

## Suspected hepatotoxicity by *Cimicifugae racemosae rhizoma* (black cohosh, root): Critical analysis and structured causality assessment

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### Abstract

Severe hepatotoxicity has been described as spontaneous or case reports in 42 patients in assumed causal relationship with the treatment by *Cimicifugae racemosae rhizoma* corresponding to the root of black cohosh (BC) for postmenopausal symptoms. However, an assessment by EMEA (European Medicines Agency) has shown a possible or probable causality in only 4 out of 42 patients. A diagnostic algorithm was now applied in the 4 patients with suspected BC hepatotoxicity, which included the qualitative and quantitative causality assessment of the updated system of the Council for International Organizations of Medical Sciences (CIOMS), allowing the study to objectively assess, score and scale the probability in each case. Due to incomplete data, the case of 1 patient was not assessable. In the remaining 3 patients, a severe course of liver disease was apparent, and steroid therapy was initiated under the provisional diagnosis of drug-induced hepatic injury. The analysis shows, however, that the observed liver diseases were unrelated to drugs. Only 1 patient had a favourable course under continued steroid therapy, and the final diagnosis was autoimmune hepatitis. The 2 other patients required liver transplantation under the final diagnosis of herpetic hepatitis established now. Quantitative evaluation showed no causality for BC in all 3 patients regarding the observed severe liver disease. Using a thorough causality assessment in the form of a diagnostic algorithm we have shown that there is no evidence for a causal relationship between treatment by black cohosh and the observed liver disease in the 4 patients.

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**Keywords:** Hepatotoxicity; *Cimicifugae racemosae* rhizome; Black cohosh; Menopause

### Introduction

Idiosyncratic hepatotoxicity is a rare feature of drug therapy, and its diagnosis is challenging due to the lack of a specific aid (Navarro and Senior, 2006; Watkins and Seeff, 2006). It is therefore essential that differential diagnoses are thoroughly considered to confidently exclude other diseases unrelated to drug-induced liver

injury (DILI). In a routine setting this is commonly achieved by the use of a combination of serologic tests, imaging studies, and clues from the patient's history (Watkins and Seeff, 2006; Bénichou, 1990; Danan and Bénichou, 1993; Bénichou et al., 1993). A diagnostic work-up is necessary in view of possible misdiagnoses in patients with a primarily suspected but later on not a confirmed and established diagnosis of DILI (Bénichou et al., 1993).

There are currently no validated animal models for studying idiosyncratic DILI, and humans as a group are not appropriate subjects for study since they are only

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occasionally susceptible to the toxicity (Navarro and Senior, 2006). Therefore, the best approach to define characteristics of idiosyncratic DILI is the assessment of patients who have already experienced the phenomenon of DILI with confirmation by a positive re-exposure (Bénichou, 1990; Danan and Bénichou, 1993; Bénichou et al., 1993). With this group of patients various characteristics of the natural course, including liver function tests, were established, leading to a structured causality assessment.

In addition to drugs, anecdotal, spontaneous and case reports have suggested that dietary supplements including botanicals may cause toxic liver disease, but causality was mostly based on circumstantial evidence and temporal association (Willett et al., 2004; Adachi et al., 2003; Estes et al., 2003; Durazo et al., 2004; Teschke et al., 2003). The shortcomings of most of these reports include difficulties regarding the assessment of co-medication with drugs and dietary supplements (DDS) and inaccuracies regarding the treatment duration, dose, natural course of the liver function tests and exclusion of unrelated diseases. Under these conditions a solid diagnosis is rarely achieved in what is a potentially life-threatening disease.

Recently, EMEA (European Medicines Agency) has proposed a causal relationship for acute liver disease observed in a total of 4 patients under treatment with *Cimicifugae racemosae rhizoma* corresponding to the root of black cohosh (BC) for postmenopausal symptoms (EMEA, 2006; Cohen et al., 2004; Levitsky et al., 2005; Lynch et al., 2006). In other primarily suspected cases there was insufficient documentation in 26 patients, unrelated causality in 5 patients and an unlikely one in 7 patients (EMEA, 2006).

The present report analyses the cases of 4 female patients with assumed hepatotoxicity by the root of black cohosh (BC) (EMEA, 2006), based on 3 published case reports (Cohen et al., 2004; Levitsky et al., 2005; Lynch et al., 2006) and a spontaneous one submitted to a national regulatory agency referred to previously (EMEA, 2006). A diagnostic algorithm including a structured causality assessment was used considering all drugs and dietary supplements (DDS) taken by the individual patients.

## Patients and methods

### Patients

Details regarding the clinical course, medication including co-medicated drugs (CD), and diagnostic work-up have been derived from various sources for each of the 4 cases: patient 1 (Cohen et al., 2004; O'Connor et al., 2003; Cohen, 2004a), patient 2 (Levitsky et al., 2005; Strom, 2006), patient 3 (Lynch et al., 2006; Cohen, 2004b), and patient 4 (EMEA, 2006).

