Review Article

Clinical Review: Herbal Hepatotoxicity and the Call for Systematic Data Documentation of Individual Cases

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Abstract

Considerable clinical and regulatory interests exist for herbal hepatotoxicity, also called herb induced liver injury [HILI]. It often is uncertain whether causality can firmly be attributed to a specific herbal preparation marketed as tea, vegetable, herbal drug, herbal dietary supplement [HDS], or herbal traditional Chinese medicine [TCM]. Confounding variables and methodological problems of poor case data documentation require substantial improvements in future presentations of suspected HILI cases to clarify these discrepancies. Essentials of systematic data documentation of individual HILI cases focus on complete narrative case details extracted from raw data, herbal product identification, herbal treatment modalities, symptom latency, liver enzyme evaluation, laboratory hepatotoxicity criteria, liver injury pattern, biliary tract imaging, hepatitis serology, comedication, exclusion of alternative causes, and causality estimation by the CIOMS scale [Council for International Organizations of Medical Sciences], syn. RUCAM [Roussel Uclaf Causality Assessment Method], best to be used as its update. For HILI cases, we strongly recommend clinical evaluation and concomitant causality assessment by the updated CIOMS scale, which considers all core elements of hepatotoxicity, is specific and validated for hepatotoxicity, structured, itemized, and quantitative, with obligatory transparent documentation of each CIOMS item and an individual score for each patient with suspected HILI; an optional expert opinion that is based on scored CIOMS items may follow, if uncertainty remains. Thus, a diagnostic framework with systematic data management and mandatory documentation of individual cases with suspected HILI will provide the basis for robust and transparent clinical and causality evaluation. This is highly appreciated by the scientific community and regulatory agencies for reasons of reassessing and gaining valid information of HILI caused by a specific plant.

ABBREVIATIONS

AIH: Auto Immune Hepatitis; ALP: Alkaline Phosphatase; ALT: Alanine AminoTransferase; AMA: Antimitochondrial Antibodies; ANA: Antinuclear Antibodies; AST: Aspartate Aminotransferase; BC: Black Cohosh; BfArM: Bundesinstitut für Arzneimittel und Medizinprodukte in Bonn, Germany; CADRMP: Canadian Adverse Drug Reaction Monitoring Program in Toront, Canada; CAM: Complementary and Alternative Medicine; CD: Comedicated Drug[s]; CIOMS: Council for International Organizations of Medical Sciences; CMV: Cytomegalovirus; EBV: Epstein Barr virus; EMA: European Medicines Agency in London, United Kingdom; ERCP: Endoscopic Retrograde Cholangiopancreaticography; FDA: Federal Drug Administration in Washington DC, USA; GC: Greater Celandine; HAV: Hepatitis A Virus; HBc: Hepatitis B Core; HBV: Hepatitis B Virus; HCV: Hepatitis C Virus; HEV: Hepatitis E Virus; HDS: Herbal Dietary Supplement; HILI: Herb Induced Liver Injury; HSV: Herpes Simplex Virus; LKM: Liver

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Kidney Microsomal antibodies; MRCP: Magnetic Resonance Cholangiopancreaticography; MRT: Magnetic Resonance Tomography; N: Normal range as multiple of its upper limit; PCR: Polymerase Chain Reaction; PS: *Pelargonium Sidoides*; R: Ratio; RUCAM: Roussel Uclaf Causality Assessment Method; SMA: Smooth Muscle Antibodies; TCM: Traditional Chinese Medicine; TGA: Therapeutic Goods Administration, Australia; USP: United States Pharmacopeia; VZV: Varicella Zoster Virus; WHO: World Health Organization

INTRODUCTION

Over the past few years, the use of medicinal herbs has increased worldwide [1,2], with regulatory surveillance of these products differing from country to country due to lack of international harmonization [1,3]. The world market for herbal medicines that are based on traditional knowledge, is estimated at US$ 60 billion annually [4], according to a United Nations report dating back to 2000 [5]. In the United States alone, the total estimated herb retail sales in all channels rose from $ 4,230 million in 2000 to $ 6,032 million in 2013, equaling to 42.6% overall and 3.3% annual increase according to the data of the American Botanical Council [6]. These figures are comparable to the increased use of complementary and alternative Medicine [CAM], since an estimated $ 27 billion was spent by consumers of CAM in the United States in 1997 [7] and $ 33.9 billion in 2007 [8], equaling to a 25.5% rise. These figures combine all CAM related expenditures spent out of pocket on visits to CAM practitioners and purchases of CAM products, classes, and materials in the Unites States in 2007, with $14.5 billion spent on the purchase of nonvitamin, nonmineral, and natural products [8]. The use of herbal medicines exerts a high economic impact on our society with special financial benefits for herb producers, providers, and healers. Considering this enormous economic impact and the resulting expenditures, it still remains unclear whether these high costs for the consumers and the society are warranted. In addition, herbal medicines are increasingly discussed due to concerns of their efficacy and safety [9], especially with respect to adverse reactions [2,10] including serious liver injury [9]. However, cases of assumed herbal hepatotoxicity often are poorly documented and rarely allow robust conclusion of causality.

In this review article, we focus on the need for a stringent case documentation of herbal hepatotoxicity, also called herb induced liver injury [HILI], to improve transparency required for both a comprehensive assessment of this specific disease including a valid causality assignment and an optional causality reevaluation by other physicians, scientists and regulatory agencies.

NARRATIVE CASE DETAILS

Clinicians are interested in clinical features observed in individual HILI cases and expect appropriate information; however, the description commonly is insufficiently presented in publications of most assumed HILI cases, hampering causality assignment as criticized for several examples [11-17], including approaches used by the German regulatory agency BfArM [Bundesinstitut für Arzneimittel und Medizinprodukte] [11-14,18], the European Medicines Agency [EMA] [15,19], the United States Pharmacopeia [USP] [15,20], and the World Health Organization [WHO] [14,21]. Obligatory documentation

is required for the age and sex of the patient, description of the herbal product with type and amount of ingredients, treatment modalities with daily dose and duration, first symptoms and subsequent clinical course, diagnostic approaches with results, and outcome. Several of these items have been reported in published cases [22-28] or spontaneous reports [29] of suspected Greater Celandine [GC] hepatotoxicity, some of these are compiled as an example for a good case documentation (Table 1) [30], with additional causality results published earlier [30]. Similar compilations have been presented for other cases of primary suspicion but not necessarily confirmation of HILI by several herbs or herbal products such as black cohosh [BC] [31-33], *Pelargonium sidoides* [PS] [16,17], or kava [12]. Supporting evidence of liver specific, structured, and quantitative causality evaluation and clinical data have been tabulated in detail for all herbs mentioned above [12,16,17,31-33]. Case details of HILI caused by herbal TCM were not tabulated in a recent report [34] but provided within the text. Clearly, for a single case report a detailed description of clinical findings within the text is sufficient, provided appropriate details are included, as exemplified in a case of hepatotoxicity by Indian Ayurveda herbs [35]. Still, tabulated narrative case details (Table 1) [30] are the preferred tools for case documentation [12,16,17,30-33,36,37] and will increase transparency, thereby improving data quality of HILI reports.

Case data completeness

Another contentious issue is case data completeness, which is rarely achieved, limiting any conclusion whether and on which data basis causality had been assumed. For reasons of data transparency and completeness, tabulations with details preferentially extracted from raw data are useful as key elements for a thorough documentation and provided data on a case by case basis in a few case series of initially assumed HILI by GC [30,36,37], BC [32,33,38], Herbalife® [39], and PS [16,17], exemplifying good clinical documentation (Table 2) [15].This tabulation serves both as documentation for each individual patient, and as a checklist during HILI case assessment with several items combined in ten domains: [1], herbal product identification; [2], herbal treatment modalities; [3], symptom latency; [4], liver enzyme value evaluation; [5], laboratory hepatotoxicity criteria; [6], liver injury pattern; [7], biliary tract imaging; [8], hepatitis serology including hepatitis E; [9], comedication; and [10], causality assessment and exclusion of alternative diagnoses.

Herbal product identification

In HILI cases, herbal product name identification often is fragmentary, sufficient identification was lacking in 31.9% in a recent study with 22/69 cases shown in a preferred documentation as example (Table 2) [15]. Clearly, whenever the herbal product was not identifiable, a robust causality assignment is not possible [15], despite other views [20]. The product identification rate was high in some spontaneous HILI reports [16,17,36], but low in another case series being as low as 42.9% [37] of the assessed cases. Apart from the product name, complete identification of all actual ingredients of the

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Table 1: Preferred documentation as example: Compilation of narrative case details and clinical data of patients with HILI by Greater Celandine [GC] and established causality.

