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ORIGINAL ARTICLE

Kava hepatotoxicity: comparative study of two structured quantitative methods for causality assessment

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SUMMARY

Background and objective: **Ingestion of the medicinal herb kava has been associated with hepatotoxicity. We aimed to compare two different quantitative methods of causality assessment of patients with assumed hepatotoxicity by the herb.**

Methods: **We assessed causality in 26 patients from Germany and Switzerland, using two structured quantitative analytical methods: the system of Maria and Victorino (MV) and that of the Council for International Organizations of Medical Sciences (CIOMS). In all 26 patients, regulatory *ad hoc* evaluation had suggested a causal relationship between liver disease and kava use.**

Results and discussion: **Assessment with the MV scale resulted in no or low graded causality for kava in the 26 patients with liver disease. Causality was probable (n = 1), possible (n = 2), unlikely (n = 7), and excluded (n = 16). Causality for kava was more evident with the CIOMS scale: highly probable (n = 1), probable (n = 2), possible (n = 6), unlikely (n = 2) and excluded (n = 15). However, the results of both quantitative causality assessments are not supportive for most of the regulatory *ad hoc* causality assessments of the 26 patients.**

Conclusion: **Grades of causality for suspected hepatotoxicity by kava were much lower when evaluated by structured quantitative causality assessment scales than by regulatory *ad hoc* judgements. The quantitative CIOMS scale is the preferable tool for causality assessment of spontaneous reports of hepatotoxcity involving kava.**

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INTRODUCTION

Chemical drugs, herbal remedies and dietary supplements are commonly considered as safe and devoid of major side effects, but in usually rare instances hepatotoxic reactions may emerge in a few susceptible individuals despite adherence to the recommended daily dose and treatment duration (1–4). Under these conditions, the diagnosis of toxic liver disease represents a major clinical challenge and may only be established when other causes of the observed liver disease have been excluded with certainty. Indeed, there is no biomarker or surrogate marker commonly available which might facilitate the diagnosis of toxic liver disease (4). By clinical criteria a differentiation between toxic and genuine liver disease is commonly not possible, because symptoms and clinical findings are similar in both conditions, including icterus, fatigue, right upper abdominal discomfort, dark urine, pale stool, pruritus and weight loss (3, 4).

In the last few years, a world-wide discussion emerged on whether and, if so, to what extent, treatment with the anxiolytic herb kava is hepatotoxic (5–15). Kava has been used as ethanolic and acetonic extracts of the rhizome of the pepper plant *Piper methysticum G. Forster* (5, 9). The initial causality assessment was a regulatory one achieved on an *ad hoc* basis. An association was assumed in 26 patients from Germany and Switzerland (16). Based on identical data, the regulatory judgement of causality was not substantiated by another regulatory agency (17) and health institute (18). It was criticized by various scientific groups (7–14), especially when additional data were evaluated (5, 7, 12–14). Moreover, quantitative causality

assessments yielded conflicting results in two reports (14, 15). Supportive data in favour of the regulatory assessment were obtained in one study (15) using the quantitative scale of MV, acronym for the authors Maria and Victorino (MV) (19), but not in another assessment (14) using the quantitative scale of Council for International Organizations of Medical Sciences (CIOMS), the acronym for the Council for International Organizations of Medical Sciences (20).

In the present study, we have evaluated causality for all 26 patients with liver disease, assumed in a regulatory assessment to be causally associated with kava treatment. We retrieved additional data and used both the quantitative MV method and the quantitative CIOMS scale. We found that, in the setting of regulatory evaluation of the observed liver disease in assumed relationship with kava, the MV scale performed poorly compared with the CIOMS scale. With a few exemptions, both scales failed to support the regulatory *ad hoc* causality assessments for kava. It appears that the CIOMS scale is the preferred tool for causality assessment in a setting of assumed kava hepatotoxicity.

