NGT subjects ingested a single dose of 500 mg metformin, and the T2DM subjects ingested their prescribed dose of metformin (250–850 mg per day) plus 120 mg ginkgo extract. Blood and urine samples were collected over 8 hours from both the NGT and T2DM subjects and for the first 2 hours of the next 3 days from the T2DM subjects. Hematologic, lipid, glucose, and insulin concentrations were measured, and renal function was tested.

The ingestion of ginkgo extract for 3 months had no significant effect on renal function or lipid, glucose, insulin, or hematologic concentrations in either group, except for a significant decrease (from $7.7 \pm 1.2\%$ to $7.2 \pm 0.9\%$; $P < 0.05$) in glycated hemoglobin concentrations in the T2DM subjects. The ingestion of ginkgo extract did not significantly affect the urinary excretion rate of metformin in either group; however, metformin excretion decreased significantly with ginkgo extract ingestion in those subjects who consumed 850 mg metformin. The ingestion of ginkgo extract did not significantly effect any of the pharmacokinetic variables of metformin measured in either the NGT or T2DM group, except for a significant increase (from 0.117 ± 0.085 to 0.141 ± 0.100; $P < 0.05$) in the elimination rate in the T2DM group.

The results indicate that the ingestion of 120 mg of ginkgo extract did not significantly affect the clinical variables measured, and co-ingestion of this extract and metformin had no significant effect on the pharmacokinetic variables measured at a metformin dose of 500 mg or less. The authors conclude that ginkgo extract does not produce insulin resistance in NGT subjects or exacerbate the condition in those with impaired glucose tolerance or T2DM. Thus, "it appears that it is probably safe to co-ingest ginkgo extract with metformin." However, the authors note that it cannot be predicted how doses larger than 120 mg per day will interact with the doses of metformin evaluated in this study (i.e., 250–850 mg per day).

It bears emphasis that the authors used the term "EGb 761," a registered trademark of Willmar Schwabe Pharmaceutical Co., Karlsruhe, Germany), in the title of and throughout this article to describe the preparation studied in this trial. The true EGb 761® is the world's first and leading standardized extract made from the ginkgo leaves and is the subject of over 100 published clinical trials covering mainly the effects of EGb 761 on cognitive functions

in normal and cognitively-impaired adults as well as effects on peripheral circulation, e.g. peripheral arterial occlusive disease (a.k.a. intermittent claudication). This patented ginkgo extract is licensed as a medicine and/or sold as a dietary supplement in many countries. In a personal communication with the primary author (GB Kudolo, 2006), Mark Blumenthal (Founder & Executive Director of the American Botanical Council) confirmed that a generic extract of ginkgo provided by Whole Health Nutrition (Edmonds, WA) was actually employed in this trial; thus, the term "EGb 761" should not have been used in this article. Kudolo stated that the extract in this study "contained constituents which compare favorably with the famed standardized 50:1 EGb 761 (of approx. 24% flavonol glycosides and 6% terpenes)." This is however not achieved by the product tested according to the analysis of the product, which was provided by the authors. The extract used contained 10% of the pharmacologically active terpene lactones, which may result in a very different efficacy than achieved by EGb 761. Also the interaction potential might be changed, which means that the results described are valid only for this specific extract, but not for ginkgo extracts in general. In addition, as Blumenthal responded in a letter to the editor of the journal: "such chemical and biological equivalence is not technically possible" because simply relying on attempts to concentrate a ginkgo extract to a 50:1 concentration and to standardize the terpenes (ginkgolides A and B and bilobalides) to 6% and the flavonoids (rutin, quercetin, and kaempferol) to 24% accounts for only approximately 30% of the extract. This obviously leaves 70% of the extract uncharacterized, and no publications in the literature have provided the chemical characterization of this fraction. Thus, it is inaccurate and potentially misleading (obviously not the intent of the authors) to claim that the ginkgo extract used in this study compared favorably with EGb 761, i.e., based solely on these chemical standardization parameters.

Furthermore, Blumenthal asserts in his letter that the alfalfa-based placebo used in this study may have been inappropriate since alfalfa contains nutrients and other phytochemicals that cannot be considered inert; thus, these active ingredients may have produced clinically observable results that may have confounded the statistical comparisons between groups. Kudolo defends the use of the alfalfa-based placebo on the basis that this was a crossover study (i.e., both groups ingested the placebo in different cycles) and that "any change in the outcome could be ascribed to the active ingredient of the Ginkgo extract, rather than to a non-specific plant constituent."

—Brenda Milot, ELS

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