



Comfrey

Updated: May 24, 2022.

OVERVIEW

Introduction

Comfrey is a plant belonging to the Boraginaceae family, extracts of the leaves and roots of which has been used as an herbal to treat wounds and to decrease pain and inflammation associated with arthritis, sprains and bone fractures. Comfrey, however, also contains pyrrolizidine alkaloids and, when taken orally, can cause sinusoidal obstruction syndrome and severe liver injury.

Background

Common comfrey (*Symphytum officinale*) is a perennial herb belonging to the family Boraginaceae which is native to Europe and Asia, but is now found worldwide. Leaf and root extracts have many constituents including allantoin, rosmarinic acid, triterpene saponins, silicic acid, and tannins, believed to be the basis for its antiinflammatory and wound healing activity. However, comfrey also contains several pyrrolizidine alkaloids (symphytine, echimidine, symglandine and lycopsamine) which are toxic and capable of causing sinusoidal obstruction syndrome (previously called veno-occlusive disease) and severe liver injury. Comfrey has been shown to cause similar liver injury in laboratory animals and has also been linked to liver cancer. Comfrey products are marketed as herbal teas, root powders and as capsules. Oral comfrey has been banned or restricted in most countries, but topical forms (ointments, creams and liniments) are available and advertised as useful for wound healing sprains and bone fractures. Human studies have shown that comfrey creams have mild analgesic effects and decreases muscle and joint pain.

Hepatotoxicity

Several cases of acute liver injury resembling sinusoidal obstruction syndrome (SOS) due to oral comfrey have been published. The injury usually arises within 1 to 2 months of starting the comfrey product (either extract in tablet form or large amounts of comfrey tea) with onset of right upper quadrant pain, nausea and weight gain (from fluid retention) followed by jaundice. Serum aminotransferase levels are usually only mildly elevated with a hepatocellular pattern of injury, although they may be markedly increased if tested during the early phases of the injury. Immunoallergic and autoimmune features are usually not present. The injury can be severe and rapidly lead to acute liver failure (acute sinusoidal obstruction syndrome), but more commonly presents insidiously with weight gain, ascites, weakness, and minimal serum aminotransferase elevations (subacute or chronic sinusoidal obstruction syndrome).

Likelihood score: C (when taken orally, a probable cause of clinically apparent liver injury due to sinusoidal obstruction syndrome).

Mechanism of Injury

The pyrrolizidine alkaloids contained in comfrey include intermedine, lycopsamine, symphytine and echnimidine, which are metabolized by the cytochrome P450 enzymes into highly toxic pyrrole metabolites which have alkylating properties that can damage hepatic endothelial cells and can cause sinusoidal obstruction. The amount of pyrrolizidine alkaloids in comfrey varies by the part of the plant used, its age and time of harvesting. The toxicity of pyrrolizidine containing substances is increased by microsomal enzyme inducers such as phenobarbital. Infants appear to be particularly susceptible to pyrrolizidine alkaloid injury.

Outcome and Management

Hepatotoxicity from comfrey is now rare, as it is widely accepted as being toxic when taken internally and oral formulations are restricted or banned in most countries. Management should be directed at limiting further injury and specific treatment of complications (ascites, variceal bleeding). Anticoagulants have not been shown to be beneficial. Difibrotide (a complex mixture of single stranded DNA prepared from pig intestine) has recently been approved for therapy of severe SOS accompanied by renal or pulmonary failure occurring after myeloablation for hematopoietic cell transplantation. More extensive description of sinusoidal obstruction syndrome and its management are given in the introductory section and in discussion of the antineoplastic alkylating agents.

Other Names: Black root, common comfrey, knitbone

Drug Class: [Herbal and Dietary Supplements](#)

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Comfrey – Generic

DRUG CLASS

Herbal and Dietary Supplements

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Comfrey	84696-05-9	Herbal mixture	Not applicable

ANNOTATED BIBLIOGRAPHY

References updated: 24 May 2022

Abbreviations used: HDS, herbal and dietary supplements; SOS, sinusoidal obstruction syndrome.

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; comfrey is discussed as a pyrrolizidine containing herbal that has been linked to veno-occlusive disease which is now referred to as sinusoidal obstruction syndrome [SOS]).