Patient	Identification	Specific information for each individual patient
01	Strahl et al., 1998 [22] 42 years Female	GC extract of known brand name and manufacturer [3 capsules/d containing each 200 mg of probably dried herb for 9 months]. Bloating as indication for treatment. Latency period of 2 months for first symptoms of itching and jaundice, at rechallenge 1 month. ALT 755 U/L, AST 350 U/L, ALP 221 U/L. Upon cessation of GC treatment, rapid decrease but not normalization of ALT values reported. Readministration of GC with positive result. Exclusion of virus hepatitis A-C and infections of other hepatotropic viruses reported, with lack of any details regarding hepatitis A, B, and C, CMV, EBV, HSV or VZV. Exclusion of biliary obstruction by sonography. Exclusion of autoimmune hepatitis reported with lack of specified parameters. Normal values of iron and copper parameters. Liver histology: Acute hepatitis with confluent liver cell necroses and little inflammation. **Final diagnosis: Highly probable GC hepatotoxicity.**
02	Benninger et al., 1999 [23], their case 5 37 years Female	GC extract as drug of known brand name and manufacturer [unknown dose/d for 3 months]. Atopic eczema as indication for GC treatment. Various herbal and homeopathic drugs as CD. Latency period of 3 months until symptoms of nausea and jaundice. ALT 813 U/L, AST 898 U/L, ALP 249 U/L. ALT course described. Positive reexposure test.for GC. Five months after GC discontinuation, normalization of liver parameters reported. Exclusion of infections by HAV, HBV, HBC, HEV, CMV, and EBV. SMA 1:40, exclusion of AIH. Ultrasound examination with normal bile ducts. Liver histology not done. **Final diagnosis: Highly probable GC hepatotoxicity.**
03	Benninger et al., 1999 [23], their case 6 65 years Female	GC extract of unknown brand name and manufacturer [unknown dose/d for 3 months]. Dyspepsia as indication for GC treatment. Latency period and symptoms not recorded. No CD. ALT 152 U/L, AST 89 U/L, ALP 451 U/L. After GC discontinuation, ALT course not sufficiently documented. Normalization of liver values 3 months after GC withdrawal. Exclusion of common causes for hepatitis reported, but lack of information regarding specific parameters. Lack of ultrasound data. Liver histology: Moderate drug induced hepatitis with low grade single cell necrosis. **Final diagnosis: Probable GC hepatotoxicity.**
04	Crijns et al., 2002 [24] 42 years Female	Herbal mixture of GC and curcuma root [*Curcuma longa rhizoma*] of known brand name and manufacturer [unknown dose/d for 2 months]. Not further described skin complaints as indication for treatment. Before admission, paracetamol [500 mg] tablet on one day. Latency period: 5 weeks until jaundice. Fever 40.5⁰ C for 2 weeks, starting 2 weeks after initiation of GC treatment. ALT 1490 U/L, AST 838 U/L, ALP 265 U/L. Following cessation of the herbal mixture, ALT course described with normalization of liver values after 2 months. Exclusion of acute hepatitis A-C and infections by CMV, and EBV, but HSV and VZV not assessed. Normal titres of ANA, but no data of AMA, SMA, and LKM. Sonography with normal biliary tract. Liver histology: Severe acute hepatitis of viral or toxic drug cause. **Final diagnoses: Probable GC hepatotoxicity and possible curcuma hepatotoxicity.**
05	Stickel et al., 2003 [25], their case 2 69 years Male	GC extract as drug of known brand name and manufacturer [80 capsules within 5-6 weeks]. Postprandial abdominal discomfort as indication for GC treatment. Latency period of 5-6 weeks until symptoms of weakness, abdominal pain in the right upper quadrant, nausea, jaundice, and dark brown urine. Medical history included cholecystectomy 4 years ago. Lack of regular comedication. Alcohol consumption below 20 g/d. ALT 881 U/L, AST 466 U/L, ALP 312 U/L. ALT course not recorded. Exclusion of acute viral hepatitis including HAV, HBV, HCV, CMV, EBV. Autoimmune parameters not assessed. By abdominal ultrasound and magnetic resonance tomography common and intrahepatic bile ducts inapparent. Liver histology: Cholestatic hepatitis compatible with drug toxicity. **Final diagnosis: Probable GC hepatotoxicity.**
06	Rifai et al., 2006 [26] 58 years Male	GC extract as drug of known brand name and manufacturer [unknown amounts of tablets/d for 3 weeks]. Biliary spasms as indication for GC treatment. Latency period: of 3 weeks until fatigue, dark urine, itching, jaundice, and pale stool. No CD. ALT 903 U/L, AST 380 U/L, ALP 516 U/L. After GC withdrawal well documented ALT course with ALT normalization within 4 weeks. Well documented exclusion of hepatitis A-C, and E, and of infections by CMV, EBV, HSV, and VZV reported. Well documented exclusion of infectious, autoimmune, metabolic, and genetic causes of acute hepatitis. Sonography with slightly thickening of the gall bladder and otherwise normal biliary tract. Liver histology: Lobular hepatitis with severe cholestasis and moderate inflammation that included also the bile ducts. **Final diagnosis: Probable GC hepatotoxicity, but also possible causality for biliary disease.**
07	Conti et al., 2008 [27] 46 years Female	GC extract as solution of known brand name and manufacturer, containing also other herbs as are *Lycopodium serrata, Carduus marianus, Hamamelis, Ruta, Sepia, Pulsatilla, Collinsonia,* and *Hydrastis* [50 drops/d for 8 weeks]. Insomnia and for sedation as indication for treatment. Latency period of 8 weeks until symptoms of nausea, anorexia, asthenia, and abdominal discomfort. Herbal mixture with various herbs and the potentially hepatotoxic *Lycopodium serrata* as CD. ALT 2,364 U/L, AST 737 U/L, ALP 255 U/L. Rapid decrease of ALT in the further course following treatment cessation with normalization after 2 months. Exclusion of HAV, HBV, HCV, CMV, EBV, and HSV. Specified serological tests for autoimmune diseases negative. Sonography without reported biliary tract abnormalities. Liver histology: Moderate mixed inflammatory infiltrate with eosinophils.. **Final diagnoses: Probable GC hepatotoxicity, probable *Lycopodium serratum* hepatotoxicity.**