### Causality assessment

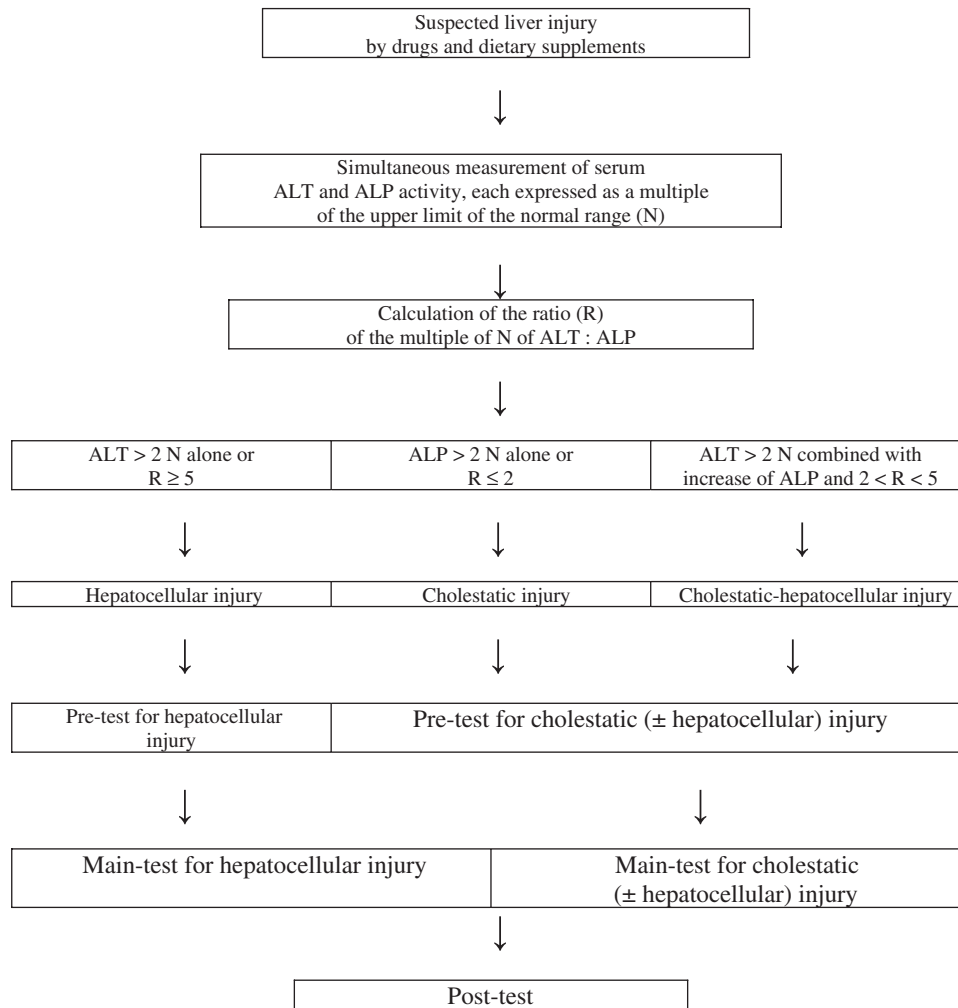
This was achieved for each case and for all used DDS by both clinical evaluation as well as a structured qualitative and quantitative causality assessment originally established as score by CIOMS (Council for International Organizations of Medical Sciences) (Bénichou, 1990; Danan and Bénichou, 1993; Bénichou et al., 1993). For the present evaluation, a slightly modified score was used as some updates regarding precision and diagnostic procedures were necessary. The causality assessment proceeds via an algorithm with 3 steps, the pre-test, main-test, and post-test. Prerequisite is the determination of the particular type of toxic liver disease by means of laboratory tests (ALT, ALP). Differentiation is thereby achieved regarding hepatocellular and cholestatic ( $\pm$  hepatocellular) injury (Fig. 1). Since all 4 patients experienced a hepatocellular injury, the following pre-test and main-test for this entity will be used. The post-test is identical for both the hepatocellular and the cholestatic ( $\pm$  hepatocellular) injury.

### Pre-test

The first step of the structured causality algorithm in toxic liver disease by DDS is a qualitative oriented pre-test which serves to clarify, with a minimum of questions, if causality is unrelated or not assessable. The items of the pre-test are based on qualitative criteria described in the qualitative CIOMS (Bénichou, 1990) and the CIOMS (Danan and Bénichou, 1993; Bénichou et al., 1993). Each DDS has to be assessed separately.

### Main-test

The main-test should be used in the second step. Each individual DDS has to be evaluated by itself. The question regarding actual measurements of DDS constituents or their metabolites in the plasma and the urine should be answered in advance, since it may facilitate causality assessment. The main-test corresponds otherwise to the well-validated assessment scores of CIOMS (Danan and Bénichou, 1993) with various modifications for reasons of precision and actualisation. In the main-test there are no more qualitative items as in the CIOMS scores (Danan and Bénichou, 1993), all of which have been transferred to the pre-test administered before. In the main-test actualisation for the exclusion of hepatitis B and C was achieved by the inclusion of HBV-DNA and HCV-RNA determination. Similarly, the use of color Doppler sonography for the assessment of hepatic vessels was added. For the exclusion of EBV, CMV, HSV, and VZV infection, the determination of PCR as well as IgM and IgG antibodies with titer changes in the further course is required to maintain precision. All



**Fig. 1.** Diagnostic algorithm for the diagnosis of liver injury by drugs and dietary supplements.

other items of the CIOMS scale (Danan and Bénichou, 1993) have been incorporated in the main-test, making a new validation unnecessary. Some items such as risk factors of advanced age, alcohol consumption, and pregnancy might be open for minor discussion, but alternatives were not convincingly presented (Zimmerman, 1999; Kaplowitz, 2001). The validation of the CIOMS scale includes a sensitivity of 86%, a specificity of 89%, a positive predictive value of 93%, and a negative predictive value of 78% (Bénichou et al., 1993).

The respective answers may be scored quantitatively with points ranging from  $-3$  to  $+3$ , with total number of score showing the grade of causality as follows:  $<0$  points, causality excluded;  $1-2$  points, unlikely;  $3-5$  points, possible;  $6-8$  points, probable;  $>8$  points, highly probable (Danan and Bénichou, 1993).

### Post-test

The post-test as the third diagnostic step evaluates other hepatic and extra-hepatic diseases which are rare

and not necessarily considered previously in the main-test. This approach is essential under circumstances diagnosis has been unclear at this point and progression to acute liver failure (ALF) may occur. The post-test is qualitative and requires an answer of either yes or no.

### Results

The overview of the pertinent characteristics of all 4 cases shows that little if any is declared concerning the brand name of the BC product, its ingredients (other than BC), its manufacturer, the plant part used, and the solvent (Table 1). There are also open questions regarding dosage and possible overdoses. Moreover, the data of some of the patients have been reported in different publications, yielding partially conflicting statements for the same patient.