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] mentions that comfrey is one of more than 350 plant species that contain pyrrolizidine alkaloids and is capable of causing sinusoidal obstruction syndrome).

Comfrey. In, PDR for Herbal Medicines. 4th ed. Montvale, New Jersey: Thomson Healthcare Inc. 2007: pp. 291-22.

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

McGee J, Patrick RS, Wood CB, Blumgart LH. A case of veno-occlusive disease of the liver in Britain associated with herbal tea consumption. *J Clin Pathol.* 1976;29:788-94. PubMed PMID: 977780.

(26 year old woman developed abdominal pain and ascites, having used herbal tea for 2 years [bilirubin 0.8 mg/dL, ALT 28 U/L, Alk P 303 U/L], with splenomegaly, varices and intractable ascites, biopsy showing sinusoid obstruction syndrome; dying after failed portocaval shunt, analysis of tea showed pyrrolizidine alkaloids).

Stillman AS, Huxtable R, Consroe P, Kohnen P, Smith S. Hepatic veno-occlusive disease due to pyrrolizidine (Senecio) poisoning in Arizona. *Gastroenterology.* 1977;73:349-52. PubMed PMID: 873137.

(6 month old developed distended abdomen and vomiting [bilirubin 0.5 mg/dL, AST 794 U/L] and was found to have ascites and biopsy showed sinusoidal obstruction syndrome; child had been fed large quantities of locally brewed tea which was made from Senecio longilobus).

Fox DW, Hart MC, Bergeson PS, Jarrett PB, Stillman AE, Huxtable RJ. Pyrrolizidine (Senecio) intoxication mimicking Reye's syndrome. *J Pediatr.* 1978;93:980-2. PubMed PMID: 722447.

(2 month old boy developed vomiting and hematemesis and hepatic encephalopathy after being given herbal tea [gordolobo] for 4 days [bilirubin normal, but rising to 19.3 mg/dL, ALT 1860 U/L] initially diagnosed as Reye syndrome, dying after 3 days, autopsy showing severe acute sinusoidal obstruction syndrome).

Mattocks AR. Toxic pyrrolizidine alkaloids in comfrey. *Lancet.* 1980;2:1136-7. PubMed PMID: 6107747.

(Measured pyrrolizidine alkaloids in dried comfrey leaves, finding lowest concentration in mature large leaves and variation by time of harvesting).

Roitman JN. Comfrey and liver damage. *Lancet.* 1981;1:944. PubMed PMID: 6112346.

(Analysis of tea made from commercially available comfrey found a cup to contain 26 mg of pyrrolizidine alkaloids, well above the amount that has been linked to serious hepatic injury when taken long term).

Editorial. Pyrrolizidine alkaloids. *Lancet.* 1984;1:201-2. PubMed PMID: 6141340.

(Plants have evolved poisons that are toxic to insects, but can also cause hepatic sinusoidal obstruction syndrome (veno-occlusive disease) in grazing animals and in humans who ingest these in teas and herbal medications: "a disastrous discontinuity of tradition").

Ridker PM, Ohkuma S, McDermott WV, Trey C, Huxtable RJ. Hepatic venoocclusive disease associated with the consumption of pyrrolizidine-containing dietary supplements. *Gastroenterology.* 1985;88:1050-4. PubMed PMID: 3972224.

(49 year old woman developed edema and ascites after taking comfrey capsules and tea for 6 months [no liver test results provided], biopsy showing sinusoidal obstruction syndrome, ultimately requiring portocaval shunt with subsequent slow clinical improvement after stopping comfrey ingestion).

Kumana CR, Ng M, Lin HJ, Ko W, Wu PC, Todd D. Herbal tea induced hepatic veno-occlusive diseases; quantification of toxic alkaloid exposure in adults. *Gut.* 1985;26:101-4. PubMed PMID: 3965360.

(Four young women brewed Indian herbal tea to treat psoriasis and 3 developed ascites from sinusoidal obstruction syndrome 19-45 days later [bilirubin 0.6, 0.6 and 3.3 mg/dL, ALT 63, 122 and 69 U/L], one dying of hepatic failure, analysis of tea revealed pyrrolizidine alkaloids).