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08	Moro et al., 2009 [28] 65 years Male	GC extract as herbal tea derived from GC leaves [1 cup/d for 1 month]. Pyrosis as indication for GC treatment. Lansoprazole 15 mg/d for 2 years as current CD. Latency period of 1 month. Asthenia, dyspepsia, dark urine, and jaundice as symptoms. ALT 4,765 U/L, AST 3,235 U/L, ALP not reported. ALT course not reported, but normalization of all liver parameters within 2 months. Three months before symptom onset, treatment with clarithromycin and amoxicillin for 1 week. All antibodies for not further specified hepatic viruses resulted negative except for anti-HCV that was found positive despite negative HCV-PCR. Autoimmune parameters not reported. Hepatomegaly by ultrasound examination. Liver histology: Moderate drug induced hepatitis. **Final diagnosis: Probable GC hepatotoxicity.**
09	BfArM, 2005 [29] 95003848 32 years Male	GC extract as drug of known brand name and manufacturer [2 capsules/d for not clearly defined duration]. Upper abdominal pains as indication for treatment. Latency period not report ed, jaundice as symptom. ALT 2,196 U/L, AST 714 U/L, ALP 256 U/L. Upon cessation of GC treatment, decrease but not normalization of ALT and AST values, with lack of reported ALP value. Readministration of GC with pruritus and not further specified increases of liver values and lack of complete resolution upon dechallenge. Overall course of ALT not sufficiently documented, neither at first and second dechallenge, nor in the interval and after the second challenge. Undulating ALT values of unknown clinical significance. Exclusion of virus hepatitis reported, with lack of any details regarding hepatitis A, B, and C, CMV, EBV, HSV or VZV. Exclusion of biliary obstruction by sonography and ERCP. Exclusion of autoimmune hepatitis with lack of reported parameters. Normal values of ceruloplasmin, α-1 Antitrypsin, and electrophoresis. Liver histology: Unspecific hepatitis with liver cell necroses. Poorly documented case including questionable rechallenge and lack of ALT normalization. **Final diagnosis: Probable GC hepatotoxicity.**
10	BfArM, 2005 [29] 96026841 55 years Female	GC extract as drug of known brand name and manufacturer [3 capsules/d for 6 weeks]. Upper abdominal pains as indication for treatment. Latency period of 6 weeks with jaundice as symptom. Diltiazem 90 for several years and doxycycline for 10 days [start prior to jaundice] for treatment of erythema migrans as CD. ALT 2,016 U/L, AST 620 U/L, ALP 398 U/L. After cessation of GC treatment, normalization of ALT not reported and with 201 U/L on day 19 still increased. Overall ALT course poorly documented. Exclusion of hepatitis A, B, and C reported without details of assessed parameters. Lack of exclusion of virus infections by CMV, EBV, HSV, and VZV. Negative results for AMA, SMA, LKM, and actin. Exclusion of biliary obstruction by sonography and ERCP. Liver histology: Compatible with drug induced liver injury **Final diagnosis: Highly probable GC hepatotoxicity.**
11	BfArM, 2005 [29] 98000501 65 years Male	GC extract as drug of known brand name and manufacturer [2-3 capsules/d for 42 days]. To increase bile flow after cholecystectomy 20 years ago as indication for treatment. Latency period of 42 days with itching and jaundice as symptoms. ALT 461 U/L, AST 355 U/L, ALP 260 U/L, normalization not reported. After GC discontinuation, on day 12 ALT 235 U/L. Exclusion of hepatitis A-C and of infections by CMV, EBV, HSV, and VZV. AMA negative, exclusion of autoimmune hepatitis reported but individual parameters not described. Upon sonography and ERCP normal bile ducts after cholecystectomy. **Final diagnosis: Highly probable GC hepatotoxicity.**
12	BfArM, 2005 [29] 98001447 49 years Female	GC extract as drug of known brand name and manufacturer [3 tablets/d for 4 weeks]. Upper abdominal pains as indication for treatment. Latency period of 3.5 weeks with reduced appetite, bloating, epigastric pain, nausea, vomiting, and jaundice as symptoms. ALT 2928 U/L, AST 1116 U/L, ALP 408 U/L. After GC discontinuation, on day 7 ALT was 1356 U/L, and on day 20 it was 426 U/L. Normalization of ALT has not been reported. Exclusion of hepatitis A-C, E and F, and of infections by CMV, EBV, and HSV, but not of VZV. Normal values of ANA, AMA, and SMA. Upon ultrasound and ERC, normal bile ducts and cholecystolithiasis or cholesterol polyps of the gallbladder, by ultrasound questionable cholecystitis. Liver histology: Severe portal hepatitis with beginning fibrosis. **Final diagnosis: Probable GC hepatotoxicity.**
13	BfArM, 2005 [29] 98001607 59 years Female	GC extract as drug of known brand name and manufacturer [3 tablets/d for 7 weeks]. Vomiting, upper abdominal pains and gastro-esophageal reflux as indications for treatment. Latency period o 20 days with tiredness, exhaustion, nausea, vomiting, and jaundice as symptoms. Asthma, treated with various sprays, and latent hyperthyroidism without treatment as comorbidities. Maximum values reported for ALT 960 U/L, AST 421 U/L, and ALP 425 U/L, with decrease but not normalization following GC discontinuation, but actual results have not been reported. Through histology, ERCP, and serology [HAV, HBV, HCV] other hepatobiliary diseases excluded, but details not reported. Missing exclusion of infections by CMV, EBV, HSV, and VZV. Poorly documented case. **Final diagnosis: Probable GC hepatotoxicity.**
14	BfArM, 2005 [29] 98008527 60 years Female	GC extract as drug of known name and manufacturer [3 capsules/d for several weeks]. General discomfort as indication for treatment. Latency period of several weeks with abdominal pains, nausea, and jaundice as symptoms. Crataegus extract as CD. ALT 420 U/L, AST 451 U/L, ALP 288 U/L. At discharge after 4 weeks, ALT with 26 U/L still slightly elevated. Exclusion of acute hepatitis A-C and infections by CMV, and EBV, but HSV and VZV not assessed. Normal titres of ANA, AMA, SMA, and LKM. Sonography and ERCP with normal biliary tract. Liver histology: AIH or dug induced liver injury. **Final diagnosis: Probable GC hepatotoxicity.**

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15	BfArM, 2005 [29] 00000278 65 years Male	GC extract as drug of known brand name and manufacturer [3 capsules/d for 4 weeks]. Bloating as indication for treatment. Latency period of 3.5 weeks with jaundice as symptom. Diclofenac [intermittent], sitosterols, butizide, raubasine, rescinnamine, and reserpine as CD. ALT 950 U/L, AST 570 U/L, normal ALP. Under treatment with cortisone and at discharge, ALT 193 U/L, but normalization of ALT with and without cortisone not reported. Exclusion of hepatitis A-C and of infections by CMV, EBV, and HSV reported. Normal titres of ANA, AMA, and SMA. Sonography and ERCP with normal biliary tract. Liver histology: Hepatitis with cholestasis. **Final diagnosis: Probable GC hepatotoxicity.**
16	BfArM, 2005 [29] 02001171 66 years Female	GC extract as drug of known brand name and manufacturer [0-2 capsules/d for 4.5 months]. Dyspepsia as indication for treatment. Latency period of 4.5 months with reduced appetite and jaundice as symptoms. ALT 760 U/L, AST 408 U/L, ALP 337 U/L. On day 14 after GC cessation, ALT 379 U/L, and on day 24 ALT 207 U/L. Normalization of ALT not reported. Exclusion of hepatitis A-C reported, but details not presented. No exclusion of infections by CMV, EBV, HSV, and VZV. Autoimmune parameters not done. Sonography, MRCP and MRT with normal biliary tract. Insufficiency of the mitral valve. **Final diagnosis: Probable GC hepatotoxicity.**

Preferred documentation: Narrative compilation with details of relevant clinical data of 16 patients with liver injury by the use of the herb GC, derived from a review article [30] based on previous analyses [36,37]. In these studies, highly probable and probable causality levels for GC were established in all patients presented as final diagnoses, using the updated CIOMS scale for the individual causality assessment. Half of the patients [cases 01-08] were derived from published case reports [22-28], the other half [cases 09-16] from spontaneous reports of the German regulatory agency BfArM [29]. Outcome was favourable in all cases.

Abbreviations: AIH: Autoimmune Hepatitis; ALP: Alkaline Phosphatase; ALT: Alanine Aminotransferase; AMA: Antimitochondrial Antibodies; ANA: Antinuclear Antibodies; AST: Aspartate Aminotransferase; BfArM: Bundesinstitut für Arzneimittel und Medizinprodukte, Bonn; CD: Comedicated Drug[s]; CIOMS: Council for International Organizations of Medical Sciences; CMV: Cytomegalovirus; EBV: Epstein Barr Virus; ERCP: Endoscopic Retrograde Cholangiopancreaticography; GC: Greater Celandine; HAV: Hepatitis A Virus; HBV: Hepatitis B Virus; HCV: Hepatitis C Virus; HEV: Hepatitis E Virus; HSV: Herpes Simplex Virus; LKM: Liver Kidney Microsomal Antibodies; MRCP: Magnetic Resonance Cholangiopancreaticography; MRT: Magnetic Resonance Tomography; PCR: Polymerase Chain Reaction; SMA: Smooth Muscle Antibodies; VZV: Varicella Zoster Virus

Table 2: Preferred documentation as example: Overview of known information regarding all 69 patients with primarily suspected but not established HILI by black cohosh [BC].

