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File: ■ Ginkgo (*Ginkgo biloba*, Ginkgoaceae)
■ Toxicology
■ Tolerability and Safety

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RE: Comprehensive Assessment Concludes Ginkgo Leaf Extract Is Safe and Well Tolerated

Heinonen T, Gaus W. Cross matching observations on toxicological and clinical data for the assessment of tolerability and safety of *Ginkgo biloba* leaf extract. *Toxicology*. 2015;327:95-115.

Ginkgo (*Ginkgo biloba*, Ginkgoaceae) leaf extract is one of the herbal products most commonly used in the United States and Europe. The most popular ginkgo formulation is the standardized extract EGb 761® (Tebonin®; Dr. Willmar Schwabe GmbH & Co. KG; Karlsruhe, Germany). The purpose of this review was to analyze the tolerability and safety of ginkgo in humans. The authors used a tool that they designed called cross matching. The purpose of cross matching is to combine different fields of knowledge and types of data into a consolidated result. It is important to evaluate not only ginkgo but also its components because various manufacturers produce ginkgo preparations differently. It is also important to evaluate the animal data because, at this time, in vivo animal tests are the first screening methods for safety and tolerability. Therefore, the authors cross matched toxicological data, adverse events (AEs) from clinical trials, epidemiological data, and data reported in the scientific and medical literature.

The pharmacologically active components of ginkgo are terpene trilactones (ginkgolides and bilobalide), flavonoid glycosides (metabolized by intestinal microflora to release quercetin, kaempferol, and isorhamnetin), ginkgolic acids, and organic acids. Products contain differing amounts of these constituents.

Data pertaining to hepatic metabolism in mice, rats, and humans were extracted from the literature. Animal metabolic enzymes differ between species and between animals and humans. The authors conclude that ginkgo is an inducer of various cytochrome P450 (CYP) and conjugation enzymes in mice. Bilobalide, but not the other terpene trilactones, can induce isoforms of CYP and DT-diaphorase in mice. Ginkgolide A and bilobalide induce glutathione S-transferase in mice. In rats, ginkgo is a potent inducer of hepatic metabolic enzymes. Bilobalide is an inducer of CYP isoenzymes in rats. The flavonoids are mainly conjugated with uridine 5'-diphospho (UDP)-glucuronide. In

humans, chronic therapeutic doses have demonstrated no definitive inhibitory or inducing effect on major human CYPs.

Data pertaining to the pharmacokinetics of ginkgo in mice, rats, and humans were also extracted and showed differences among species. Mice and rats were exposed in toxicity studies to several hundred- to several thousand-fold higher doses of ginkgo constituents than would be used therapeutically in humans. Accordingly, the peak plasma levels of ginkgolides A and B and bilobalide were several ten- to hundred-fold higher than in humans at therapeutic doses.

Data pertaining to the genotoxicity (damage to the genetic material, which can lead to cancer) and mutagenicity (mutations in the genetic material) of ginkgo in mice and rats were reviewed. Very high concentrations of ginkgo or its components caused cytotoxicity, which appeared positive on in vitro genotoxic tests. Even doses much higher than what would be used therapeutically were not genotoxic or mutagenic in vivo. There was no indication of carcinogenicity in mice and rats with dose levels of EGb 761 25 or 50 times greater than the human therapeutic dosage.

The National Toxicology Program conducted studies that showed thyroid and liver tumor induction in ginkgo-treated mice and rats. The mechanism for this effect was increased activity of hepatic drug metabolism enzymes, which caused accelerated cell proliferation and concomitant liver neoplasm (tumor), while thyroid proliferation from elevated thyroid-stimulating hormone resulted from increased glucuronidation of rodent thyroid hormones. Increased olfactory epithelium pigmentation and hyaline drop accumulation in the nose without carcinogenicity and benign respiratory tumors (adenomas) were observed in two rats treated with an intermediate dose (300 mg/kg). These findings may be random or caused by esophageal reflux due to gavage administration. There is no indication of ginkgo carcinogenicity in humans.

The clinical tolerability and safety of ginkgo were also evaluated via a literature search. The specific search engine and terms were not reported. A total of 88 publications describing 75 studies were included. Nearly all of the studies were conducted with EGb 761. Only tolerability and safety data were extracted. Patients receiving placebo or another comparative treatment other than ginkgo were excluded from the analysis. The 75 studies include a total of 7115 ginkgo-treated patients. The authors evaluated all 75 clinical trials and "saw no specific and serious undesired drug reaction of *G. biloba*. If adverse events were observed, they were as frequent with *G. biloba* as with placebo treatment." The authors calculated an AE rate and confidence interval. The calculation showed that the probability for one person to have a specific adverse reaction from ginkgo is ≤0.000518. They calculate that at least 1930 patients have to be treated with ginkgo to find one patient with an adverse drug reaction.

Possible adverse reactions to ginkgo have been reported; specifically, bleeding of individual organs (eye, nose, cerebral, and gastrointestinal hemorrhage), headache, dizziness, mild gastrointestinal complaints (such as diarrhea, abdominal pain, nausea, and vomiting), hypersensitivity reactions (allergic shock), and allergic skin reactions (erythema, edema, itching, and rash). However, these AEs are based on spontaneous reports. In controlled, clinical trials, AEs have never exceeded placebo rates. The authors conclude that they are unable to establish that ginkgo provokes any specific adverse reaction.

None of the animal studies provide ample evidence of the toxicity of ginkgo in humans. The data necessitated cross matching as many sources as possible because there is a poor relationship between animal and clinical results. Hence, the following four sources were cross matched: (1) In controlled, clinical trials including a total of 7115 patients, ginkgo was well tolerated. The numerous clinical studies evaluated different diseases, doses, duration of treatment, populations, and diagnostic measures; nonetheless, "no reasonable suspicion of an adverse drug reaction to *G. biloba* was found." (2) A long history of modern commercial use (since 1965) supports the tolerability observed in the clinical studies. According to the manufacturer of EGb 761, on average for the past 25 years, approximately 360 million doses/year or 1 million doses/day of EGb 761 have been consumed. (3) There are a wide variety of preclinical toxicological studies with reports from independent sources on diverse ginkgo preparations and doses used. (4) A long history of traditional use without expressed safety concerns suggests good tolerability.

The authors "certify" that adverse reactions to ginkgo would be extremely rare. They conclude that ginkgo leaf extract is well tolerated and safe. Despite the cross matching, this does not mean that AEs are not possible. In particular, there could be adverse herb-drug interactions to new drugs under development. It is well known that the elderly population often take numerous drugs simultaneously and this same population would be interested in taking ginkgo preparations. The authors do discuss the possibility of pharmacokinetic ginkgo-drug interactions, but did not find evidence of suggesting such interactions.

—Heather S. Oliff, PhD

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