PATIENTS AND METHODS

Patients

Twenty-six patients originating from Germany (n = 20) and Switzerland (n = 6) were studied. In all patients, liver disease was causally attributed to treatment with kava extracts, and the regulatory assessment of causality for kava gave scores ranging from certain (n = 3) and probable (n = 15) to possible (n = 8) (16). For each of the patients, essential data were collected from various sources including the German and Swiss regulatory agencies, drug manufacturers, primary-care physicians, treating hospital physicians and pharmacists as described previously (14). Additional data were obtained from published reports quoted by the regulators (16).

MV scale

All 26 patients underwent the structured quantitative causality assessment reported by MV (19). The MV scale is a short and modified version of the structured quantitative causality assessment of CIOMS (20). The scale was applied to kava and each co-medicated chemical drug, herbal remedy and dietary supplement. If there was more than one co-medication, only the co-medicated compound with the highest total score was considered in the final assessment.

The scores of the MV system relate to temporal relationships regarding onset of clinical or laboratory manifestation, and normalization of laboratory values after drug discontinuation, exclusion of alternative causes, extrahepatic immuno-allergic manifestations, results of re-exposure and previous published reports of cases of drug-induced liver injury with the alleged drug (19). It provides for each of these items a range of scores. The total score is then computed and used to assign causality as being highly probable, probable, possible, unlikely or excluded.

CIOMS scale

The quantitative CIOMS scale (20) was applied to all 26 patients (14, 16). Causality assessment for kava and co-medication was as described for the MV evaluation. The quantitative CIOMS uses items such as time to onset, course of improvement of laboratory data, risk factors, concomitant drugs, search for non-drug causes, previous information on hepatotoxicity of the drug and response to re-administration (20). It provides with each of these parameters a range of scores. The total score is then computed and this is used for causality assessment as described above for the MV scale.

Comparative assessment

The results presently obtained with the MV scale were compared with the CIOMS scores for kava and co-medications for all 26 patients (14).

RESULTS

General characteristics

In the mostly female patients, daily overdose of kavapyrones (kavalactones), prolonged treatment and co-medication were common features (Table 1), considering that the regulatory recommendation includes 60–120 mg kavalactones daily as maximum intake for no longer than 3 months.

Table 1. Clinical data of all patients (n = 26) with regulatory suspected liver disease in assumed association with the treatment by kava extracts

Patient	Identification	Age (years)	Sex	Kava extract	Duration of therapy (months)	Kavapyrones (mg/day)	Co-medication	Outcome (f = favourable, d = died)	Regulatory information	Additional information	Regulatory *ad hoc* causality assessment		Additional references
											Kava	Co-medication	
01	BfArM 93015209	38	f	Acetonic	3·5	210	Oral contraceptive Diazepam L-Thyroxine	f	Exclusion of non-kava causes not reported	Daily kava overdose Prolonged kava treatment Exclusion of hepatitis A, B, C, CMV, EBV, but not of HSV Exclusion of biliary obstruction and alcoholism Course of ALT not sufficiently documented, still increased after 6 weeks Normalisation of ALT not documented Autoimmunological parameters not assessed Wilson's disease not excluded	++	–	(7, 12, 13)

Table 1. (Continued)

02	BfArM 94006568	68	f	Acetonic	24	210	St John's wort Aluminium hydroxide	f	Exclusion of non-kava causes not communicated Observed recurrent increase of ALT during kava discontinuation not mentioned and its relevance for kava unrelated causality (qualitative CIOMS assessment) not discussed Existing increased ANA and AMA titres not mentioned Alternative diagnosis of AIH and PBC or overlap syndrome not discussed	Daily kava overdose Prolonged kava treatment (2 years) Exclusion of hepatitis A, B, C, CMV, EBV, but not of HSV Ultrasonography data not presented Kava unrelated causality due to recurrent increase of ALT ALT normalisation documented after 3 months Alternative diagnosis of AIH, PBC or overlap syndrome	+	−	(7, 12, 18)
03	BfArM 94901308	50	f	Acetonic	1·5	210	Furosemide Atenolol Terfenadine	f	Exclusion of non-kava causes not documented Existing recurrent increase of ALT during kava discontinuation not mentioned and its relevance for a kava unrelated causality (qualitative CIOMS assessment) not discussed Daily overdose of terfenadine not reported and not assessed Existing increased HSV-IgM titre not reported and alternative diagnosis of herpetic hepatitis not evaluated	Daily kava overdose ALT normalisation not documented after 2 months Kava unrelated cause due to recurrent increase of ALT Known terfenadine overdose with up to 300 mg daily (allowed maximal 120 mg) Complete exclusion diagnostic work-up, but HSV-IgM positive Cessation of initial steroid treatment at time when HSV hepatitis was diagnosed HSV-hepatitis as alternative cause	++	+	(7, 12–14)