Presented information	Cases	Individual cases
Brand name	22/69	1,5,11,12,13,14,15,16,17,18,19,20,21,22,23,24,28,29,30,31,32,33
Manufacturer	12/69	1,5,11,17,18,20,28,29,30,31,32,33
Plant part	06/69	1,5,8,11,28,33
Solvent	02/69	1,11
Daily dose	11/69	1,3,5,6,7,11,12,13,16,17,18
BC drug	07/69	1,11,19,21,23,24,31
BC herbal supplement	01/69	5
BC polyherbal product	14/69	2,3,12,13,14,15,16,17,18,20,22,28,30,33
Date of BC start	20/69	1,3,4,5,6,7,8,10,11,12,13,15,18,20,21,22,27,28,29,33
Date of BC end	17/69	1,3,4,5,6,7,8,10,11,12,13,15,18,19,20,21,22
Date of symptoms	24/69	1,2,3,4,5,6,7,8,10,11,12,13,14,15,16,18,19,20,21,22,23,27,32,33
Temporal association	12/69	1,4,5,6,8,10,12,13,18,20,21,22
Time on BC	16/69	1,3,4,5,6,7,8,10,11,12,13,15,18,20,21,22
Time to onset	19/69	1,3,4,5,6,7,8,9,10,11,12,13,18,20,21,22,27,28,33
ALT value	15/69	1,2,3,4,5,6,7,8,10,11,12,13,15,23,32
ALP value	12/69	1,2,3,4,5,6,7,11,12,13,23,32
Hepatotoxicity criteria	14/69	1,2,3,4,5,6,7,8,10,11,12,13,23,32
ALT de-challenge	06/69	4,6,7,10,11,15
Biliary tract imaging	08/69	4,5,6,7,9,10,15,28
HAV	13/69	1,2,3,4,5,6,7,8,9,10,11,14,15
HBV	12/69	1,3,4,5,6,7,8,9,10,11,14,15
HCV	13/69	1,2,3,4,5,6,7,8,9,10,11,14,15
HEV	0/69	-

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CMV	09/69	1,4,5,6,8,10,11,14,15
EBV	09/69	1,4,5,6,8,10,11,14,15
HSV	03/69	4,6,8
VZV	01/69	8
Co-medication/ herbal mixture	23/69	2,3,4,5,6,7,11,12,13,14,15,16,17,18,20,22,23,27,28,29,30,32,33
BC undetermined product	13/69	4,6,7,8,9,10,25,26,27,29,32,34-69

Preferred documentation: The group of the 69 cases consisted of 11 case reports [cases 1-11], 13 TGA cases from Australia [cases 12-24], 2 CADRMP cases from Canada [cases 25 and 26], 7 MedWatch/ FDA cases from the United States [cases 27-33], and 33 EMA cases from the European Union [cases 34-69]. Details and references of the 69 cases were adapted and published earlier [15].

Abbreviations: 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; HEV: Hepatitis E ; HSV: Herpes Simplex Virus; VZV: Varicella Zoster Virus

incriminated herbal product is another crucial issue, violated not only by mislabelled herbs [20] but also missing labelling contaminants and adulteration by synthetic drugs that were added to enhance efficacy of the herbal preparation [15].

Herbal treatment modalities

Duration of herbal use is an essential criterion for a temporal association and requires a correct documentation. Failure to provide the temporal association between herbal use and the unfolding liver disease (Table 2) [15] inevitably leads to lack of an established causality [15,17,20]. In HILI case series, documentation of a temporal association was successfully reported in 66.7% [16], 38.5% [17], 90.9% [36], and 95.2% [37] of the evaluated cases. Documentation of daily doses was variably reported in 53.3% [16], 69.2% [17], 90.9% [36], and 19.1% [37] in all cases.

Symptom latency

The exact dates of the first symptom observations or transaminases or alkaline phosphatase [ALP] elevations, found for instance by chance at a routine check up, are required and should be part of any case documentation (Table 2) [15] to safely exclude symptoms that existed prior to herbal use initiation, or herbs that were used to treat preexisting symptoms of an already unfolding disease unrelated to the later assumed HILI. The latency period provides additional support for or against a temporal association and often clarifies causality. In HILI case series, documentation of dates of first symptoms that allowed assessment of a temporal association was provided for 66.7% [16], 76.7% [17], 68.2% [36], and 1.1% [37] of the cases.

Liver enzyme evaluations

Values of transaminases ALT [alanine aminotransaminase] and AST [aspartate aminotransaminase], and of ALP are corner stones to definitively diagnose liver disease and provide guidance for the further clinical course during dechallenge after cessation of herbal use; mandatory documentation of these values facilitates HILI case assessment, as exemplified for a BC case series (Table 2) [15]. In this series, documentation was unacceptable: out of 69 cases, initial values of ALT were available in 15 patients [21.7%] and in six patients [8.7%] during dechallenge, raising serious doubts of an existing liver disease in most of the reported cases [15]. In other case series, frequency of documented initial ALT values was higher with figures of 80.0% [16], 53.9% [17], 86.4% [36], and 100% [37] in all cases.

Laboratory hepatotoxicity criteria

HILI case assessment mandates internationally accepted hepatotoxicity criteria for disease characterization, best defined by the laboratory values ALT and/or ALP, expressed as N in multiples of the upper limit of their normal range [39-41]. Recommended criteria of HILI for ALT were previously >2N [42,43], and are currently >5N [39,40,44] or 3N if total bilirubin values exceed 2N [44]; for ALP, values of >2N are commonly considered diagnostic [42-44]. Neglecting hepatotoxicity criteria by failure of documentation in 23.2% of suspected HILI cases (Table 2) invalidates any attempt to construct a causal association between herbal use and liver disease [15], although opposing views have been published [20]. Problems of criteria neglect were not evident in analyses of EMA [19] but in WHO assessments [21] and other reports of purported HILI, with frequencies of reported criteria of 80.0% [16], 38.5% [17], 86.4 [36] %, and 85.5% [37] of all cases.

Liver injury pattern

Based on laboratory constellations, all HILI cases should undergo mechanistic differentiation into hepatocellular, cholestatic or the mixed form of hepatotoxicity. This is feasible by comparing serum activities of ALT and ALP at diagnosis of suspected herbal hepatotoxicity [42,43]. Enzyme activity is expressed as a multiple of the upper limit of the normal range [N], and the ratio [R] of ALT/ALP is calculated. Liver injury is classified as hepatocellular, if ALT > 2N alone or R ≥ 5; cholestatic, when there is an increase of ALP > 2N alone or when R ≤ 2; of the mixed type, if ALT > 2N, ALP is increased and 2 < R < 5 [40,41]. Differentiation of liver injury pattern guides in selecting the correct criteria for assessing causality by positive test results of unintentional reexposures [40-45,46] and by the CIOMS [Council for International Organizations of Medical Sciences] scale, also called RUCAM [Roussel Uclaf Causality Assessment Method] [40-43]. Documentation of liver injury pattern was provided in 53.3% [16], 38.5% [17], and 68.2% [36] of the HILI cases.

Biliary tract imaging

Biliary tract diseases are easily overlooked in primarily assumed HILI cases, especially in the absence of biliary tract imaging data to exclude biliary stone disease. It shows poor clinical management when only 8/69 patients [11.6%] in a case series of initially assumed HILI received the benefit of some kind of a biliary tract imaging (Table 2) [15]; data in other suspected

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HILI case series show variable frequencies of 0% [13], 20% [16], 38.5% [17], 59.1% [36], and 52.4% [37] of all cases. Biliary tract diseases are among the diagnoses most often missed in primarily suspected HILI cases [47].

Hepatitis serology

All forms of hepatitis are diseases with potential comorbidity to HILI, causing problems in causality assessment if not adequately documented and excluded, done in the HILI case series of 69 patients (Table 2) [15]. Among these, hepatitis A-C was excluded in only <19% and others forms of hepatitis in <13% of all cases, with hepatitis E in none [15]. Hepatitis A-C exclusion has been documented in other spontaneous HILI reports for <20% [13], <27% [16], <39% [17], and <64% [36] of all cases, with much lower rates for other hepatitis types including especially hepatits E [13,16,17,36,37]. Therefore, causality for the initially incriminated herb remains disputable unless hepatitis exclusion is done with the appropriate scrutiny and careful documentation.

Comedication

Accurate documentation of any comedication in each case of suspected HILI is mandatory and may be compiled in the narrative case documentation (Table 1) [30] or in a summarizing documentation (Table 2) [15]. Comedication includes any synthetic drug and herbal preparation, each undergoing a separate causality assessment procedure including individual data sets of treatment modalities, especially start and end of use. Appropriate documentation of comedication in HILI case series was presented for 100% [13], 33.3% [16], 69.2% [17], 59.1% [36], and 71.4% [37] of the cases.

Causality evaluation

For HILI cases, we strongly recommend clinical evaluation and concomitant prospective causality assessment by the updated CIOMS scale [40,41,48], which is liver specific, considers all core elements of hepatotoxicity, is well validated for hepatotoxicity, and should be presented as tabulated document (Table 3) [36];

Table 3: Preferred documentation as example: Tabulated causality assessment of 15 patients with primarily suspected HILI by *Pelargonium sidoides* [PS].

