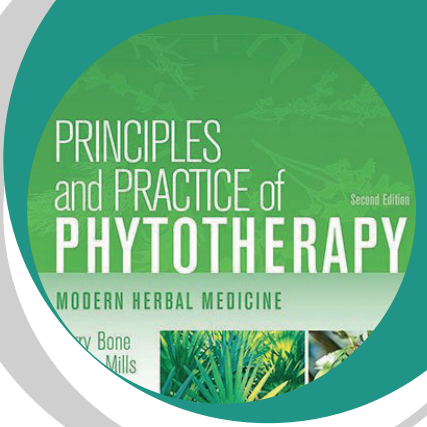
SOCIETY OF WELLNESS
NUTRITIONAL SYSTEMS




Functional Herbal Therapy and Cancer: Module 5

# Black Cohosh Monograph

## An excerpt from Part III: Materia Medica Principles and Practice of Phytotherapy, 2nd Edition

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### General side effects

High doses of black cohosh can cause a frontal headache, with a dull, full or bursting feeling. This headache is the most characteristic effect observed when giving even therapeutic doses.[98] A review published in 2000 found that mild gastrointestinal upset was the most frequent minor adverse event reported in clinical studies (average of 5.6% of patients across five studies). Other minor adverse events reported in clinical studies included headache, vertigo, weight gain, mastalgia, heavy feeling in the legs and a stimulant effect. Vaginal bleeding has also been reported.[2]

Two reviews published in 2003 confirm that adverse events with black cohosh are rare, mild and reversible. Gastrointestinal upsets and rashes are the most common adverse events. There is record of a few serious adverse events, including hepatic and circulatory conditions, but causality could not be determined.[99,100] Details of some of the case reports follow.

A case was reported in 2001 of a woman diagnosed with grade 1 endometrioid adenocarcinoma of the endometrium „whose history was notable for extensive use of supplemental phytoestrogens“. Herbs included chaste tree, dong quai, black cohosh and licorice.[101] No causality was demonstrated.

A 45-year-old woman who had been taking separate bottled products of black cohosh, *Vitex agnus-castus* and evening primrose oil for 4 months had 3 nocturnal seizures within a 3-month period. The patient had also consumed one to two beers 24 to 48 h prior to each incident.[102] It was not established whether the herbal preparations caused the seizures.

A 26-year-old woman presented at a hospital with chest pain. Her heart rate and blood pressure dropped temporarily during the course of monitoring. Her urine digoxin level was „elevated“ at 0.9 ng/mL (but within the normal therapeutic range (0.5 to 2.0 ng/mL)). However, she was not taking digoxin. In addition to the contraceptive pill, she was taking a herbal preparation containing black cohosh, skullcap (Scutellaria lateriflora), lousewort *(Pedicularis canadensis)*, hops *(Humulus lupulus)*, valerian *(Valeriana officinalis)* and cayenne pepper *(Capsicum annuum)*. The product was not available for analysis. The chest pain had started during her shift as a topless dancer, during which she had consumed four alcoholic drinks, but no illicit drugs.[103] This study inappropriately

speculated on „digoxin-like factors" with cardiotonic activity claimed to be „commonly" found in herbal teas. The source of the patient's symptoms remains a mystery, but factors that interfere with digoxin assays yet are without cardiotonic activity have been reported in some herbs. (Refer to the Siberian ginseng *(Eleutherococcus senticosus)* monograph by way of example.)