Table 1. (Continued)

04	BfArM 98004297	81	f	Ethanolic	10	120	Hydrochlorothiazide Crataegus extract	d	Exclusion of non-kava causes not reported Observed recurrent increase of ALT during kava discontinuation not mentioned and its relevance for kava unrelated causality (qualitative CIOMS assessment) not discussed Existing increased titres of LKM antibodies not recorded and alternative diagnosis of LKM-AIH not evaluated	Prolonged kava treatment (10 months) No exclusion of hepatitis A and C, CMV, EBV, HSV, but LKM positive No ultrasound results Chronic pancreatitis at autopsy Recurrent ALT increase despite kava cessation, suggesting kava independent cause No further ALT follow up due to early death LKM positive AIH as alternative diagnosis	++	–	(12–14)
05	BfArM 99006005	33	f	Ethanolic	4	180	Cisapride	f	Exclusion of non-kava causes not documented Not further specified antibodies described and attributed to a kava induced AIH but not discussed regarding a genuine AIH Normalisation of liver values under cortisone treatment	Daily kava overdose Prolonged kava treatment Exclusion of non-kava causes not presented Course of ALT under cortisone therapy for AIH fails to represent the natural enzyme course, therefore not assessable Diagnosis of genuine AIH, suggested by reporting physician without information of specific antibodies AIH as alternative diagnosis accepted	++	++	(7, 12–14)

Table 1. (Continued)

06	BfArM 99006200	35	f	Ethanolic	3	120	St John's wort	f	Exclusion of non-kava causes not communicated and also not available Nevertheless, the regulator states that non-kava causes are not evident	Data for exclusion of non-kava causes not available Exact ALT course and date of normalisation not reported Multiple sclerosis as comorbidity Possible treatment also with acetaminophen Poorly documented case	++	–	(7, 12)
07	BfArM 00005994	50	f	Ethanolic	7	60	Estrogens Gestagens Metformin Glimepiride St John's wort	LTX	Exclusion of non-kava causes not reported Existing increased titres of EBV-IgM antibodies, ANA and SMA not mentioned and alternative diagnosis of EBV hepatitis, EBV-AIH or genuine AIH not discussed	Prolonged kava treatment (7 months) ALT course not assessable due to LTX Exclusion of hepatitis A, B, C, CMV, EBV, HSV, biliary obstruction, alcoholism Positive titres for EBV-IgM, ANA, ASMA and significant increases of VZV-IgG Cortisone treatment Alternative diagnosis of AIH, EBV-AIH, EBV hepatitis, possibly also of VZV hepatitis	++	++	(7, 12–14)
08	BfArM 00008627	23	f	Ethanolic	4	240	Rizatriptan Oral contraceptive	LTX d	Exclusion of non-kava causes not documented Observed recurrent increase of ALT during kava discontinuation not mentioned and its relevance for a kava unrelated causality (qualitative CIOMS assessment) not discussed Existing increased titres of CMV-IgM antibodies not recorded and alternative diagnosis of CMV hepatitis not discussed	Daily kava overdose Prolonged duration of kava treatment Kava unrelated cause due to recurrent increase of ALT Further ALT course not assessable due to LTX Exclusion of hepatitis A, B, C, biliary obstruction, alcoholism, Wilson's disease No exclusion of EBV and HSV, positive titre for CMV-IgM CMV hepatitis as alternative diagnosis	++	–	(7, 12–14)