The key element for the following causality assessment by both the pre-test (Tables 2 and 3) and the main-test (Tables 4 and 5) is the information regarding the

**Table 1.** Clinical data of all 4 patients with primarily suspected hepatotoxicity by black cohosh (BC)

Characteristics	Case 1	Case 2	Case 3	Case 4
Age (years)	57	50	54	n.a.
Reported herb	BC tablets	BC root	BC product	n.a.
Manufacturer	n.a.	Pharmavite/ Nutraceutical Corp.	n.a.	n.a.
Plant part	n.a.	Root	n.a.	n.a.
Solvent	n.a.	n.a.	n.a.	n.a.
Daily dose	n.a.	500 mg	1000 mg	80 mg
Duration of therapy	3 weeks	5 months	3 or 8 months	n.a.
Co-medication	Labetolol, fosinopril, verapamil, metformin, insulin, aspirin, and aminosalicylic acid	Valaciclovir, pseudo- ephedrine, and ibuprofen	Fluoxetine, propoxyphene, acetaminophen, and levothyroxine	n.a.
Co-morbidity	Polymyositis, diabetes mellitus, arterial hypertension, and obstructive sleep apnoea	n.a., but substantiated as evidenced by listed co-medication	Fibromyalgia, osteoarthritis, depression, and hypothyroidism	n.a.
Provisional diagnosis	Drug induced autoimmune hepatitis, most likely due to BC	Autoimmune hepatitis, fulminant liver failure due to BC	Autoimmune hepatitis, fulminant liver failure associated with BC	Liver disease caused by BC
Outcome	Good	Liver transplantation, recovered	Liver transplantation, died	Good
Final diagnosis of this analysis	Liver disease unrelated to BC or CD, autoimmune hepatitis	Liver disease unrelated to BC or CD, herpetic hepatitis	Liver disease unrelated to BC or CD, herpetic hepatitis	Liver disease unrelated to BC or CD, not further assessable

BC denotes black cohosh, CD co-medicated drugs, n.a. not assessable.

accurate natural course of the ALT decrease following cessation of DDS therapy. When the respective data are lacking, problems emerge for the causality assessment. Under these conditions, some items are not assessable in the pre-test (Tables 2 and 3) and yield no point for item 2 in the main-test and indicate 0 points for item 3 due to missing information regarding the natural course of ALT (Tables 4 and 5). Each co-medicated drug was evaluated separately for the pre-test and main-test, and only the drug with the highest score was included in the subsequent assessment. Hence, a subtle analysis of each case is essential for causality assessment, supported also by the post-test (Table 6).

### Case 1

The 57-year-old female patient suffered from multi-morbidity including polymyositis (Cohen et al., 2004), diabetes mellitus, hypertension (Cohen et al., 2004; O'Connor et al., 2003; Cohen, 2004a), as well as obstructive sleep apnoea (EMEA, 2006; Cohen et al., 2004). Long-term medication for more than 2 years comprised labetalol, fosinopril, verapamil, metformin, insulin (Cohen et al., 2004; O'Connor et al., 2003; Cohen, 2004a), aspirin (Cohen et al., 2004; O'Connor

et al., 2003), and aminosalicylic acid (ASA) (Cohen, 2004a). With the exception of insulin, all mentioned drugs are known to be potentially hepatotoxic (Zimmerman, 1999). Three weeks before presentation she started with BC treatment, and liver-associated symptoms were noticed after only 1 week of treatment (Cohen et al., 2004). BC treatment was discontinued, and a tapering steroid course was instituted, since drug-induced autoimmune hepatitis, most likely due to BC, was suspected. Resolution of the abnormal liver function tests occurred within 9 weeks, and follow-up liver chemistries remained normal 2 months after steroid discontinuation. At 4 months the liver disease recurred with rapid improvement by a second course of steroids and long-term azathioprine.

The case report was published (Cohen et al., 2004) and subsequently discussed by experts at a workshop on the safety of black cohosh in clinical studies organized by the National Institutes of Health (Cohen, 2004a). The discussion of this case revealed that there is no certainty that the product taken by this patient included only BC or any BC. The patient recalled seeing the words “black cohosh” on the bottle but could not remember any details about the label or the bottle, which she had discarded. Participants noted problems ascertaining precisely what product or material was

**Table 2.** Pre-test for hepatocellular and cholestatic ( $\pm$  hepatocellular) injury

Hepatocellular injury	Patient		Cholestatic ( $\pm$ hepatocellular) injury	Patient	
	Yes	No		Yes	No
<i>I. Causality unrelated</i>					
1. Reaction occurred before starting the drug	<input type="checkbox"/>	<input type="checkbox"/>	1. Reaction occurred before starting the drug	<input type="checkbox"/>	<input type="checkbox"/>
2. Reaction occurred more than 15 days after stopping the drug (except for slowly metabolised drugs)	<input type="checkbox"/>	<input type="checkbox"/>	2. Reaction occurred more than 30 days after stopping the drug (except for slowly metabolised drugs)	<input type="checkbox"/>	<input type="checkbox"/>
3. Non-drug cause highly probable	<input type="checkbox"/>	<input type="checkbox"/>	3. Non-drug cause highly probable	<input type="checkbox"/>	<input type="checkbox"/>
4. Decrease of ALT $<50\%$ after the 30th day of drug discontinuation	<input type="checkbox"/>	<input type="checkbox"/>			
5. Recurrent increase of ALT during drug discontinuation	<input type="checkbox"/>	<input type="checkbox"/>			
<i>II. Causality not assessable</i>					
1. No information to calculate time to onset	<input type="checkbox"/>	<input type="checkbox"/>	1. No information to calculate time to onset	<input type="checkbox"/>	<input type="checkbox"/>
2. No information about the course of ALT	<input type="checkbox"/>	<input type="checkbox"/>	2. No information about the course of ALP	<input type="checkbox"/>	<input type="checkbox"/>
3. Continued drug therapy	<input type="checkbox"/>	<input type="checkbox"/>	3. Continued drug therapy	<input type="checkbox"/>	<input type="checkbox"/>
4. Decrease of ALT $\geq 50\%$ after the 30th day of drug discontinuation	<input type="checkbox"/>	<input type="checkbox"/>	4. Persistence or increase of ALP after drug discontinuation	<input type="checkbox"/>	<input type="checkbox"/>

When at least one question is answered with yes, causality is unrelated or not assessable, respectively. The pre-test and the main-test evaluate the hepatocellular injury separately from the cholestatic ( $\pm$  hepatocellular) one.