Culvenor CCJ. Pyrrolizidine alkaloids: some aspects of the Australian involvement. *Trends Pharmacol Sci.* 1985;6:18–22.

(Presence of pyrrolizidine alkaloids in several common Australian weeds is a health hazard to livestock and humans; these include Heliotropium europaeum, Echium plantagineum, Senecio and Crotalaria species).

Huxtable RJ, Luethy J, Zweifel U. Toxicity of comfrey-pepsin preparations. *N Engl J Med.* 1986;315:1095. PubMed PMID: 3762623.

(Analysis of two commercial brands of comfrey-pepsin preparations sold as a digestive aid demonstrated pyrrolizidine alkaloids [symphytine and symglandine] in concentrations that could cause sinusoidal obstruction syndrome after a few months of regular intake).

Weston CF, Cooper BT, Davies JD, Levine DF. Veno-occlusive disease of the liver secondary to ingestion of comfrey. *Br Med J (Clin Res Ed).* 1987;295:183. PubMed PMID: 3115370.

(13 year old boy developed fever, abdominal pain and ascites after several years of treatment with an herbal tea containing comfrey for Crohn's disease [bilirubin 1.5 mg/dL, AST 87 U/L, Alk P normal], biopsy showing sinusoidal obstruction syndrome).

Roulet M, Laurini R, Rivier L, Calame A. Hepatic veno-occlusive disease in a newborn infant of a woman drinking herbal tea. *J Pediatr.* 1988;112:433–6. PubMed PMID: 3346784.

(5 day old girl found to have jaundice, hepatomegaly and ascites [bilirubin 9.6 mg/dL, ALT 760 U/L, protime 13%], biopsy and autopsy showing severe sinusoidal obstruction syndrome and analysis of an herbal tea taken daily by the mother during pregnancy revealed pyrrolizidine alkaloids).

Bach N, Thung SN, Schaffner F. Comfrey herb tea-induced hepatic veno-occlusive disease. *Am J Med.* 1989;87:97–9. PubMed PMID: 2741990.

(47 year old woman developed liver test abnormalities and ascites having taken comfrey pills and tea daily for more than a year [bilirubin 1.2 mg/dL, ALT 24 U/L, Alk P 27 U/L], biopsy showing chronic sinusoidal obstruction syndrome).

Ridker PN, McDermont WV. Hepatotoxicity due to comfrey herb tea. *Am J Med.* 1989;87:701. PubMed PMID: 2629737.

(Letter in response to Bach [1989] reviewing the history of the association of comfrey and pyrrolizidine alkaloids and sinusoidal obstruction syndrome).

Huxtable RJ, Awang DV. Pyrrolizidine poisoning. *Am J Med.* 1990;89:547–8. PubMed PMID: 2220897.

(Letter in response to Bach [1989] and Ridker [1989] calling for better documentation of components of implicated hepatotoxic herbs in view of the variable amounts of pyrrolizidine alkaloids found in different comfrey samples due to different species of Symphytum, problems of contamination, mislabeling, use of leaves vs roots and variability in alkaloid content by time of harvest and growing conditions).

Ridker PM, McDermott WV. Comfrey herb tea and hepatic veno-occlusive disease. *Lancet.* 1989;1:657–8. PubMed PMID: 2564469.

(Concise review of the hepatotoxicity of comfrey herb tea and its association with sinusoidal obstruction syndrome, probably due to the presence of pyrrolizidine alkaloids which comprise more than 180 compounds and occur in at least 8 plant families; four genera – Heliotropium, Crotalaria, Senecio and Symphytum – accounting for most toxic ingestions).

Yeong ML, Swinburn B, Kennedy M, Nicholson G. Hepatic veno-occlusive disease associated with comfrey ingestion. *J Gastroenterol Hepatol.* 1990;5:211–4. PubMed PMID: 2103401.

(23 year old man who had eaten young comfrey leaves for 1-2 weeks developed fatigue and abdominal pain followed in the next 2 months by swelling and edema [bilirubin 1.6 mg/dL, AST 365 U/L, Alk P 475 U/L, INR 1.4], with intractable ascites and hepatic failure; autopsy showed sinusoidal obstruction syndrome).