Table 1. (Continued)

09	BfArM 01003950	48	f	?	?	?	?	f	Virtually no data reported Brand name of the kava extract unknown No information of time to onset from the beginning of kava and from cessation of kava presented Course with actual ALT values not mentioned Exclusion of non-kava causes not reported Unclear case, not suitable as index case for a possible subsequent re-administration (see case 10, identical patient)	No data available Unassessable case	?	?	(7, 12, 13)
10	BfArM 01003951	56	f	Ethanolic	?	?	L-Thyroxine Estradiol Omeprazole Losartan	f	Exclusion of non-kava causes only for HBV, HCV, CMV, EBV and HSV, but not for HAV reported No information of time to onset from the beginning of kava and from cessation of kava presented Course with actual ALT values not given ALT values just before questionable kava re-administration not presented This case and the former one (identical patient) are unsuitable for assessment as a positive rechallenge test	Daily dose of kava and duration of treatment unknown Course of ALT not evaluable Hepatitis A not excluded Exclusion of hepatitis B and C, CMV, EBV, HSV Titre of ANA not increased, other autoimmune parameters not assessed Treatment with cortisone for unknown reason Various other co-medicated dietary supplements	+++	+	(7, 12, 13)

Table 1. (Continued)

11	BfArM 01006229	32	m	Ethanolic	3	240	Valerian extract	LTX(2x)	Exclusion of non-kava causes incomplete, details also regarding hepatitis and AIH not presented Recurrent increase of ALT during kava cessation not mentioned and its relevance for a kava unrelated causality (quantitative CIOMS assessment) not discussed Existing increased AMA titres not reported and alternative diagnosis of PBC not discussed	Daily kava overdose Exclusion of hepatitis A, B, C, CMV, biliary obstruction EBV and HSV not excluded Recurrent ALT increase, suggesting kava independent cause Adipositas Cortisone treatment for unknown indication Increased AMA titres Alternative diagnosis of PBC	++	–	(7, 12, 14)
12	BfArM 01006939	36	m	Acetonic	1·5	70	–	f	Exclusion of non-kava causes incompletely communicated, details also regarding virus and autoimmune genesis not reported Existing hepato-splenomegaly, increased MCV and pancytopenia (anaemia, leucopenia, thrombocytopenia) not mentioned and not evaluated regarding another underlying disease	Exclusion of hepatitis A, B, C, E, CMV, EBV, alcoholism, bile duct obstruction and negative results for ANA, AMA, LKM, c-ANCA, p-ANCA, SLA, ASMA HSV not excluded ALT normalisation not documented after 2 months Thickening of wall of gallbladder, suspected cholecystolithiasis, liver histology also with cholangitis and bile duct proliferations Cholecystitis and/or cholangitis as possible alternative diagnosis Myelodysplastic syndrome as possible alternative diagnosis	++		(12)

Table 1. (Continued)

13	BfArM 01010536	45	f	Ethanolic	4	45	Cynara scolymus extract	f	Exclusion of non-kava causes incompletely documented The information that serological results were negative is not precise enough	Exclusion of hepatitis A, B, C, bile duct obstruction, alcoholism CMV, EBV and HSV not excluded and autoimmune parameters not assessed ALT course not described in detail	++	–	(12)
14	BfArM 02000370	50	f	Ethanolic	3·5	240	Oral contraceptive Cyclandelat	f	Exclusion of non-kava causes incompletely documented An infection and an autoimmune disease excluded without further details Report came from pharmacist, not from treating physician who denied a possible causality for kava Cryptogenic liver cirrhosis diagnosed in spring 1998, start with kava treatment 20 February 1998	Daily kava overdose Prolonged duration of kava treatment Virtually no data available ALT course not documented Case not assessable Preexisting cryptogenic liver cirrhosis as alternative diagnosis	+	–	(12)
15	BfArM 02001414	46	f	Ethanolic	1	360	–	f	Exclusion of non-kava causes incompletely presented regarding specific parameters for hepatitis A–C and lack of HSV as well as ultrasonography results Existing chronic epigastric pain, increased lipase and decreasing under i.v. infusion therapy, increased y-GT and ALP not mentioned, alternative diagnosis of pancreatitis not discussed	Daily kava overdose Course of ALT poorly and normalisation not documented Exclusion of hepatitis A, B, C mentioned, but no details documented EBV and HSV not excluded Ultrasound data not reported Pancreatitis as alternative diagnosis	++		(12, 14)

