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Black Cohosh

Updated: May 20, 2014.

OVERVIEW

Introduction

Black cohosh is a popular herbal medication derived from a plant of the buttercup family indigenous to North America (Actaea racemosa, syn Cimicifuga racemosa), which is claimed to have estrogen-like effects and is used primarily for relief of symptoms of menopause. In recent years, products labeled as black cohosh has been implicated in many instances of clinically apparent, acute liver injury, some cases of which have been severe and led to emergency liver transplantation or death.

Background

Black cohosh (Cimicifuga racemosa; Actaea racemosa) is a perennial plant indigenous to the eastern United States and Canada. It has been long employed as a traditional Native American medicine to treat malaise, gynecological disorders, kidney disorders, malaria, rheumatism, and sore throat. The plant is referred to by many names, including black root, black snakeroot, bugbane, cimicifuga, cohosh bugbane, macrotnys, and rattlesnake root. Black cohosh supplements are made from its roots and rhizomes. Black cohosh is commonly used for the relief of symptoms associated with menopause and has been shown to be effective in ameliorating these symptoms in controlled trials. The constituents of black cohosh include triterpenes glycosides and polyphenols. Black cohosh was initially believed to have estrogen-like activity and modulate tissue specific subtypes of the estrogen receptor; more recent investigations suggest that it may have serotonergic activity. Black cohosh is available in multiple preparations either as an herbal product on its own or as a component of an herbal supplement. Phytochemical analyses have shown that some black cohosh products are mislabeled and contain Chinese Actaea species instead. Side effects of black cohosh may include hypotension, bradycardia, central nervous system effects, nausea, and vomiting.

Hepatotoxicity

In prospective clinical trials involving more than 1200 patients, black cohosh was not associated with serum enzyme elevations during treatment and no cases of clinically apparent liver injury were reported. However, products labeled as black cohosh have been linked to more than fifty instances of clinically apparent liver injury that have ranged in severity from symptomatic elevations in serum enzymes without jaundice, to acute self-limited hepatitis, prolonged hepatitis with cholestasis, autoimmune hepatitis, and acute liver failure requiring liver transplantation or with a fatal outcome. The latency to onset of liver injury ranged from 1 to 48 weeks, but was usually within 2 to 12 weeks. The clinical presentation was typically with jaundice and a markedly hepatocellular pattern of injury with liver biopsy histology resembling acute viral hepatitis. Some instances of an autoimmune hepatitis-like clinical syndrome have been described with high levels of autoantibodies, chronic

hepatitis on liver biopsy and a clinical response to prednisone. In some cases, black cohosh appeared to have precipitated an autoimmune hepatitis that was self sustained and relapsed when immunosuppression was withdrawn; while in other instances the hepatitis with autoimmune features resolved spontaneously after discontinuation of black cohosh or after a short course of prednisone. In several instances, the implicated product has been retrieved and found to contain Chinese Actaea species rather than black cohosh, and the role of Actaea racemosa in causing liver injury remains controversial.

Mechanism of Injury

Black cohosh does not appear to be inherently hepatotoxic, and the clinical features of cases suggest that the liver injury is an idiosyncratic reaction which may be immunologically mediated. The specific component of black cohosh responsible for the hepatic injury is not known. As with many HDS products, unknown adulterants or herbals mislabeled as black cohosh may be the actual cause of hepatic injury.

Outcome and Management

The severity of liver injury ranges from moderate elevations in liver enzymes to acute hepatic failure and death. However, mild disease with spontaneous resolution with stopping the herbal is more common. Cases with autoimmune features or prolonged symptomatic cholestasis may benefit for a course of immunosuppression with prednisone, with or without azathioprine. However, the dose of prednisone should be kept to a minimum and attempts should be made to withdraw immunosuppression once the hepatitis has resolved. There is no evidence for cross sensitivity to the liver injury between black cohosh and more conventional estrogen preparations nor with other herbals.

Drug Class: Herbal and Dietary Supplements

CASE REPORTS

Case 1. Acute liver failure after taking an herbal preparation with black cohosh.

[Modified from: Lontos S, Jones RM, Angus PW, Gow PJ. Acute liver failure associated with the use of herbal preparations containing black cohosh. Med J Aust 2003; 179: 390-1. PubMed Citation]

A 52 year old woman developed fatigue and lethargy, followed by jaundice approximately 3 months after starting a liquid herbal preparation that contained black cohosh. She stopped the botanical when she became ill, but subsequently developed jaundice. The preparation was made and provided by a pharmacist and contained fluid extracts of several botanicals, including ground ivy (Nepeta hederacea), golden seal (Hydrastis canadensis), ginkgo (Ginkgo biloba), oats seed (Avena sativa) and black cohosh (Cimicifuga racemosa). She had no history of liver disease, alcohol abuse or risk factors for viral hepatitis and was not taking other medications. On examination, she was deeply jaundiced, but had no signs of hepatic encephalopathy. Serum bilirubin was 21.5 mg/dL, ALT 1380 U/L, alkaline phosphatase 230 U/L and INR 3.0. Other causes of acute liver failure were said to be excluded. During the initial week, she developed evidence of hepatic failure with progressive hepatic encephalopathy and worsening coagulation, leading to liver transplantation approximately 4 weeks after admission. The explanted liver showed massive necrosis.

