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Review

Suspected black cohosh hepatotoxicity—Challenges and pitfalls of causality assessment

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ABSTRACT

Objectives: Black cohosh (BC) is a herbal drug or herbal dietary supplement used for treatment of menopausal symptoms. Recently, however, reports have appeared about the occurrence of rare toxic liver disease in an assumed relationship with the use of BC.
Methods: We have analyzed and reviewed the data of all 69 reported cases with suspected BC hepatotoxicity. Causality for BC was assessed utilizing the scale of the original structured quantitative Council for International Organizations of Medical Sciences (CIOMS), or the main-test as its updated form.
Results: With the hepatotoxicity specific causality assessment methods, there was an excluded, unlikely, unrelated or unassessable causality for BC in 68 of 69 cases with liver disease. One patient had a possible causality for BC and a symptomatic cholelithiasis with confounding variables of fatty liver of unknown etiology; unknown BC brand including possible herbal mixture; unknown daily BC dosage; and an unassessable duration of BC usage. In general, the cases of the 69 patients were poorly documented. Confounding variables were: failure to identify the BC product; use of herbal mixtures with multiple ingredients in addition to BC; co-medication with synthetic drugs and dietary supplements including herbal ones; missing temporal association between BC use and development of liver disease; not specified modalities of BC treatment; failure of dechallenge after BC discontinuation; pre-existing liver diseases; insufficiently excluded other liver diseases; presence of alternative liver diseases.
Conclusions: The analysis of 69 cases shows little, if any, supportive evidence for a significant hepatotoxic risk of BC.

Contents

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1. Introduction

The diagnosis of idiosyncratic hepatotoxicity by drugs and dietary supplements (DDS) continues to be a challenge for clinical hepatologists [1–6]. It is well recognized that for the diagnosis of DDS hepatotoxicity a diagnostic biomarker is not available [5]. The diagnosis may therefore only be established when other liver diseases have been excluded [2,5]. However, even in a clinical setting of liver diseases, this diagnostic approach is not always successful. And in up to 30% of patients with acute liver failure its cause remains undetermined [7–10]. The way to prove or disprove the diagnosis of DDS hepatotoxicity is therefore cumbersome and characterized by challenges and pitfalls.

Recent interest has emerged regarding the question whether the use of black cohosh (BC) may cause idiosyncratic hepatotoxicity [11–22]. BC is the synonym for *Actaea racemosa* and *Cimicifuga racemosa*, and its rhizome and roots are raw materials for herbal drugs and herbal dietary supplements to treat menopausal symptoms. In few published case reports with liver disease causality for BC has been suggested [11–19]. Spontaneous reports were also presented to regulatory agencies [20–22]. For all these cases, additional information was provided and questions were raised [23–41]. Causality for BC was declined for most cases using a systematic quantitative causality assessment method specific for the evaluation of DDS hepatotoxicity [21,39,40]. A possible causality for BC was proposed in other poorly documented cases using a not hepatotoxicity specific method [22]. It is generally agreed, however, that in the suspected cases poor data quality and various other confounding variables prevail [21,22,39–41]. These circumstances certainly complicate a sound quantitative causality assessment.

In the present review we focus on the available evidence regarding causality for BC in patients with liver disease.

2. Challenging evaluation of suspected BC hepatotoxocity

Ascertaining causality for BC in patients with liver disease requires a step-by-step approach. First of all, documentation of the used BC product and of treatment modalities is essential. Missing data may lead to the conclusion that causality of the case is not assessable [21,22,39,40]. Second, criteria for liver disease in assumed connection with the use of BC have to be defined, based on actual data of liver values [39]. In the final stage, a structured quantitative causality method specified for DDS hepatotoxicity is mandatory [21,39,40]. This includes various items such as temporal course of the liver values and exclusion of other, BC unrelated causes [5].

Reviewing the cases with presumed BC hepatotoxicity, in all three key areas of interest shortcomings are evident. These are the basis of a world-wide discussion [21,22,39–41].

3. Identification problems of BC products

Products of BC derived from its roots and rhizome are sold as dried plant material and as fluid or dried extracts [21,22]. They are marketed as herbal drugs under regulatory supervision or as unregulated herbal dietary supplements. The quality of the raw material contained in BC dietary supplements may be of some concern due to confusion of *Actaea racemosa* with other *Actaea* species [22]. Among these are *A. podocarpa* (yellow cohosh), *A. cimicifuga*, *A. dahurica*, and *A. heracleifolia*. Adulteration or substitution of BC with ingredients of similar binominal name or similar common name such as blue cohosh has also been reported. Various BC-based dietary supplements are used as polyherbal mixtures (Table 1) [22,39,40], causing problems regarding identification of potentially hepatotoxic ingredients [12,24,25] and subsequent causality assignment [21].

In the majority of cases with suspected BC liver disease, BC as a product was not identified or characterized [22,39,40]. This applies to published case reports (Table 1) [39,40] and to spontaneous reports presented by various regulatory agencies [21,22]. These include the European Medicines Agency (EMEA) [21], the Canadian Adverse Drug Reaction Monitoring Program (CADRMP), the Australian Therapeutic Goods Administration (TGA), and the MedWatch of the US Food and Drug Administration (FDA) [22]. Information regarding daily dosage of the BC product and duration of treatment is lacking in most cases (Tables 1 and 2) [21,22,39,40], with reported daily overdosage in 2 cases [21]. Attributing causality to BC, used at normal daily dosage, may therefore be difficult under these conditions of uncertainty.

4. Qualifying criteria for BC hepatotoxicity

Prerequisite for causality assessment in hepatotoxicity by DDS, including BC, is a clear definition of criteria qualifying for this disease entity. DDS hepatotoxicity requires for its diagnosis values of alanine aminotransferase (ALT) and/or alkaline phosphatase (ALP) to be at least 2*N* (*N* corresponds to the upper limit of the normal range) [5,39,40]. Other values such as aspartate aminotransferase (AST), gamma-glutamyltranspeptidase (GGT), or bilirubin are not considered of diagnostic value in this particular context. DDS hepatotoxicity may exhibit a hepatocellular, cholestatic or mixed form of liver injury. Differentiation of these entities is prerequisite for further causality evaluation [5,39,40,42–44]. Therefore, serum activities of alanine aminotransferase (ALT) and alkaline phosphatase (ALP) are measured on the day the diagnosis of DDS hepatotoxicity is suspected. Each activity is expressed as multiple of the upper limit of the normal range (*N*), and the ratio (*R*) of ALT:ALP is calculated. Liver injury is (1) hepatocellular, when ALT > 2*N* alone or $R \geq 5$, (2) cholestatic when there is an increase of ALP > 2*N* alone or when $R \leq 2$, and (3) of the mixed type when ALT > 2*N*, ALP is increased and $2 < R < 5$. For causality evaluation by quantitative causality assessment methods [5,43,44], each case has to be evaluated separately for BC and co-medicated drugs (CDs). These include synthetic drugs, herbal drugs and dietary supplements. Consequently, results of ALT and ALP have to be available, and a temporal association between BC use and the emerging ALT and/or ALP values is mandatory.