Items	Score	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
1. Time to onset from the beginning of the drug • 5 – 90 days	+2	?	+2		+2		+2		+2	+2		+2	+2	?	?	
• < 5 or > 90 days	+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	+1	?	+1	+1	?	?	+1
3. Course of ALT after cessation of the drug • Decrease ≥ 50 % within 8 days	+3				+3								+3			
• Decrease ≥ 50 % within 30 days	+2									+2						+2
• No information	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					?										
4. Risk factor ethanol • Alcohol use [drinks/d: > 2 for woman, > 3 for men]	+1			?											?	
• No alcohol use [drinks/d: ≤ 2 for woman, ≤ 3 for men]	0	0	0		0	0	0		0	0	0	0	0	0	?	0
5. Risk factor age • ≥ 55 years	+1	+1						+1							+1	
• < 55 years	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	0		0	0	0	0		
• Concomitant drug with incompatible time to onset	0										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
• 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							-			-	-				-
• Hepato-biliary sonography / colour Doppler sonography of liver vessels							-			-					-

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	Score															
• 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 titre change for																
CMV [Anti-CMV-IgM / IgG]									-							
EBV [Anti-EBV-IgM / IgG]									-							
HEV [Anti-HEV-IgM / IgG]																
HSV [Anti-HSV-IgM / IgG]																
VZV [Anti-VZV-IgM / IgG]																
Evaluation of group I and II • All causes - group 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				-2				-2							
• Non drug cause highly probable	-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
• Reaction published but unlabelled	+1															
• Reaction unknown	0															
9. Response to readministration • Doubling of ALT with the drug alone	+3															
• Doubling of ALT with the drugs already given at the time of first 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		0	+2	-1	+5	+1	+2	+2	+1	+4	0	+2	+5	-1	+1	+1

Preferred documentation of causality assessment using the scale of CIOMS [Council for International Organizations of Medical Sciences], considering the items for the hepatocellular type of liver injury and the data of a previous report of 15 patients with primarily suspected HILI by *Pelargonium sidoides* [PS] [36]. In the above section 6 of concomitant drug[s], the following products were considered: synthetic drugs, dietary supplements including herbal ones, and polyherbal products. In the 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.

Abbreviations: ALT: Alanine Aminotransferase; 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; HEV: Hepatitis E Virus; HSV: Herpes Simplex Virus; PCR: Polymerase Chain Reaction; VZV: Varicella Zoster Virus; Total points / causality: ≤ 0 / excluded; 1-2 / unlikely; 3-5 / possible; 6-8 / probable; ≥ 9 / highly probable.

an optional expert opinion that is based on scored CIOMS items may follow, if uncertainty remains [40,48]. Thus, a diagnostic framework and systematic data management with mandatory documentation of individual cases with suspected HILI will provide the basis for robust clinical and causality evaluation and transparency. This is highly appreciated by the scientific community and regulatory agencies; it should provide valid information of HILI caused by a specific plant.

The CIOMS scale is worldwide used for hepatotoxicity assessments in epidemiological studies, clinical trials, case reports, case series, regulatory analyses, and genotyping studies, as partially compiled previously [41]. Navarro as a member of the Drug-Induced Liver Injury Network [DILIN] correctly acknowledged that CIOMS/RUCAM is the causality assessment method mostly used and internationally best accepted for DILI cases [49]; this also applies to HILI cases, in line with views of our group [40,41,48]. Actually, CIOMS also was the causality assessment scale most frequently used in a recent large study of HILI case series [47].

Occasional attempts to downplay the relevance of CIOMS/ RUCAM [50] are unwarranted and should be resisted on scientific grounds and clinical usability as provided earlier [40,41,48]; in addition, it appears inappropriate to question the role of two of the participating international experts [50] from the United States [42], who efficiently co-established some criteria of CIOMS/RUCAM but were not co-authors of the validated final CIOMS/ RUCAM scale [49]. In fact, co-authorship was never offered, and hence could not have been declined [Gaby Danan, personal communication 2015].

Advantages and disadvantages of CIOMS/RUCAM have been extensively discussed [40,41,48]. CIOMS provides a pragmatic prospective tool for a robust causality assessment by physicians still at the bedside and at a time when HILI is unfolding and discussed as potential diagnosis. This scale is applicable in any country without delays by final expert evaluations, which may be a crucial issue in a clinical setting. Relying on expert circles alone [50] is ambiguous [47,48] and a step back to the pre-CIOMS era

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in the late eighties of the past century when DILI decisions were made on poorly defined and unscored items, not validated by a gold standard; actually, this situation led to the development of CIOMS/RUCAM, which was validated on positive reexposure test results as gold standard [42,43].

Another approach for causality evaluation consists of assessing results obtained by unintentional reexposures with application of accepted diagnostic criteria; these were fulfilled in some HILI cases [46] and in 1/8 Herbalife® cases [39], again transparent and valid documentation is prerequisite.

For each individual case of primarily suspected HILI, a careful exclusion of possible alternative differential diagnoses including hepatitis E is mandatory, using a standard form as published recently [40,41].

HILI case series characteristics

Attempts of HILI case documentation and causality assessment are not confined to academic interest but fulfil a major requirement of clinicians and practioners during the treatment of patients with HILI. A careful HILI case analysis and documentation facilitates a sound clinical decision and the characterization of a liver injury caused by a single herb, as shown for GC (Table 4) [30]. A similar documentation was feasible and published for kava hepatotoxicity [51]. Exclusion of other causes is required as tabulated (Table 5).

HILI case compilations

HILI case compilations have been published for commonly used herbal drugs and other herbal products [39,52], herbal TCM [traditional Chinese medicine] products [34,53-55], and Indian Ayurveda herbs [35]. For some of these HILI cases, causality assessment results have been published in these reports [34,35,39,53-55], or elsewhere [30,36,37,50,51].

Legal aspects

The current call for systematic data documentation of HILI cases as basis for subsequent case analyses was also stimulated by legal considerations. In the past and in court, judges commonly ask for appropriate case documents and sound evaluation methods in disputed HILI cases. Two court decisions merit special attention, one relates to BC in the United States [56-58] and the other one to kava in Germany [59,60].

In 2005, the case of a 50 year old woman was published with fulminant liver failure and liver transplantation in assumed connection with the use of BC [56]. A product liability action was filed in the United States by the patient after her recovery [57]. The court decision answered the question whether in this specific case sufficient evidence establishes the herb as a generally or individually specific cause for the observed liver disease; for BC, both aspects of causation were denied. General

Table 4: Preferred documentation as example: Clinical characteristics of GC hepatotoxicity.

Characteristics of HILI by GC	
1.	Characterization of GC hepatotoxicity as a specific disease entity was feasible and based on high causality levels for GC in 16 patients with liver disease
2.	Causality for GC was graded highly probable and probable in 4 and 12 patients, respectively
3.	Among these 16 patients, there was an additional causality for comedicated curcuma graded as possible, for comedicated Lycopodium serratum graded as probable, and for biliary disease graded as possible
4.	The existence of GC hepatotoxicity has been verified by a positive reexposure test in two patients
5.	Ages of the 16 patients ranged from 32 to 69 years with an average of 54.7 years, and the ratio of females: males was 10: 6
6.	Comedication with synthetic or herbal drugs and dietary supplements including herbal ones and herbal mixtures was used in the majority of assessable cases
7.	On average, the patients used 10 mg chelidonine daily with lack of daily overdose in any of the cases
8.	Treatment duration was 3 weeks to 9 months with an average of 2.4 months
9.	Latency period until first symptoms was 3 weeks to 4.5 months with an average of 1.7 months, which was considerably shorter than the treatment duration
10.	Jaundice was the most frequently reported symptom, rarely also weakness, anorexia, nausea, vomiting, abdominal pains, dark urine, pale stools, and itching
11.	High serum activities are found for ALT but not for ALP, suggestive of a hepatocellular type of toxic liver injury in patients with GC hepatotoxicity
12.	Histology showed predominantly liver cell necrosis and hepatitis
13.	Outcome was favorable in all 16 patients, with lack of both acute liver failure and requirement of a liver transplant
14.	In one patient, good prognosis was sustained even after 7 months of continued GC Use despite presence of emerging GC hepatotoxicity
15.	GC hepatotoxicity usually represents the hepatocellular and idiosyncratic type of liver injury with its metabolic subgroup, characterised as acute clinical course
16.	The underlying mechanism[s] leading to GC hepatotoxicity as well as possible culprit[s] are still unknown
17.	Due to lack of epidemiologic data, the incidence of GC hepatotoxicity cannot accurately be calculated but appears to be low
18.	In cases of liver disease, causality for GC was verified and creates concern regarding safety of patients and pharmacovigilance considerations

Preferred documentation: The data are based on the cases of 16 patients with GC hepatotoxicity and highly probable or probable causality levels for GC and derived from a previous report [30].

