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Ginkgo

Updated: March 14, 2018.

OVERVIEW

Introduction

Ginkgo is a popular herbal medication and extract derived from the leaves and seeds of the tree Ginkgo biloba. Ginkgo has not been implicated in causing liver injury.

Background

Ginkgo (ging' koe) is a widely used herbal derived from the leaves and seeds of the Ginkgo biloba tree, a "living fossil", being the only extant species of what was a large order of plants (Ginkgoales) more than 200 million years ago. Ginkgo is native to central China, but has been introduced worldwide. The word ginkgo derives from a Japanese approximation of the Chinese word for "silver apricot" referring to the tree's fruit. Extracts from ginkgo leaves and seeds were used in traditional Chinese medicine for centuries for a multitude of illnesses and conditions. Ginkgo extracts contain multiple compounds, but ginkgolides and bilobalide are unique to this herb. Ginkgo extracts have been shown to have antioxidant, antiinflammatory and antihistaminic activity. Current uses are many and include dementia, memory loss, headache, dizziness, tinnitus, hearing problems, difficulty concentrating, mood disturbances, peripheral vascular disease, asthma, and bronchitis. Ginkgo is purported to increase mental acuity and delay the effects of aging on the brain, as well as improve peripheral circulation, prevent macular degeneration and decrease symptoms of claudication and Raynaud's syndrome. Ginkgo leaf extract is also used in foods, cosmetics, and skin lotions. The scientific bases for the purported effects of ginkgo are not well established and clinical trials have shown no or only modest clinical effects in dementia, claudication and tinnitus. Ginkgo is available in a variety of formulations (tablets, capsules, powder, teas, and lotions) and the typical oral dosage is 120 to 240 mg per day in 2 to 3 divided doses. Side effects of ginkgo are uncommon and mild, and include gastrointestinal upset, nausea, diarrhea, headache, dizziness, increased bleeding tendency and rash. In clinical trials, both serious and common side effects have been no more frequent with ginkgo than placebo.

Hepatotoxicity

Despite wide spread use, ginkgo has not been specifically linked to liver injury, either in the form of transient serum enzyme elevations or clinically apparent acute liver injury. Indeed, ginkgo is sometimes used to treat acute or chronic liver injury. Gingko demostrates some degree of inhibition of cytochrome P450 activity in vitro, but in doses used in humans it appears to have little effect on drug metabolism. Several instances of excessive bleeding during therapy with ginkgo have been attributed to drug interactions with antiplatelet medications or anticoagulants.

Likelihood score: E (unlikely cause of clinically apparent liver injury).

Other Names: Maidenhair tree, fossil tree, kew tree, Japanese silver apricot

Drug Class: Herbal and Dietary Supplements

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Ginkgo – Generic

DRUG CLASS

Herbal and Dietary Supplements

SUMMARY INFORMATION

Fact Sheet at National Center for Complementary and Integrative Health, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Ginkgo	90045-36-6	Herbal mixture	Not applicable

ANNOTATED BIBLIOGRAPHY

References updated: 14 March 2018

Zimmerman HJ. Unconventional drugs. Miscellaneous drugs and diagnostic chemicals. In, Zimmerman, HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott,1999: pp. 731-4.

(Expert review of hepatotoxicity published in 1999; ginkgo is not discussed).

Liu LU, Schiano TD. Hepatotoxicity of herbal medicines, vitamins and natural hepatotoxins. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 2nd ed. New York: Informa Healthcare USA, 2007, pp. 733-54.

(Review of hepatotoxicity of herbal and dietary supplements [HDS] published in 2007; ginkgo is listed as nonhepatotoxic).

Ginkgo. In, PDR for Herbal Medicines. 4th ed. Montvale, New Jersey: Thomson Healthcare Inc. 2007: pp. 371-84.

(Compilation of short monographs on herbal medications and dietary supplements).

Kleijnen J, Knipschild P. Ginkgo biloba. Lancet 1992; 340: 1136-9. PubMed PMID: 1359218.

(Review of history, mechanism of action, clinical and adverse effects of ginkgo; "no serious side effects have been noted in any trial"; rarely, there are mild gastrointestinal complaints, headaches or allergic skin reactions).

De Smet PAGM. Herbal remedies. N Engl J Med 2002; 347: 2046-56. PubMed PMID: 12490687.

(Review of status and difficulties of herbal medications, including lack of standardization, federal regulation, contamination, safety, hepatotoxicity and drug-herb interactions; specific discussion of 4 herbs with therapeutic promise: ginkgo, hawthorn, saw palmetto and St. John's wort).