Reviewing the cases with liver disease in primarily assumed causal relationship with the use of BC, there were reports lacking ALT and/or ALP values [21,22,39,40]. These cases were therefore not suitable for causality assessment. Moreover, in other cases there was no clear temporal association between the use of BC and the increase of ALT or ALP [32,34]. Again, this condition excludes a causal relationship between liver disease and BC use in these cases.

5. Pitfalls of ad hoc and liver-unspecific causality assessment for assumed BC hepatotoxicity

An ad hoc causality assessment is initially necessary in all suspected cases of assumed hepatotoxicity by DDS including BC. However, some shortcomings of this approach are evident, especially regarding missed diagnoses [4,5]. These shortcomings are also observed in cases of primarily suspected BC hepatotoxicity (Table 1) [39,40]. It is noteworthy that the published case reports of assumed BC hepatotoxicity commonly used the ad hoc causality approach alone [11–14,16–19]. In only one single case report was the scale of the hepatotoxicity-specific structured quantitative Council for International Organizations of Medical Sciences (CIOMS) additionally applied [15].

Table 1
Overview of all 11 case reports with primarily suspected BC hepatotoxicity.

Patients/authors	BC product/BC treatment	Co-medication/co-morbidity	Original information	Additional information	Comments/final diagnosis	Additional references
Patient 01 47 years, female Whiting et al. [11], their case 01.	BC, Remifemin, Schaper & Brümmer, Rhizome. Ethanolic extract. 40 mg/d, 6 days.	None.	Use of BC for 1 week for relief of menopausal symptoms.	Two years later [23]: Dark urine on day 6 of BC use, which was discontinued.	Short-term use of BC for only 6 days.	EMEA [20,21]
			BC daily dose and brand name not declared.	Negative results for HBV–DNA, HCV–RNA, CMV, EBV.	Clinical course suggestive of pre-existing liver disease [20,21,40].	Kerlin [23]
			Discontinuation of BC treatment when jaundice appeared.	On admission: bilirubin 32 mg/dL, ALT 1276 U/L.	Piecemeal necrosis suggestive of Wilson's disease (not excluded by urine copper/24 h) or AIH, but parameters such as SLA/LP, anti-ASGPR, anti-LKM-1, 2, 3 were not assessed.	Teschke et al. [40]
			LTX later, but date not defined, good outcome.	BC brand name declared.	Other causes not excluded: hepatitis E, HSV, VZV.	USP [22]
			Peak values of 2295 U/L for ALT and 19.7 mg/dL for bilirubin.	Temporal association claimed by USP [22], but rejected by EMEA [20,21].	Inconsistency regarding bilirubin levels: peak value declared as 19.7 mg/dL [11], but admission value with 32 mg/dL much higher [23].	
			Negative results for hepatitis A (anti-HAV-IgM), hepatitis B (HBsAg), hepatitis C (anti-HCV), ANA, SMA, AMA.		No ALT dechallenge reported despite BC cessation [11,23], indicating BC is not the causative agent [40].	
			Normal imaging of the liver.		For an ALF case other diagnoses insufficiently excluded.	
			Histology: Piecemeal necrosis and early fibrosis.		No imaging data for biliary tract.	
			Initial diagnosis: Fulminant hepatic failure caused by BC.		Short time between BC intake and transplantation, according to EMEA improbable relation between early cirrhosis and BC intake [20,21].	
					Final diagnosis: Fulminant hepatic failure due to pre-existing liver disease of unknown etiology.	
Patient 02, 43 years, female, Whiting et al. [11], their case 02.	BC, herbal mixture. Not assessable: brand name, manufacturer, plant part, solvent. Not assessable: daily dose, time on herbs.	Herbal mixture: Chasteberry, Chinese angelica, Hops, Oats seed, Passionflower, Skullcap, Valerian. Ovarian adenocarcinoma (shortly after presented with hepatitis).	Use of BC mixture for general health promotion.	Temporal association claimed by USP, but data not presented [22].	Poorly documented case [40].	EMEA [20,21]
			Not assessable: time to symptoms, time from diagnosis to normal laboratory values.		Temporal association not evident.	Teschke et al. [40]
			Further clinical course unclear.		Diarrhoe not compatible with DDS hepatotoxicity, symptom for an intestinal disease combined with liver disease.	USP [22]
			Symptoms included diarrhoe.		A negative HBsAg alone does not rule out hepatitis B.	
			Negative results for anti-HAV-IgM. HBsAg, anti-HCV, SMA, AMA.		No data available for hepatitis E, CMV, EBV, HSV, VZV, SLA/LP, anti-ASGPR, anti-LKM-1, 2, 3, urinary cooper/24 h.	
			ANA 1:40.		ALP with 80 U/L in the lower area of the normal range (40–250), suggestive of Wilson's disease.	
			Data on bile duct imaging not presented.		No bile duct imaging.	
			Liver histology with severe interface hepatitis (piecemeal necrosis).		No ALT dechallenge after BC discontinuation, suggesting BC unrelated cause.	
			Initial diagnosis: Hepatitis caused by BC.		No analysis of herbal mixture, causality assessment for BC according to EMEA thereby not possible [20,21].	
					Final diagnosis: Chronic hepatitis unrelated to BC, possibly ANA-positive AIH, other forms of AIH, hepatitis B, Wilson's disease.	