ALT denotes alanine aminotransferase, ALP alkaline phosphatase. The term drug refers to any chemically defined drug or dietary supplement.

**Table 3.** Pre-test for cases 1–4 with hepatocellular injury

Hepatocellular injury	Case 1		Case 2		Case 3		Case 4	
	BC	CD	BC	CD	BC	CD	BC	CD
<i>I. Causality unrelated</i>								
Q 1	No	No	No	No	n.a.	n.a.	n.a.	n.a.
Q 2	No	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Q 3	Yes	Yes	Yes	Yes	Yes	Yes	n.a.	n.a.
Q 4	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Q 5	Yes	Yes	n.a.	n.a.	Yes	n.a.	n.a.	n.a.
<i>II. Causality not assessable</i>								
Q 1	No	No	No	Yes	No	n.a.	n.a.	n.a.
Q 2	Yes	Yes	Yes	Yes	Yes	n.a.	n.a.	n.a.
Q 3	No	Yes	Yes	Yes	No	Yes	n.a.	n.a.
Q 4	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.

BC denotes black cohosh, CD co-medicated drugs, Q questions as outlined in Table 2, n.a. not assessable.

taken in case reports and the importance of this step before an assignment of association can be properly made. It was also stressed that the lack of authentication of material poses significant difficulties in the interpretation of case reports.

Retrospectively, the diagnosis of autoimmune hepatitis possibly being caused or triggered by BC is open for discussion. Drugs associated with this form of liver disease have commonly been taken for long periods of time and continued long after hepatic injury has begun (Zimmerman, 1999), conditions not applicable to the present case. Moreover, failure of the autoimmune hepatitis to return after steroid withdrawal would

support the interference that the initially suspected drug was the cause (Zimmerman, 1999), a situation not described for the present patient. It appears, therefore, that the autoimmune hepatitis may not have been caused or triggered by BC.

In contrast to BC, treatments with the other medications were long standing and have obviously not been discontinued at the first presentation and on follow up, raising the question whether autoimmune hepatitis might have been caused or triggered by one of these drugs. The hepatotoxic potency of labetalol, fosinopril, verapamil, metformin, aminosalicic acid, or aspirin is well established, but none of these drugs has

**Table 4.** Main-test for hepatocellular and cholestatic ( $\pm$  hepatocellular) injury

Hepatocellular injury	Score	Patient	Cholestatic ( $\pm$ hepatocellular) injury	Score	Patient
<i>1. Time to onset from the beginning of the drug</i>			<i>1. Time to onset from the beginning of the drug</i>		
● 5–90 days (rechallenge: 1–15 days)	+2	–	● 5–90 days (rechallenge: 1–90 days)	+2	–
● <5 or >90 days (rechallenge: >15 days)	+1	–	● <5 or >90 days (rechallenge: >90 days)	+1	–
<i>2. Time to onset from cessation of the drug</i>			<i>2. Time to onset from cessation of the drug</i>		
● $\leq 15$ days (except for slowly metabolized drugs: >15 days)	+1	–	● $\leq 30$ days (except for slowly metabolized drugs: >30 days)	+1	–
<i>3. Course of ALT after cessation of the drug</i>			<i>3. Course of ALP after cessation of the drug</i>		
Difference between peak of ALT and upper limit of normal range			Difference between peak of ALP and upper limit of normal range		
● Decrease $\geq 50\%$ within 8 days	+3	–	● Decrease $\geq 50\%$ within 180 days	+2	–
● Decrease $\geq 50\%$ within 30 days	+2	–	● Decrease <50% within 180 days	+1	–
● No information	0	–	● Persistence, increase or no information	0	–
● Decrease $\geq 50\%$ after the 30 <sup>th</sup> day	0	–			
● Decrease <50% after the 30 <sup>th</sup> day or recurrent increase	–2	–			
<i>4. Risk factor ethanol</i>			<i>4. Risk factor ethanol or pregnancy</i>		
● Yes	+1	–	● Yes	+1	–
● No	0	–	● No	0	–
<i>5. Risk factor age</i>			<i>5. Risk factor age</i>		
● $\geq 55$ years	+1	–	● $\geq 55$ years	+1	–
● <55 years	0	–	● <55 years	0	–
<i>6. Concomitant drug(s)</i>			<i>6. Concomitant drug(s)</i>		
● None or no information	0	–	● None or no information	0	–
● Concomitant drug with incompatible time to onset	0	–	● Concomitant drug with incompatible time to onset	0	–
● Concomitant drug with compatible or suggestive time to onset	–1	–	● Concomitant drug with compatible or suggestive time to onset	–1	–
● Concomitant drug known as hepatotoxin and with compatible or suggestive time to onset	–2	–	● Concomitant drug known as hepatotoxin and with compatible or suggestive time to onset	–2	–
● Concomitant drug with evidence for its role in this case (positive rechallenge or validated test)	–3	–	● Concomitant drug with evidence for its role in this case (positive rechallenge or validated test)	–3	–
<i>7. Search for non drug causes</i>			<i>7. Search for non drug causes</i>		
<i>Group I (6 causes)</i>			<i>Group I (6 causes)</i>		
● Anti-HAV-IgM			● Anti-HAV-IgM		
● Anti-HBc-IgM/HBV-DNA			● Anti-HBc-IgM/HBV-DNA		
● Anti-HCV-IgM/HCV-RNA			● Anti-HCV-IgM/HCV-RNA		
● Hepatobiliary sonography/color Doppler sonography of liver vessels			● Hepatobiliary sonography/color Doppler sonography of liver vessels		
● Alcoholism (AST/ALT $\geq 2$ )			● Alcoholism (AST/ALT $\geq 2$ )		
● Acute recent hypotension history (particularly if underlying heart disease)			● Acute recent hypotension history (particularly if underlying heart disease)		
<i>Group II</i>			<i>Group II</i>		
● Complications of underlying disease(s)			● Complications of underlying disease(s)		
● Infection suggested by PCR and titer change for CMV (anti-CMV-IgM/IgG), EBV (anti-EBV-IgM/IgG), HSV (anti-HSV-IgM / IgG), VZV (anti-VZV-IgM/IgG)			● Infection suggested by PCR and titer change for CMV (anti-CMV-IgM/IgG), EBV (anti-EBV-IgM/IgG), HSV (anti-HSV-IgM/IgG), VZV (anti-VZV-IgM/IgG)		
<i>Evaluation of group I and II</i>			<i>Evaluation of group I and II</i>		
● All causes-groups I and II – reasonably ruled out	+2	–	● All causes-groups I and II – reasonably ruled out	+2	–