Abbreviations: ALP: Alkaline Phosphatase; ALT: Alanine Aminotransferase; GC: Greater Celandine

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Table 5: Data checklist for HILI diagnosis assessment.

Items to be assessed	Information obtained			Individual result
	Yes	**No**	**Partial**	
● **Brand name** with batch number and expiration date	☐	☐	☐	
● **Indication** of herb use	☐	☐	☐	
● **Begin of symptoms** leading to herb treatment	☐	☐	☐	
● **Daily dose**	☐	☐	☐	
● **Application form** of herb product	☐	☐	☐	
● **Exact date of drug/herb start**	☐	☐	☐	
● **Exact date of drug/herb end**	☐	☐	☐	
● **Exact dates of emerging new symptoms** after drug/herb start in chronological order	☐	☐	☐	
● **Exact date of initially increased liver values**	☐	☐	☐	
● **Time frame of challenge**	☐	☐	☐	
● **Time frame of latency period**	☐	☐	☐	
● **Time frame of dechallenge**	☐	☐	☐	
● **Verification of temporal association**	☐	☐	☐	
● **Exclusion of temporal association**	☐	☐	☐	
● **Gender, age, body weight, height, BMI**	☐	☐	☐	
● **Ethnicity, profession**	☐	☐	☐	
● **Preexisting general diseases with past medical history and actual assessment**	☐	☐	☐	
● **Preexisting liver diseases with past medical history and actual assessment regarding**	☐	☐	☐	
● **Risk factors such as age and alcohol**	☐	☐	☐	
● **Alcohol use with quantification**	☐	☐	☐	
● **Comedication** by synthetic drugs, herbal drugs, herbal and other dietary supplements with all details of product, daily dose, exact dates of start and end of use, indication	☐	☐	☐	
● **ALT value initially** including exact date and normal range	☐	☐	☐	
● **ALT values during dechallenge** at least on days 8 and 30, and later on, with exact dates	☐	☐	☐	
● **ALT values during dechallenge** to exclude a second peak, with exact dates	☐	☐	☐	
● **ALT normalization** with exact date and actual value	☐	☐	☐	
● **ALP value initially** including exact date and normal range	☐	☐	☐	
● **ALP values during dechallenge** at least on days 8 and 30, and later on, with exact dates	☐	☐	☐	
● **ALP values during dechallenge** to exclude a second peak, with exact dates	☐	☐	☐	
● **ALP normalization** with exact date and actual value	☐	☐	☐	
● **AST value initially** including normal range	☐	☐	☐	
● **Laboratory criteria for hepatotoxicity**	☐	☐	☐	
● **Laboratory criteria for injury pattern**	☐	☐	☐	
● **Liver and biliary tract imaging** including hepatobiliary sonography, CT, MRT, MRC	☐	☐	☐	
● **Color Doppler sonography** of liver vessels	☐	☐	☐	
● **Unintended reexposure**	☐	☐	☐	
● **Known hepatotoxicity** caused by the drug/herb	☐	☐	☐	
● **Other possible causes,** consideration and exclusion	☐	☐	☐	
● **Hepatitis A** - Anti-HAV-IgM	☐	☐	☐	
● **Hepatitis B** - HBsAg, anti-HBc-IgM, HBV-DNA	☐	☐	☐	
● **Hepatitis C** - Anti-HCV, HCV-RNA	☐	☐	☐	
● **Hepatitis E** - Anti-HEV-IgM, anti-HEV-IgG, HEV-RNA	☐	☐	☐	
● **Cytomegalovirus (CMV)** - CMV-PCR, titer change for anti-CMV-IgM and anti-CMV-IgG	☐	☐	☐	
● **Epstein Barr virus (EBV)** - EBV-PCR, titer change for anti-EBV-IgM and anti-EBV-IgG	☐	☐	☐	
● **Herpes simplex virus (HSV)** - HSV-PCR, titer change for anti-HSV-IgM and anti-HSV- IgG	☐	☐	☐	

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Item				
● **Varicella zoster virus (VZV)** - VZV-PCR, titer change for anti-VZV-IgM and anti-VZV- IgG	□	□	□	
● **Other virus infections** - Specific serology of Adenovirus, Coxsackie-B-Virus, Echovirus, Measles virus, Rubella virus, Flavivirus, Arenavirus, Filovirus, Parvovirus, HIV, and others	□	□	□	
● **Other infectious diseases** - Specific assessment of bacteria (such as Campylobacter, Coxiella, Leptospirosis, Listeria, Salmonella, Treponema pallidum), fungi, parasites, worms, tropical diseases, and others	□	□	□	
● **Autoimmune hepatitis (AIH)** type I - Gamma globulins, ANA, SMA, AAA, SLA/LP	□	□	□	
● **Autoimmune hepatitis (AIH)** type II - Gamma globulins, anti-LKM-1 (CYP 2D6), anti-LKM-2 (CYP 2C9), anti-LKM-3	□	□	□	
● **Primary biliary cirrhosis (PBC)** - AMA, anti PDH-E2	□	□	□	
● **Primary sclerosing cholangitis (PSC)** - p-ANCA, MRC	□	□	□	
● **Autoimmune cholangitis (AIC)** - ANA, SMA	□	□	□	
● **Overlap syndromes** - See AIH, PBC, PSC, and AIC	□	□	□	
● **Non alcoholic steatohepatitis (NASH**) - BMI, insulin resistance, hepatomegaly, echogenicity of the liver	□	□	□	
● **Alcoholic liver disease (ALD)** - Patient's history, clinical and laboratory assessment, sonography	□	□	□	
● **Drug/herb induced liver injury** - Patient's history, clinical and laboratory assessment, sonography, use of the CIOMS scale	□	□	□	
● **Toxin Screening** - Cocaine, ecstasy and other amphetamines	□	□	□	
● **Rare intoxications** - Toxin screening for household and occupational toxins	□	□	□	
● **Hereditary hemochromatosis** - Serum ferritin, total iron-binding capacity, genotyping for C2824 and H63D mutation, hepatic iron content	□	□	□	
● **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 work-up, genotyping	□	□	□	
● **Porphyria** - Porphobilinogen in urine, total porphyrines in urine	□	□	□	
● **α_1 – Antitrypsin deficiency** - α_1 – Antitrypsin in serum	□	□	□	
● **Biliary diseases** - Clinical and laboratory assessment, hepatobiliary sonography, endosonography, CT, MRT, MRC	□	□	□	
● **Pancreatic diseases** - Clinical and laboratory assessment, sonography, CT, MRT	□	□	□	
● **Celiac disease -** TTG antibodies, endomysium antibodies, duodenal biopsy	□	□	□	
● **Anorexia nervosa** - Clinical context	□	□	□	
● **Parenteral nutrition** - Clinical context	□	□	□	
● **Cardiopulmonary diseases with shock liver** (cardiac hepatopathy, ischemic hepatitis) - Cardiopulmonary assessment of congestive heart disease, myocardial infarction, cardiomyopathy, cardiac valvular dysfunction, pulmonary embolism, pericardial diseases, arrhythmia, hemorrhagic shock, and various other conditions	□	□	□	
● **Addison's disease** - Plasma cortisol	□	□	□	
● **Thyroid diseases** - TSH basal, T4, T3	□	□	□	
● **Grand mal seizures** - Clinical context of epileptic seizure (duration > 30 min)	□	□	□	
● **Heat stroke** - Shock, hyperthermia	□	□	□	
● **Polytrauma** - Shock, liver injury	□	□	□	
● **Systemic diseases** - Specific assessment of M. Boeck, amyloidosis, lymphoma, other malignant tumors, sepsis, and others	□	□	□	
● **Graft vs. host disease** - Clinical context	□	□	□	
● **Other diseases** - Clinical context	□	□	□	

This checklist is derived from a previous report (40) and is far from complete, considered as a reminder for the physician. Some listed liver diseases like AIH require a liver biopsy to establish the diagnosis. Few elements are not directed to causality assessment but are important for overall case evaluation.