Table 1. (Continued)

16	BfArM 02002090	26	f	Ethanolic	0·25	50	Sulfasalazine Diclofenac Progesterone Omeprazole Butylscopolaminium-bromide	f	Age not assessed by regulator but generally known Exclusion of non-kava causes not documented	ALT course poorly documented Exclusion of hepatitis A, B, C, EBV, CMV mentioned but specific data not documented AMA, SLA/LP, LKM with negative results, but ANA not reported Known Bechterew's disease and adipositas as co-morbiditiy	++	–	(12, 13)
17	BfArM 02002378	61	f	Ethanolic	3	120	Omeprazole Hymecromon Ginkgo biloba extract	LTXd	Time to onset from cessation of kava not documented Exclusion of non-kava causes not presented	Virtually no data available The use of hymecromon suggests pre-existing hepato-biliary disease Case is not assessable	++	–	(7, 12)
18	BfArM 02003010	48	f	Ethanolic	6	850	Silymarin Rheumeda (homeopathic preparation) Gelum (mineral supplement) Polilevo (amino acid complex)	LTX	Partial exclusion of non-kava causes with not clearly documented antibodies (HAV, HBV, HCV, CMV) and lack of ultrasonography results Recurrent increase of ALT during kava discontinuation not mentioned and its relevance for a kava unrelated causality (qualitative CIOMS assessment) not discussed Known regular alcohol consumption not documented and not discussed Existing data of cirrhosis and fatty liver not mentioned and not discussed Existing increased lipase and edematous pancreatitis shown by ultrasound examination not reported and not discussed Existing increased y-globulins and enhanced AMA titres not documented and not discussed regarding PBC as an alternative diagnosis	Daily kava overdose Prolonged duration of kava treatment Well documented case with all necessary details Recurrent ALT increase suggests kava independent cause Increased AMA titres and y-globulins PBC or pre-existing liver cirrhosis of unknown cause as alternative diagnosis	+	–	(12–14)

Table 1. (Continued)

19	BfArM NN	39	f	Ethanolic	6	60	Oral contraceptive Paroxetine St John's wort	f	Exclusion of non-kava causes not presented Existing positive rechallenge test reported	Well documented case with exclusion of all relevant kava independent causes Positive re-challenge test, thereby highly probable causality	+++	–	(7, 12–14)
20	BfArM NN	60	f	Ethanolic	12	1200	Etilefrine Piretanide	LTX	Exclusion of non-kava causes fairly well reported, except results of ultrasound examination, ANA and urinary copper excretion/24 h BMI 31·8 kg/m^2 not mentioned	Daily kava overdose Prolonged duration of kava treatment Well documented case Negative results for AMA and LMA, data for ANA not available Adipositas (BMI 31·8 kg/m^2) as comorbidity	++	–	(7, 12–14)
21	IKS 2000–3502	50	m	Acetonic	2	280	–	LTX	Daily overdose of kava Fever, rash Asthenia as first symptom, continuation of kava treatment for one more week Occasional alcohol consumption Exclusion of hepatitis A, B and C, EBV, CMV LTX 9 days after hospitalization	Exclusions of hepatitis E Denied alcohol consumption MCV, amylase and lipase not reported ALT course not available Exclusion of biliary obstruction No exclusion of HSV, AIH or Wilson's disease	++		(12–14)