Sierpina VS, Wollschlaeger B, Blumenthal M. Ginkgo biloba. Am Fam Physician 2003; 68: 923-6. PubMed PMID: 13678141.

(Ginkgo is used in the treatment of cerebrovascular disease and dementia and is generally well tolerated, but can increase risk of bleeding when used in combination with antiplatelet therapy or anticoagulants).

Schiano TD. Hepatotoxicity and complementary and alternative medicines. Clin Liver Dis 2003; 7: 453-73. PubMed PMID: 12879994.

(Comprehensive review of herbal associated hepatotoxicity; ginkgo is not listed as causing hepatotoxicity).

Russo MW, Galanko JA, Shrestha R, Fried MW, Watkins P. Liver transplantation for acute liver failure from drug-induced liver injury in the United States. Liver Transpl 2004; 10: 1018-23. PubMed PMID: 15390328.

(Among ~50,000 liver transplants reported to UNOS between 1990 and 2002, 270 [0.5%] were done for drug induced acute liver failure, including 7 [5%] for herbal medications, none attributed to ginkgo).

Naik SR, Panda VS. Antioxidant and hepatoprotective effects of Ginkgo biloba phytosomes in carbon tetrachloride-induced liver injury in rodents. Liver Int 2007; 27: 393-9. PubMed PMID: 17355462.

(In rats, ginkgo extract decreased the toxic injury induced by carbon tetrachloride, decreased free radical oxidative stress and increased glutathionine, superoxide dismutase and glutathione reductase levels).

Yuan G, Gong Z, Li J, Li X. Ginkgo biloba extract protects against alcohol-induced liver injury in rats. Phytother Res 2007; 21: 234-8. PubMed PMID: 17154234.

(Ginkgo extract decreased steatosis and inflammation and serum ALT levels in a rat model of alcohol liver injury, which was likely mediated by a decrease in oxidative stress and prevention of glutathione depletion).

Sener G, Omurtag GZ, Sehirli O, Tozan A, Yüksel M, Ercan F, Gedik N. Protective effects of ginkgo biloba against acetaminophen-induced toxicity in mice. Mol Cell Biochem 2006; 283: 39-45. PubMed PMID: 16444584.

(Ginkgo extracts decreased cell injury, ALT and TNFα levels in a mouse model of acetaminophen hepatotoxicity perhaps mediated by its antioxidant activity).

García-Cortés M, Borraz Y, Lucena MI, Peláez G, Salmerón J, Diago M, Martínez-Sierra MC, et al. [Liver injury induced by "natural remedies": an analysis of cases submitted to the Spanish Liver Toxicity Registry]. Rev Esp Enferm Dig 2008; 100: 688-95. Spanish. PubMed PMID: 19159172.

(Among 521 cases of drug induced liver injury submitted to Spanish registry, 13 [2%] were due to herbals but none attributed to ginkgo).

Chalasani N, Fontana RJ, Bonkovsky HL, Watkins PB, Davern T, Serrano J, Yang H, Rochon J; Drug Induced Liver Injury Network (DILIN). Causes, clinical features, and outcomes from a prospective study of drug-induced liver injury in the United States. Gastroenterology 2008; 135: 1924-34. PubMed PMID: 18955056.

(Among 300 cases of drug induced liver disease in the US collected between 2004 and 2008, 9% of cases were attributed to herbal medications, but none were attributed to ginkgo).

DeKosky ST, Williamson JD, Fitzpatrick AL, Kronmal FA, Ives DG, Saxton JA, Lopez OL, et al. Ginkgo biloba for prevention of dementia: a randomized controlled trial. JAMA 2008; 300: 2253-62. PubMed PMID: 19017911.

(Controlled trial of long term [median 6.1 years] administration of ginkgo vs placebo in ~3000 elderly patients with no or mild impairment of cognition, showing no effect in preventing dementia; "The adverse event profiles for G. biloba and placebo were similar and there were no statistically significant differences in the rates of serious adverse events").

Navarro VJ. Herbal and dietary supplement hepatotoxicity. Semin Liver Dis 2009; 29: 373-82. PubMed PMID: 19826971.

(Overview of the regulatory environment, clinical patterns, and future directions in research with HDS; ginkgo is not listed as a potentially hepatotoxic botanical).

Jacobsson I, Jönsson AK, Gerdén B, Hägg S. Spontaneously reported adverse reactions in association with complementary and alternative medicine substances in Sweden. Pharmacoepidemiol Drug Saf 2009; 18: 1039-47. PubMed PMID: 19650152.