Carlsson C. Herbs and hepatitis. *Lancet*. 1990;336:1068. PubMed PMID: 1977040.

(Analysis of laboratory results from 395 patients found higher ALT levels among 53 patients taking herbals [55 U/L] than among those who did not [12 U/L]).

Huxtable RJ. The myth of beneficent nature: the risks of herbal preparations. *Ann Intern Med*. 1992;117:165–6. PubMed PMID: 1605432.

(Editorial on problems of herbal poisoning highlighting pyrrolizidine alkaloids, comfrey, germander, and suggesting guidelines on their use [never during pregnancy or while nursing, avoiding daily and high doses of a single agent, using products from reputable sources and never using comfrey]).

Miskelly FG, Goodyer LI. Hepatic and pulmonary complications of herbal medicines. *Postgrad Med J*. 1992;68:935. PubMed PMID: 1494520.

(77 year old woman developed fatigue followed by jaundice 6 months after starting an herbal product with comfrey and skullcap [bilirubin 3.5 mg/dL, AST 520 U/L, Alk P 390 U/L], resolving within 6 months of stopping).

Sperl W, Stuppner H, Gassner J, Judmaier W, Dietze O, Vogel W. Reversible hepatic veno-occlusive disease in an infant after consumption of pyrrolizidine-containing herbal tea. *Eur J Pediatr*. 1995;154:112–6. PubMed PMID: 7720737.

*(18 month old boy treated with locally prepared herbal tea for over a year presented with ascites and hepatic encephalopathy [bilirubin 2.8 mg/dL, ALT 124 rising to 923 U/L], biopsy showing sinusoidal obstruction syndrome, but gradual improvement and resolution of clinical symptoms and signs after stopping the tea; the plant leaves were likely *Adenostyles alliariae* [Alpendost], which is known to contain pyrrolizidine alkaloids).*

Stickel F, Seitz HK. The efficacy and safety of comfrey. *Public Health Nutr*. 2000;3(4A):501–8. PubMed PMID: 11276298.

(Review of comfrey which has a long tradition as an external treatment for inflammatory arthritis and trauma; for internal application it was claimed to be beneficial for gastritis, ulcers, diarrhea and various allergies including asthma; the pyrrolizidine content of comfrey products varies greatly, and hepatic toxicity largely associated with daily intake of tablets or multiple cups of tea).

Stickel F, Seitz HK, Hahn EG, Schuppan D. *Z Gastroenterol*. 2001;39:225–32, 234–7. [Liver toxicity of drugs of plant origin]. German. PubMed PMID: 11324140.

(Review of hepatotoxicity of botanicals including comfrey, pyrrolizidine alkaloids, germander, celandine, chaparral, Chinese herbs and pennyroyal).

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; comfrey is listed as a health tonic that contains toxic pyrrolizidine alkaloids capable of causing sinusoidal obstruction syndrome).

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

(Comprehensive review of herbal associated hepatotoxicity; discusses comfrey as a cause of sinusoidal obstruction syndrome).

Pak E, Esrason KT, Wu VH. Hepatotoxicity of herbal remedies: an emerging dilemma. *Prog Transplant*. 2004;14:91–6. PubMed PMID: 15264453.

(Review of hepatotoxicity of herbal medications stressing the recent rise in numbers of cases, with literature review of comfrey).

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%] due to herbal medications, but comfrey is not mentioned as a cause).

Seeff LB. Herbal hepatotoxicity. *Clin Liver Dis.* 2007;11:577–96. PubMed PMID: 17723921.

(Review of herbal induced hepatotoxicity, with detail of specific herbal compounds including review of the literature on comfrey hepatotoxicity).

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

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

Chalasan 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 comfrey).

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; comfrey is discussed in the context of pyrrolizidine alkaloid hepatotoxicity).

Giannetti BM, Staiger C, Bulitta M, Predel HG. Efficacy and safety of a Comfrey root extract ointment in the treatment of acute upper or low back pain: results of a double-blind, randomized, placebo controlled, multicentre trial. *Br J Sports Med.* 2010;44:637–41. PubMed PMID: 19460762.