Patient 03, 52 years, female, Lontos et al. [12].	BC, herbal mixture provided by local pharmacist. Not assessable: plant part, solvent. 750 mg/d, 3 months, with treatment free interval of 4 weeks preceding hospitalization.	Ground ivy, Golden seal, Gingko, Oats seed. Tinnitus.	Herbal mixture used for tinnitus. Jaundice on admission, after 1-week hepatic encephalopathy and hepatorenal failure, required LTX. Reported extensive investigation to exclude other recognized causes of acute liver failure, but no parameters were presented. No data of ALT dechallenge and hepato-biliary imaging. Uncertainty, which ingredient caused acute liver failure. *Initial diagnosis*: Acute liver failure by herbal preparation containing BC.	Temporal association claimed by USP [22], but not evident [12]. Negative serology for hepatitis A, B, and C, but individual parameters not reported [23]. Questions regarding quality of the used herbal mixture [20,24,25].	Poorly documented case [40]. No temporal association evident with long drug free interval of 4 weeks [40]. Details for exclusion of hepatitis A, B, and C not reported. Uncertainty, whether other liver diseases were excluded. No data of hepato-biliary imaging. No results of ALT dechallenge available. Not substantiated evidence for herbal mixture as causative agent [20,24,25,40]. *Final diagnosis*: Acute liver failure unrelated to herbal preparation containing BC.	Cumming and Kelly [25] EMEA [20,21] Kerlin [23] Teschke et al. [40] Thomsen et al. [24] USP [22]
Patient 04, 57 years, female, Cohen et al. [13].	BC tablets. Not assessable: brand name, manufacturer, plant part, solvent. Not assessable: daily dose. 1 week.	Labetolol [13,26,27], Fosinopril, Verapramil, Metformin, Insulin, Aspirin [13,26] and Aminosalicylic acid [27]. Polymyositis [13], Diabetes mellitus [13,26,27], arterial hypertension [13,26,27], obstructive sleep apnoe [13,20].	BC treatment for 1 week and than stopped due to liver associated symptoms. ANA 1:640, liver histology with piecemeal necrosis (autoimmune hepatitis). Resolution of liver function tests within 9 weeks under steroid treatment. Recurrence after 4 months without steroids and again improvement by steroids and long-term azathioprine. Exclusion of few other liver diseases. *Initial diagnosis*: Drug induced autoimmune hepatitis, most likely due to BC.	Various inconsistencies in different reports on the same case [13,26,27], discussed by EMEA [21], Teschke and Schwarzenboeck [39], and USP [22]. Uncertainty, whether the product includes only BC or any BC [21,27,39].	Pre-existing genuine autoimmune hepatitis, unrelated to BC or CD [39]. BC treatment for only 1 week, and recurrence despite BC discontinuation, incompatible with BC-AIH [39]. Autoimmune hepatitis and autoimmune polymyositis as poly-autoimmune syndrome [17,39]. *Final diagnosis*: Pre-existing genuine autoimmune hepatitis. Liver disease unrelated to BC or CD.	Cohen [27] EMEA [20,21] O'Connor et al. [26] Teschke and Schwarzenboeck [39] USP [22]
Patient 05, 50 years, female, Levitsky et al. [14].	BC root, Pharmavite/Nutraceutical Corp., solvent not assessed. 500 mg/d, 5 months.	Primarily no co-medication declared [14]. Valaciclovir [28], Pseudo-ephedrine [28] and Ibuprofen [28]. Comorbidity not assessed, but substantiated as evidenced by listed CD.	Fulminant liver failure requiring LTX. Steroid treatment, since AIH was initially suspected. Alcohol consumption and co-medication denied. Exclusion of hepatitis A–C, CMV, EBV, negative results for ANA, SMA, anti-LKM-1. Liver histology: Acute hepatitis. *Initial diagnosis*: Autoimmune hepatitis. Only later fulminant liver failure due to BC.	In front of court, alcohol consumption on a regular basis and co-medication admitted [28]. Use of Valaciclovir for 2 years as herpes prophylaxis until the time of her liver transplant.	Various inconsistencies in different reports on the same patient [14,28,29,30]. No data presented for HEV, HSV, VZV, anti-LKM-2, anti-LKM-3, urinary copper (24 h) to exclude Wilson's disease. *Final diagnosis*: Herpetic hepatitis. Liver disease unrelated to BC or CD.	EMEA [21] Levitsky et al. [30] Strohm [28] Strom [29] Teschke and Schwarzenboeck [39]

Table 1 (*Continued*)

Patients/authors	BC product/BC treatment	Co-medication/co-morbidity	Original information	Additional information	Comments/final diagnosis	Additional references
Patient 06, 54 years, female, Lynch et al. [15].	Not assessable: brand name, manufacturer, plant part, solvent. 1000 mg/d, 3 months [31] or 8 months [15].	Fluoxetine [31], Propoxyphene [31], Acetaminophen [31], Levothyroxine [15,31]. Fibromyalgia [31], osteoarthritis [31], depression [31], hypothyrodism [15,31].	Presentation with an 8-week history of fatigue, forgetfulness and weight loss.	Positive titer for anti-HSV-IgM [31].	Various inconsistencies in different reports on the same case [15,31].	Cohen [31]
			Alcohol consumption (2 glasses wine nightly for several years).	BC cessation at first presentation [31], not reported in subsequent case report [15].	Multimorbid patient.	EMEA [20,21]
			Exclusion of various forms of hepatitis, AIH, Wilson's disease, hemochromatosis.	Co-medication consisted also of fluoxetine, propoxyphene, and acetaminophen [31], not mentioned in case report [15].	Positive titer for anti-HSV-IgM.	Teschke and Schwarzenboeck [39]
			Prednisone treatment for possible AIH. LTX 39 days after admission, death due to intraoperative uncontrollable hemorrhage. *Initial diagnosis*: Autoimmune hepatitis, fulminant liver failure associated with BC.	Uncertainty, whether CDs were discontinued [15,31]. Drop and second peak of ALT after BC cessation [15,31].	Unclear duration of BC treatment of 3 [31] or 8 [15] months. Discontinuation of CDs not described [15,31], possible role of CD for liver disease. High alcohol consumption. Drop and second peak of ALT after BC cessation [15,31] exclude BC as causative agent [39]. *Final diagnosis*: Herpetic hepatitis. Liver disease unrelated to BC. Hepatotoxicity possibly by CD.	
Patient 07, 50 years, female, Nisbeth and O'Connor [16].	Not assessable: brand name, manufacturer, plant part, solvent. 40 mg/d, 2 weeks.	Lansoprazole. Cholecystolithiasis (multiple stones), gastroesophageal reflux disease, anxiety.	Two weeks before presentation, start of symptoms and BC treatment.	CMV, EBV, HSV, and VZV not excluded [33].	Pre-existing hepato-biliary disease [32].	Nisbeth and O'Connor [33]
			Later on, pains after eating fatty foods in a fast food restaurant. Cholelithiasis with freely moving gallstones in the gallbladder. Assumed possible role of cholelithiasis at initial presentation. ALT dechallenge, but normalization not reported. Unclear, whether lansoprazole has been discontinued. Exclusion of differential diagnoses poorly documented. Hepatic serologies were reported to be normal, no details regarding hepatitis A, B, C and other infections available. *Initial diagnosis*: BC hepatitis.	Temporal association and role of cholelithiasis debated [32,33].	Poorly documented exclusion of differential diagnoses [32]. Normalization of ALT not reported. Debate on temporal association and role of cholelithiasis [32,33]. Lack of temporal relationship evident, hence no causal association for BC [32]. *Final diagnosis*: Pre-existing hepato-biliary disease. BC and CD unrelated liver disease, cholecystolithiasis with multiple stones.	Teschke [32] Teschke et al. [40]
Patient 08, 41 years, female, Dunbar and Solga [17].	BC root. Not assessable: brand name, manufacturer, solvent. Not assessable: daily dose. 2 weeks.	None.	Two-week use of BC for menopausal symptoms (with 41 years?). Discontinuation of BC use when icterus appeared, LTX 2.5 months thereafter. Persistence of increased liver functions tests despite BC cessation, but actual ALT data not provided. Unusual liver histology with giant cell hepatitis, subsequent increasing in severity despite BC cessation. *Initial diagnosis*: Acute liver failure due to BC.	Giant cell hepatitis not known for DDS hepatotoxicity, differentiation necessary from DDS induced giant cells within hepatic granulomas [39,40].	Giant cell hepatitis best attributed to virus infection such as paramyxo-like virus or paramyxovirus (measles) [39,40]. Menopausal symptoms unusual at age of 41 years. Clinical picture suggestive of virus infection with hepatitis rather than of menopausal symptoms and BC hepatitis [39,40]. *Final diagnosis*: Giant cell hepatitis by virus infection, unrelated to BC.	Teschke and Schwarzenboeck [39] Teschke et al. [40]