A case report exists of a 54-year-old woman who developed severe asthenia and high blood levels of creatine phosphokinase (230 to 237 U/L), lactate dehydrogenase (LDH 504 to 548 U/L) and total cholesterol, while taking a supplement derived from black cohosh for the management of vasomotor symptoms related to menopause. Notably the woman had previously taken the product for 12 months with no alteration in biochemistry and had restarted the product after a 3-month break. The black cohosh tablets contained 20 mg of dried rhizome and root extract. No other cause could be identified for her symptoms and she was advised to discontinue the product, after which a progressive normalisation of biochemical parameters and improvement in clinical symptoms occurred.[104]

A case report described a 56-year-old woman diagnosed with cutaneous pseudolymphoma after taking a black cohosh product for 12 months. The localised erythematous plaques on her arms and legs appeared after 6 months and completely disappeared with withdrawal of the product for 3 months.[105]

Other adverse reactions attributed to black cohosh use include cutaneous vasculitis106 and coagulation activation with fluid retention (secondary to a transient autoimmune hepatitis).[107]

## Liver injury

On the 9 February 2006, the Australian TGA announced the following:

"The Therapeutic Goods Administration (TGA) reviewed the safety of Black cohosh *(Cimicifuga racemosa)* following reports of possible liver problems internationally and in Australia. At the time of the review, there were 47 cases of liver reactions worldwide, including 9 Australian cases. In Australia, 4 patients were hospitalised, including two who required liver transplantation. Although some reports are confounded by multiple ingredients, by more than one medication or by other medical conditions, there is sufficient evidence of a causal association between Black cohosh and serious hepatitis. However, considering the widespread use of Black cohosh, the incidence of liver reaction appears to be very low. Following the safety review, the TGA has decided that medicines containing Black cohosh should include the following label statement: „Warning: Black cohosh may harm the liver in some individuals. Use under the supervision of a healthcare professional"."

On July 18, 2006, the Medicines and Healthcare Products Regulatory Agency (MHRA) in the UK issued a press release stating that all black cohosh products sold there should carry the following label warning: "Black cohosh may rarely cause liver problems. If you become unwell (yellowing eyes/ skin, nausea, vomiting, dark urine, abdominal pain, unusual tiredness) stop taking immediately and seek medical advice. Not suitable for patients with a previous history of liver disease."

Notwithstanding the Australian TGA's claim at the time concerning the number of cases of liver damage linked to black cohosh (which include the adverse reaction reports filed with the UK MHRA and other health authorities) only 5 papers or letters had been published purporting to demonstrate a link between black cohosh *(Actaea racemosa)* ingestion and subsequent liver injury. It is important to closely examine these published reports since, because of the process of peer review, these represent the best-documented evidence of any association with liver injury. The first publication, from doctors at the Princess Alexandra Hospital in Brisbane, Australia, described 6 patients with evidence of severe hepatitis that was linked to taking a range of herbal products.108 Two of these patients were taking black cohosh, although one was also taking other herbs including skullcap, a herb which can be substituted by *Teucrium species*, a known hepatotoxic genus.109

The one case attributed to black cohosh alone (Case 1) was truly dramatic. Of the cases reported, the most serious illness occurred in this 47-year-old woman who was taking black cohosh for menopausal symptoms. She required liver transplantation even though, according to the publication, the patient had been taking the black cohosh for just one week. Histological examination of her liver confirmed severe hepatitis and early fibrosis. The patient did not exhibit eosinophilia and had no signs of any systemic disturbance. Serology for hepatitis A, B and C was negative, but rechallenge with the herb was not performed "for ethical reasons". The dose of black cohosh taken was not specified, neither was the product.

The second publication, also from Australia, describes a 52-year-old woman with acute liver failure (Case 2).110 She had been taking an herbal formula containing 1:1 liquid extracts prescribed by a pharmacist. Black cohosh 1:1 was 10% of the mixture and the daily dose of the combination was 7.5 mL twice a day. The patient underwent successful liver transplantation. Although the authors stated that: "Extensive investigation excluded other recognised causes of liver failure", they provided no details of what these investigations were. Analysis by the TGA was said to confirm the presence of golden seal, black cohosh and Ginkgo in the herbal mixture. Other stated ingredients were ground ivy and oats seed.