Table 1. (Continued)

22	IKS 2000–0014	33	f	Acetonic	1·5	210	Exsepta (homeopathic medication)	f	Daily overdose of kava Continuation of kava treatment for another week despite symptoms Still slightly increased aminotransferases 5 months after kava cessation Occasional alcohol consumption, 60 g alcohol the day before clinical symptoms Persistent increased titres of EBV-IgM Not further specified tests for autoantibodies and virus negative Exclusion of biliary obstruction	Recurrent increase of ALT 16 days after kava cessation, in line with kava unrelated liver disease Increased EBV-IgM with normal EBV-IgG, suggestive for alternative diagnosis of EBV-hepatitis Histology includes destruction of interlobular bile ducts, suggesting alternative diagnosis of bile duct destruction of unknown cause Normalization of ALT 2 months after kava cessation Lymphocyte transformation test reactive for kavapyrones. CYP 2D6 deficiency Hepatitis A and C as well as CMV and HIV sufficiently excluded HBc-IgM, HEV and HSV not assessed ANA, AMA, SMA, c-ANCA, p-ANCA all negative	++	−	(12–14)
23	IKS 1999–2596	46	f	Acetonic	3	140	Hydrochlorothiazide Valsartan Propanolol	f	Daily overdose of kava Not further declared exclusion of common drug unrelated causes Improvement of laboratory values starting 13 days after cessation of all medications including kava	Not further specified exclusion of hepatitis and EBV Not reported data on CMV, HSV and autoimmune parameters Course of ALT values not reported Normal ultrasound results Poorly documented case	+	−−	(12–14)

Table 1. (Continued)

24	IKS 2000–2330	59	f	Acetonic	2	70	Estradiol Norethisterone acetate Celecoxib	LTX	Suspected AIH with positive ANA and AMA (anti-M2 negative) Liver cirrhosis, Child C Increased y-globulins and MCV Not further specified exclusion of acute hepatitis A, B, C and negative IgM titres for CMV and EBV Course of ALT values not reported LTX 7 months after kava cessation Insignificant alcohol consumption Exclusion of biliary obstruction	No further data available Poorly documented case AIH, PBC or overlap syndrome as alternative diagnosis MCV increased, possibly alcohol related HSV not excluded Question of cortisone treatment Course of ALT not mentioned Overweight	+	–	(14)
25	IKS 2001–2046	39	f	Acetonic	0·3	140	–	f	Daily overdose of kava ALT 100 U/L, AST 44 U/L (date not listed) Denied alcohol consumption Not further specified hepatitis serology, negative 11 months before increased ALT Kava treatment August 2000 for 10 days First symptoms October 2000 Carbimazole since 26 October 2000 Normal liver values 2 November 2000	Poorly documented case Kava medication August 2000 for 8–10 days Nervosity as indication for kava Increased liver values 2 months after kava cessation, concomitant with diagnosis of hyperthyreosis (Basedow) Rapid regression of ALT due to carbimazole treatment Thyreotoxic hepatopathy as alternative diagnosis Retrospective assessment includes nervosity in August 2000 due to hyperthyreosis, treatment by kava ineffective, cessation of kava, 2 months later diagnosis of hyperthyreosis with increased ALT, subsiding under thyreostatic therapy No causal relationship for kava	+		(14)

Table 1. (Continued)

26	IKS 2000–0219	56	f	Acetonic	1	70	St John's wort Silymarin	f	ALT 115 U/L, AST 53 U/L Increased liver values in January 2000 Kava treatmnet from December 1999 until 8 September 2000, no discontinuation despite slightly increased ALT Denied alcohol consumption Hypocaloric diet, reduction of body weight by 18 kg down to 52 kg in the 4 months preceding increased ALT values Not further specified negative results for hepatitis serology and autoimmune antibodies Normal ultrasound results Liver biopsy 9 months after initial ALT increase with balooning liver cell degeneration without inflammation or necrosis Normalization of ALT 3 months after kava cessation	Adipositas as co-morbidity declared Increased ALT values obviously not ascribed primarily to kava since no cessation was considered Poorly documented case Increased ALT values due to adipositas as alternative diagnosis	+	–	(14)

