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Herb induced liver injury presumably caused by black cohosh: A survey of initially purported cases and herbal quality specifications

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ABSTRACT

Herb induced liver injury (HILI) is a particular challenge that also applies to purported cases presumably caused by black cohosh (BC), an herb commonly used to treat menopausal symptoms. We analyzed and reviewed all published case reports and spontaneous reports of initially alleged BC hepatotoxicity regarding quality of case details and causality assessments. Shortcomings of data quality were more evident in spontaneous reports of regulatory agencies compared to published case reports, but assessments with the scale of CIOMS (Council for the International Organizations of Sciences) or its updated version revealed lack of causality for BC in all cases. The applied causality methods are structured, quantitative, and liver specific with clear preference over an *ad hoc* causality method or the liver unspecific Naranjo scale. Reviewing the case data and the reports dealing with quality specifications of herbal BC products, there is general lack of analysis with respect to authentication of BC in the BC products used by the patients. However, in one single regulatory study, there was a problem of BC authentication in the analysed BC products, and other reports addressed the question of impurities and adulterants in a few BC products. It is concluded that the use of BC may not exert an overt hepatotoxicity risk, but quality problems in a few BC products were evident that require additional regulatory quality specifications.

Key words. Herb induced liver injury. Drug induced liver injury. Hepatotoxicity. Herbal hepatotoxicity. Black cohosh induced liver injury. Black cohosh. Actaea cimicifuga.

INTRODUCTION

Drug-induced liver injury (DILI) is a major challenge for hepatologists, toxicologists, regulatory agencies, health institutes, and manufacturers,[1-4] but this applies even more to cases of herb-induced liver injury (HILI).[4-6] DILI is normally connected with the use of a single and well defined synthetic chemical, which is produced according to the rules of specific manufacturing requirements and may be obtained as a regulatory approved drug in a regulated market as a treatment for a specific disease. However, conditions for herbs and especially herbal mixtures in association with the development of purported HILI are quite different and much more complex.

Recent discussions emerged regarding alleged HILI by black cohosh (BC),[7-13] an herb that is also known as *Actaea cimicifuga* L., syn. *Cimicifuga racemosa* L. used previously. BC has gained world wide popularity as an herbal treatment for menopausal symptoms[14,15] with well established good safety records also with respect to the liver.[16] Critical evaluations focused now not only on the presented cases of HILI presumably induced by BC,[10-12] but also on the quality of the used BC products.[13] Analyses of the cases showed primarily lack or rarity of basic preconditions that are required for sound clinical assessments as well as pharmacovigilance evaluations.[10-12] For cases of supposed HILI by BC, the regulatory pharmacovigilance view clearly pre-

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fers quantity of cases *vs.* quality of case data in connection with causality assessment.[17]

Opposed to this preference, a good clinical assessment with a thorough causality evaluation relies on appropriate data of each individual case, preferring quality *vs.* quantity.[10-12,17,18] Moreover, highly applauded and based on alert regulatory actions, the problem of alleged HILI in connection with the use of BC was further investigated by assessing the quality of the BC products that led to purported HILI in individual affected patients. Unexpectedly, the examined BC products did not contain authentic black cohosh.[13] These conditions create concern regarding validity of causality assignments of the reported HILI cases as well as efficacy, safety, or both in the course of BC treatment.

The present cumulation of clinical and regulatory problems related to BC is challenging and encourages to urgently needed improvements in the area of HILI by BC and other herbs. This review summarizes present key issues of supposed HILI cases in association with assumed BC use and related quality specifications of BC as an herbal product.

CASES OF INITIALLY PURPORTED BC HEPATOTOXICITY

In none of the numerous clinical trials using BC drugs was there any suspicion of adverse reactions related to liver injury.[16,19] In particular, lack of hepatotoxicity by BC was confirmed in a recent metaanalysis of randomized, double blind controlled clinical trials.[16] Despite these studies, some risks remain that rare hepatotoxicity may affect a few susceptible individuals as a consequence of BC used by a larger population.