Patient 09, 50 years, female, Joy et al. [18], their case 01.	Not assessable: brand name, manufacturer, plant part, solvent. Not assessable: daily dose, duration of treatment.	Co-medication: none. Chronic fatigue, hypertension.	Reported clinical symptoms compatible with virus infection. Bilirubin, ALP and other liver values in the normal range, except AST 70 U/L and GGT 571 U/L. Exclusion of various hepato-biliary diseases reported. *Initial diagnosis*: BC liver toxicity.	None.	Not further specified virus infection with some liver involvement [40]. By definition, no evidence for BC hepatotoxicity, requiring increased values for ALT and/or ALP >2N [40]. *Final diagnosis*: Virus infection with some liver involvement.	Teschke et al. [40]
Patient 10, 51 years, female, Joy et al. [18], their case 02.	Not assessable: brand name, manufacturer, plant part, solvent. Not assessable: daily dose. 2 months.	Co-medication: none declared. Cholelithiasis, fatty liver, well controlled asthma (medication?).	Two-week history of epigastric pain. Increased ALT and ALP. Hepatitis A, B, C, E and other differential diagnoses fairly well ruled out. Dechallenge of ALT and ALP following BC cessation. *Initial diagnosis*: BC hepatotoxicity.	None.	No information regarding BC product: drug under regulatory supervision, unregulated dietary supplement, or unregulated herbal mixture containing BC. Unknown daily BC dosage. Poorly documented case, ascertaining causality for BC thereby more difficult. BC basically a candidate for cause of liver disease, when co-morbidity (symptomatic cholecystolithiasis and fatty liver of unknown cause), unassessable BC product and unassessable daily BC dosage are considered as confounding factors. *Final diagnosis*: Possible BC hepatotoxicity with special consideration of various confounding factors such as symptomatic cholelithiasis, fatty liver of unknown etiology, unknown BC product and unknown daily BC dosage.	Teschke et al. [40]
Patient 11, 50 years, female, Chow et al. [19].	BC, Remifemin. Schaper & Brümmer. Rhizome. Isopropanolic extract. 40 mg/d, 2 months.	Multivitamins. Gastric bypass, obesity, alcoholism [34,35].	Use of BC 20 mg/d intermittenly for 3 years, then 40 mg daily for 2 months.	Age 50 years [34], not 51 [19].	No temporal association between BC and start of liver symptoms, excluding thereby a causal relationship [34]. Debated case [34–36].	Chow et al. [36]
			Presentation with a 2-month history of lethargy, nausea, and arthralgia, and 2 weeks of jaundice.	Body weight 88 kg [34].	Pre-existing alcoholic or non-alcoholic liver cirrhosis due to risk factors such as obesity, gastric bypass, and alcoholism [34,35].	Naser and Liske [35]
			Development of acute liver failure requiring LTX.	First presentation on 23 May 2006. Back calculation shows symptom onset around 23 March 2006 but dose increase of BC only later on 31 March 2006 [34].	Co-medication with not further specified multivitamins [19,22,35].	Teschke [34]
			Dechallenge of ALT but not of bilirubin.	Symptoms emerged 1 week before dose increase, thereby no temporal association [34].	*Final diagnosis*: Pre-existing alcoholic or non-alcoholic liver cirrhosis with liver failure (obesity, gastric bypass, alcoholism, and undefined multivitamins as risk factors). Liver disease unrelated to BC.	Teschke et al. [40]
			No history of significant alcohol consumption reported. *Initial diagnosis*: Liver failure associated with the use of BC.	Daily intake of 3–4 units of alcohol with 1–2 alcohol free days per week [34]. Diagnostic workup incomplete [34,35].		

The group of the 11 cases consists of 11 published cases. Details of the cases, BC products and treatment modalities as well as original informations are derived from the original reports [11–19]. Additional information of the cases and comments are substantiated, as outlined, by additional Refs. [22–41]. AIH denotes autoimmune hepatitis, ALF acute liver failure, ALT alanine aminotransferase, ALP alkaline phosphatase, AMA antimitochondrial antibodies, ANA antinuclear antibodies, ASGPR asialo-glycoprotein-receptor, AST aspartate aminotransferase, BC black cohosh, CD co-medicated drugs, CMV cytomegalovirus, DDS drugs and dietary supplements. EBV Epstein-Barr virus, EMEA European Medicine Agency, GGT gamma-glutamyltranspeptidase, HAV hepatitis A virus, HBsAg hepatitis B surface antigen, HBV hepatitis B virus, HCV hepatitis C virus, HEV hepatitis E virus, HSV herpes simplex virus, LKM liver kidney microsomes, LTX liver transplantation, SLA/LP soluble liver antigen/liver-pancreas antigen, SMA smooth muscle antibodies, USP United States Pharmacopeia, and VZV varizella zoster virus.