**Table 4.** (continued)

Hepatocellular injury	Score	Patient	Cholestatic ( $\pm$ hepatocellular) injury	Score	Patient
● The 6 causes of group I ruled out	+1	–	● The 6 causes of group I ruled out	+1	–
● 5 or 4 causes of group I ruled out	0	–	● 5 or 4 causes of group I ruled out	0	–
● Less than 4 causes of group I ruled out	–2	–	● Less than 4 causes of group I ruled out	–2	–
● Non drug cause highly probable	–3	–	● Non drug cause highly probable	–3	–
8. Previous information on hepatotoxicity of the drug			8. Previous information on hepatotoxicity of the drug		
● Reaction labelled in the product characteristics	+2	–	● Reaction labelled in the product characteristics	+2	–
● Reaction published but unlabelled	+1	–	● Reaction published but unlabelled	+1	–
● Reaction unknown	0	–	● Reaction unknown	0	–
9. Response to readministration			9. Response to readministration		
● Doubling of ALT with the drug alone	+3	–	● Doubling of ALP with the drug alone	+3	–
● Doubling of ALT with the drugs already given at the time of 1 st reaction	+2	–	● Doubling of ALP with the drugs already given at the time of 1 st reaction	+2	–
● Increase of ALT but less than N in the same conditions as for the first administration	+1	–	● Increase of ALP but less than N in the same conditions as for the first administration	+1	–
● Other situation	0	–	● Other situation	0	–
Total points			Total points		

Total points/causality:  $\leq 0$  = excluded, 1–2 = unlikely; 3–5 = possible; 6–8 = probable;  $> 8$  = highly probable.

ALT denotes alanine aminotransferase, ALP alkaline phosphatase, AST aspartate aminotransferase, HAV hepatitis A virus, HbC hepatitis B core, HBV hepatitis B virus, HCV hepatitis C virus, CMV cytomegalovirus, EBV Epstein Barr virus, HSV herpes simplex virus, VZV varicella zoster virus. The term drug refers to any chemically defined drug or dietary supplement.

**Table 5.** Main-test for cases 1–4 with hepatocellular injury

Hepatocellular injury	Case 1		Case 2		Case 3		Case 4	
	BC	CD	BC	CD	BC	CD	BC	CD
Q 1	+2	+1	+1	+1	+1	+1	n.a.	n.a.
Q 2	+1	n.a.	n.a.	n.a.	+1	n.a.	n.a.	n.a.
Q 3	–2	0	0	0	–2	0	0	0
Q 4	0	0	+1	+1	+1	+1	n.a.	n.a.
Q 5	+1	+1	0	0	0	0	n.a.	n.a.
Q 6	–2	–1	–2	–1	–2	–1	0	0
Q 7	–3	–3	–3	–3	–3	–3	–2	–2
Q 8	+1	+2	+1	+2	+1	+2	+1	0
Q 9	0	0	0	0	0	0	0	0
Total points	–2	0	–2	0	–3	0	–1	–2
Causality	Excluded	Excluded	Excluded	Excluded	Excluded	Excluded	Excluded	Excluded

BC denotes black cohosh, CD co-medicated drugs, Q questions as outlined in Table 4, n.a. not assessable.

previously been shown to cause autoimmune hepatitis (Zimmerman, 1999), a situation to be considered in the present case.

The presentation of laboratory tests was complete, except that the usual exclusion of EBV, CMV, and HSV has not been done. In the present case, ANA was positive, and the liver histology showed changes

compatible with autoimmune hepatitis (Cohen et al., 2004). The patient was multimorbid with diabetes mellitus, hypertension, and obstructive sleep apnoea (Table 1) and had also a polymyositis, another autoimmune disease. The combination of two or more autoimmune entities is a well-known clinical phenomenon, commonly described as poly-autoimmune syndrome