Case reports have been published with initially presumed liver injury by the use of BC[20-28] and subsequent discussions.[7-11,29-42] Concerns prevailed regarding causation in view of prevailing poor data presentation associated with numerous confounding variables.[10,11,42] Other recent case reports have not been subjected to a further thorough causality assessment due to lack of BC product identification and debated, highly questionable BC use,[17,43] genuine autoimmune hepatitis as primary diagnosis with relapse after discontinuation of BC and immunosuppressive therapy,[44] unusual prolonged dechallenge period for several years, use of a herbal mixture, and unclear temporal association,[17,45] undetermined fluctuating liver values, major comorbidity, and comedication,[17,45] DILI by nonsteroidal and anti-inflammatory drugs,[46,47] and case duplication.[46,47]

Some concern emerged initially when spontaneous reports of primarily purported HILI cases by BC have been evaluated by the EMA (European Medicines Agency), but this uncertainty vanished subsequent to its own pharmacovigilance studies and concomitant causality assessments.[48] EMA suggested a possible causality in only two single cases of spontaneous reports[48] that were later on criticized regarding causality due to various confounding variables and uncertainties.[10,11] Concomitantly, EMA declined a causal relationship of BC in the remaining 34 cases of spontaneous reports on the basis of being unrelated, unlikely, excluded, or not assessable.[48] The overall cases of spontaneous reports analyzed by EMA originated from EU countries (n = 31) and non-EU countries (n = 5);[48] they were of no support for an evident hepatotoxic potency of BC[42,47] and the cautionary warning for BC consumers that was issued by regulatory agencies.[48,49]

Other spontaneous reports of cases with initially purported BC hepatotoxicity from Canada, Australia, and the US have emerged, but causality for BC had to be declined using a thorough analytical approach,[12] similar to the one applied by EMA for its spontaneous BC cases.[48] The cases have primarily been collected by the USP (United States Pharmacopeia),[49] but there are possibly rare case duplications with non EU cases already presented by EMA.[48] A total of 22 spontaneous cases had to be analyzed, and upon initial assessment USP attributed a uniform possible causality for BC to all cases, not considering an excluded, unlikely, probable or highly probable causality in any of these cases.[49] This uniform grading of a possible causality was facilitated by the use of the Naranjo scale that allows such a low level of causation under practically any circumstances.[12] Although with a possible causality already low graded,[49] these cases have been a matter of major discussions,[12,42,47] with the result that the possible causality level could not be sustained upon further analysis in any of these cases.[12] Low quality of case data as well as various confounding variables and inconsistencies prevailed in both, the EMA and the USP series of spontaneous reports,[48,49] but striking differences of evaluating quality existed between EMA and USP. In contrast to USP,[49] the EMA cases of spontaneous reports underwent a thorough and qualified assessment.[48] In addition, for case evaluation USP explicitly preferred quantity of individual cases rather than quality of causality evaluation,[17] whereas the philosophy of others preferred quality *vs.* quantity[10-12,17,18,42,47] in line with the EMA approach.[48]

DEFINITION OF HERB-INDUCED LIVER INJURY

The initial proposal that BC may be the causative agent in cases with liver disease required a clear definition of the adverse reaction; otherwise any attribution of causation to BC is not founded on clinical, scientific, or regulatory grounds. Common criteria required for establishing the diagnosis of liver injury are available and have been published before as part of the scale of CIOMS (Council for International Organizations of Medical Sciences).[50] They include ALT or ALP values of > 2N,[4,50,51] or better > 3N,[52] where N is the upper limit of the normal range. As simple as these initial requirements of ALT and ALP values are, they have rarely been considered in spontaneous cases of primarily purported cases of BC hepatotoxicity[12,48,49] (Table 1), whereas the respective data have well been presented by published case reports (Table 1).[10,11] Lack of appropriate definitions led to misinterpretation and inclusion of not validated cases in the assessment approach even when ALT results were not available, not reported, or very low with values not compatible with liver injury.[10-12,42,47-49] Similarly, even isolated and marginally increases of GGT levels led to the

Table 1. Overview of available information regarding cases of published case reports and spontaneous reports with initially purported BC hepatotoxicity.