The phenomenon of idiosyncratic hepatic reactions to drugs is well documented. It also appears that this reaction does occur to certain herbs, eg chaparral *(Larrea tridentata)* and germander *(Teucrium species)*. By definition, such reactions are rare and unpredictable and are not dose related. There are two types of idiosyncratic hepatic injury: hypersensitivity and aberrant metabolism. The former develops 1 to 5 weeks after exposure to the drug and, since it is immune-mediated and acute, also involves a systemic reaction including rash, fever and eosinophilia. The latter takes weeks to months to develop and symptoms are confined to the liver. Diagnosis of drug-induced idiosyncratic liver injury (DILI) is very difficult and relies largely on circumstantial evidence. Factors taken into account include a temporal association, exclusion of other possible causes, a consistent latency period to those described above, presence or absence of hypersensitivity (systemic) features, positive response to drug removal (dechallenge), positive response to rechallenge and a positive lymphocyte stimulation test (this last factor is quite controversial). Complicating this is the fact that DILI can mimic every known human liver disease.[111] There are many confounding factors that could lead to incorrect associations between ingested medications or herbs and idiosyncratic liver injury. Many viruses that cause liver disease are still to be identified[112] and there are no tests for

them. Even known viruses are not always tested for. For example, a Dutch study published this year found that Hep E virus was a significant cause of unexplained hepatitis.[113] Occult coeliac disease has been suggested as a cause of unexplained raised ALT and AST.[114] Rare liver diseases may not be excluded.[115,116] Other environmental factors could be implicated.

The experience of a liver transplant unit highlights some key issues behind the history and incidence of severe acute hepatitis (fulminant hepatic failure, FHF). All adult cases of FHF presenting to the Victorian Liver Transplant Unit (Australia) from 1988 to 2002 were analysed. Eighty patients (mostly female) were referred, at a rate of approximately one case per million population per year. Mean age was about 38 years. Most cases were due to paracetamol poisoning (36%) or idiopathic hepatitis (34%).[110] Only 5 of the 80 cases were classified as drug induced, making this causality a rare factor. Other main causes included hepatitis A (3 cases), hepatitis B (8 cases) and Wilson's disease (6 cases). The 27 cases (34%) of hepatitis due to unknown causes (idiopathic) is a surprising rate. These cases are also described as non-A non-B hepatitis, since patients are not positive for hepatitis A or B. In the USA one study found that the most common cause of FHF was non-A non-B (idiopathic) hepatitis.[117] (Note that this US study was published in 1995, well before the dramatic rise in herbal use in that country). Presumably unidentified infectious or environmental factors could cause these cases of idiopathic hepatitis. However, the authors of the Australian study state: "The strong female predominance of cases argues against a viral cause and raises the possibility that hormonal factors are involved, or that the condition is linked to autoimmune liver diseases. There is clearly a need for large, detailed, multicentre epidemiological studies, to provide further clues to a possible aetiology/ies of this syndrome".

The demographics of idiopathic hepatitis (female, late 30s to early 50s) and black cohosh use strongly overlap. Hence, there is a distinct possibility that some patients who develop idiopathic hepatitis might also be coincidentally taking black cohosh. The herb could then be mistakenly attributed as the cause.

Since these initial series of cases attributing idiosyncratic hepatotoxicity to black cohosh, more cases have been reported. There have also been several publications analysing these and the earlier case reports, especially from the team headed by Teschke.

In 2009 the group rigorously analysed all 69 reported cases (at the time) and found no likelihood of causality in 68.[118] Most cases were marred by confounding variables, misreported data and a lack of critical information.[119] In particular, there was a lack of identification of the herb involved in the initial cases.[120]

Of high relevance here are the findings of Health Canada. From January 2005 to March 2009, Health Canada received 6 domestic reports of liver adverse reactions suspected of being associated with black cohosh. Analysis of 3 products associated with these reports revealed that they did not contain authentic black cohosh. Their phytochemical profiles were consistent with the presence of other related herbal species. A review of the authenticity of all licensed products containing black cohosh resulted in the voluntary withdrawal of several products not containing authentic black cohosh, including the products reported in 4 of the adverse reaction cases.[121]