**Table 6.** Post-test for hepatocellular and cholestatic ( $\pm$  hepatocellular) injury

Differential diagnosis exclusion	Diagnostic evaluation/symptoms	Patient
1. Autoimmune hepatitis (AIH) Typ I	Gamma globulins, ANA, SMA, AAA, SLA/LP, anti-LSP, anti-ASGPR	Yes/no
2. Autoimmune hepatitis (AIH) Typ II	Gamma globulins, anti-LKM-1 (CYP 2D6), anti-LKM-2 (CYP 2C9), anti-LKM-3	Yes/no
3. Primary biliary cirrhosis (PBC)	AMA, anti PDH-E2	Yes/no
4. Primary sclerosing cholangitis (PSC)	p-ANCA, MRC, ERCP	Yes/no
5. Autoimmune cholangitis (AIC)	ANA, SMA	Yes/no
6. Overlap syndromes	See 1–5	Yes/no
7. Wilson's disease	Copper excretion (24 h urine), ceruloplasmin in serum, free copper in serum, Coombs-negative hemolytic anemia, hepatic copper content, Kayser-Fleischer-ring, neurologic-psychiatric diagnostic, genotyping	Yes/no
8. Hereditary hemochromatosis	Serum ferritin, total iron-binding capacity, genotyping for C2824 and H63D mutation, hepatic iron content	Yes/no
9. Porphyria	Porphobilinogen in urine, total porphyrines in urine	Yes/no
10. $\alpha_1$ – Antitrypsin deficiency	$\alpha_1$ – Antitrypsin in serum	Yes/no
11. Non-alcoholic steatohepatitis (NASH)	Adipositas, insulin resistance, hepatomegaly, echogenicity of the liver	Yes/no
12. Toxic liver diseases	Toxicological assessment by occupational and household toxins	Yes/no
13. Hepatitis E	Anti-HEV-IgM, anti-HEV-IgG, HEV-RNA	Yes/no
14. Other viral infections Adenovirus, Cocksackie-B-Virus, Echovirus, Measlesvirus, Rubellavirus, Flavivirus, Arenavirus, Filovirus, Parvovirus, HIV	Specific serology	Yes/no
15. Additional infectious diseases Bacteria, parasites, worms, mycosis	Specific assessment	Yes/no
16. Systemic diseases M. Boeck, amyloidosis Lymphoma and other malignant tumors, sepsis	Specific assessment	Yes/no
17. Celiac disease	TTG antibodies, endomysium antibodies, duodenal biopsy	Yes/no
18. Addison's disease	Plasma cortisol, ACTH	Yes/no
19. Thyroid diseases	TSH basal, freeT <sub>4</sub> , freeT <sub>3</sub>	Yes/no
20. Heat stroke	Shock, hyperthermia	Yes/no
21. Grand mal seizures	Status epilepticus (duration > 30 min)	Yes/no
22. Rare intoxications	Toxin screening	Yes/no
23. Cocain, ecstasy and other amphetamines Anorexia nervosa	Toxin screening Clinical context	Yes/no Yes/no
25. Cardiopulmonary diseases Congestive heart disease, myocardial infarction, cardiomyopathy, cardiac valvular dysfunction, pulmonary embolism, pericardial diseases, arrhythmia by hemorrhagic shock	Cardiopulmonary assessment	Yes/no
26. Other diseases	Clinical context	Yes/no

ANA denotes antinuclear antibodies, SMA smooth muscle antibodies, AAA anti-actin antibodies, SLA soluble liver antigen, LP liver-pancreas antigen, LSP liver specific protein, ASGPR asialo-glycoprotein-receptor, LKM liver kidney microsomes, CYP cytochrome P450, AMA antimitochondrial antibodies, PDH pyruvate dehydrogenase, p-ANCA perinuclear antineutrophil cytoplasmic antibodies, MRC magnetic resonance cholangiography, HEV hepatitis E virus, HIV human immunodeficiency virus, TTG tissue transglutaminase, TSH thyroid stimulating hormone.

and applicable to the present case with polymyositis and autoimmune hepatitis.

The pre-test for BC and co-medicated drugs showed an unrelated causality, since a non-drug cause (autoimmune hepatitis) is highly probable (Tables 2, 3, and 7) and a recurrent increase of ALT during discontinuation of BC and steroids was observed (Cohen et al., 2004).

Moreover, causality is partly not assessable for BC since the values of ALT represent the effect of steroid treatment for autoimmune hepatitis. The pre-test is also not evaluable for the co-medicated drugs since treatment has not been discontinued.

Using the main-test causality for BC was excluded with  $-2$  points (Tables 4, 5, and 7). The low score was

**Table 7.** Summary of causality assessments for cases 1–4

Hepatocellular injury	Case 1		Case 2		Case 3		Case 4	
	BC	CD	BC	CD	BC	CD	BC	CD
Pre-test I causality	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.a.	n.a.
Pre-test II causality	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Main-test								
Total points	–2	0	–2	0	–3	0	n.a.	n.a.
Causality	Excluded	Excluded	Excluded	Excluded	Excluded	Excluded	n.a.	n.a.
EMEA								
Total points	+7	n.a.	+6	n.a.	+3	n.a.	+4	n.a.
Causality	Probable	n.a.	Probable	n.a.	Possible	n.a.	Possible	n.a.

BC denotes black cohosh, CD co-medicated drugs, n.r. not related, n.a. not assessable. The data for the pre-tests are derived from Tables 2 and 3, for the main-test from Tables 4 and 5, and for EMEA (European Medicines Agency) from reference 11.

partially due to the recurrent increase of ALT during discontinuation of BC and steroids (Cohen et al., 2004). For the main-test regarding the co-medicated drugs there was no information of the course of ALT, since cessation of the drugs was not documented and obviously not initiated. The score reached a total of 0 points (Tables 4 and 5), corresponding to an excluded causality (Table 7). According to the reported data (Cohen et al., 2004; O'Connor et al., 2003; Cohen, 2004a) only a few differential diagnosis of the post-test have been ruled out (Table 6).

EMEA (European Medicines Agency) classified BC with +6 points and a probable causality (Table 7) (EMEA, 2006). There was no mention or causality assessment of the co-medicated drugs with the exemption of verapamil, which was described and denoted as possible allergic hepatotoxic. A causality was denied on the basis that this particular drug was administered over a period of 2 years before the onset of reaction.

Taken together, the patient had an autoimmune hepatitis responsive to steroid treatment, recurring after steroid cessation and responding again upon treatment. The observed liver disease was causally unrelated to both BC and CD.

## Case 2

The patient, a 50-year-old woman, took BC root, 500 mg daily, for 5 months prior to the presentation with clinical signs of liver disease. In the case report both alcohol consumption and co-medication were denied (Levitsky et al., 2005). In particular, it was stated that she used no illicit drugs and no medications including herbal medications, acetaminophen, or non-steroidal anti-inflammatory drugs. Later, however, alcohol consumption on a regular basis was admitted, and co-medication was documented (Strom, 2006). The co-

medication taken suggests major co-morbidity. In particular, she was using, or had used, medications that are known or potential hepatotoxins. She had taken erythromycin for 2.5 years ending just 4 months before her liver transplant. She also took such large doses of ibuprofen in the 1990s that she developed anemia. The patient was presently taking valaciclovir, pseudo-ephedrine, and ibuprofen at the time of her liver transplant (Strom, 2006), but the duration of this therapy is not documented. On these and other grounds it was stated that there was no evidence to establish either general or specific causation regarding BC as cause for the liver disease (Strom, 2006).