Key Points

Medication:	Herbal mixture with black cohosh
Pattern:	Hepatocellular (R=11.3)
Severity:	5+ (liver transplantation for acute liver failure)

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Medication:	Herbal mixture with black cohosh
Latency:	3 months
Recovery:	None
Other medications:	Other herbals in the liquid mixture included ground ivy, goldenseal, ginkgo and oats seed

Comment

This patient developed an acute liver failure of unknown cause approximately 3 months after starting an herbal preparation that was claimed to contain black cohosh. The other components have not been implicated in cases of acute liver failure, but may have contributed due to herb-herb interactions. This case was the initial report of hepatotoxicity attributed to black cohosh. The possibility that the liver injury was unrelated to black cohosh and due to a adulterant or mislabeled herbal or was due to a coincidental, idiopathic or unusual viral cause of acute liver failure cannot be completely excluded. However, the clinical presentation with a strongly hepatocellular pattern of injury and a gradual progression to hepatic failure over several weeks, even after stopping the herbal, has been described in other cases of severe acute liver injury attributed to black cohosh.

Case 2. Acute liver failure arising during chronic therapy with black cohosh.

[Modified from: Lynch CR, Folkers ME, Hutson WR. Fulminant hepatic failure associated with the use of black cohosh: a case report. Liver Transpl 2006; 126: 989-92. PubMed Citation]

A 54 year old woman developed fatigue and weight loss 6 months after starting black cohosh (1000 mg daily) for menopausal symptoms. She had a history of hypothyroidism and was receiving levothyroxine (100 µg daily). The fatigue persisted, and she noted onset of forgetfulness and loss of 10 pounds before seeking medical help. She had no history of liver disease, drank alcohol regularly but not to excess, and had no risk factors for viral hepatitis. On examination, she had tenderness over the liver but was not obviously jaundiced. Serum aminotransferase levels were markedly elevated (ALT 1003 U/L, AST 1014 U/L) with modest increases in alkaline phosphatase (266 U/L) and total bilirubin (2.4 mg/dL). Tests for hepatitis A, B and C were negative as were tests for herpes simplex, cytomegalovirus and Epstein-Barr virus infection. Autoantibodies were negative. Ultrasound and computerized tomography of the abdomen showed no evidence of biliary obstruction or abnormalities of the liver. The prothrombin time was elevated (INR 1.4). A liver biopsy showed severe bridging hepatocellular necrosis and with panlobular inflammation and interface hepatitis, but without fibrosis, compatible with a severe acute hepatitis. Prednisone was started, but her condition worsened. After two weeks, serum aminotransferase levels were still high and total bilirubin rose to 20.6 mg/dL. She developed hepatic encephalopathy and worsening coagulation (INR 2.6). Repeat ultrasonography showed reduced liver size. She underwent deceased donor liver transplantation 39 days after admission, but expired during the operation as a result of excessive hemorrhage. Autopsy showed a shrunken liver with extensive necrosis, minimal inflammation and regenerative nodules.

Key Points

Medication:	Black cohosh
Pattern:	Hepatocellular (R=10.9)
Severity:	5+ (acute hepatic failure, liver transplantation and death)
Latency:	6 months to initial symptoms, 8 months to jaundice
Recovery:	None

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Medication:	Black cohosh
Other medications:	Levothyroxine 100 µg daily

Comment

Acute hepatitis with progressive hepatic failure arose 6 to 8 months after starting black cohosh for menopausal symptomatology. No other obvious cause was present and the patient was taking no other medication that might be considered hepatotoxic. While autoimmune hepatitis was considered and she was treated with prednisone, there were no autoantibodies or other features of this diagnosis and there appeared to be little response to immunosuppression. The clinical presentation and course was similar to other cases of liver injury attributed to black cohosh. The longer latency to onset was atypical, but similar variability in latency to onset of severe hepatotoxicity occurs with other agents that cause idiosyncratic acute liver injury, such as isoniazid and troglitazone.

Case 3. Chronic hepatitis associated with black cohosh use.

[Modified from case 2 of: Pierard S, Coche JC, Lanthier P, Dekoninck X, Lanthier N, Rahier J, Geubel AP. Severe hepatitis associated with the use of black cohosh: a report of two cases and an advice for caution. Eur J Gastroenterol Hepatol 2009; 21: 941-5. PubMed Citation]

A 58 year old woman developed fatigue and weakness while taking black cohosh (80 mg of root extract daily) in addition to medications for hypertension (irbesartan 150 mg daily), hypothyroidism (levothyroxine 100 µg daily), hypercholesterolemia (simvastatin 20 mg daily), and diabetes (insulin). She had no history of liver disease, alcohol abuse, or risk factors for viral hepatitis. Physical examination was unremarkable. Laboratory testing, however, showed elevations in serum ALT (318 U/L), AST (214 U/L) and GGT (95 U/L) with normal bilirubin, albumin, total protein, INR, platelet and white blood cell counts. Tests for hepatitis A, B and C as well as Epstein Barr virus and cytomegalovirus infection were negative. Smooth muscle antibody was weakly positive (titer 1:40). A liver biopsy showed interface hepatitis and lobular inflammation with portal fibrosis suggestive of chronic hepatitis. Simvastatin was stopped, but she did not improve (Table). Accordingly, three months later black cohosh was discontinued. Within two weeks serum aminotransferase levels decreased and two months later her symptoms had resolved and liver tests were normal.