	Case Reports		Spontaneous Reports	
Presented information	Cases	Individual cases	Cases	Individual cases
Brand name	06/16	1,5,11,13,14,15	17/24	3,4,5,6,7,8,9,10,11,12,13, 14,15,17,19,20,22
Manufacturer	04/16	1,5,11,13	09/24	8,9,11,17,18,19,20,21,22
Plant part	06/16	1,5,8,11,13,15	03/24	17,22,24
Solvent	02/16	1,11	0/24	-
Daily dose	09/16	1,3,5,6,7,11,13,14,15	06/24	3,4,7,8,9,23
BC drug	01/16	1	05/24	10,12,14,15,20
BC polyherbal product	04/16	2,3,14,16	12/24	3,4,5,6,7,8,9,11,13,17,19,22
Date of BC start	04/16	4,5,14,15	11/24	3,4,6,9,11,12,13,16,17,18,22
Date of BC end	01/16	4	08/24	3,4,6,9,10,11,12,13
Date of symptoms	02/16	4,5	14/24	3,4,5,6,7,9,10,11,12,13,14, 16,21,22
Temporal association	08/16	4,5,6,8,10,12,13,14	08/24	3,4,9,11,12,13,23,24
Time on BC	13/16	1,3,4,5,6,7,8,10,11,12,13,14,16	08/24	3,4,6,9,11,12,13,24
Time to onset	14/16	1,3,4,5,6,7,8,9,10,11,12,13,14,16	09/24	3,4,9,11,12,13,16,17,22
ALT value	16/16	1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16	05/24	3,4,6,14,21
ALP value	14/16	1,2,3,4,5,6,7,8,9,10,11,13,14,16	04/24	3,4,14,21
Hepatotoxicity criteria	15/16	1,2,3,4,5,6,7,8,10,11,12,13,14,15,16	04/24	3,4,14,21
ALT dechallenge	04/16	10,11,12,15	01/24	6
Biliary tract imaging	12/16	2,4,5,6,7,9,10,12,13,14,15,16	02/24	6,17
HAV	16/16	1,2,3,4,5,6,7,8,9,10, 11,12,13,14,15,16	02/24	5,6
HBV	15/16	1,3,4,5,6,7,8,9,10,11,12,13,14,15,16	02/24	5,6
HCV	16/16	1,2,3,4,5,6,7,8,9,10, 11,12,13,14,15,16	02/24	5,6
CMV	11/16	1,4,5,6,8,10,11,12,13,14,15	02/24	5,6
EBV	11/16	1,4,5,6,8,10,11,12,13,14,15	02/24	5,6
HSV	04/16	4,6,8,12	0/24	-
VZV	01/16	8	0/24	-
Comedication/herbal mixture	11/16	2,3,4,5,6,7,11,12,14,15,16	19/24	1,2,3,4,5,6,7,8,9,11,13,14, 16, 17,18,19,21,22,24
Undetermined BC product	10/16	2,3,4,6,7,8,9,10,12,16	07/24	1,2,16,18,21,23,24

The analysis refers to initially purported cases of BC hepatotoxicity derived from 16 published case reports[20-28,43-46] and 24 spontaneous reports.[48,49] Additional details of all cases have been presented in earlier reports.[10-12,42,47] The group of the 16 case reports represents in the table the following individual cases: cases 1 and 2;[20] case 3;[21] case 4;[22] case 5;[23] case 6;[24] case 7;[25] case 8;[26] cases 9 and 10;[27] case 11;[28] case 12;[43] case 13;[44] cases 14 and 15;[45] and case 16, published as their case 2.[46] The group of the 24 spontaneous cases consists of 2 CADRMP cases from Canada, 13 TGA cases from Australia, 7 MedWatch/FDA cases from the US,[12,49] and 2 cases from EMA with 1 case from an EU country, its case 28, and 1 case from a non-EU country, its case 4.[48] These 24 cases represent in the table the following individual cases: CADRMP, cases 1 and 2; TGA, cases 3-15; MedWatch/FDA, cases 16-22; EMA EU, case 23; and EMA non EU, case 24. ALP: Alkaline phosphatase. ALT: Alanine aminotransferase. BC: Black cohosh. CMV: cytomegalovirus. EBV: Epstein Barr virus. HAV: Hepatitis A virus. HBV: Hepatitis B virus. HCV: Hepatitis C virus. HSV: Herpes simplex virus. VZV: Varicella zoster virus.

erroneous assumption of liver injury.[12,49] Therefore, lack or inaccuracy of HILI definitions has been a problem for the required causality assessment regarding alleged BC cases.[10-12,42,47]

CHALLENGE, DECHALLENGE, AND REEXPOSURE

Key criteria for the diagnosis of DILI and HILI are evaluations of challenge, dechallenge, and reexposure characteristics.[1-6,50-52] With respect to cases of initially purported BC hepatotoxicity, the required data have incompletely been presented in published case reports as well as spontaneous reports (Table 1). Under these conditions and for cases of poorly documented cases, any causation assignment to BC may be open for discussions.[10-12]