The patient was put on steroid treatment for the initial diagnosis of autoimmune hepatitis and not for the diagnosis of BC-induced autoimmune hepatitis, which was obviously considered only later (Levitsky et al., 2005). Consecutively, the coagulopathy worsened and encephalopathy developed. Five weeks after initial presentation the patient underwent successful orthotopic liver transplantation. She was discharged 1 week after an uneventful postoperative course of treatment.

The patient has taken drugs previously as well as at the time of her liver transplant (Strom, 2006). Potentially hepatotoxic drugs such as valaciclovir and ibuprofen had obviously not been discontinued up to her liver transplant, raising the question whether one of these drugs may have caused severe hepatotoxicity and subsequent acute liver failure. It is also not documented that BC treatment has been stopped at first presentation or some time before liver transplantation (Levitsky et al., 2005), since BC was not known to the treating physician (Strom, 2006). Of major concern is the reported treatment of the patient with valaciclovir (Strom, 2006), a drug exclusively used for infections by either herpes simplex or herpes zoster. It is highly probable that the patient has had an infection by herpes simplex or zoster and experienced a herpetic liver

disease. There is thus little, if any evidence for a causal relationship between BC and the observed acute liver disease when all clinical aspects are considered.

In the pre-test for BC, causality is unrelated since a non-drug cause (herpetic hepatitis) is highly probable. Data related to the ALT course cannot be evaluated (Tables 2, 3, and 7), since BC treatment has not been discontinued (Levitsky et al., 2005). The pre-test for co-medicated drugs is not applicable since treatment was not stopped (Tables 2, 3, and 7).

The main-test for BC (Tables 4, 5, and 7) is rarely applicable since discontinuation of BC treatment is not documented (Levitsky et al., 2005; Strom, 2006). Similarly, co-medication was taken up to the liver transplantation (Strom, 2006), the main-test is therefore difficult to evaluate (Tables 4, 5, and 7). It was assumed that co-medicated drugs could have been taken for more than 90 days (Table 5). With the post-test (Table 6), some other hepatic diseases have been excluded according to the published laboratory data (Levitsky et al., 2005).

The EMEA classified the case for BC with +6 points, rendering a probable causality (Table 7) (EMEA, 2006). Causality for co-medicated drugs was not assessed, since the respective data have only been documented later (Strom, 2006) and were not known at the time of the evaluation by EMEA (2006).

It thus appears that the patient experienced a herpetic liver disease treated with valaciclovir. A causative role of BC and CD for the observed liver disease could not be demonstrated by qualitative and quantitative causality assessment.

### Case 3

The patient, a 54-year-old multimorbid female, had a past medical history not only of hypothyroidism (Lynch et al., 2006; Cohen, 2004b) but also of fibromyalgia, osteoarthritis, and depression (Cohen, 2004b). She had taken BC 1000 mg daily for the preceding 3 (Cohen, 2004b) or 8 (Lynch et al., 2006) months which was stopped at first presentation (Cohen, 2004b), a fact not stated in the subsequent case report (Lynch et al., 2006). She also used for an unknown period of time not only levothyroxine (Lynch et al., 2006; Cohen, 2004b) but also fluoxetine, proboxyphen, and paracetamol (Cohen, 2004b), not mentioned in the detailed case report (Lynch et al., 2006). Although discontinuation of BC (and alcohol) was described, this was not the case for co-medicated drugs such as fluoxetine, proboxyphen, and paracetamol (Cohen, 2004b). The initial laboratory data showed grossly elevated liver enzyme levels especially of the aminotransferases (Lynch et al., 2006; Cohen, 2004b). However, levels dropped unexpectedly in a few days (Cohen,

2004b) and then rose again to levels above the initial values (Lynch et al., 2006; Cohen, 2004b). The patient did not respond to subsequent steroids and underwent orthotopic liver transplantation 39 days after admission. She expired in the operation room due to uncontrolled hemorrhage (Lynch et al., 2006; Cohen, 2004b). Anti-HSV-IgM was positive (Cohen, 2004b), suggesting a recent HSV infection with a foudroyant course of herpetic liver disease.

The pre-test for BC (Tables 2, 3, and 7) showed an unrelated causality, since a non-drug cause is highly probable (herpetic liver disease), and there was a drop and recurrent increase of ALT described during BC discontinuation (Cohen, 2004b). The pre-test for co-medicated drugs such as fluoxetine, proboxyphen, and paracetamol can hardly be applied since discontinuation has not been stated (Cohen, 2004b).

The main-test for BC renders, with a total of only –3 points, an excluded causality assuming a treatment of 8 months (Tables 4, 5, and 7). The main-test for the co-medicated drugs fluoxetine, proboxyphen, and paracetamol (Cohen, 2004b) is poorly applicable (Tables 4, 5, and 7) since these drugs have obviously not been discontinued (Cohen, 2004b). Under the assumption that the therapy with these drugs lasted for more than 90 days, a total of 0 points is achieved (Tables 4 and 5), equivalent to an unrelated causality (Table 7). With regard to the post-test (Table 6), only some additional differential diagnosis have been excluded as assessed by the published laboratory data (Lynch et al., 2006; Cohen, 2004b).

The authors of the case report validated the causality regarding BC as probable (+6 points) (Lynch et al., 2006), EMEA suggested a possible causality (+3 points) (EMEA, 2006), and we found that causality is excluded (–3 points) (Table 4). Co-medication was not taken into consideration by both the authors (O'Connor et al., 2003; Cohen, 2004b) and EMEA (2006).

The patient suffered, therefore, most probably from herpetic liver disease, whereas causality was not related to BC and co-medication.

### Case 4

The patient of not declared age used 80 mg BC daily for an unknown period of time (EMEA, 2006). Due to lack of other data (Table 1) (EMEA, 2006), the case is not assessable by the pre-test (Tables 2, 3, and 7) and the main-test (Tables 4, 5, and 7). At best, with the main-test for BC and CD a total of –1 and –2 points are achievable, respectively, provided some co-medication was used (Table 5). The overall causality was not assessable (Table 7). EMEA evaluated for BC a possible causality (+4 points) on the basis of data not presented in detail (Table 7) (EMEA, 2006).