Key Points

Medication:	Black cohosh (80 mg daily)
Pattern:	Undefined, probably hepatocellular
Severity:	1+ (enzyme elevations and symptoms without jaundice)
Latency:	Unclear
Recovery:	2 months after stopping
Other medications:	Simvastatin, irbesartan, levothyroxine, insulin

Laboratory Values

Time After Presentation	ALT (U/L)	AST (U/L)	Bilirubin (mg/dL)	Other
0	183	214	Normal	Asthenia
	Simvastatin discontinued			
3 months	527	663		
	Black cohosh discontinued			

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Time After Presentation	ALT (U/L)	AST (U/L)	Bilirubin (mg/dL)	Other
3.3 months	85	96		
5 months	45	43		Symptoms resolved
Normal Values	**<34**	**<44**	**<1.2**	

Comment

The case report lacked information on duration of black cohosh use and several important clinical details (alkaline phosphatase levels, ANA results), but the timing of improvement in relationship to stopping black cohosh was very supportive of the link between the herbal and the chronic hepatic injury. Drugs that cause idiosyncratic acute hepatitis arising within 6 months of starting therapy may, if continued long term, also cause chronic hepatitis, sometimes with autoimmune features (examples being methyldopa, nitrofurantoin, isoniazid). In these instances, the time to onset of injury can be many months or years after starting the medication, particularly if it is given intermittently.

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Black Cohosh – Generic

DRUG CLASS

Herbal and Dietary Supplements

SUMMARY INFORMATION

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

Fact Sheet at Office of Dietary Supplements, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Black Cohosh	84776-26-1	Herbal mixture	Not applicable

ANNOTATED BIBLIOGRAPHY

References updated: 20 May 2014

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; black cohosh 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];

black cohosh is mentioned as having been linked to cases of acute hepatitis, acute liver failure and autoimmune hepatitis, the mechanism of injury being unknown and the actual relationship to black cohosh being controversial).

Black cohosh. In, PDR for Herbal Medicines. 4th ed. Montvale, New Jersey: Thomson Healthcare Inc. 2007: pp. 95-100.

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

Lieberman S. A review of the effectiveness of Cimicifuga racemosa (black cohosh) for the symptoms of menopause. J Womens Health 1998; 7: 525-9. PubMed PMID: 9650153.

(History of the development of black cohosh and series of open label and controlled trials showing its efficacy in decreasing symptoms of menopause).

American College of Obstetricians and Gynecologists Committee on Practice Bulletins–Gynecology. Clinical management guidelines for obstetrician-gynecologists: use of botanicals for management of menopausal symptoms. Obstet Gynecol 2001; 97: 1-11. PubMed PMID: 11501568.

(Review of evidence of benefit of various botanicals for menopausal symptoms: "Black cohosh may be helpful in the short-term treatment of women with vasomotor symptoms").

Whiting PW, Clouston A, Kerlin P. Black cohosh and other herbal remedies associated with acute hepatitis. Med J Aust 2002; 177: 440-3. PubMed PMID: 12381254.

(6 cases of severe hepatitis in patients taking herbal medications, including 1 on black cohosh alone and 5 taking multiple herbals including skullcap [n=3], valerian [n=2], chaparral [n=1] and greater celandine [n=1] for 1 to 14 weeks, presenting with jaundice [bilirubin 9.9-62.7 mg/dL, ALT 1293-3764 U/L, Alk P 80-219 U/L], the 1 on black cohosh alone requiring emergency liver transplantation, the other 5 resolving in 7-25 weeks, 3 treated with prednisone for prolonged cholestasis).

Vitetta L, Thomsen M, Sali A. Black cohosh and other herbal remedies associated with acute hepatitis. Med J Aust 2003; 178: 411-2. PubMed PMID: 12697018.

(Letter in response to Whiting [2002] suggesting that hepatitis may have been due to a contaminant and without verification, the link to black cohosh cannot be made).

Thomsen M, Schmidt M. Hepatotoxicity from Cimifuga Racemosa? Recent Australian case report not sufficiently substantiated. J Alt Complement Med 2003; 9: 337-40. PubMed PMID: 12697018.

(Authors argue that case series of Whiting [2002] lacked essential information such as analytic verification of components and was weakened by insufficient exclusion of other causes, implausible mechanism of injury, overrating of dangers of herbals and lack of previous reports of hepatotoxicity in multiple prospective studies).