The problems of ad hoc evaluation are not solved when liver-unspecific causality assessment methods, such as the Naranjo scale, are applied instead of liver-specific ones. USP (United States Pharmacopeia) used the Naranjo scale and assessed a possible causality in 30 patients with suspected BC hepatotoxicity [22]. The Naranjo scale rather than the CIOMS scale was preferred by USP on the basis of low data quality, which was considered as being unsuitable for the assessment by the CIOMS scale. There was some discussion around the applied Naranjo scale [37], audit was finally opined, that the results of the USP review were based on consensus opinion, with the Naranjo scale being only used as an adjunct [38]. In the original USP review, however, consensus opinion was not addressed, nor were there any definitions on which criteria the consensus was based [22]. The value of expert groups on grounds of individual opinions is a matter of general debate [5,42–46]. Consequently, it appears that the USP approach [22] lacked fundamental criteria for a sound causality evaluation.

The review of USP and the use of the Naranjo scale for causality assessment [22] was criticized on various grounds [37]. In particular, the Naranjo scale was published in 1981, long before disease-specific causality assessment methods had been established. It has, among other shortcomings, large interobserver variations and lacks both a gold standard and evaluation regarding sensitivity, specificity, and predictive value. These factors make it unsuitable as a substitute for the CIOMS scale. Moreover, in 16 of 30 patients, alternative causes of their own could have initiated the reaction. In the remaining 14 patients, other causes have not been ruled out [22,37]. It was also criticized that in 28 of 30 patients, the adverse reaction did not improve with drug discontinuation, or the specific situation was unknown or unclear [37]. These factors signify problems with dechallenge, one of the key elements for a sound causality assessment.

In the USP review referring to BC case reports of assumed hepatotoxicity, the definition of this particular disease is lacking [22]. The reported cases of the US MedWatch/FDA assessed various pathologies including elevated GGT (>120) associated with alcohol consumption. In addition, not further specified elevated liver enzymes with reported alcohol use were communicated. Among the pathologies of the Australian TGA cases, there were examples such as hepatitis and jaundice after only 3 days of a BC mixture; hepatic steatosis; not further specified abnormal hepatic function tests; or isolated GGT increases, one of these up to only 58 U/L. Not further specified elevated liver enzymes were described by the Canadian CADRMP in patients with an unidentified BC product under conditions of co-medication or alcohol use. These few details illustrate the weakness of the USP review in the face of poor data quality.

Table 2
Overview of known information regarding all 11 case reports with primarily suspected BC hepatotoxicity.

Known information	Cases	Individual cases
Brand name	03/11	1, 5, 11
Manufacturer	03/11	1, 5, 11
Plant part	04/11	1, 5, 8, 11
Solvent	02/11	1, 11
Daily dose	06/11	1, 3, 5, 6, 7, 11
Time on BC	09/11	1, 3, 4, 5, 6, 7, 8, 10, 11
Time to onset	07/11	1, 4, 6, 8, 9, 10, 11
ALT dechallenge	04/11	4, 6, 10, 11
Biliary tract imaging	07/11	2, 4, 5, 6, 7, 9, 10
HAV	11/11	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11
HBV	10/11	1, 3, 4, 5, 6, 7, 8, 9, 10, 11
HCV	11/11	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11
CMV	07/11	1, 4, 5, 6, 8, 10, 11
EBV	07/11	1, 4, 5, 6, 8, 10, 11
HSV	03/11	4, 6, 8
VZV	01/11	8
Co-medication/herbal mixture	07/11	2, 3, 4, 5, 6, 7, 11

The group consists of 11 published cases. Details of the cases are presented in Table 1, and additional data are derived from the herein quoted references. For abbreviations see legend to Table 1.

6. Challenges of liver-specific quantitative causality assessment methods suitable for suspected BC hepatotoxicity

There are 69 cases with primarily suspected BC hepatotoxicity, when duplicates and triplicates were excluded [21,22,39,40]. They have been evaluated by the scale of the structured, quantitative and hepatotoxicity specific CIOMS [43] or by its updated form as main-test [5]. The main-test is part of a causality algorithm, consisting also of a pre-test and a post-test, and was published recently [5,39]. The 69 cases are derived from various sources: EMEA ($n = 36$), case reports ($n = 11$), and USP ($n = 22$) [20–22,39,40]. EMEA contributed 36 cases of spontaneous reports, consisting of 31 EU cases and 5 non-EU cases [20,21]. There were also 11 case reports published since 2002 (Tables 1–5) [39,40]. Finally, 22 of 30 USP cases, not yet assessed by other groups, were included [22].

In none of the 36 EMEA cases causality for co-medicated drugs (CD) had been separately evaluated [20,21]. This was assessed in the 11 case reports (Tables 1 and 4) [39,40], but not thoroughly in the 22 USP cases due to poor data constellation [22]. CD refers to synthetic drugs as well as herbal and other dietary supplements.

6.1. EMEA cases

With the original CIOMS scale, EMEA attributed no causality for BC in 30 EU cases with primarily suspected BC hepatotoxicity, collected from European national competent authorities [20,21]. In particular, causality for BC was excluded ($n = 5$), unlikely ($n = 7$), unrelated ($n = 7$), or unassessable ($n = 11$). In 4 non-EU cases [16], no causality for BC was described by EMEA [20,21]. For these patients causality was unlikely ($n = 1$), unrelated ($n = 2$), or unassessable ($n = 1$) [21]. Therefore, EMEA classified 34 EU and non-EU cases with a lack of causality for BC [20,21]. For two cases of EMEA, one EU case [20,21] and one non-EU case [21], EMEA classified a possible causality for BC [21]. Re-assessment of these 2 cases with the main-test showed an excluded causality for BC (Table 6) [39,40].

6.2. Case reports

In the group of 11 case reports (Table 1) evaluated with the main-test (Table 3), a detailed analysis has been made (Tables 1-4) in addition to previous assessments [39,40]. This group consisted also of 6 published cases [11–15], pre-assessed by EMEA with a probable ($n = 2$), possible ($n = 1$), unlikely ($n = 1$), and unassessable ($n = 2$) causality for BC [20,21]. These 6 case reports received a possible causality for BC by USP with the Naranjo scale [22] and an unlikely ($n = 1$) or excluded ($n = 5$) causality with the main-test (Tables 3–5) [39,40]. Finally, five other cases of the group had been published as case reports [16–19] and were evaluated with the main-test (Tables 1–5) [40]: In 1 of 5 cases causality was possible for BC and symptomatic cholelithiasis, but various confounding variables such as unknown BC product, unknown daily dosage, and presence of fatty liver of unknown etiology have to be considered (Table 1) [40]. With the main-test applied to all 11 cases, causality for BC was possible ($n = 1$), unlikely ($n = 3$), or excluded ($n = 7$) (Tables 3–5). In all 11 cases a further thorough assessment was undertaken (Tables 1–5).