Abbreviations: AAA: Anti-Actin Antibodies; AMA: Anti Mitochondrial Antibodies; ANA: Antinuclear Antibodies; BMI: Body Mass Index; CT: Computed Tomography; CYP: Cytochrome P450; HAV: Hepatitis A Virus; HBC: Hepatitis B Core; HBsag: Hepatitis B Antigen; HBV: Hepatitis B Virus; HCV: Hepatitis C Virus; HEV: Hepatitis E Virus; HILI: Herb Induced Liver Injury; HIV: Human Immunodeficiency Virus; LKM: Liver Kidney Microsomes; LP: Liver-Pancreas Antigen; MRC: Magnetic Resonance cholangiography; MRT: Magnetic Resonance Tomography; P-ANCA: Perinuclear Antineutrophil Cytoplasmatic Antibodies; PDH: Pyruvate Dehydrogenase; PCR: Polymerase Chain Reaction; SLA: Soluble Liver Antigen, SMA: Smooth Muscle Antibodies; TSH: Thyroid Stimulating Hormone; TTG: Tissue Transglutaminase.

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causation refers to the previously established hepatotoxicity by the same herb, which was denied because of lack of convincing data. Specific causation refers to the case under discussion; this also was refuted on grounds of conflicting case data, poor case data quality, and numerous confounding variables [57]. The judge actually excluded both involved experts from expert testimony as to causation according to Daubert, rule 702 [57]. As explained in detail, this rule requires that an expert be qualified to render a testimony on the subject, and that his testimony be reliable and relevant. None of the experts obviously met these and other qualification requirements [57]. Following the trial, USP reduced the causality for BC in this case from a probable to a possible level [20]; an erratum clarified the case conditions [58]. Our clinical diagnosis in this case was herpes virus hepatitis and liver disease unrelated to BC or comedicated drugs; CIOMS based assessment led to causality exclusion for both BC and comedications [31]. In retrospect, this court case calls for a thorough clinical documentation of HILI cases, associated with an unbiased expert opinion.

Kava was the focus of another trial after it was withdrawn from the market by the German regulatory agency BfArM due to alleged liver toxicity [59,60]. Almost 12 years after the BfArM preliminary withdrawal of the market authorization for products containing extracts of kava [*Piper methysticum*, Piperaceae] root and/or rhizoma [18], the case has been reviewed by the German administrative court in Cologne [59]. According to the court's ruling on June 11, 2014, the ban of kava medicinal products as issued by BfArM was not justified [59,60], as based on available evidence. The benefit/risk ratio of kava medicinal products was confirmed as positive and must be considered as positive [59], with credit given to previous scientific and clinical work [60], which assessed causality in cases of assumed kava hepatotoxicity with the CIOMS scale [12,13,51,61] . As a consequence of the court's ruling, German kava products have been formally restored to their market status prior to June 2002. In the meantime, BfArM appealed the court's ruling, but justification for the appeal has not yet been published [60]. The next court session will be on February 25, 2015, this time in Muenster. Clearly, the ruling is a major breakthrough, as it strengthens the legal certainty and predictability of regulatory decisions for herbal medicinal product manufacturers in general. It is also a call upon BfArM and other regulatory agencies to supply transparent and appropriate clinical documentations of future HILI cases to be evaluated by well trained assessors and external experts, to be more introspective, not to dismiss differing expert views a priori, and to provide rather than refute complete original raw data of HILI cases in anonymous form for reanalysis to interested scientists.

CONCLUSIONS

The current presentation of HILI case details commonly is incomplete and often lacks essential items for a profound clinical assessment including causality evaluation. Consequently, concern and increased interest in HILI mandates an appropriate case data documentation, which allows transparency and reconstruction of a comprehensive clinical picture including verified causality. Future HILI cases will substantially benefit from a structured case management and documentation in the clinical setting, as spontaneous report to a regulatory agency, or as case report or case series submitted to scientific journals.

REFERENCES

1. WHO. World Health Organization. WHO traditional medicines strategy 2014-2023. Geneva: WHO. 2013.

2. Ekor M. The growing use of herbal medicines: issues relating to adverse reactions and challenges in monitoring safety. Front Pharmacol. 2014; 4: 177.

3. WHO. Regulatory situation of herbal medicines. A worldwide review. Edited by X. Zhang. 2005.

4. WHO. World Health Organization. WHO traditional medicines strategy. 2002-2005. Geneva: WHO. 2002.

5. UN. United Nations Conference on Trade and Development. Systems and National Experiences for Protecting Traditional Knowledge, Innovations and Practices. Background Note by the UNCTAD Secretariat. Geneva. United Nations Conference on Trade and Development, 2000.

6. Lindstrom A, Ooyen C, Lynch ME, Blumenthal M, Kawa K. Sales of herbal dietary supplements increase by 7.9% in 2013, marking a decade of rising sales. HerbalGram. 2014; 103: 52-56.

7. Eisenberg DM, Davis RB, Ettner SL, Appel S, Wilkey S, Van Rompay M. Trends in alternative medicine use in the United States, 1990-1997: results of a follow-up national survey. JAMA. 1998; 280: 1569-1575.

8. Nahin RL, Barnes PM, Stussman BJ, Bloom B. Costs of complementary and alternative medicine [CAM] and frequency of visits to CAM practitioners: United States 2007. National health statistics reports; no. 18. Hyattsville, MD: National Center for Health Statistics. 2009.

9. NIH. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases [NIDDK]. LiverTox. Agents included in LiverTox by drug class. 2014.

10. Posadzki P, Watson LK, Ernst E. Adverse effects of herbal medicines: an overview of systematic reviews. Clin Med. 2013; 13: 7-12.

11. Schmidt M, Morgan M, Bone K, McMillan J. Kava: a risk-benefit assessment. In: Mills M, Bone K [eds]. The essential guide to herbal safety. Elsevier Churchill Livingstone, St. Louis [Missouri], 2005; 155-221.

12. Teschke R, Schwarzenboeck A, Hennermann KH. Kava hepatotoxicity: a clinical survey and critical analysis of 26 suspected cases. Eur J Gastroenterol Hepatol. 2008; 20: 1182-1193.

13. Teschke R, Wolff A. Kava hepatotoxicity: regulatory data selection and causality assessment. Dig Liver Dis. 2009; 41: 891-901.

14. Teschke R, Wolff A. Regulatory causality evaluation methods applied in kava hepatotoxicity: are they appropriate? Regul Toxicol Pharmacol. 2011; 59: 1-7.

15. Teschke R. Black cohosh and suspected hepatotoxicity - inconsistencies, confounding variables, and prospective use of a diagnostic causality algorithm: A critical review. Menopause. 2010; 17: 426-440.

16. Teschke R, Frenzel C, Schulze J, Eickhoff A. Spontaneous reports of primarily suspected herbal hepatotoxicity by Pelargonium sidoides: Was causality adequately ascertained? Regul Toxicol Pharmacol. 2012; 63: 1-9.

17. Teschke R, Frenzel C, Wolff A, Herzog J, Glass X, Schulze J. Initially purported hepatotoxicity by Pelargonium sidoides: the dilemma of pharmacovigilance and proposals for improvement. Ann Hepatol. 2012; 11: 500-512.

18. BfArM. Bundesinstitut füer Arzneimittel und Medizinprodukte, Bonn. Federal Institute for Drugs and Medicinal Products in Germany. Rejection of Drug Risks, Step II. As related to: Kava-Kava [Piper

Teschke et al. (2015)
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methysticum]-containing, and kavain-containing drugs, including homeopathic preparations with a final concentration up to, and including D4. 2002.

19. EMA. Assessment of case reports connected to herbal medicinal products containing cimicifugae racemosae rhizoma [black cohosh, root]. 2007.

20. Mahady GB, Low Dog T, Barrett ML, Chavez ML, Gardiner P, Ko R. United States Pharmacopeia review of the black cohosh case reports of hepatotoxicity. Menopause. 2008; 15: 628-638.

21. WHO. World Health Organization. Assessments of the risk of hepatotoxicity with kava products. WHO Document Production Services: Geneva, Switzerland; 2007.