Lontos S, Jones RM, Angus PW, Gow PJ. Acute liver failure associated with the use of herbal preparations containing black cohosh. Med J Aust 2003; 179: 390-1. PubMed PMID: 14503910.

(52 year old woman developed jaundice 3 months after starting an herbal mixture including black cohosh [bilirubin 21.5 mg/dL, ALT 1380 U/L, Alk P 230 U/L, INR 3.0], with progressive hepatic failure and liver transplantation 1 month later: Case 1).

Pittler MH, Ernest E. Systematic review: hepatotoxic events associated with herbal medicinal products. Aliment Pharmacol Ther 2003; 18: 451-71. PubMed PMID: 12950418.

(Systematic review of published cases of hepatotoxicity due to herbal medications listing 52 case reports or case series, most common agents being celandine [3], chaparral [3], germander [8], Jin Bu Huan [3], kava [1], Ma Huang [3], pennyroyal [1], skullcap [2], Chinese herbs [9], valerian [1]).

Estes JD, Stolpman D, Olyaei A, Corless CL, Ham JM, Schwartz JM, Orloff SL. High prevalence of potentially hepatotoxic herbal supplement use in patients with fulminant hepatic failure. Arch Surg 2003; 138: 852-8. PubMed PMID: 12912743.

(Among 20 patients undergoing liver transplantation for acute liver failure during 2001-2, 10 were potentially caused by herbals; none were attributed to black cohosh).

Thomsen M, Vitetta L, Sali A, Schmidt M. Acute liver failure associated with the use of herbal preparations containing black cohosh. Med J Aust 2004; 180: 598-9. PubMed PMID: 15175000.

(Authors challenge the relationship between black cohosh and liver injury [Lontos 2003], on the basis that the herbal mixture also contained group ivy which has pulegone and that black cohosh has "a very good safety record").

Cumming FJ, Kelly L. Acute liver failure associated with the use of herbal preparations containing black cohosh. Med J Aust 2004; 180: 599-600. PubMed PMID: 15175000.

(Reply to letter [Thomsen 2004] by the Office of Complementary Medicines indicating that the herbal product was analyzed and pulegone levels were below the level of detection).

Cohen SM, O'Connor AM, Hart J, Merel NH, Te HS. Autoimmune hepatitis associated with the use of black cohosh: a case study. Menopause 2004; 11: 575-7. PubMed PMID: 15356412.

(57 year old woman developed fatigue 3 weeks after starting black cohosh for hot flashes [bilirubin normal, ALT 1220 U/L, Alk P minor elevations], with ANA 1:640 and liver biopsy suggesting autoimmune hepatitis, resolving with prednisone therapy and relapsing with stopping [bilirubin 9.2 mg/dL, ALT 1694 U/L]).

National Center for Complementary and Integrative Health, NIH. Workshop on safety of black cohosh in clinical studies. November 22, 2004. Available at: http://nccih.nih.gov/news/events/blackcohosh/blackcohosh_mtngsumm.pdf

(Workshop on black cohosh and its association with liver injury including two case reports from Australia: 47 year old woman developed acute liver failure 3 weeks after starting black cohosh for menopausal symptoms [bilirubin 32 mg/dL, ALK 1276 U/L, Alk P 153 U/L, INR 5.0], leading to emergency liver transplant and explant showing massive necrosis [Whiting 2002]; 52 year old woman developed acute liver failure presenting 1 month after taking a 3 month course of black cohosh [bilirubin 20 mg/dL, ALT 1380 U/L, Alk P 230 U/L, INR 3.0] undergoing liver transplant and explant showing massive necrosis).

Australian Therapeutic Goods Administration Statement. New labelling requirements and consumer information for medicines containing Black cohosh(Cimicifuga racemosa). 2006. Available at: http://www.tga.gov.au/safety/alerts-medicine-black-cohosh-070529.htm

(Labeling requirements for black cohosh from the Therapeutic Goods Administration of Australia: "Warning: Black cohosh may harm the liver in some individuals").

Huntley A. The safety of black cohosh(Actaea racemosa, Cimicifuga racemosa). Expert Opin Drug Saf 2004; 3: 615-23. PubMed PMID: 15500420.

(Review of experimental animal and human studies of black cohosh focusing upon mechanism of action, clinical efficacy and adverse events; in human trials few adverse events were reported and no liver side effects were encountered; in spontaneous reporting systems worldwide there have been 8 reports of liver and biliary adverse events).

Levitsky J, Alli TA, Wisecarver J, Sorrell MF. Fulminant liver failure associated with the use of black cohosh. Dig Dis Sci 2005; 50: 538-9. PubMed PMID: 15810638.

(50 year old woman developed jaundice 5 months after starting black cohosh [500 mg daily] for menopausal symptoms [bilirubin 7.6 g/dL, ALT 1474 U/L, Alk P 232 U/L, INR 2.5], with subsequent worsening despite prednisone therapy leading to liver transplantation 5 weeks after first presentation).