The analysis of these 11 case reports shows that in the original presentation the brand name and the manufacturer were unknown in 8 patients (Tables 1 and 2). Other uncertainties include missing data of the plant part used, and the solvent. Questions are also open as to whether the BC product was a herbal drug under regulatory

Table 3
Main-test for causality assessment of all 11 case reports with primarily suspected BC hepatotoxicity.

	Score	Patients																	
		1 BC	2 BC	2 CD	3 BC	3 CD	4 BC	4 CD	5 BC	5 CD	6 BC	6 CD	7 BC	7 CD	8 BC	9 BC	10 BC	11 BC	11 CD
1. Time to onset from the beginning of the drug																			
5–90 days	+2	+2					+2								+2	+2	+2		
<5 or >90 days	+1				+1	+1		+1	+1	+1	+1	+1		+1					+1
2. Time to onset from cessation of the drug																			
≤15 days	+1	+1					+1				+1				+1	+1	+1	+1	
3. Course of ALT after cessation of the drug																			
Decrease ≥50% within 8 days	+3																+3		
Decrease ≥50% within 30 days	+2																	+2	
No information	0	0	0	0	0	0		0	0	0		0	0	0	0	0			
Decrease ≥50% after the 30th day	0																		
Decrease <50% after the 30th day or recurrent increase	−2						−2				−2								
4. Risk factor ethanol																			
Yes	+1								+1	+1	+1	+1						+1	+1
No	0	0	0	0	0	0	0	0					0	0	0	0	0		
5. Risk factor age																			
≥55 years	+1						+1	+1											
<55 years	0	0	0	0	0	0			0	0	0	0	0	0	0	0	0	0	0
6. Concomitant drug(s)																			
None or no information	0	0													0	0	0		
Concomitant drug with incompatible time to onset	0																		
Concomitant drug with compatible or suggestive time to onset	−1																	−1	
Concomitant drug known as hepatotoxin and with compatible or suggestive time to onset	−2		−2	−2	−2	−2	−2	−2	−2	−2	−2	−2	−2	−2					−2
Concomitant drug with evidence for is role in this case (positive rechallenge or validated test)	−3																		
7. Search for non-drug causes																			
Group I (6 causes)																			
Anti-HAV-IgM		−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
Anti-HBc-IgM/HBV–DNA		−			−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
Anti-HCV-IgM/HCV–RNA		−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
Hepatobiliary sonography/colour doppler sonography of liver vessels			−	−			−	−	−	−	−	−	−	−		−	−		
Alcoholism (AST/ALT ≥2)		−	−	−			−	−	−	−	−	−	−	−	−				
Acute recent hypotension history (particularly if underlying heart disease)													−	−			−		
Group II																			
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)															−				

Table 3 (*Continued*)

	Score	Patients																			
		1 BC	2 BC	2 CD	3 BC	3 CD	4 BC	4 CD	5 BC	5 CD	6 BC	6 CD	7 BC	7 CD	8 BC	9 BC	10 BC	11 BC	11 CD
Evaluation of groups I and II																			
All causes-groups I and II–reasonably ruled out	+2																		
The 6 causes of group I ruled out	+1																		
5 or 4 causes of group I ruled out	0																		
Less than 4 causes of group I ruled out	−2																		
Non-drug cause highly probable	−3	−3	−3	−3	−3	−3	−3	−3	−3	−3	−3	−3	−3	−3	−3	−3	−3	−3	−3
8. Previous information on hepatotoxicity of the drug																			
Reaction labelled in the product characteristics	+2	+2	+2		+2	+2	+2	+2	+2	+2	+2	+2	+2	+2	+2	+2	+2	+2	
Reaction published but unlabelled	+1			+1															
Reaction unknown	0																		0
9. Response to re-administration																			
Doubling of ALT with the drug alone	+3																		
Doubling of ALT with the drugs already given at the time of 1st reaction	+1																		
Increase of ALT but less than N in the same conditions as for the first administration	−2																		
Other situations	0																		
Total points for patient		+2	−3	−4	−2	−2	−1	−1	−1	−1	−2	−1	−3	−2	+2	0	+5	+2	−3

Individual data of the cases 1–11 and the corresponding references are presented in Table 1. Causality assessment with the main-test was performed for all 11 patients regarding black cohosh (BC) ± co-medicated drugs (CD). The group of the 11 cases consists 11 published cases. In Section 7 (search for non-drug causes), the symbol of − denotes that the obtained result was negative and that of + was positive, whereas lack of a symbol indicates that assessment was not performed. ALT denotes alanine aminotransferase, AST asparate 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. Total points/causality: ≤0 = excluded; 1–2 = unlikely; 3–5 = possible; 6–8 = probable; >8 = highly probable.

control; a herbal dietary supplement; or a mixture of various herbal ingredients (Table 1). Therefore, lack of basic information about the used BC product seriously interferes with causality assessment.

The temporal association between BC use and the development of liver disease is a key element for causality assessment [5,43]. Data as to time to onset, from the beginning and from the cessation of the drug, was incompletely reported (Tables 1 and 2), and the course of ALT after cessation of the drug has been rarely communicated (Tables 2 and 3). In particular, ALT dechallenge data were provided in only 4 of 11 patients (Table 2). Therefore, causality assessment is difficult to perform.

DDS hepatotoxicity is basically a diagnosis by exclusion of other diseases unrelated to DDS [5,43]. In patients with primarily suspected BC hepatotoxicity, exclusion of hepatitis A, B, and C was almost complete (Tables 2 and 3). CMV and EBV have been excluded in 7 of 11 patients, HSV in 3 patients, and VZV in 1 patient. Biliary tract imaging was reported in 7 of 11 cases. Therefore, the exclusion of major BC unrelated liver diseases was incomplete, and this is a burden for making an unequivocal causality assessment of BC hepatotoxicity.

Co-medication with synthetic drugs, herbal drugs, or herbal and non-herbal dietary supplements was evident in 7 of 11 patients (Tables 1–3). Co-medication is a major confounding factor in assigning BC causality.

The analysis of causality for BC with the scale of the main-test as the updated form of the CIOMS scale [39,40] reveals little, if any, evidence for BC-related hepatotoxicity (Tables 3–5). Item by item had to be assessed for a sound causality assessment (Table 3). This data was listed on grounds of transparency with the option of re-assessing causality by other experts.