Since temporal associations were not appropriately documented in half of the published case reports[20-28] (Table 1), questions remained that led to some uncertainty.[10,11] Even worse, time frames for BC use and the evolution of the disease were only fragmentary described in the regulatory cases (Table 1) that were presented by the Australian TGA (Therapeutic Goods Administration), the Canadian CADRMP (Canadian Adverse Drug Reaction Monitoring Program, now Health Canada), the USMedWatch/FDA through USP,[12,49] and by EMA.[48] It is generally understood, however, that temporal association is only one single qualifying factor for a causal association. When a temporal association is lacking in a particular case under consideration, causality is primarily not assessable or negative for the suspected herb,[51] including BC.[10-12] Temporal association alone without clinical assessment and exclusion of any alternative diagnoses is in no way sufficient to establish a possible causality for BC, as proposed by EMA in its 2 spontaneous cases.[48] With respect to BC, ALT dechallenge after discontinuation of BC use has been reported in only a few cases of published case reports[10,11,20-28] (Table 1) and in one single case of spontaneous reports[12,48,49] (Table 1). Excluded from assessment of ALT dechallenge are cases with a dechallenge period of several years or with the primary diagnosis of genuine autoimmune hepatitis responding to immunosuppressive therapy. The scattered results of ALT dechallenge are open for some speculations, since lack of these data may imply preexisting liver disease before BC use or persistence of any other liver disease unrelated to BC use. Therefore, case reports and spontaneous reports without ALT dechallenge data are difficult to be used for causality assessments.

In view of the lack of a convincing surrogate marker, a positive reexposure test is commonly considered as gold standard for the diagnosis of DILI and HILI.[4,51] However, even in the absence of a reexposure test probable causality grading is achievable, provided the case is well documented.[53] Using the reexposure test with a positive result, the existence of HILI has been confirmed for a variety of herbs[6,54-70] (Table 2). In none of the cases with initially purported BC hepatotoxicity, was a valid positive reexposure test with BC described,[10-12,48] with one single case proposed and debated[12,49] but not confirmed.[12]

CLINICAL DATA OF INITIALLY PURPORTED CASES OF BC HEPATOTOXICITY

General agreement exists on the normally poor data quality of spontaneous reports[12,48,49] that were

Table 2. Purported HILI cases by herbs and herbal mixtures in relation to reexposure test.

Herbs/Herbal mixtures	Positive reexposure test	References
Ayurvedic herbs	No	53
Black cohosh	No	10-12,48,49
Chaparral	Yes	54
Chinese herbal mixture	Yes	55-57
Chinese Jin Bu Huan	Yes	58,59
Chinese Ma-huang	Yes	60
Chinese Syo-saiko-to	Yes	61
Germander	Yes	62,63
Greater Celandine	Yes	64-66
Herbalife®	Yes	67,68
Kava	Yes	64
Mistletoe	Yes	69
Senna	Yes	70

presented to and provided by EMA[48] and by USP regarding Health Canada, TGA in Australia, and MedWatch/FDA in the US.[49] This is not unexpected since, for instance, MedWatch/FDA provides a forum mainly for patients rather than their health care providers who could provide much more detailed information. An additional problem was apparent when clinical data of BC cases presented by regulatory agencies have been transferred and included in the USP data collection.[12,49] Important data have been misinterpreted or ignored, a situation that fails to contribute to a transparent case assessment.[12] Similarly, for various published case reports, conflicting data have been reported, compared to data provided by the regulatory agency or other publications on the same patients,[10,11,42] not considering also retracted case details.[34,35,48] Thus, good quality of case data is a key element for appropriate assessments, otherwise alternative diagnoses may emerge[10-12,71-78] (Table 3).

Detailed analyses of initially proposed cases of BC hepatotoxicity have shown quality deficits regarding assessment of the respective indication for treatment by BC.[10-12] BC may have been used for indications other than menopausal symptoms, since the age of the patients ranged from 30 to 72 years.[10-12,20-28,42-49] This raised the question whether BC treatment may have been inaugurated at a time when unspecific symptoms of a liver disease became apparent.