Low Dog T. Menopause: a review of botanical dietary supplements. Am J Med. 2005; 118 Suppl 12B: 98-108. PubMed PMID: 16414334.

(Systematic review of 19 controlled trials found evidence that black cohosh is beneficial for relief of menopause related symptoms, but recommendations are tempered by methodologic problems with the published trials, questions about its mechanism of action, and 4 recent reports of severe liver injury suspected to be due to black cohosh).

Lynch CR, Folkers ME, Hutson WR. Fulminant hepatic failure associated with the use of black cohosh: a case report. Liver Transpl 2006; 126: 989-92. PubMed PMID: 16721764.

(54 year old woman developed fatigue 6 months after starting black cohosh [1 gram daily] and jaundice in next 2 months [bilirubin 2.4 mg/dL, ALT 1003 U/L, Alk P 266 U/L, INR 1.4], with subsequent worsening leading to liver transplantation; explant showed shrunken liver with marked centrilobular necrosis and regenerative nodules: Case 2).

Dugoua J-J, Seely D, Perri D, Koren G, Mills E. Safety and efficacy of black cohosh(Cimifuga racemosa) during pregnancy and lactation. Can J Clin Pharmacol 2006; 13: e257-e61. PubMed PMID: 17085773.

(Systematic review of literature on efficacy and safety of black cohosh during pregnancy concluded that it should be used with caution; no mention of hepatotoxicity).

Nisbet BC, O'Connor RE. Black cohosh-induced hepatitis. Del Med J 2006; 79: 441-4. PubMed PMID: 18203607.

(50 year old woman developed abdominal pain 2 weeks after starting black cohosh [40 mg/day] for menopausal symptoms [bilirubin 1.1 mg/dL, ALT 691 U/L, Alk P 117 U/L], with rapid resolution on stopping).

Newton KM, Reed SD, LaCroix AZ, Grothaus LC, Erlich K, Guiltinan J. Treatment of vasomotor symptoms of menopause with black cohosh, multibotanicals, soy, hormone therapy, or placebo. Ann Intern Med 2006; 145: 869-79. PubMed PMID: 17179056.

(Controlled trial of black cohosh [160 mg/day], vs a multibotanical with black cohosh, vs a mutlibotanical with dietary soy, vs estrogen vs placebo in 351 women with vasomotor symptoms attributed to menopause found no difference between herbals and placebo in improving symptoms or in rates of adverse events; no hepatotoxicity or ALT results reported).

Briese V, Stammwitz U, Friede M, Henneicke-von Sapelin HH. Black cohosh with or without St. John's wort for symptom-specific climacteric treatment–results of a large-scale, controlled, observational study. Maturitas 2007; 57: 405-14. PubMed PMID: 17590291.

(Open label observation study of 6141 women receiving either black cohosh alone or combined with St. John's wort for menopausal symptoms showed similar improvements with either treatment; only 2.2% developed adverse events and there were no case of liver dysfunction reported, but laboratory data were not collected).

Gori L, Firenzuoli F. Is black cohosh a hepatotoxic medicinal herb? Forsch Komplementarmed 2007; 17: 109-10. PubMed PMID: 17464162.

(The European Medicines Agency [EMEA] announced that 42 cases of liver injury attributed to black cohosh have been reported; however, authors argue that many cases were poorly documented and the possibility of contamination and other comorbidities raise issue of whether black cohosh was the cause; concluding that black cohosh hepatotoxicity is probably rare).

Herbal Medicinal Products Committee, European Medicines Agency. Assessment of case reports connected to herbal medicinal products containing Cimicifugae racemosae rhizoma (black cohosh, root). 2007. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Herbal_-_HMPC_assessment_report/2010/02/WC500074167.pdf

(Assessment of reported cases of black cohosh hepatotoxicity by the Committee on Herbal Medicinal Products of the European Medicines Agency using the RUCAM scoring system, concluded that most cases were inadequately documented and only 3 could be considered possible and 2 probable).

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

(Review of HDS associated hepatotoxicity, with review of the literature including 4 reports of hepatic injury due to black cohosh).

Dunbar K, Solga AF. Black cohosh, safety, and public awareness. Liver International 2007; 27: 1017-8. PubMed PMID: 17696943.

(41 year old woman developed fatigue 2 weeks after starting black cohosh and developed progressive jaundice, ascites and hepatic encephalopathy leading to transfer to a transplant center [bilirubin 13.1 mg/dL, ALT 393 U/L, INR 2.0], undergoing liver transplant 2.5 months after onset).

Walji R, Boon H, Guns E, Oneschuk D, Younus J. Black cohosh(Cimifuga racemosa [L.] Nutt.): safety and efficacy for cancer patients. Support Care Cancer 2007; 15: 913-21. PubMed PMID: 17602247.

(Systematic review of literature of safety and efficacy of black cohosh in patients with cancer concluded that evidence for benefit as well as for liver toxicity was "inconclusive").

Teschke R. Questions regarding causality in presumed black cohosh hepatotoxicity. Del Med J 2008; 80: 233-4; author reply 235. PubMed PMID: 18714667.