(Controlled trial of comfrey root extract ointment versus placebo in 120 patients with acute back pain found significant effect of comfrey ointment on pain intensity and movement; side effects were mild and transient and no more common than with placebo).

Mei N, Guo L, Fu PP, Fuscoe JC, Luan Y, Chen T. Metabolism, genotoxicity, and carcinogenicity of comfrey. *J Toxicol Environ Health B Crit Rev.* 2010;13:509–26. PubMed PMID: 21170807.

(Overview of the metabolism and toxicity of comfrey, which refers to several species in the genus Symphytum, most frequently “common comfrey” or S. officinale; the herbal is prepared from leaves and dried roots but is a potential health risk due to pyrrolizidine alkaloids which include retronecine mono- and diesters that are hepatotoxic and carcinogenic in laboratory animals).

Staiger C. Comfrey: a clinical overview. *Phytother Res.* 2012;26:1441–8. PubMed PMID: 22359388.

(Review of the efficacy and safety of topical comfrey in treatment of arthritis, myalgias, contusions and strains).

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 including five publications on comfrey).

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 discusses pyrrolizidine alkaloids including comfrey as causing sinusoidal obstruction syndrome).

Abdualmjid RJ, Sergi C. Hepatotoxic botanicals - an evidence-based systematic review. *J Pharm Pharm Sci.* 2013;16:376–404. PubMed PMID: 24021288.

(A systematic review of hepatotoxic botanicals mentions that comfrey is a common garden plant and consists of several species which contain pyrrolizidine alkaloids that can lead to sinusoidal obstruction syndrome, when taken orally and brewed as teas).

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 herbal hepatotoxicity mentions that comfrey is used topically for pain relief, but when taken orally or brewed as a tea it can be associated with sinusoidal obstruction syndrome).

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 comfrey).

Licata A, Macaluso FS, Craxì A. Herbal hepatotoxicity: a hidden epidemic. *Intern Emerg Med.* 2013;8:13–22. PubMed PMID: 22477279.

(Review and commentary on herbal hepatotoxicity discusses pyrrolizidine alkaloids [including comfrey] which are dose dependent hepatotoxins that cause vino-occlusive disease, probably as a result of biotransformation by the liver to pyrrole derivatives that act as alkylating agents).

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 HDS induced liver injury including regulatory problems, difficulties in diagnosis and assessing causality; discusses comfrey which has been used for pain relief, but has been banned in most countries because of its association with severe SOS).

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 specifically to a comfrey containing product).

Navarro VJ, Lucena MI. Hepatotoxicity induced by herbal and dietary supplements. *Semin Liver Dis.* 2014;34:172–93. PubMed PMID: 24879982.

(Review of HDS induced liver injury including regulatory problems, difficulties in diagnosis and assessing causality; mentions that the FDA issued a warning in 2001 about the hepatotoxicity of comfrey).

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.e3. PubMed PMID: 25500423.

(Extensive review of possible beneficial as well as harmful effects of herbal products on the liver mentions that comfrey contains pyrrolizidine alkaloids that can cause SOS).

Stickel F, Shouval D. Hepatotoxicity of herbal and dietary supplements: an update. *Arch Toxicol.* 2015;89:851–65. PubMed PMID: 25680499.

(Extensive review of liver injury due to HDS, discusses the pyrrolizidine alkaloids and the clinical features, diagnosis and management of SOS).

Chalasanani 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.e7. 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%], however, none of the HDS products listed included comfrey as a known component).

Frenzel C, Teschke R. Herbal hepatotoxicity: clinical characteristics and listing compilation. *Int J Mol Sci.* 2016;17:E588. pii. PubMed PMID: 27128912.

(Extensive listing of herbal products that have been implicated in causing liver injury, including comfrey).

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;17:537. PubMed PMID: 27070596.

(Review and tabulation of HDS causes of liver injury focusing upon illicit anabolic steroids, green tea, linoleic acid, usnic acid, Herbalife and Hydroxycut products, OxyELITE Pro, vitamin A, Ma Huang [ephedra] and Garcinia cambogia).