## Discussion

A total of 4 cases with previously suspected hepatotoxicity by *Cimicifugae racemosae rhizoma* corresponding to the root of black cohosh (BC) (EMEA, 2006) were evaluated in the present report regarding causal association (Tables 1–7). The clinical analysis and structured causality assessment reveal that in 1/4 patients (case 4) there was no valid evaluation possible due to lack of basic information. Of the remaining 3 cases, 1 patient had an autoimmune hepatitis unrelated to BC (case 1), and 2 other ones (cases 2 and 3) have had obviously a herpetic liver disease. All 3 patients experienced a severe course of their liver disease, and steroid therapy was initiated under various provisional diagnoses (Table 1) such as drug-induced autoimmune hepatitis, most likely due to BC (case 1), (Cohen et al., 2004; O'Connor et al., 2003; Cohen, 2004a), autoimmune hepatitis and fulminant liver failure due to the use of BC (case 2) (Levitsky et al., 2005; Strom, 2006), and autoimmune hepatitis and fulminant hepatic failure associated with the use of BC (case 3) (Lynch et al., 2006; Cohen, 2004b). Only one patient with the final diagnosis of autoimmune hepatitis (case 1) had a favourable course under continued steroid therapy. The 2 other patients (cases 2 and 3), with the final diagnosis of herpetic hepatitis, required liver transplantation. In all 3 patients there was no convincing evidence that the observed liver diseases might have been caused by BC (Tables 5 and 7).

Interestingly, all 3 patients who could be evaluated had a substantial co-medication with up to 7 additional medications (Table 1) (Cohen et al., 2004; Levitsky et al., 2005; Lynch et al., 2006; O'Connor et al., 2003; Strom, 2006; Cohen, 2004b). Most of the co-medicated drugs (Table 1) are potentially hepatotoxic (Zimmerman, 1999), and clinical studies have shown that the combination of 2 or more potentially hepatotoxic drugs increases substantially the risk regarding hepatotoxicity by a factor of 6 compared to one single drug, which by itself, shows a risk factor of 1.7 to develop acute liver injury (de Abajo et al., 2004). In other studies with botanicals such as kava there was co-medication documented with up to 7 drugs, botanicals, or dietary supplements, a situation which does not facilitate causality assessment (Teschke et al., 2003). Nevertheless, co-medication has not been shown in the present cases to be causally related to the observed liver disease (Tables 5 and 7).

In 38 out of 42 patients, a causal relationship between BC treatment and the development of liver disease could not be established, whereas such a condition was suspected in the remaining 4 patients (EMEA, 2006). Reanalyzing the latter group showed incorrect diagnoses including herpetic liver disease in 2 patients (cases 2 and 3), with the requirement of liver transplantation following treatment with valaciclovir combined with steroids

or with steroids alone (Tables 5 and 7). Fulminant hepatitis by herpes simplex virus (HSV) occurs in previously healthy adults including pregnant women (Luzar et al., 2005; Velasco et al., 1999; Pinna et al., 2002) and is one of a few causes of fulminant hepatic failure for which a potentially effective therapy is available. The patient's life depends on early diagnosis followed by antiviral therapy. Untreated HSV hepatitis is usually fatal. Among 93 reported patients with HSV hepatitis, 63 had no antiviral treatment, most of them died and only 11% survived (Pinna et al., 2002). A similar clinical picture has been described for varicella-zoster virus (VZV) hepatitis with fulminant hepatic failure (Pishvaian et al., 2006). It is therefore necessary to exclude HSV and VZV hepatitis in all patients with unclear liver diseases including those with suspected drug-induced hepatotoxicity. Finally, as long as other forms of viral hepatitis including HSV, VZV, CMV, and EBV are not safely excluded, steroid treatment should not be considered.

There is no evidence that steroids have a benefit in patients with acute drug-induced hepatocellular jaundice with or without fulminant hepatic failure (Zimmerman, 1999). While it was considered reasonable to treat patients with overt evidence of hypersensitivity, such as rash, fever, and eosinophilia, with steroids despite the lack of evidence of benefit, these findings were not reported for the patients of the present study.

A more recent case report appeared describing a 41-year-old female with acute liver failure in assumed causal relationship with the use of black cohosh for menopausal symptoms (Dunbar and Solga, 2007). Liver histology showed, among other features, a giant cell hepatitis which has not yet been described for drug-induced liver disease (Zimmerman, 1999). Differentiation is essential between giant cell hepatitis which is unrelated to drugs, as in the present case report (Dunbar and Solga, 2007), and giant cells within hepatic granulomas which may be drug related (Zimmerman, 1999). Since giant cell hepatitis is not compatible with liver diseases by drugs including black cohosh, other diseases have to be evaluated. Various differential diagnoses have already been considered in the case report, and virtually all important hepatic and infectious diseases with the potency of causing giant cell hepatitis have been ruled out, with the exception of paramyxovirus-like virus and paramyxovirus infection leading to measles (Dunbar and Solga, 2007). The hallmark of this entity is a pronounced giant cell hepatitis with a possible severe clinical course (Phillips et al., 1988, 1991; Fimmel et al., 1998). The histological and clinical pattern of the reported case is consistent with severe liver disease by a virus infection such as measles rather than by black cohosh. Spotted exanthema, fever, and night sweats are common in measles, mimicking similar symptoms of menopause such as hot flushes, night

sweats, and increased core temperature. The conclusion may be reached that, prior to treatment, the patient initially experienced symptoms of some virus infection such as measles but not of menopause, considering also the young age of the 41-year-old female. Under these aspects it appears that the patient had a severe and prolonged course of a virus infection such as measles with giant cell hepatitis and acute liver failure, rather than two different clinical entities of a menopausal syndrome and acute liver failure by black cohosh.

In conclusion, a vigorous causality assessment using a diagnostic algorithm is essential to evaluate the relationship between the observed liver disease and the treatment by DDS, to include black cohosh. Using this approach there was no evidence in the present analysis of the evaluated 4 patients for a causal association between black cohosh and liver injury.

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