(Letter in response to Nisbet [2006] suggesting that symptoms predated time of starting black cohosh and that other diagnoses were not adequately excluded; reply by authors stating that symptoms arose soon after starting black cohosh and that other diagnoses were either excluded or highly unlikely).

Joy D, Joy J, Duane P. Black cohosh: a cause of abnormal postmenopausal liver function tests. Climacteric 2008; 11: 84-8. PubMed PMID: 18202968.

(Two cases: 50 year old woman developed headaches and mild AST [53-70 U/L] and GGT [213-571 U/L] elevations on black cohosh, which resolved on stopping; 51 year old woman developed abdominal pain and liver test abnormalities [bilirubin normal, ALT 722 U/L, Alk P 226 U/L] after taking black cohosh for 2 months, values normalizing within 2 weeks of stopping).

Chow EC, Teo M, Ring JA, Chen JW. Liver failure associated with the use of black cohosh for menopausal symptoms. Med J Aust 2008; 188: 420-2. PubMed PMID: 18393750.

(51 year old woman developed fatigue followed by jaundice 3 years after starting intermittent doses of black cohosh [20 mg daily], [bilirubin 6.2 mg/dL, ALT 1230 U/L, Alk P 191 U/L, INR 1.8], with progressive liver failure leading to liver transplantation; explant showed massive necrosis and collapse).

Borrelli F, Ernst E. Black cohosh (Cimicifuga racemosa) for menopausal symptoms: a systematic review of its efficacy. Pharmacol Res 2008; 58: 8-14. PubMed PMID: 18585461.

(Systematic review of six randomized placebo controlled trials of black cohosh in women with menopausal symptoms found no consistency in support of beneficial effects, but that such an effect could not be excluded; no discussion of adverse events).

Mahady GB, Low Dog T, Barrett ML, Chavez ML, Gardiner P, Ko R, Marles RJ, et al. United States Pharmacopeia review of the black cohosh case reports of hepatotoxicity. Menopause 2008; 15: 628-38. PubMed PMID: 18340277.

(Expert committee review of case reports of hepatotoxicity related to black cohosh from all possible sources found 30 separate reports, but on analysis none were considered "certain" or even "probable", which, nevertheless, led to recommendation that black cohosh be labeled with a cautionary statement regarding liver injury).

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, none were attributed to black cohosh).

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 or dietary supplements, but none were attributed to black cohosh).

Pierard S, Coche JC, Lanthier P, Dekoninck X, Lanthier N, Rahier J, Geubel AP. Severe hepatitis associated with the use of black cohosh: a report of two cases and an advice for caution. Eur J Gastroenterol Hepatol 2009; 21: 941-5. PubMed PMID: 19404202.

(Two cases with histological features of chronic hepatitis during black cohosh therapy for menopausal symptoms: 62 year old woman developed abdominal pain 3 months after starting black cohosh [bilirubin normal, ALT 322 U/L, GGT 320 U/L, ANA 1:320], with resolution upon stopping [transient worsening when given prednisolone and azathioprine]; 58 year old woman developed fatigue sometime after starting black cohosh for menopausal symptoms [bilirubin normal, ALT 318 U/L, GGT 95 U/L], with persistence of abnormalities on continuing and rapid improvement upon stopping black cohosh: Case 3).

Naser B, Liske E. Teschke R. Liver failure associated with the use of black cohosh for menopausal symptoms. Med J Aust 2009; 190: 99-100; author reply 100. PubMed PMID: 19278034.

(Two letters in response to Chow [2008] raising the issue of alcohol as a cause of the liver injury and the possibility of other causes such as herpes simplex, adenovirus and Wilson disease; reply by authors stating that these etiologies were unlikely).

Teschke R. A U.S. review determined that black cohosh products should be labeled with a cautionary statement. Menopause 2009; 16: 214; author reply 214-5. PubMed PMID: 19131847.

(Letter in response to Mahady [2008] questioning the use of the Naranjo rather than the RUCAM scale in assessing causality in cases of black cohosh hepatotoxicity; authors reply stating that the causality assessment was done by expert consensus opinion and the Naranjo scale was used only as an aid).

Teschke R, Schwarzenboeck A. Suspected hepatotoxicity by Cimifugae racemosae rhizome (black cohosh, root): Critical analysis and structured causality assessment. Phytomedicine 2009; 16: 72-84. PubMed PMID: 19010650.

(Among 42 reports of severe hepatotoxicity received by the European Medicine Agency, only 4 were considered as possible or probable; application of RUCAM to these 4 cases by the author yielded scores in the "excluded" range [-1 to -3], largely because of other possible diagnoses [autoimmune hepatitis, herpes] and other drugs used).

Teschke R, Bahre R, Fuchs J, Wolff A. Black cohosh hepatotoxicity: quantitative causality evaluation in nine suspected cases. Menopause 2009; 16: 956-65. PubMed PMID: 19339903.