Basic data were obtained from various sources (7, 12–14, 16). Regulatory information and *ad hoc* causality assessment was presented by the database of BfArM (16) and the Swiss regulatory agency. Regulatory causality assessment was highly probable (+++), probable (++), possible (+), unlikely (–) or excluded (––). Regarding additional informations, a recurrent increase of ALT was found in some patients, indicating a kava independent cause of the liver disease as outlined previously in the qualitative CIOMS assessment (20). AIH, autoimmune hepatitis; AMA, antimitochondrial antibodies; ALT, alanine aminotransferase; ANA, antinuclear antibodies; BMI, body mass index; CIOMS, Council for International Organization of Medical Sciences; CMV, cytomegalovirus; EBV, Epstein Barr virus; HAV, hepatitis A virus; HBV, hepatitis B virus; HCV, hepatitis C virus; HSV, herpes simplex virus; LKM, liver kidney microsomal antibodies; LTX, liver transplantation; MCV, median cell volume; PBC, primary biliary cirrhosis; SMA, smooth muscle antibodies.

Details described for the individual cases implicate poor regulatory data presentation in some of the patients as well as laboratory and clinical manifestations suggestive of kava- and drug-unrelated causes in others. Moreover, in a few patients a temporal association between kava use and the development of liver disease was not convincingly presented in the regulatory data information.

MV causality assessment for kava

Using the MV scale for all 26 patients, there were only three cases with a score ≥10, implying causality for kava (Table S1 and Table 2). Causality was probable for one patient with 16 points (case 19) and possible for two of the cases with 10 points (case 16) and 13 points (case 21). The score for the remaining 23 patients was low, suggesting kava to be an unlikely or excluded cause in another seven and 16 patients, respectively.

The low MV scores may be attributed to various conditions such as the presence of several alternative kava-independent causes of the observed liver disease, giving a −3 point score; only partial exclusion of kava-independent causes, resulting in 0 point; missed extrahepatic manifestations like rash, fever, arthralgia, peripheral eosinophilia and cytopenia, yielding 0 points; and latency period of mostly >8 weeks, giving only 1 point (Table S1). Laboratory signs of acute drug-induced hepatocellular toxicity commonly subside within a short time, and ALT values are normalized 2 months after drug discontinuation. This results in 3 points, but was applicable to only some patients. Instead, the others reached only 0 points on various grounds. For instance, ALT values were still high or unknown 2 months after kava cessation, or the natural course of ALT within 2 months was not assessable because of early death, liver transplantation (LTX) or cortisone treatment of autoimmune

Table 2. Comparison of causality assessments of 26 suspected cases of kava or co-medication hepatotoxicity using the MV and the CIOMS scales

Patient	MV causality for kava	MV causality for co-medication	CIOMS causality for kava	CIOMS causality for co-medication
1	Excluded	Excluded	Possible	Possible
2	Excluded	Excluded	Excluded	Excluded
3	Excluded	Excluded	Excluded	Excluded
4	Excluded	Excluded	Excluded	Excluded
5	Excluded	Excluded	Excluded	Excluded
6	Unlikely	Excluded	Unlikely	Excluded
7	Excluded	Excluded	Excluded	Excluded
8	Excluded	Excluded	Excluded	Excluded
9	Excluded		Excluded	
10	Excluded	Excluded	Unlikely	Possible
11	Excluded	Excluded	Excluded	Excluded
12	Unlikely		Probable	
13	Unlikely	Excluded	Possible	Possible
14	Excluded	Excluded	Excluded	Excluded
15	Excluded		Possible	
16	Possible	Excluded	Possible	Possible
17	Unlikely	Unlikely	Excluded	Excluded
18	Excluded	Excluded	Excluded	Excluded
19	Probable	Unlikely	Highly probable	Excluded
20	Unlikely	Unlikely	Probable	Probable
21	Possible		Possible	
22	Unlikely	Excluded	Excluded	Excluded
23	Excluded	Excluded	Possible	Possible
24	Unlikely	Excluded	Excluded	Excluded
25	Excluded		Excluded	
26	Excluded	Excluded	Excluded	Excluded