(Review of 778 spontaneous reports of adverse reactions to herbals to Swedish Registry found 52 related to ginkgo [6.7%], including 2 reports of serum enzyme elevations; no details given).

Fransen HP, Pelgrom SM, Stewart-Knox B, de Kaste D, Verhagen H. Assessment of health claims, content, and safety of herbal supplements containing Ginkgo biloba. Food Nutr Res 2010; 54. PubMed PMID: 20927202.

(Efficacy and safety of Ginkgo leaf products found little support for health claims, variability in the content of Ginkgo components and concern about drug-herb interactions particularly in coagulation).

Ihl R, Bachinskaya N, Korczyn AD, Vakhapova V, Tribanek M, Hoerr R, Napryeyenko O; on behalf of the GOTADAY Study Group. Efficacy and safety of a once-daily formulation of Ginkgo biloba extract EGb 761 in dementia with neuropsychiatric features: a randomized controlled trial. Int J Geriatr Psychiatry 2011; 26: 1186-94. PubMed PMID: 21140383.

(Controlled trial of ginkgo [240 mg once daily] vs placebo in 410 patients with suspected Alzheimer's disease or vascular dementia for at least 24 weeks; adverse event rates were similar for both groups and no liver related events were reported).

Herrschaft H, Nacu A, Likhachev S, Sholomov I, Hoerr R, Schlaefke S. Ginkgo biloba extract EGb 761® in dementia with neuropsychiatric features: a randomised, placebo-controlled trial to confirm the efficacy and safety of a daily dose of 240 mg. J Psychiatr Res 2012; 46: 716-23. PubMed PMID: 22459264.

(Controlled trial of ginkgo [240 mg once daily] vs placebo in 410 patients with suspected Alzheimer's disease or vascular dementia for at least 24 weeks; no hepatic adverse events were reported and "...laboratory tests did not reveal any conspicuous or systematic changes").

Diamond BJ, Bailey MR. Ginkgo biloba: indications, mechanisms, and safety. Psychiatr Clin North Am 2013; 36: 73-83. PubMed PMID: 23538078.

(Review of results of clinical trials of ginkgo focusing largely on EGb 761, a standardized product used in Europe given in doses of 80 to 240 mg daily; side effects have included bleeding abnormalities perhaps due to antiplatelet activity and interactions with warfarin; no mention of hepatotoxicity).

Unger M. Pharmacokinetic drug interactions involving Ginkgo biloba. Drug Metab Rev 2013; 45: 353-85. PubMed PMID: 23865865.

(Extensive review of evidence for drug interactions by ginkgo concludes that interactions are minimal with standard doses of gingko).

Björnsson ES, Bergmann OM, Björnsson HK, Kvaran RB, Olafsson S. Incidence, presentation and outcomes in patients with drug-induced liver injury in the general population of Iceland. Gastroenterology 2013; 144: 1419-25. PubMed PMID: 23419359.

(In a population based study of drug induced liver injury from Iceland, 96 cases were identified over a 2 year period, including 15 [16%] due to herbal and dietary supplements, but none were attributed to ginkgo).

Dağ MS, Aydınlı M, Oztürk ZA, Türkbeyler IH, Koruk I, Savaş MC, Koruk M, et al. Drug- and herb-induced liver injury: a case series from a single center. Turk J Gastroenterol 2014; 25: 41-5. PubMed PMID: 24918129.

(Between 2008 and 2012, 82 patients with drug or herbal supplement induced liver injury were seen at a single referral center in Turkey, 10 [12%] of which were due to HDS products, including 7 due to Teucrium polium [mountain germander] and 3 to green tea extract, but none to ginkgo containing products).

Navarro VJ, Barnhart H, Bonkovsky HL, Davern T, Fontana RJ, Grant L, Reddy KR, et al. Liver injury from herbals and dietary supplements in the U.S. Drug-Induced Liver Injury Network. Hepatology 2014; 60:1399-408. PubMed PMID: 25043597.

(Among 85 cases of HDS associated liver injury [not due to anabolic steroids] enrolled in a US prospective study between 2004 and 2013, none were attributed to ginkgo).

Seeff LB, Bonkovsky HL, Navarro VJ, Wang G. Herbal products and the liver: a review of adverse effects and mechanisms. Gastroenterology 2015; 148: 517-32. PubMed PMID: 25500423.

(Extensive review of possible beneficial as well as harmful effects of herbal products mentions that ginkgo biloba can interact with warfarin and aspirin and affect platelet function, increasing the risk of abnormal bleeding).

