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NLM Citation: LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012-. Licorice. [Updated 2023 Mar 20].
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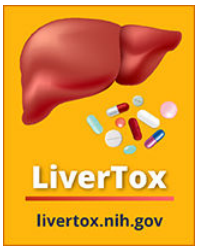


Licorice

Updated: March 20, 2023.

OVERVIEW

Introduction

Licorice is the common name of the plant *Glycyrrhiza glabra*, the roots of which are widely used as a flavoring in food, candy and tobacco, and extracts of which have been used in traditional medicine for the treatment of many conditions, including gastrointestinal disorders, upper respiratory infections, and symptoms of menopause and premenstrual tension. Licorice when given in high doses has many serious adverse events, but has not been reported to cause serum aminotransferase elevations or clinically apparent liver injury.

Background

Licorice is a flavoring agent as well as an herbal supplement prepared from the roots and runners of *Glycyrrhiza glabra*, a herbaceous flowering plant found in Mediterranean areas of Europe and Africa, the Middle East, and Asia. The roots of *Glycyrrhiza glabra* have a sweet aroma, and extracts are used to sweeten and flavor tobacco, food, and candy. Extracts of licorice root have also been used in traditional medicine for a variety of conditions including ulcer disease, constipation, nausea, upper respiratory illnesses, cough, fever, and menopausal and premenstrual symptoms of women. The constituents in licorice root responsible for its sweetness and aroma are volatile oils similar to those found in anise and fennel flavorings. The medicinal components of licorice are not precisely known but are usually attributed to flavonoids, flavones, saponins, and chalcones. A major component of licorice root (ranging from 4% to 12%) is glycyrrhizin or glycyrrhizinic acid, an astringent molecule with corticosteroid-like activities. Glycyrrhizin has been used to treat several disorders including chronic hepatitis C, where it is given intravenously two or three times weekly. The evidence for its efficacy in hepatitis C, however, is not widely accepted, and it has now been replaced by the highly efficacious direct acting HCV antivirals. Nevertheless, studies in cell culture and in animal models have repeatedly found that glycyrrhizin and licorice extracts decrease or prevent liver injury from a variety of insults including chemotherapeutic agents, acetaminophen, prescription drugs, obesity and ischemia. However, glycyrrhizin also has known toxicities in animals and humans that are attributed to its mineralocorticoidal actions, for which reason some licorice extracts are deglycyrrhinized. Orally available licorice with or without glycyrrhizin is used in many herbal preparations for its purported medicinal activities as well as for its flavor and sweetness. Licorice is not licensed for any medical condition in the United States by the FDA, but over-the-counter extracts are available and purported to be beneficial for general health, gastrointestinal health, liver wellness, menopausal symptoms and many other conditions. None of these claims, however, has been demonstrated in properly designed and adequately powered prospective studies. While generally regarded as safe (GRAS) in amounts found in food, licorice extracts in high doses can cause serious adverse effects due to its mineralocorticoidal activities resulting in systemic arterial hypertension, hypokalemia, sodium and water retention, muscle weakness, paralysis, and cardiac arrhythmias. Deaths from hypermineralocorticoidal effects have been reported in patients taking high

doses of oral licorice in teas or as extracts in capsules or tablets. Licorice is also an abortifacient and has estrogenic and corticosteroid effects that can result in fetal toxicity or loss and should not be used during pregnancy.

Hepatotoxicity

In multiple clinical studies of different preparations of licorice or glycyrrhizin in conventional doses, adverse side effects were usually described as uncommon and transient. In studies that included measurements of routine liver tests, there were no episodes of serious elevations in serum ALT or AST and no instances of clinically apparent liver injury. There have been no single case reports of liver injury due to licorice and large case series and registries of drug- and dietary supplement induced liver injury, and licorice has not been listed as an implicated agent.

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

Mechanism of Injury

The mechanism by which licorice extracts and glycyrrhizin might cause liver injury is unknown.

Outcome and Management

Hepatotoxicity from licorice extracts or glycyrrhizin has not been reported.

Drug Class: Herbal and Dietary Supplements

Other names: Glycyrrhizin, Sweet Root, Liquorice

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Licorice – Generic

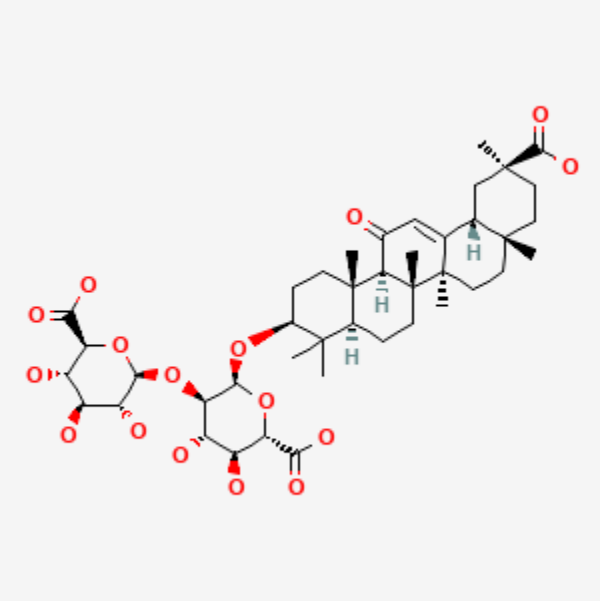
DRUG CLASS

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
Glycyrrhizin	1405-86-3	C42-H62-O16	