22. Strahl S, Ehret V, Dahm HH, Maier KP. [Necrotizing hepatitis after taking herbal remedies]. Dtsch Med Wochenschr. 1998; 123: 1410-1414.

23. Benninger J, Schneider HT, Schuppan D, Kirchner T, Hahn EG. Acute hepatitis induced by greater celandine (Chelidonium majus). Gastroenterology. 1999; 117: 1234-1237.

24. Crijns AP, de Smet PA, van den Heuvel M, Schot BW, Haagsma EB. [Acute hepatitis after use of a herbal preparation with greater celandine (Chelidonium majus)]. Ned Tijdschr Geneeskd. 2002; 146: 124-128.

25. Stickel F, Pöschl G, Seitz HK, Waldherr R, Hahn EG, Schuppan D. Acute hepatitis induced by Greater Celandine (Chelidonium majus). Scand J Gastroenterol. 2003; 38: 565-568.

26. Rifai K, Flemming P, Manns MP, Trautwein C. [Severe drug hepatitis caused by Chelidonium]. Internist (Berl). 2006; 47: 749-751.

27. Conti E, De Checchi G, Mencarelli R, Pinato S, Rovere P. Lycopodium similiaplex-induced acute hepatitis: a case report. Eur J Gastroenterol Hepatol. 2008; 20: 469-471.

28. Moro PA, Cassetti F, Giugliano G, Falce MT, Mazzanti G, Menniti-Ippolito F. Hepatitis from Greater celandine (Chelidonium majus L.): review of literature and report of a new case. J Ethnopharmacol. 2009; 124: 328-332.

29. BfArM. Bundesinstitut für Arzneimittel und Medizinprodukte [German regulatory agency]. Bekanntmachung. Abwehr von Gefahren durch Arzneimittel, Stufe II, Anhörung: Schöllkraut-haltige Arzneimittel zur innerlichen Anwendung. 2005.

30. Teschke R, Frenzel C, Glass X, Schulze J, Eickhoff A. Greater Celandine hepatotoxicity: a clinical review. Ann Hepatol. 2012; 11: 838-848.

31. Teschke R, Schwarzenboeck A . Suspected hepatotoxicity by Cimicifugae racemosae rhizoma (black cohosh, root): critical analysis and structured causality assessment. Phytomedicine. 2009; 16: 72-84.

32. Teschke R, Bahre R, Fuchs J, Wolff A. Black cohosh hepatotoxicity: quantitative causality evaluation in nine suspected cases. Menopause. 2009; 16: 956-965.

33. Teschke R, Schmidt-Taenzer W, Wolff A. Spontaneous reports of assumed herbal hepatotoxicity by black cohosh: Is the liver unspecific Naranjo scale precise enough to ascertain causality? Pharmacoepidemiol Drug Saf. 2011; 20: 567-582.

34. Teschke R. Traditional Chinese Medicine induced liver injury. J Clin Translat Hepatol. 2014; 2: 80-94.

35. Teschke R, Bahre R. Severe hepatotoxicity by Indian Ayurvedic herbal products: a structured causality assessment. Ann Hepatol. 2009; 8: 258-266.

36. Teschke R, Glass X, Schulze J. Herbal hepatotoxicity by Greater Celandine (Chelidonium majus): causality assessment of 22 spontaneous reports. Regul Toxicol Pharmacol. 2011; 61: 282-291.

37. Teschke R, Glass X, Schulze J, Eickhoff A. Suspected Greater Celandine hepatotoxicity: Liver specific causality evaluation of published case reports from Europe. Eur J Gastroenterol Hepatol. 2012; 24: 270-280.

38. Teschke R, Bahre R, Genthner A, Fuchs J, Schmidt-Taenzer W, Wolff A. Suspected black cohosh hepatotoxicity--challenges and pitfalls of causality assessment. Maturitas. 2009; 63: 302-314.

39. Teschke R, Frenzel C, Schulze J, Schwarzenboeck A, Eickhoff A. Herbalife hepatotoxicity: Evaluation of cases with positive reexposure tests. World J Hepatol. 2013; 5: 353-363.

40. Teschke R, Wolff A, Frenzel C, Schwarzenboeck A, Schulze J, Eickhoff A. Drug and herb induced liver injury: Council for International Organizations of Medical Sciences scale for causality assessment. World J Hepatol. 2014; 6: 17-32.

41. Teschke R, Schwarzenboeck A, Eickhoff A, Frenzel C, Wolff A, Schulze J. Clinical and causality assessment in herbal hepatotoxicity. Expert Opin Drug Saf. 2013; 12: 339-366.

42. Danan G, Bénichou C. Causality assessment of adverse reactions to drugs – I. A novel method based on the conclusions of international consensus meetings: application to drug-induced liver injuries. J Clin Epidemiol. 1993; 46:1323-1330.

43. Benichou C, Danan G, Flahault A. Causality assessment of adverse reactions to drugs--II. An original model for validation of drug causality assessment methods: case reports with positive rechallenge. J Clin Epidemiol. 1993; 46: 1331-1336.

44. Aithal GP, Watkins PB, Andrade RJ, Larrey D, Molokhia M, Takikawa H. Case definition and phenotype standardization in drug-induced liver injury. Clin Pharmacol Ther. 2011; 89: 806-815.

45. Sarma DN, Barrett ML, Chavez ML, Gardiner P, Ko R, Mahady GB, et al. Safety of green tea extract: a systematic review by the US Pharmacopeia. Drug Saf. 2008; 31: 469-484.

46. Teschke R, Genthner A, Wolff A, Frenzel C, Schulze J, Eickhoff A. Herbal hepatotoxicity: analysis of cases with initially reported positive re-exposure tests. Dig Liver Dis. 2014; 46: 264-269.

47. Teschke R, Schulze J, Schwarzenboeck A, Eickhoff A, Frenzel C. Herbal hepatotoxicity: suspected cases assessed for alternative causes. Eur J Gastroenterol Hepatol. 2013; 25: 1093-1098.

48. Teschke R, Frenzel C, Schulze J, Eickhoff A. Herbal hepatotoxicity: challenges and pitfalls of causality assessment methods. World J Gastroenterol. 2013; 19: 2864-2882.

49. Fenkel JM, Navarro VJ. Herbal and dietary supplement-induced liver injury. Gastroenterol Hepatol (N Y). 2011; 7: 695-696.

50. Lewis JH. Causality assessment: which is best – expert opinion or RUCAM? Clin Liv Dis. 2014; 4: 4-8.

51. Teschke R. Kava hepatotoxicity--a clinical review. Ann Hepatol. 2010; 9: 251-265.

52. Teschke R, Wolff A, Frenzel C, Schulze J, Eickhoff A. Herbal hepatotoxicity: a tabular compilation of reported cases. Liver Int. 2012; 32: 1543-1556.

53. Teschke R, Wolff A, Frenzel C, Schulze J. Review article: herbal hepatotoxicity - an update on traditional Chinese medicine preparations. Aliment Pharmacol Ther. 2014; 40: 32-50.

54. Teschke R, Zhang L, Long H, Schwarzenboeck A, Schmidt-Taenzer W, Genthner A. Traditional Chinese Medicine and herbal hepatotoxicity: a tabular compilation of reported cases. Ann Hepatol. 2015; 14: 7-19.

55. Teschke R, Zhang L, Melzer L, Schulze J, Eickhoff A. Green tea extract and the risk of drug-induced liver injury. Expert Opin Drug Metab

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Toxicol. 2014; 10: 1663-1676.

56. Levitsky J, Alli TA, Wisecarver J, Sorrell MF. Fulminant liver failure associated with the use of black cohosh. Dig Dis Sci. 2005; 50: 538-539.

57. Nebraska Court. Nebraska judgement of 8 September 2006.

58. Levitsky J, Alli TA, Wisecarver J, Sorrell MF. Fulminant liver failure associated with the use of black cohosh. Dig Dis Sci. 2005; 50: 538-539.

59. Cologne Court. Administrative Court, Cologne, Germany. Court ruling 7 K 2197/12 of May 2010, 2014.

60. Schmidt M. German court ruling reverses kava ban; German regulatory authority appeals decision. HerbalGram. 2014; 103: 38-42.

61. Teschke R, Fuchs J, Bahre R, Genthner A, Wolff A. Kava hepatotoxicity: comparative study of two structured quantitative methods for causality assessment. J Clin Pharm Ther. 2010; 35: 545-563.

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