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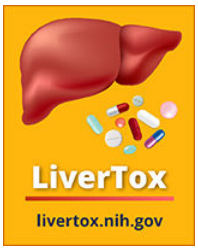

Ginseng

Updated: March 14, 2018.

OVERVIEW

Introduction

Ginseng is a popular herbal medication and extract derived from the roots of a perennial plant (Panax ginseng) found mostly in China, Korea and Siberia. Ginseng is used is to promote health and improve wellness, as well as to treat stress and as a mild stimulant. Ginseng has not been implicated in causing liver injury although it may have the potential of causing significant herb-drug interactions that can lead to liver injury.

Background

Ginseng (jin' seng) is a widely used herbal derived from the roots of eleven distinct species of plants belonging to the genus Panax and family Araliaceae. Ginseng grows in the Northern Hemisphere in eastern Asia, mostly China, Korea and Siberia. The form of ginseng most commonly used is Asian (or Chinese) ginseng made from the dried roots of Panax ginseng. American ginseng (Panax quinquefolius) has similar properties. The word ginseng derives from the Chinese character "rénshen" meaning "man root", which refers to the ginseng root's characteristic forked shape. The botanical name Panax is derived from the Greek word meaning "all-heal" as in the term panacea. Ginseng is taken promote health and healing, as an adaptogen (to treat stress and enhance recovery from illness), aphrodisiac (to aid in sexual desire and performance) and a stimulant (wakefulness and mental acuity). Ginseng is also claimed to lower blood glucose levels and to be beneficial in diabetes. Ginseng is found in energy drinks as well as in many cosmetic preparations. The scientific bases for the purported effects of ginseng are not well established. Ginseng contains 30 different triterpene saponins, referred to as ginsenosides and panaxosides, which are considered the active compounds and which have antioxidant and stimulatory activities. Commercial preparations of ginseng vary widely in ginsenoside content (some have none at all), which may cause variation in their biologic effects. The recommended daily dose varies widely (100 to >1,000 mg daily), depending on the preparation used (capsules, tablets, liquid, root extract, tea) and indications. Side effects of ginseng are uncommon and mild, and include inability to sleep, nausea, morning diarrhea, headaches and nose bleeds.

Hepatotoxicity

Despite wide spread use, ginseng by itself has not been linked to liver injury, either in the form of transient serum enzyme elevations or clinically apparent acute liver injury. Indeed, ginseng is sometimes used to treat acute or chronic liver injury, although its efficacy and safety in this situation have not been proven. Nevertheless, ginseng has been reported to affect cytochrome P450 activity and cause significant herb-drug interactions that can lead to adverse events including liver injury. In vitro studies have found that different gensinosides have different effects on cytochrome P450 activity, and some may inhibit CYP 3A4 sufficiently to affect the

metabolism of other drugs, increasing or decreasing their activity. Thus, different ginseng preparations may exhibit varying degrees of herb-drug interaction. Liver injury has been reported to develop 1 to 3 months after starting ginseng in patients who previously tolerated the potentially toxic agent (imatinib, raltegravir) without liver injury and who later tolerated restarting the medication without concurrent ginseng use.

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

Drug Class: Herbal and Dietary Supplements

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Ginseng – Generic

DRUG CLASS

Herbal and Dietary Supplements

SUMMARY INFORMATION

(Ginseng, American) Fact Sheet at MedlinePlus/Natural Medicines Comprehensive Database

(Ginseng, Siberian) Fact Sheet at MedlinePlus/Natural Medicines Comprehensive Database

(Ginseng, Asian or N. American) Fact Sheet at National Center for Complementary and Integrative Health

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Ginseng	50647-08-0	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; ginseng is not discussed).

Seeff L, Stickel F, Navarro VJ. Hepatotoxicity of herbals and dietary supplements. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2013, pp. 631-58. *(Review of hepatotoxicity of herbal and dietary supplements [HDS]*;

ginseng is not discussed).

Ginseng. In, PDR for Herbal Medicines. 4th ed. Montvale, New Jersey: Thomson Healthcare Inc. 2007: pp. 384-92.

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

Cui J, Garle M, Eneroth P, Bjorkhem I. What do commercial ginseng preparations contain? Lancet 1994; 344: 134. PubMed PMID: 7912373.

(Analysis of 50 commercial ginseng products sold in 11 countries found concentration of ginsenosides varied from 1.9-9%, and 6 [12%] had none and were likely not made from ginseng).

Janetzky K, Morreale AP. Probable interaction between warfarin and ginseng. Am J Health Syst Pharm 1997; 54: 692-3. PubMed PMID: 9075501.

(47 year old man on anticoagulation for a mechanical heart valve with INR maintained between 3.0 and 4.0 started ginseng capsules three times daily and, two weeks later, INR was 1.5, returning to previous level upon stopping ginseng).

Vogler BK, Pittler MH, Ernst E. The efficacy of ginseng. A systematic review of randomised clinical trials. Eur J Clin Pharmacol 1999; 55: 567-75. PubMed PMID: 10541774.

(Systematic review of the literature found 16 trials of ginseng root extract, but found that evidence for benefit was not compelling for any indication: physical and psychomotor performance, cognitive function, diabetes and herpes simplex).

Kitts D, Hu C. Efficacy and safety of ginseng. Public Health Nutr 2000; 3: 473-85. PubMed PMID: 11276295.