(Analysis of 9 cases of suspected black cohosh hepatotoxicity using RUCAM suggested that none could be considered even possibly related, largely because of competing diagnoses, other medications being taken and lack of information on course and outcome).

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

(Review of the problems of causality assessment in herbal and dietary supplement [HDS] associated liver disease, including the variable clinical presentations, the complexity and lack of information on their components, absence of controlled trials demonstrating safety and efficacy, the possibility of contamination or incorrect labeling and frequent underreporting of herbal use by patients. Black cohosh is discussed as a potential cause of severe acute hepatitis).

Vannacci A, Lapi F, Gallo E, Vietri M, Toti M, Menniti-Ippolito F, Raschetti R, et al. A case of hepatitis associated with long-term use of Cimicifuga racemosa. Altern Ther Health Med 2009; 15: 62-3. PubMed PMID: 19472866.

(37 year old woman developed jaundice 6-8 months after starting black cohosh for menopausal symptoms [bilirubin 1.5 mg/dL, ALT 20 times ULN, GGT slightly increased], with persistent ALT abnormalities until use of the herbal was admitted, resolution occurring within 1 month of stopping).

Guzman G, Kallwitz ER, Wojewoda C, Chennuri R, Berkes J, Layden TJ, Cotler SJ. Liver injury with features mimicking autoimmune hepatitis following the use of black cohosh. Case Report Med 2009; PubMed PMID: 20130783.

(Two women, ages 42 and 53, developed fatigue 6 and 8 months after starting black cohosh for menopausal symptoms [bilirubin 3.1 and 2.0 mg/dL, ALT 1457 and 443 U/L, Alk P 94 and 188 U/L, ANA 1:20-1:40], biopsy showing changes suggestive of chronic hepatitis and both responding to corticosteroids).

Mahady G, Low Dog T, Sarma DN, Giancaspro GI. Suspected black cohosh hepatotoxicity—causality assessment versus safety signal. Maturitas 2009; 64: 139-40. PubMed PMID: 19781876.

(Letter in response to Teschke [2009] mentioning that there have been 82 reports of hepatotoxicity attributed to black cohosh and that a product warning is warranted).

Betz JM, Anderson L, Avigan MI, Barnes J, Farnsworth NR, Gerden B, Henderson L, et al. Black Cohosh: considerations of safety and benefit. Nutrition Today 2009; 44: 155-62. [Not in PubMed].

(Summary of a 2007 NIH workshop on the safety of black cohosh and making recommendations for future research and analysis).

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 adverse event reports of herbals to the Swedish Registry includes 38 [5%] related to black cohosh, including 3 related to enzyme elevations and 3 various hepatic reactions).

Barnes J. Black cohosh (black snakeroot, Cimicifuga racemosa (L.) Nutt., Actaea racemosa L.). J Prim Health Care 2010; 2: 79-80. PubMed PMID: 20690409.

(Review mentions that a systematic review conducted in 2007 of 6 controlled trials of black cohosh extracts in 1112 women found evidence of efficacy to be "uncertain" and several spontaneous reports of hepatotoxicity have been published).

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, 1 to black cohosh).

Teschke R. Black cohosh and suspected hepatotoxicity: inconsistencies, confounding variables, and prospective use of a diagnostic causality algorithm. A critical review. Menopause 2010; 17: 426-40. PubMed PMID: 20216279.

(Author performed a reanalysis of 69 cases of suspected liver injury from black cohosh using RUCAM and concluded that 27 were excluded, 21 unlikely, 8 unrelated, 12 unassessable, and only 1 possibly related).

Mahady G, Low Dog T, Sarma ND, Giancaspro GI, Griffiths J. The causal relationship between the use of black cohosh-containing products and hepatotoxicity. Menopause. 2010;17:1088-9; author reply 1089. PubMed PMID: 20827114.

(Letter in response to Teschke [2010] arguing that the modified RUCAM he used made most cases unassessable and that several groups have agreed that black cohosh has a "signal of safety concern"; author replies addressing the need of an improved causality instrument).

Painter D, Perwaiz S, Murty M. Black cohosh products and liver toxicity: update. Can Adverse Reaction Newsl 2010; 20: 1-2 [Not in PubMed]

(Among 4 cases of suspected black cohosh hepatotoxicity reported to Health Canada, analysis of retrieved samples showed that none contained authentic black cohosh, but had phytochemical profiles consistent with presence of other related herbal species).

Firenzuoli F, Gori L, Roberti di Sarsina P. Black Cohosh Hepatic Safety: Follow-Up of 107 patients consuming a special Cimicifuga racemosa rhizome herbal extract and review of literature. Evid Based Complement Alternat Med 2011; 2011: 821392. PubMed PMID: 21660145.

(Among 107 women treated with black cohosh extract for at least one year, none had clinical or biochemical evidence of liver injury).

Jiang B, Ma C, Motley T, Kronenberg F, Kennelly EJ. Phytochemical fingerprinting to thwart black cohosh adulteration: a 15 Actaea species analysis. Phytochem Anal 2011; 22: 339-51. PubMed PMID: 21337649.