Chalasani N, Bonkovsky HL, Fontana R, Lee W, Stolz A, Talwalkar J, Reddy KR, et al.; United States Drug Induced Liver Injury Network. Features and outcomes of 899 patients with drug-induced liver injury: The DILIN Prospective Study. Gastroenterology 2015; 148: 1340-52. PubMed PMID: 25754159.

(Among 899 cases of drug induced liver injury enrolled in a prospective database between 2004 and 2012, HDS were implicated in 145 [16%], none of which were primarily attributed to ginkgo: see Navarro [2014]).

García-Cortés M, Robles-Díaz M, Ortega-Alonso A, Medina-Caliz I, Andrade RJ. Hepatotoxicity by Dietary Supplements: A tabular listing and clinical characteristics. Int J Mol Sci 2016; 17. pii: E537. PubMed PMID: 27070596.

(Listing of published cases of liver injury from HDS products does not include ginkgo in the listings]).

Avigan MI, Mozersky RP, Seeff LB. Scientific and regulatory perspectives in herbal and dietary supplement associated hepatotoxicity in the United States. Int J Mol Sci 2016; 17: 331. PubMed Citation (Overview of the US regulations regarding herbal and dietary supplements and role of FDA, Department of Agriculture, Federal Trade Commission and Office of Dietary Supplements of the NIH in assessment of safety of HDS products including actions taken against commercial products when reports of liver injury appeared in postmarketing phase).

Brown AC. An overview of herb and dietary supplement efficacy, safety and government regulations in the United States with suggested improvements. Part 1 of 5 series. Food Chem Toxicol 2017; 107(Pt A): 449-71. PubMed PMID: 27818322.

(Summary of the US regulations on safety and efficacy of herbal and dietary supplements).

Brown AC. Liver toxicity related to herbs and dietary supplements: Online table of case reports. Part 2 of 5 series. Food Chem Toxicol 2017; 107(Pt A): 472-501. PubMed PMID: 27402097.

(Description of an online compendium of cases of liver toxicity attributed to HDS products, does not mention ginkgo).

Wong LL, Lacar L, Roytman M, Orloff SL. Urgent liver transplantation for dietary supplements: an under-recognized problem. Transplant Proc 2017; 49: 322-5. PubMed PMID: 28219592.

(Among 2048 adult liver transplants recipients enrolled in the Scientific Registry of Transplant Recipients [SRTR] between 2003 and 2015, 625 were done for acute hepatic necrosis due to drug induced liver injury, half being due to acetaminophen and the 4th most frequent cause [n=21] being HDS products, but none were attributed specifically to ginkgo).

de Boer YS, Sherker AH. Herbal and dietary supplement-induced liver injury. Clin Liver Dis 2017; 21: 135-49. PubMed PMID: 27842768.

(Review of the frequency, clinical features, patterns of injury and outcomes of HDS hepatotoxicity; ginkgo is not included as a potential cause of liver injury).

Pawar RS, Handy SM, Cheng R, Shyong N, Grundel E. Assessment of the authenticity of herbal dietary supplements: comparison of chemical and DNA barcoding methods. Planta Med 2017; 83: 921-36. PubMed PMID: 28454189.

(Chemical and DNA barcoding methods were applied to 112 marketed samples of herbal supplements and among 20 labelled as ginkgo, all had evidence of ginkgolides but 16 samples had evidence of contamination with other flavonoid-rich extracts).

Li S, Zhang X, Fang Q, Zhou J, Zhang M, Wang H, Chen Y, et al. Ginkgo biloba extract improved cognitive and neurological functions of acute ischaemic stroke: a randomised controlled trial. Stroke Vasc Neurol 2017; 2: 189-97. PubMed PMID: 29507779.

(Among 348 Chinese adults with recent onset of an acute ischemic stroke treated with ginkgo biloba extract or placebo for up to 6 months, adverse events were uncommon and similar in the two groups including results of 'the laboratory evaluation").

Vega M, Verma M, Beswick D, Bey S, Hossack J, Merriman N, Shah A, et al; Drug Induced Liver Injury Network (DILIN). The incidence of drug- and herbal and dietary supplement-induced liver injury: preliminary findings from gastroenterologist-based surveillance in the population of the State of Delaware. Drug Saf 2017; 40: 783-7. PubMed PMID: 28555362.

(A prospective, population based registry of cases of drug induced liver injury occurring in Delaware during 2014, identified 20 cases [2.7 per 100,000] overall, including 6 due to HDS products, all of which were proprietary multiingredient products, none specifically mentioning ginkgo).