(Review of the history, composition, purported effects, clinical efficacy and safety of ginseng).

Stedman C. Herbal hepatotoxicity. Semin Liver Dis 2002; 22: 195-206. PubMed PMID: 12016550.

(Review and description of patterns of liver injury, including discussion of potential risk factors, and herb-drug interactions; ginseng may interact with warfarin causing a decrease in anticoagulation).

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).

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

(Comprehensive review of herbal associated hepatotoxicity; ginseng 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 ginseng use).

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 a Spanish registry, 13 [2%] were due to herbals, but none were attributed to ginseng).

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 linked to ginseng use).

Saxena A, Tripathi KP, Roy S, Khan F, Sharma A. Pharmacovigilance: effects of herbal components on human drugs interactions involving cytochrome P450. Bioinformation 2008; 3: 198-204. PubMed PMID: 19255634.

(Review of effects of St. John's wort, piperine, ginsenosides and ginkgolic acid on cytochrome P450 activity; in vitro ginsenosides have inhibitory activity against CYP 2E1 and CYP 3A4).

Hao M, Zhao Y, Chen P, Huang H, Liu H, Jiang H, Zhang R, Wang H. Structure-activity relationship and substrate-dependent phenomena in effects of ginsenosides on activities of drug-metabolizing P450 enzymes. PLoS One 2008; 3: e2697. PubMed PMID: 18628990.

(Ginsenosides with different structures have different effects on cytochrome P450 activity).

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; ginseng 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 14 [2%] attributed to ginseng, including 2 with a "mixed liver reaction" and 2 with enzyme elevations, but no details given).

Bilgi N, Bell K, Ananthakrishnan AN, Atallah E. Imatinib and Panax ginseng: a potential interaction resulting in liver toxicity. Ann Pharmacother 2010; 44: 926-8. PubMed PMID: 20332334.

(26 year old man with CML on imatinib for 7 years developed symptomatic liver injury 3 months after starting daily use of an energy drink with Panax ginseng [bilirubin 1.4 mg/dL, ALT 1069 U/L, Alk P 124 U/L] which resolved with stopping both medications, but he was able to restart imatinib without recurrence of liver injury after recovery and while remaining off of ginseng).

Mateo-Carrasco H, Gálvez-Contreras MC, Fernández-Ginés FD, Nguyen TV. Elevated liver enzymes resulting from an interaction between Raltegravir and Panax ginseng: a case report and brief review. Drug Metabol Drug Interact 2012; 27: 171-5. *(Abstract only: Patient with chronic hepatitis C and HIV infection on long term antiretroviral therapy with raltegravir, lopinavir and ritonavir developed jaundice 39 days after starting ginseng tablets, resolving with stopping herbal intake*). PubMed PMID: 23092794.

Bunchorntavakul C, Reddy KR. Review article: herbal and dietary supplement hepatotoxicity. Aliment Pharmacol Ther 2013; 37: 3-17. PubMed PMID: 23121117.

(Systematic review of literature on HDS associated liver injury mentions that ginseng can have significant herb-drug interactions).

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 ginseng containing products).

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 ginseng).

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 a known ginseng containing product).

Seeff LB, Bonkovsky HL, Navarro VJ, Wang G. Herbal products and the liver: a review of adverse effects and mechanisms. Gastroenterology 2015; 148: 517-532. PubMed PMID: 25500423.

(Extensive review of possible beneficial as well as harmful effects of herbal products on the liver mentions that there have been numerous reports of liver injury from germander).

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 germander: 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 discuss ginseng 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).

Kim TW. Ginseng for Liver Injury: Friend or Foe? Medicines (Basel) 2016; 3. pii: E33. PubMed PMID: 28930143.

(Review of literature on hepatoprotective and hepatotoxic effects of ginseng which is active in decreasing hepatic injury in several animal models of liver disease and which is largely safe although has important drug-herb interactions because of inhibition of CYP 3A4 activity which can raise levels of other medications that are more hepatotoxic at higher doses).

Dong H, Ma J, Li T, Xiao Y, Zheng N, Liu J, Gao Y, et al. Global deregulation of ginseng products may be a safety hazard to warfarin takers: solid evidence of ginseng-warfarin interaction. Sci Rep 2017; 7: 5813. PubMed PMID: 28725042.

(Studies in rats demonstrate that purified ginseng extracts increase CYP 3A4 activity and inhibit the effects of warfarin on coagulation factors, suggesting that use of ginseng may cause reversal of warfarin's protective effects against thomboembolic events).

Myers AP, Watson TA, Strock SB. Drug reaction with eosinophilia and systemic symptoms syndrome probably induced by a lamotrigine-ginseng drug interaction. Pharmacotherapy 2015; 35: e9-e12. *(44 year old man developed rash and eosinophilia 35 days after starting lamotrigine for seizures and while taking ginseng daily for general health [bilirubin 1.4 mg/dL, ALT 473 U/L, Alk P 465 U/L, eosinophils 3040/μ* PubMed PMID: 25756365.

L], resolving within 3 weeks of stopping lamotrigine).

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, mentions that germander was the most frequently implicated herb in causing liver injury listing 23 references of single case reports and case series).

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 ginseng was not implicated in any case).

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 with specific mention of anabolic steroids, black cohosh, germander, green tea, pyrrolizidine alkaloids and proprietary multiingredint nutrition supplements [MINS]).

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: 783-787. 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 ginseng).