Frequency of comedication was high in all BC cases[10-12] (Table 1), suggesting substantial comorbidity.[42,47] Comedication was found in published case reports[10,11] (Table 1) and in spontaneous cases[12,48,49] (Table 1). In the evaluated cases, comedication consisted of conventional synthetic drugs and other herbs including mixtures containing various herbs.[10-12,42,47-49]

HEPATOTROPIC VIRUS INFECTIONS AND HEPATOBILIARY IMAGING

Infections by hepatotropic viruses may simulate the clinical picture of DILI and HILI, which necessitates exclusion of these infections. The most important hepatotropic viruses are:

- Hepatitis A virus (HAV).
- Hepatitis B virus (HBV).
- Hepatitis C virus (HCV).
- Cytomegalovirus (CMV).
- Epstein-Barr virus (EBV).
- Herpes simplex virus (HSV).
- Varicella zoster virus (VZV).

Other viruses are considered less frequent.[4,51]

In the published case reports, exclusion of infections by HAV, HBV, or HCV was virtually complete, but only scattered results were provided for CMV, EBV, HSV, and VZV[10,11,42] (Table 1). Analysis of the spontaneous reports presented by EMA[48] and USP[49] shows that in only 2 cases are infections by HAV, HBV, HCV, CMV, and EBV excluded, and in none of the cases HSV or VZV was considered and excluded (Table 1). Since HILI in general and primarily purported HILI by BC in particular are diagnoses of exclusion of other diseases, these criteria are fulfilled only marginally in the USP cases[49] and do not allow the regulatory diagnoses of HILI induced by BC in most cases.[12] This again is a situation where diagnoses of other viral infections may have easily been overlooked, as shown in other studies concerned with DILI or HILI (Table 3). Based on the present experience, special care should be provided that data of hepatotropic virus infections including also hepatitis E are complete,[4,51] whenever cases of DILI or HILI are presented as spontaneous reports to regulatory agencies or as case reports to be considered for publication.

For exclusion of alternative diagnoses, imaging data of the liver and the biliary system are mandatory, preferentially also color Doppler sonography of the liver vessels.[4,10-12,51] Imaging data have fairly well been published by case reports but not by spontaneous reports[10-12,42,47-49] (Table 1). This is a major diagnostic flaw in a cohort of female patients with their increased risk of biliary stone diseases.

BASIC DIAGNOSTIC WORKUP AND ALTERNATIVE DIAGNOSES

Increased liver values may normally be attributed to some hundreds of different diseases related to the liver, biliary system, other organs, and systemic disorders with hepatic involvement.[4,51] Based on clinical experience of skilled hepatologists associated with few technical workups, liver diseases unrelated to DILI or HILI are usually recognized within a short time. Basic support is provided through a variety of reports with appropriate recommendations.[1,4,47,51] The diagnosis of BC hepatotoxicity is only warranted when other differential diagnoses have been excluded with certainty. However, this was rarely done with the required expertise,[20-28,48,49] resulting in a variety of alternative diagnoses[10-12] (Table 3).

Alcohol has a high prevalence of abuse in Western countries and is potentially toxic to the liver,[79] as are herbs and synthetic drugs.[1-6,50-78] This

is why alcoholic liver disease is an alternative diagnosis and important confounding variable found in cases of initially purported DILI and HILI (Table 3). With respect to BC cases, alcohol use has been reported in spontaneous cases and published case reports, and details have been analyzed.[47] Accor-

Table 3. Alternative diagnoses in cases of initially purported hepatotoxicity by BC in comparison to other herbs and conventional synthetic drugs.