Studies in black cohosh users have also sought to understand its impact on the liver. A prospective, longitudinal study recruited 100 healthy postmenopausal women from a hospital in Egypt. The women received black cohosh extract (40 mg/day) for relief of menopausal symptoms and were followed up for 12 months. Eighty-seven women completed the study, which included evaluation of total hepatic blood flow and liver function. The study sought to investigate potential mechanisms of hepatotoxicity: compromise of blood flow to the liver or a direct toxic effect on liver cells. The following results were obtained after 12 months of treatment:

- No significant changes in hepatic artery blood flow, portal vein blood flow or total hepatic blood flow;
- No significant changes in any liver function tests;
- A significant reduction in the prevalence, daily frequency and severity of hot flushes, compared with baseline.[122]

A meta-analysis of 5 trials involving 1,[117] women found no evidence that the isopropanolic extract of black cohosh has an adverse effect on liver function.[123]

## References


98. Felter HW. *The Eclectic Materia Medica, Pharmacology and Therapeutics*, 1922. Portland, 1983, Reprinted by Eclectic Medical Publications, p 466-469.
99. Dog TL, Powell KL, Weisman SM. *Menopause* 10(4): 299-313, 2003.
100. Huntley A, Ernst E. *Menopause* 10(1): 58-64, 2003.
101. Johnson EB, Muto MC, Yanushpolsky EH et al. *Obstet Gynecol* 98(5 Pt 2): 947-950, 2001.
102. Shuster J. *Hosp Pharm* 31(12): 1553-1554, 1996.
103. Scheinost ME. *J Am Osteopathic Assoc* 101(8): 444-446, 2001.
104. Minciullo PL, Saija A, Patafi M et al. *Phytomedicine* 13(1-2): 115-118, 2006.
105. Meyer S, Vogt T, Obermann EC et al. *Dermatology* 214(1): 94-96, 2007.
106. Ingraffea A, Donohue K, Wilkel C, Falanga V. *J Am Acad Dermatol* 56(5 Suppl): S124-S126, 2007.
107. Zimmermann R, Witte A, Voll RE et al. *Climacteric* 13(2): 187-191, 2010.
108. Whiting, PW, Clouston A, Kerlin P. *MJA* 177(8): 440-443, 2002.
109. Mills S, Bone K: *The Essential Guide to Herbal Safety*, USA, 2005, Churchill Livingstone. p. 581-584.
110. Lontos S, Jones RM, Angus PW et al. *MJA* 179(7): 390-391, 2003.
111. Pishvaian AC, Trope BW, Lewis JH. *Curr Opin Gastroenterol*, 20(3): 208-219, 2004.
112. Bowden D, Moaven LD, Locarnini S. *MJA* (164): 87-89, 1996.
113. Waar K, Herremans M, Vennema H. *J Clin Virol* 33(2): 145-149, 2005.
114. Bardella M, Vecchi M, Conte D. *Hepatology* 29(3): 654-657, 1999.
115. Tordjmann T, Grimbert S, Genestie C. *Gastroenterol Clin Biol* 22(3): 305-310, 1998.
116. Gaya D, Thorburn D, Oien K. *J Clin Pathol* 56(11): 850-853, 2003.

117. Hoofnagle J, Carithers R, Shapiro C. *Hepatology* (21): 240-252, 1995.
118. Teschke R, Bahre R, Genthner A et al. *Maturitas* 63(4): 302-314, 2009.
119. Teschke R. *Menopause* 17(2): 426-440, 2010.
120. Teschke R, Schwarzenboeck A, Schmidt-Taenzer W et al. *Ann Hepatol* 10(3): 249-259, 2011.
121. *Black cohosh products and liver toxicity*: update. 2010, Canadian Adverse Reaction Newsletter. p. 1-2.
122. Nasr A, Nafeh H. *Fertil Steril* 92(5): 1780-1782, 2009.
123. Naser B, Schnitker J, Minkin MJ et al. *Menopause* 18(4): 366-375, 2011.