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

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FILE: ▪ Ginkgo (*Ginkgo biloba*)
▪ Herb/Drug Interaction

HC 110281-374

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RE: Lack of Evidence of Ginkgo and Antiplatelet or Anticoagulant Drug Interactions

Bone KM. Potential interaction of *Ginkgo biloba* leaf with antiplatelet or anticoagulant drugs: what is the evidence? *Mol Nutr Food Res*. 2008;52(7):764-771.

Ginkgo (*Ginkgo biloba*) has become one of the best-selling herbs on the global market. Ginkgo products come in various formulations and compositions, including EGb 761® (Dr. Willmar Schwabe; Karlsruhe, Germany) which is a highly concentrated extract of ginkgo leaves, standardized by total flavonoid and terpene trilactone content. However, generic standardized ginkgo products do not reflect the same phytochemical profile as EGb 761.

Regular ginkgo intake has been linked with bleeding episodes, and the potential interaction of ginkgo with antiplatelet or anticoagulant drugs has become an accepted notion. This review sought to critically examine the likelihood that ginkgo (and specifically EGb 761 or extracts which mimic its phytochemical profile) influences normal hemostasis.

The author notes that there is no evidence from controlled studies that normal doses of EGb 761 (or closely similar extracts) have any impact on hemostasis. Furthermore, earlier ex vivo platelet aggregation studies using high doses or a concentrated ginkgolide mixture have been inappropriately extrapolated to the normal use of commercial extracts. Although in vitro studies have shown that single constituents of EGb 761 (especially ginkgolide B) inhibit platelet aggregation, the results should be interpreted with caution because there are issues of oral bioavailability and excessive concentrations. One study revealed that aggregation of human platelets was inhibited by ginkgolides at concentrations generally more than 100 times higher than the peak plasma values measured after oral intake of EGb 761.

In perhaps the most comprehensive study to date, the effect of 240 mg/day for 7 days of EGb 761 in 50 healthy male volunteers was assessed using a randomized, double-blind, placebo-controlled crossover design. None of the 29 coagulation and bleeding parameters evaluated showed any evidence of an inhibition of blood coagulation or platelet aggregation

from EGb 761 intake. Four small, controlled studies found no additional impact on hemostasis when EGb 761 was combined with either aspirin or warfarin.

The results from controlled studies appear to be at odds with the 21 case reports published between 1996 and 2005, which describe adverse bleeding events in connection with the consumption of ginkgo. Although there was a single documented case report in which it was confirmed that EGb 761 was involved in the bleeding, the patient was also taking aspirin. Establishing causality from these case reports is difficult, due to the generally low quality of the reports. Not only is there variability in herbal products, but also a lack of documentation of key factors such as product name, level of standardization, other potentially active ingredients, and type of extract used are generally absent. Further confounding any interpretation, in most of the reported cases, other clinical risk factors for bleeding were present. Nevertheless, these case reports do serve as a warning for a potential problem. The author suggests that there is scant evidence, based on either the case reports or controlled studies, to suggest that combining ginkgo with anticoagulant or antiplatelet agents increases the risk of bleeding over and above the use of these agents alone.

Reviews and meta-analyses of clinical trials have shown that EGb 761 has a remarkably low incidence of side effects. In 44 clinical trials, only 0.5% of 9772 patients reported adverse events, and none of the events were linked to abnormal bleeding. An excerpt of the Mediplus database in Germany providing information for 320,644 patients was used to evaluate reported bleeding events. Over 810,077 patient years of observation, 22,586 bleeding events were reported, giving an average of 2.79 events per 100 years of observation. The risk of bleeding with EGb 761 or any ginkgo preparation was around 1, indicating that the frequency of reported bleeding events in patients taking ginkgo was the same as that in patients not taking ginkgo. No increase in the prevalence of bleeding during EGb 761 intake compared to periods without EGb 761 was seen for coadministration of phenprocoumon, aspirin, or for any other anticoagulant or antiplatelet medication.

The author concludes that results from controlled clinical trials together with those from the surveillance (database) study suggest that concerns regarding the potential for ginkgo to interact adversely with anticoagulant and antiplatelet drugs are substantially overstated, especially if EGb 761 or phytochemically similar extracts are involved. However, the amounts and relative levels of the various ginkgolides, the fortification with added flavonoids, or the lack of removal of ginkgolic acids might account for a less favorable safety profile for other ginkgo extracts in terms of bleeding risk. On the other hand, the reported cases may represent an idiosyncratic reaction to ginkgo, but better data are required to establish this.

—Jennifer Minigh, PhD

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