Initial attribution	Alternative diagnoses	References
Black cohosh	1. Autoimmune hepatitis.	10-12
	2. Herpetic hepatitis.	10
	3. Giant cell hepatitis.	11
	4. Virus infection with hepatic involvement.	11
	5. Alcoholic liver disease/cirrhosis.	11,12
	6. Non-alcoholic liver cirrhosis, previous gastric bypass operation.	11
	7. Liver injury by fluoxetine.	12
	8. Liver injury by Interferon.	12
	9. Cardiac hepatopathy.	12
	10. Preexisting liver diseases/cirrhosis.	11,12
	11. Biliary diseases.	11,12
	12. Questionable liver disease.	10,12
	13. Crestor induced rhabdomyolysis.	12
Other herbs	1. Autoimmune hepatitis.	71,72
	2. LKM positive autoimmune hepatitis.	71,72
	3. SMA positive autoimmune hepatitis.	71,72
	4. Primary biliary cirrhosis.	71,72
	5. Overlap syndrome.	71,72
	6. EBV hepatitis.	71,72
	7. HSV hepatitis.	71,72
	8. VZV hepatitis.	71,72
	9. Liver injury by co-medication.	71,72
	10. Non-alcoholic steatohepatitis.	71,72
	11. Hyperthyroid hepatopathy.	71,72
	12. Pancreatitis.	71,72
	13. Preexisting liver cirrhosis.	71,72
	14. Questionable liver disease.	71,72
Synthetic drugs	1. Autoimmune hepatitis.	73-75
	2. Infection by cytomegalovirus (CMV).	76
	3. Infection by Epstein-Barr virus (EBV).	76
	4. Virus hepatitis.	73,74,77,78
	5. Hemochromatosis.	77,78
	6. Wilson's disease.	73,74
	7. Ischemic hepatitis.	73-75,77
	8. Cardiac hepatopathy.	77
	9. Chronic liver disease.	76
	10. Liver cirrhosis.	76,78
	11. Fatty liver.	76
	12. Non alcoholic steatohepatitis.	73,74
	13. Alcoholic liver disease.	73-75
	14. Gilbert's syndrome.	76
	15. Tumors.	73-75
	16. Lymphoma.	76
	17. Bile duct diseases.	73-75
	18. Systemic sepsis.	73-75
	19. Chlamydial infection.	77
	20. Thyroid disease.	73,74
	21. Postictal.	76

Data are derived from various reports.[10-12,71-78]

dingly, alcohol abuse and associated alcoholic liver disease may have been confounding factors, at least in six patients of the study group that used BC products.

Various alternative diagnoses were not only an issue of primarily assumed hepatotoxicity due to BC[10-12] (Table 3), but also of cases with initially proposed HILI by other herbs and with DILI[71-78] (Table 3). In cases of DILI and HILI including BC, the use of sophisticated causality assessment methods substantially facilitated the detection of alternative diagnoses.[10-12,71-78] Undetected alternative diagnoses in patients with initially purported HILI by BC or other herbs create concern, since delayed institution of the appropriate therapy is inevitably associated with the risk of health hazards. However, in any case of suspected HILI, discontinuation of the accused herb(s) is mandatory, just to be on the side of caution.

LIVER UNSPECIFIC AND SPECIFIC CAUSALITY ASSESSMENTS

The ad hoc causality approach[80] and the Naranjo scale[81] have widely been applied in published case reports of alleged BC hepatotoxicity,[20-28,43-46] with the Naranjo scale also being used for the USP cases.[49] Both assessment methods are in use for any kind of adverse reactions not related to any target organ; they have therefore to be classified as liver unrelated and unspecific evaluation approaches.[80] Due to their liver unspecificity,[80,81] these two methods are considered obsolete and should be abandoned for assessment of assumed cases of DILI and HILI.[80] In particular, the use of any of these two assessment methods runs the high risk to miss the correct diagnoses unrelated to drugs and herbs (Table 3). Regarding the Naranjo scale, a thorough analysis has shown profound shortcomings of causality assessments in DILI cases.[82] Sadly, the USP applied the Naranjo scale to cases of initially assumed HILI not only by BC[49] and also by green tea extracts;[83] consequently, it received specific criticisms with respect to both herbal products, BC[12,17,18,47] and green tea.[3]

The quantitative, structured, and liver specific CIOMS scale has been applied by EMA for its cases of initially assumed HILI by BC,[48] a sophisticated approach for causality assessment of HILI and DILI.[4,50,51,73,80,82] With the original CIOMS scale and the main test as the updated version of this scale, causality for BC has been evaluated in initially purported cases of HILI by BC.[10-12,42,47] However, causality for BC could not be substantiated in case reports[10,11,42] and spontaneous reports.[10-12,47]

IDENTIFICATION OF THE USED BC PRODUCTS

As part of the causality assessment approach, the used BC product has clearly to be identified in any case of primarily purported BC hepatotoxicity. Lack of identification inevitably leads to lack of causality attribution. In particular, there have been cases of patients who were not sure whether they used a BC product at all, but nonetheless, their cases have been published as case reports.[10,22,43] The brand name of the used BC drug or BC dietary supplement has been provided by only a few published case reports and by most spontaneous reports, whereas frequency of data regarding manufacturer, plant part, and solvent was normally lower and basically fragmentary in both subgroups (Table 1). With 10/16 cases, the rate of undetermined BC products was high in the group of published case reports and creates concern regarding validity of causation attribution.[10,11,42] Additional problems arose when the used BC product was an herbal mixture that was not further specified regarding the individual ingredients[10-12,42,47] (Table 1). There is also concern, for instance, that herbal mixtures, containing also BC, may be potentially hepatotoxic through the action of other herbal ingredients.