6.3. USP cases

We have also applied the main-test as the updated CIOMS scale for causality assessment in 22 of 30 cases reported by USP [22]. Excluding published case reports, only those cases were evaluated for BC [47] which had not yet been considered before (Table 1). Assessed were 2 CADRMP cases, 13 TGA cases, and 7 MedWatch cases. With the main-test, the CADRMP cases reached for BC maximal −1 point, the TGA cases +2 points, and the MedWatch cases +1 point. Causality for BC was therefore excluded in 17 of 22 cases and unlikely in the other 5 patients [47].

7. Confounding variables in primarily suspected BC hepatotoxicity

Causality assessment for BC in 69 patients with liver disease was complicated by various confounding factors (Tables 1–3) [21,22,39,40,47]. Examples were: failure to identify the BC product and modalities of BC treatment [21,22,39,40,47]; missing temporal association between the use of BC and the development of liver disease [21,32–34,40,47]; failure of dechallenge after BC discontinuation [22,39,40,47]; pre-existing liver diseases [21,34–36,39,40,47]; and insufficiently excluded other liver diseases [22,39,40,47]. Moreover, in some patients of case reports alternative diagnoses were evident (Table 1) [22,39,40]: genuine autoimmune hepatitis [13,39]; herpetic hepatitis [14,15,39]; alcohol abuse [22]; alcoholic and non-alcoholic liver cirrhosis [19]; liver disease caused by obesity and prior gastric bypass [19]; hepatitis by myxovirus or other virus infection [17]. Additional confounding factors were evident such as co-medication with synthetic drugs [21,22,39,40] and dietary supplements including herbal ones [22,39,40]; and the use of mixtures with multiple ingredients in addition to BC [11,12,22,39,40]. Overall poor data quality of cases with suspected BC hepatotoxicity was another major confounding factor. These various confounding variables led in most cases to

Table 4
Overview of causality assessment of all 11 case reports with primarily suspected BC hepatotoxicity.

Patient 01, Whiting et al. [11], their case 01:
The main-test rendered with +2 points an unlikely causality for BC (Table 2) [40]. EMEA rated the case with improbable causality for BC, because of the short time between BC intake and transplantation [16,17]. USP used the Naranjo scale, which yielded a possible causality [22] by a not acceptable causality assessment method for DDS hepatotoxicity [37].

Patient 02, Whiting et al. [11], their case 02:
The main-test yielded −3 and −4 points for BC and co-medicated herbs, respectively (Table 2), which corresponds to an excluded causality for each [40]. EMEA argued that it is not possible to assess the cause of the liver disease, because of the combination of different herbs that have not been analyzed for their constituents and the lack of further information [16,17]. USP attributed a possible causality for BC in this case, based on the Naranjo scale and a temporal association [22] which is not evident (Table 1) [40].

Patient 03, Lontos et al. [12]:
The main-test showed −2 points for each BC and other constituents of the herbal mixture (Table 2) [40]. EMEA stated that it is not possible to conclude that BC is the relevant cause of liver failure [16,17], confirming previous conclusions [12,24,25]. USP attributed a possible causality for BC, using the Naranjo scale [22].

Patient 04, Cohen et al. [13]:
With the main-test causality was excluded for both BC and CD with −2 points and 0 points, respectively (Table 2) [39]: EMEA classified for BC +6 points and a probable causality using the CIOMS scale, but CD were not assessed [16,17]. USP considered a possible causality for BC with the Naranjo scale [22].

Patient 05, Levitsky et al. [14]:
The main-test for BC and CD was rarely applicable (Table 2) since discontinuation of BC treatment is not documented [14,28,39] and co-medication was taken up to the liver transplant [28,30,39]. It was assumed that CD could have been taken for more than 90 days. With the main-test −2 and 0 points were achieved for BC and CD, respectively, correlating to an excluded causality for both. EMEA classified the case for BC with +6 points and a probable causality [16]. CD was not assessed, since the respective data have only been documented later [16,39]. With the additional data, EMEA left its causality assessment unchanged [17]. For UPS the case had a possible causality for BC, using the Naranjo scale [22].

Patient 06, Lynch et al. [15]:
The main-test rendered a total of −3 points and thereby an excluded causality for BC (Table 2), assuming a treatment of 8 months [15]. With the main-test for CD 0 points were achieved, equating to an excluded causality (Table 2) [39]. A possible causality (+3 points) for BC was suggested by EMEA with the CIOMS scale [16,17] and by USP with the Naranjo scale [22]. A probable causality for BC with the CIOMS scale (+6 points) was declared by the authors of the case report [15]. Causality for CD was not assessed by EMEA [20,21], USP [22], and the authors [15].

Patient 07, Nisbeth and O'Connor [16]:
The main-test resulted in an excluded causality for both BC and CD with −3 and −2 points, respectively (Table 3) [40].

Patient 08, Dunbar and Solga [17]:
The main-test provided +2 points for BC corresponding to an unlikely causality (Table 3) [40].

Patient 09, Joy et al. [18], their case 01:
The main-test resulted in 0 points and thereby in an excluded causality for BC (Table 3) [40].

Patient 10, Joy et al. [18], their case 02:
The main-test presented +5 points corresponding to a possible causality for BC (Table 3) [40], but confounding factors have to be considered [18,40]. They include unknown BC product (brand name?, drug status under regulatory control?, BC plant part?, solvent?, unregulated herbal mixture?, unregulated dietary supplement?) and undetermined daily dose (overdosage?) as well as symptomatic cholelithiasis and fatty liver of unknown etiology.

Patient 11, Chow et al. [19]:
The main-test rendered +2 points for BC corresponding to an unlikely causality, and −3 points for co-medicated multivitamins resulting in an excluded causality (Table 3) [40].

The group consists of 11 published case reports. Details of the cases are presented in Tables 1–3, and additional data are derived from references quoted in Table 1. Abbreviations are denoted in the legend of Table 1.

an excluded, unlikely, unrelated, or unassessable causality for BC [21,22,39–41,47].

8. Limitation of the analysis

Hepatotoxic side effects due to the use of BC have not been described by the USP when reviewing the pertinent literature [22]. This statement refers to experimental reports and clinical studies including postmarketing evaluations. In particular, USP noted the results of more than 2800 patients in a reviewing evaluation [22,48] and of more than 6000 women in a large-scale controlled, observational study [22,49,50]. The limitation of the present analysis consists primarily in the assessment of published case reports and spontaneous reports presented to national regulatory agencies rather than larger epidemiological studies. However, this effort may not be successful when, for instance, BC hepatotoxicity occurs in 1:100,000 or 1:1,000,000 users. Therefore, the previous studies and the present analysis may not exclude with certainty, very rare

Table 5
Summary of causality assessments for BC using the main-test for 11 case reports with primarily suspected BC hepatotoxicity.