(Analysis of 15 Actaea species by HPLC and LC-MS methods showed a characteristic pattern of polyphenols and triterpene glycosides in Actaea racemosa extracts; a specific marker compound [cimifugin] was found in most other species, but not racemosa [black cohosh]).

Naser B, Schnitker J, Minkin MJ, de Arriba SG, Nolte KU, Osmers R. Suspected black cohosh hepatotoxicity: no evidence by meta-analysis of randomized controlled clinical trials for isopropanolic black cohosh extract. Menopause 2011; 18: 366-75. PubMed PMID: 21228727.

(Meta analysis of 5 randomized controlled trials of black cohosh [Remifemin] found no significant changes in mean ALT, AST or GGT levels among black cohosh and placebo recipients; among 7 patients who developed significant rises in liver tests during therapy, none were judged to be related to black cohosh therapy).

Teschke R, Schmidt-Taenzer W, Wolff A. Spontaneous reports of assumed herbal hepatotoxicity by black cohosh: is the liver-unspecific Naranjo scale precise enough to ascertain causality? Pharmacoepidemiol Drug Saf 2011; 20: 567-82. *(2* PubMed PMID: 21702069.

2 cases of suspected black cohosh hepatotoxicity were evaluated by the RUCAM and Naranjo causality scales: scores ranged from -2 to +2 by RUCAM [none even possible] and -1 to +2 by Naranjo [6 possible]).

Teschke R, Schwarzenboeck A, Schmidt-Taenzer W, Wolff A, Hennermann KH. Herb induced liver injury presumably caused by black cohosh: a survey of initially purported cases and herbal quality specifications. Ann Hepatol 2011; 10: 249-59. PubMed PMID: 21677326.

(Review of problems of causality assessment in cases of liver injury attributed to herbal medications focusing upon black cohosh).

Naser B, Schnitker J, Minkin MJ, de Arriba SG, Nolte KU, Osmers R. Suspected black cohosh hepatotoxicity: no evidence by meta-analysis of randomized controlled clinical trials for isopropanolic black cohosh extract. Menopause 2011; 18: 366-75. PubMed PMID: 21228727.

(In a meta analysis of 5 placebo controlled trials of black cohosh including 1020 women, there were no differences in mean ALT or AST values between placebo and treatment recipients).

Wang YJ, Dou J, Cross KP, Valerio LG Jr. Computational analysis for hepatic safety signals of constituents present in botanical extracts widely used by women in the United States for treatment of menopausal symptoms. Regul Toxicol Pharmacol 2011; 59: 111-24. PubMed PMID: 20920542.

(Computer analyses of chemical structures of compounds found in botanicals used to treat menopausal symptoms identified several predicted to cause hepatic injury, including protocatechuic acid in black cohosh).

Mahady G, Low Dog T, Sarma ND, Griffiths J, Giancaspro GI. Response to Teschke et al. Pharmacoepidemiol Drug Saf 2012; 21: 339-40; author reply 336-8. 22407603. PubMed PMID: 22407603.

(Letter in response to Teschke [2011] arguing that the calculation of RUCAM scores was based upon the author's modifications of the scoring system that resulted in all cases being unlikely or excluded).

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 neither black cohosh or Cimicifuga racemosa are listed).

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

(Systematic review of the literature on HDS associated hepatotoxicity mentions that black cohosh has been implicated in causing liver injury in at least 6 publications).

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. (In a population based study of drug induced liver injury from Iceland, 96 cases were identified over a 2 year period [2010-12], including 15 attributed to herbals or dietary supplements, but none specifically to black cohosh). PubMed PMID: 23419359.

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 including discussion of black cohosh, which has been linked to liver injury ranging from asymptomatic increases in ALT levels to acute liver failure and hepatitis with autoimmune features).

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

(Extensive review of the hepatotoxicity of botanicals mentions the main active constituents of black cohosh are terpene glycosides and discusses 3 case reports of serious liver injury from its use).

Lim TY, Considine A, Quaglia A, Shawcross DL. Subacute liver failure secondary to black cohosh leading to liver transplantation. BMJ Case Rep 2013; 2013. pii: cr2013009325. PubMed PMID: 23833086.

(60 year old woman developed jaundice 2 weeks after starting black cohosh for menopausal symptoms [bilirubin 27.7 mg/dL, AST 2385 U/L, Alk P 151 U/L, INR 1.57], with progressive worsening requiring liver transplantation 3 weeks later).

Enbom ET, Le MD, Oesterich L, Rutgers J, French SW. Mechanism of hepatotoxicity due to black cohosh (Cimicifuga racemosa): Histological, immunohistochemical and electron microscopy analysis of two liver biopsies with clinical correlation. Exp Mol Pathol 2014; 96: 279-283. PubMed PMID: 24657312.

(Two women, ages 65 and 55 years, developed jaundice while taking black cohosh preparations for an unknown period [peak bilirubin 6.6 and 5.4 mg/dL, ALT 92 and 2061 U/L, Alk P 368 and 156 U/L], resolving within 3 months of stopping).