AUTHENTICATION OF BC IN DRUGS AND OTHER PRODUCTS

Details on BC composition and/or source generally were not reported in published case reports, as criticized recently.[9] This was considered as an important omission, because some commercially available products contain Asian *Cimicifuga* species which are less expensive than *C. racemosa*. Lack of analyses for authentication of *C. racemosa* in BC products taken by patients with initially presumed BC hepatotoxicity was confirmed by other evaluations on subsequently published case reports[10,11,42] and spontaneous reports.[12,47-49]

In one case report going back to 2003, an herbal mixture containing also BC was used, but again no approach for authentication of *Cimicifuga racemosa* was primarily undertaken.[21] Along with criticism as a letter to the editor, analyses have been performed in batches, which were similar but not identical to the actually used mixture and that have now been provided by the previous supplier.[30,31] Analysis was

performed by two different expert groups who agreed at least on the presence of BC in the herbal mixture. There were, however, discrepancies concerning the other ingredients and discussions around the analyzed batches,[21,30,31] a situation that complicated causality attribution,[11] which was also denied by EMA based on principal grounds.[48]

With Health Canada there is the only one single regulatory agency with recent interest for analytical assessments of BC products.[13] As late as 2010 and limited to a few spontaneous cases, other analyses of BC products taken by patients with primarily assumed BC hepatotoxicity were performed, and their results were published by the regulatory agency.[13] In the analyzed samples of four patients, there was lack of authentic BC in Swiss herbal products. The phytochemical profiles of the samples were consistent with the presence of other related herbal species. Product analysis was not done for the BC products used by two other patients. In the same report, Health Canada informs that although research has shown problems with the herbal identity of some products marketed in the United States as black cohosh, these Canadian cases demonstrate that products not containing authentic black cohosh may be associated with liver adverse reactions. As communicated by the Australian regulatory agency TGA regarding its case 19184, a Swisse BC product was used[12] which may have a similar authentication problem for BC as the Swiss herbal products analyzed by Health Canada.[13] Therefore, the initial step in making a regulatory association between BC and a reported adverse toxic liver injury must be to confirm the product's identity by the respective regulatory health agency, as now done by Health Canada.[13] This approach should also include other comedicated herbal drugs and herbal dietary supplements including herbal mixtures, provided liver injury has been assumed.

Herbs are plants with normally some dozens of different chemical substances that can be isolated upon further analyses.[84] Various but not all of these substances exhibit specific properties and are therefore preferred for human use, whereas others may be toxic and are not suitable for consumption. Preferred herbs are used as regulatory approved herbal drugs under subsequent regulatory surveillance, as medicinal herbal dietary supplements under limited regulatory surveillance, or as herbal dietary supplements, unrelated to medicinal purposes and lacking any surveillance. As for synthetic drugs, the rules of GMP are prerequisite for manufacturing herbal drugs and herbal dietary supplements, but in addition adherence to the rules of Good Manufacturing Practices (GMP) is mandatory for herbal products. Violation of the GAP or GMP rules may result in the manufacturing of herbal products that lack efficacy, safety, or both. With respect to a few BC products, there is general agreement that quality specifications are required to meet the problem of impurities, misidentification, and adulterants by other *Cimicifuga* species.[42,49,84-86]

CONCLUDING REMARKS

Herb induced liver injury presumably caused by black cohosh has thoroughly been analyzed in case reports and spontaneous reports, but there is at present no evidence for a causal relationship. Nevertheless, the cautionary statement for consumers issued by regulatory agencies[48,49] should be maintained, just to be on the side of caution.[11,47,88] Rare cases could have been escaped in the frame of the present case studies,[47] and inappropriate legal problems that emerged recently[34] in relation to a case report[23,35] might be preventable by these regulatory measures in the future. Regulatory agencies should now focus on quality specifications to overcome problems of impurities, misidentifications, and adulterations of a few BC products.

CONFLICT OF INTEREST

No conflicts of interest exist.

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