ANNOTATED BIBLIOGRAPHY

References updated: 20 March 2023

Abbreviations: HbA1c, hemoglobin A1c; HDS, herbal and dietary supplements.

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; several herbal medications are discussed, but not licorice).

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; no mention of licorice or glycyrrhizin).

Licorice. In, PDR for Herbal Medicines. 4th ed. Montvale, New Jersey: Thomson Healthcare Inc. 2007: pp. 522-530.

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

Wikipedia. Available at: https://en.wikipedia.org/wiki/Liquorice

(Wikipedia website providing a concise description of licorice, its etymology, chemistry, cultivation, uses, medical properties, and toxicities).

Tominaga Y, Nakagawa K, Mae T, Kitano M, Yokota S, Arai T, Ikematsu H, et al. Licorice flavonoid oil reduces total body fat and visceral fat in overweight subjects: a randomized, double-blind, placebo-controlled study. Obes Res Clin Pract. 2009;3:I–IV.

(Among 80 overweight adults treated with liquid licorice flavored oil [300, 600 or 900 mg] or placebo daily for 8 weeks, total body fat decreased with licorice therapy compared to placebo despite similar daily caloric intake and in higher does, total body weight was also decreased, while bilirubin, ALT, AST and alkaline phosphatase levels did not change appreciably in either group).

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 in a Swedish Registry does not list licorice among products associated with 5 or more reports).

Reuben A, Koch DG, Lee WM; Acute Liver Failure Study Group. Drug-induced acute liver failure: results of a U.S. multicenter, prospective study. Hepatology. 2010;52:2065–76. PubMed PMID: 20949552.

(Among 1198 patients with acute liver failure enrolled in a US prospective study between 1998 and 2007, 133 [11%] were attributed to drug induced liver injury of which 12 [9%] were due to herbals, including several herbal mixtures, usnic acid, Ma Huang, black cohosh, and Hydroxycut, but not licorice).

Vitalone A, Menniti-Ippolito F, Raschetti R, Renda F, Tartaglia L, Mazzanti G. Surveillance of suspected adverse reactions to herbal products used as laxatives. Eur J Clin Pharmacol. 2012;68:231–8. PubMed PMID: 21964980.

(Among 26 reports of adverse events from HDS products reported to the Italian Medicines Agency between 2002 and 2011, 7 implicated products contained licorice among other agents; the adverse reactions being urticaria in 2, gastrointestinal complaints in 2, photophobia in 1, electrolyte disturbance in 1 and only abdominal pain and aminotransferase elevations in 1 attributed to a product with 10 other herbal components including aloe vera and senna).

Teschke R, Wolff A, Frenzel C, Schulze J, Eickhoff A. Herbal hepatotoxicity: a tabular compilation of reported cases. Liver Int. 2012;32:1543–56. PubMed PMID: 22928722.

(A systematic compilation of all publications on the hepatotoxicity of specific herbals identified 185 publications on 60 different herbs, herbal drugs and supplements, but none listed licorice as an ingredient).

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 does not mention licorice).

Navarro VJ, Seeff LB. Liver injury induced by herbal complementary and alternative medicine. Clin Liver Dis. 2013;17:715–35. PubMed PMID: 24099027.

(Review of the epidemiology, regulatory status, diagnosis, pathogenesis and causes of liver injury from herbal products with specific discussion of conjugated linoleic acid, ephedra, germander, green tea, usnic acid, flavocoxid, aloe vera, chaparral, greater celandine, black cohosh, comfrey, kava, skullcap, valerian, noni juice, pennyroyal and traditional herbal remedies).

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 839 cases of liver injury from drugs collected in the US between 2004 and 2013, 130 were due to HDS products, including 45 from body building agents [probably anabolic steroids] and 85 from diverse HDS products but no case was attributed specifically to licorice or glycyrrhizin).

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

(Description of an online compendium of cases of liver toxicity attributed to HDS products that does not list or discuss licorice).

Nazari S, Rameshrad M, Hosseinzadeh H. Toxicological effects of Glycyrrhiza glabra (Licorice): a review. Phytother Res. 2017;31:1635–1650. PubMed PMID: 28833680.

(Extensive review of the animal toxicity of glycyrrhizin and licorice focusing largely on its mineralocorticoid effects and pseudohyperaldosteronism with hypokalemia, electrolyte imbalance, hypertension, weakness, asthenia, peripheral edema, and neuromuscular paralysis; no mention of liver toxicity in humans).