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 PMID: 26950122.

(Summary of the regulatory issues surrounding HDS products and hepatotoxicity in the US, including difficulties of surveillance, causality assessment, detection of contaminants and FDA regulatory actions using examples of Lipokinetix [usnic acid], OxyELITE Pro [Aegeline], Hydroxycut [possibly green tea] and designer [anabolic] steroids; no specific discussion of comfrey).

Navarro VJ, Khan I, Björnsson E, Seeff LB, Serrano J, Hoofnagle JH. Liver injury from herbal and dietary supplements. *Hepatology.* 2017;65:363–73. PubMed PMID: 27677775.

(Summary of a workshop on the increase in frequency of HDS associated liver injury in the US, focusing upon green tea extracts, OxyELITE Pro, anabolic steroid jaundice and exploring issues of chemical analysis of HDS products, possible changes in regulatory requirements and needs for future research; comfrey is not specifically discussed).

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 role of HDS in causing liver injury, mentions comfrey as a source of pyrrolizidine alkaloid associated SOS occurring in the US).

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 2408 adult urgent liver transplants enrolled in the US Scientific Registry of Transplant Recipients between 2003 and 2015, 625 [30%] were listed as drug induced, mostly due to acetaminophen [n=300, 48%], and HDS products were the 4th most common cause [n=21, 3%], seemingly increasing in proportion during the 12 years of enrollment; comfrey was not among the agents listed).

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(9):783–787. PubMed PMID: 28555362.

(In a statewide prospective registry of drug induced liver injury, 23 cases were identified during 2014 in Delaware, of which 6 [43%] were attributed to HDS products, but none listed comfrey as a component).

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, lists four publications of case reports implicating comfrey in causing liver injury, probably veno-occlusive disease due to pyrrolizidine alkaloids).

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 cause being green tea [n=8] and Herbalife products [n=6], none were attributed to comfrey).

Kucera A, Barna M, Holcova S, Horacek O, Hladiková M, Ottillinger B. Tolerability and effectiveness of an antitrauma cream with comfrey herb extract in pediatric use with application on intact and on broken skin. *Int J Pediatr Adolesc Med.* 2018;5:135–141. PubMed PMID: 30805549.

(Among 712 children treated with a topical cream containing comfrey for up to two weeks, only one had a local adverse reaction [redness and burning] and “These were otherwise no systemic or other adverse reactions”).

Avila C, Breakspear I, Hawrelak J, Salmond S, Evans S. A systematic review and quality assessment of case reports of adverse events for borage (*Borago officinalis*), coltsfoot (*Tussilago farfara*) and comfrey (*Symphytum officinale*). *Fitoterapia.* 2020;142:104519. PubMed PMID: 32105669.

(Literature review and “quality assessment” of reports of hepatotoxicity of three botanical products that can contain pyrrolizidine alkaloids including comfrey).

Kuchta K, Schmidt M. Safety of medicinal comfrey cream preparations (*Symphytum officinale* s.l.): The pyrrolizidine alkaloid lycopsamine is poorly absorbed through human skin. *Regul Toxicol Pharmacol.* 2020;118:104784. PubMed PMID: 32941922.

(In vitro assays of human skin tissue and lycopsamine [a pyrrolizidine alkaloid found in comfrey] demonstrated its poor absorption through human skin).

Wang Z, Han H, Wang C, Zheng Q, Chen H, Zhang X, Hou R. Hepatotoxicity of pyrrolizidine alkaloid compound intermedine: comparison with other pyrrolizidine alkaloids and its toxicological mechanism. *Toxins (Basel).* 2021;13:849. PubMed PMID: 34941687.

(In vitro studies of the toxicity of the pyrrolizidine alkaloid found in comfrey [intermedine] for hepatocytes suggested that injury was caused by release of reactive oxygen species leading to mitochondrial mediated apoptosis).

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 none were attributed to comfrey).

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 identified 446 publications with a total of 936 cases of liver injury attributed to 79 different herbal products, the most common being He Shou Wu [n=91], green tea [90] Herbalife products [64], kava [62] and greater celandine [48]; comfrey was listed as the cause of 8 cases).