	Patient	Reference/identification	Main-test for BC (score)	Main-test for BC (causality)
Case reports ($n = 11$)	01	Whiting et al. [11], their case 01	+2	Unlikely
	02	Whiting et al. [11], their case 02	−3	Excluded
	03	Lontos et al. [12]	−2	Excluded
	04	Cohen et al. [13]	−2	Excluded
	05	Levitsky et al. [14]	−2	Excluded
	06	Lynch et al. [15]	−3	Excluded
	07	Nisbeth and O'Connor [16]	−3	Excluded
	08	Dunbar and Solga [17]	+2	Unlikely
	09	Joy et al. [18], their case 01	0	Excluded
	10	Joy et al. [18], their case 02	+5	Possible
	11	Chow et al. [19]	+2	Unlikely

Details of the 11 cases are presented in Tables 1–4. The data of the main-test are derived from Table 3.

Table 6
Overview of 2 spontaneous EMEA cases with primarily suspected BC hepatotoxicity.

Patients/authors	BC product/BC treatment	Co-medication/co-morbidity	Original information	Comments/final diagnosis	Additional references
Patient 01, age unknown, EMEA [20], EU case 28.	Not assessable: brand name, manufacturer, plant part solvent.	None.	Time of onset of reaction with relation to BC exposure, but no details presented.	Poorly documented case.	Teschke and Schwarzenboeck [39]
	80 mg/d, duration of BC treatment not assessed.		Daily BC overdose.	Daily BC overdose.	USP [22]
			No information on differential diagnostic assessment.	The main-test for BC yielded -1 point corresponding to an excluded causality [39]. EMEA evaluated the case with a possible causality (+4 points) using the CIOMS scale [20], and USP arrived at the same level of causality with the Naranjo scale [22].	
			Hepatocellular injury with bilirubin elevation.	Final diagnosis: Daily BC overdose.	
			Initial diagnosis: BC hepatocellular injury.	Unassessable liver disease.	
Patient 02, >55 years, female, EMEA [21], its non-EU case 04.	Not assessable: brand name, manufacturer, plant part, solvent.	Atenolol, Flurazepam, Lorazepam, Lithium.	Patient with pre-existing liver disease of unknown origin and increased serum activities of liver enzymes suggestive of mild hepatocellular injury.	Poorly documented case of a multimorbid patient with pre-existing liver disease.	Teschke et al. [40], USP [22]
	80 mg/d, 5 weeks.	Pre-existing liver disease, cholecystolithiasis, psychiatric disorders, benzodiazepine abuse, hypertension.	Reported positive dechallenge for BC and atenolol with not presented actual data.	No assessment of differential diagnoses.	
			Daily BC overdose.	Daily BC overdose.	
			Initial diagnosis: Hepatotoxicity by BC and CD, pre-existing liver disease, cholecystolithiasis, psychiatric disorders, benzodiazepine abuse, hypertension.	The main-test rendered +2 points for BC and +1 point for CD, equivalent to an unlikely causality for both BC and CD [40]. EMEA used the CIOMS scale and classified the case with +5 points for BC, correlating to a possible causality [21]. Causality for CD was not quantified. USP assessed a possible causality for BC with the Naranjo scale [22].	
				Final diagnosis: Exacerbation of pre-existing liver disease, unrelated to BC and CD. Cholecystolithiasis, psychiatric disorders, benzodiazepine abuse, hypertension, daily BC overdose.	

The EMEA cases 1 and 2 have been assessed previously by EMEA [20,21] and by other reports [22,39,40]. For abbreviations see legend of Table 1.

incidences of idiosyncratic hepatotoxicity by BC in a few susceptible users.

Another limitation consists in the low quality of individual data in patients with primarily assumed BC hepatotoxicity. Poor data quality is a common challenge in causality assessment of DDS hepatotoxicity [3–5,51]. This pertains especially to questionaries of Adverse Drug Reaction (ADR) reports to regulatory agencies that are not specific for toxic liver diseases [3–5,51], a condition applicable to all 69 cases of the present analysis. It should also be acknowledged that regulatory databases may lack information required for a sound causality evaluation, unless active data collection by the regulatory agency is accomplished [3,4,51]. Reviewing the data of cases with suspected BC hepatotoxicity presented by regulatory agencies [21,22], it appears that for these cases little regulatory effort to obtain additional data from the reporting physicians was accomplished.

The diagnostic strength to prove or disprove BC hepatotoxicity is limited in view of the absence of a diagnostic biomarker [5]. However, this shortcoming is compensated by the application of the structured quantitative CIOMS scale [43] and of the main-test as its updated form [5]. The CIOMS scale has been established by international experts and is based on the results of rechallenge tests [43,44]. It has been well validated regarding sensitivity (86%), specificity (89%), positive predictive value (93%), and negative predictive value (78%) [44]. It is also considered as the most widely used causality assessment method for DDS hepatotoxicity [6]. Therefore, the used causality methods may offset missing biomarkers and possibly the opinions of expert groups.

Finally, confounding variables may limit the quality of our analysis. The used structured causality assessment methods consider in their scales some, but not all of the confounding factors. In particular, the major limitation is the uncertainty of the BC product in cases when an unregulated BC dietary supplement was used (Table 1) [21,22,39,40]. This leaves the question, for instance, whether BC was really an ingredient of the BC product [39], or whether a problem of adulteration may exist [22]. Despite these uncertainties, in the present analysis of 69 cases it was primarily assumed on pragmatic grounds that all patients had used a product which contained BC. When BC was used in a herbal mixture, causality assessment was done for BC with the understanding that the result refers to BC and the other ingredients of the mixture.

9. Concluding remarks

Causality for BC has been assessed in a total of 69 patients with primarily assumed BC hepatotoxicity. These cases refer to the evaluation by EMEA ($n = 36$), the present analysis of published case reports ($n = 11$), and the individual data of patients presented by USP for spontaneous reports of CADRMP, TGA, and MedWatch/FDA ($n = 22$). With the original CIOMS scale and the main-test as its updated scale, 68 of 69 patients reached an excluded, unlikely, unrelated, or unassessable causality for BC. For only 1 patient causality was possible for BC and also for symptomatic cholelithiasis with confounding factors of fatty liver of undefined cause, unknown BC brand including possible herbal mixture, unknown daily BC dose, and unassessable duration of BC treatment. Future strategies should focus on prospective studies for each single case with suspected BC hepatotoxicity.

Conflict of interest

No conflicts of interest exist.

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