Arentz S, Smith CA, Abbott J, Fahey P, Cheema BS, Bensoussan A. Combined lifestyle and herbal medicine in overweight women with polycystic ovary syndrome (PCOS): a randomized controlled trial. Phytother Res. 2017;31:1330–1340. PubMed PMID: 28685911.

(Among 108 overweight women [ages 18 to 44 years] with polycystic ovary syndrome treated with lifestyle modification and either two herbal preparations [one with Glycyrrhizia glabra and one with Tribulus terrestris extracts] or placebo for 3 months, oligomenorrhea was improved with the herbal therapy as were fasting insulin levels, blood pressure, body weight, and quality of life, and with no serious adverse events; no mention of ALT levels or hepatotoxicity).

Medina-Caliz I, Garcia-Cortes M, Gonzalez-Jimenez A, Cabello MR, Robles-Diaz M, Sanabria-Cabrera J, Sanjuan-Jimenez R, et al; Spanish DILI Registry. Herbal and dietary supplement-induced liver injuries in the Spanish DILI Registry. Clin Gastroenterol Hepatol. 2018;16:1495–1502. PubMed PMID: 29307848.

(Among 856 cases of hepatotoxicity enrolled in the Spanish DILI Registry between 1994 and 2016, 32 were attributed to herbal products, the most frequent implicated agents being green tea [n=8] and Herbalife products [n=6]; no mention of licorice).

Li X, Sun R, Liu R. Natural products in licorice for the therapy of liver diseases: Progress and future opportunities. Pharmacol Res. 2019;144:210–226. PubMed PMID: 31022523.

(Review of the effects of licorice on cell signaling pathways underlying its antioxidant activity and possible role as a hepatoprotective and antifibrotic agent).

Ballotin VR, Bigarella LG, Brandão ABM, Balbinot RA, Balbinot SS, Soldera J. Herb-induced liver injury: Systematic review and meta-analysis. World J Clin Cases. 2021;9:5490–5513. PubMed PMID: 34307603.

(Systematic review of the literature on herb induced liver injury identified 446 references describing 936 cases due to 79 different herbal products, the most common being He Shou Wu [91], green tea [90] Herbalife products [64], kava kava [62] and greater celandine [48];]; licorice was not listed among the 79 implicated products).

Ng SL, Khaw KY, Ong YS, Goh HP, Kifli N, Teh SP, Ming LC, et al. Licorice: a potential herb in overcoming SARS-CoV-2 infections. J Evid Based Integr Med. 2021;26:2515690X21996662.

(Commentary on licorice suggesting that its broad antiinflammatory and antimicrobial actions are reason to consider whether studies of its effects on COVID-19 are warranted).

Rostamizadeh P, Asl SMKH, Far ZG, Ahmadijoo P, Mahmudiono T, Bokov DO, Alsaikhan F, et al. Effects of licorice root supplementation on liver enzymes, hepatic steatosis, metabolic and oxidative stress parameters in women with nonalcoholic fatty liver disease: A randomized double-blind clinical trial. Phytother Res. 2022;36:3949–3956. PubMed PMID: 35785498.

(Among 52 Iranian women with nonalcoholic fatty liver treated with life-style modification and either licorice [1000 mg] or placebo daily for 3 months, weight loss was greater with licorice [-5.1 vs -3.8 kg] as was decrease in ALT levels [-6.6 vs -3.0 U/L], serum insulin [-4.5 vs -2.0 μU/L], and hepatic steatosis as assessed by ultrasound, and "no side effects were recorded").

Bessone F, García-Cortés M, Medina-Caliz I, Hernandez N, Parana R, Mendizabal M, Schinoni MI, et al. Herbal and dietary supplements-induced liver injury in Latin America: experience from the LATINDILI Network. Clin Gastroenterol Hepatol. 2022;20:e548–e563. PubMed PMID: 33434654.

(Among 367 cases of hepatotoxicity enrolled in the Latin American DILI Network between 2011 and 2019, 29 [8%] were attributed to herbal products, the most frequent being green tea [n=7], Herbalife products [n=5] and garcinia [n=3], while licorice is not mentioned).

Guo M, Wang Z, Dai J, Fan H, Yuan N, Gao L, Peng H, et al. Glycyrrhizic acid alleviates liver fibrosis in vitro and in vivo via activating CUGBP1-mediated IFN-γ/STAT1/Smad7 pathway. Phytomedicine. 2023;112:154587. PubMed PMID: 36805480.

(Glycyrrhizic acid given in vitro and in vivo inhibited fibrosis formation in cell culture and animal models and the inhibitory activity appeared to be mediated by binding of glycyrrhizic acid to CUGBP2 resulting in its inhibition and interference with the gamma interferon-STAT1-SMAD7 pathway that increases stellate cell activation and fibrogenesis).