hepatitis (AIH) as a kava-unrelated disease. Low scores were also obtained when co-medication was considered as possible or probable cause for the observed liver disease. It therefore appears that in some patients various confounding conditions preclude a high ranking of causality for kava.

MV causality assessment for co-medication

In analogy to kava (Table S1), MV scores were also low for co-medication (Table S2). Co-medication was observed in 21 of 26 patients. As MV scores were all ≤9 (Table S2), causality for co-medication was either unlikely (n = 2) or excluded (n = 19) (Table 2). The causes of low MV scores for co-medication were similar to those previously outlined for kava.

Comparison of MV with CIOMS scales

There is poor concordance of causality grades obtained using the MV and CIOMS scales for both kava and co-medication (Table 2). In general, causality assessment by CIOMS resulted in higher grades of causality for kava and co-medication. Moreover, disagreement prevails relative to the regulatory *ad hoc* causality assessment for kava and co-medication (Table 1) compared with the structured causality evaluation by MV or CIOMS scales (Table 2). In particular, the regulatory assessment of certain, probable or possible causality for kava for all 26 patients (Table 1) was not substantiated by the structured quantitative evaluation using either the MV or CIOMS scales (Table 2). These data suggest that in a setting of suspected kava hepatotoxicity, causality assessment with the quantitative CIOMS scores should be preferred over evaluation using an *ad hoc* basis or the MV scale.

DISCUSSION

The present study shows that the extent of causality varied widely depending on the system used for the quantitative evaluation (Table 2). This is a known phenomenon already described in another study of patients with liver disease because of chemical drugs (21, 22). With the quantitative MV system, causality for kava was probable and possible in only one or two patients, respectively (Tables 2 and S1) and that for co-medication excluded or unlikely (Tables 2 and S2). On the other hand, using the scores of the quantitative CIOMS scale, causality for kava was highly probable for one case, probable for two cases and possible for six cases. The causality grades were sometimes shared with the co-medication (Table 2). It was evident that the MV system and the CIOMS scales (Table 2) produced results with poor concordance.

Previous studies have shown that the MV and CIOMS scales perform equally well in the presence of signs of hypersensitivity such as rash, fever, arthralgia, peripheral eosinophilia and cytopenia. In all other cases, the CIOMS system performs better than the MV scale (21, 22). Accordingly, as the patients of the present study, with few exemptions, lacked signs of hypersensitivity (Tables S1 and S2), the CIOMS scale is the preferred tool for kava causality assessment, at least in the present setting of regulatory assumed liver disease by kava and co-medication.

The regulatory causality assessment (16) seemed to have been confirmed in one single publication (15). The latter study reports that the data of all the patients were analysed systematically using a clinical diagnostic scale (CDS). Reference was provided for CDS being identical with the MV scale (15, 23). This scale was obviously applied without item by item analysis with an additional qualitative assessment (15). Such causality assessment has been criticized for drug-induced liver injury (4, 24). The MV scale in the present study on 20 patients from Germany (cases 1–20) (Table 1), recorded causality as follows: probable (n = 1), possible (n = 1), unlikely (n = 5) and excluded (n = 13) (Table 2 and Table S1). Using the CDS approach, which corresponded to the MV scale, gave all the cases a causality of certain, probable or possible (15). It appears that in the latter study not all information (Table 1) (7, 12–14) required for a sound causality assessment was available or considered.

Causality assessment on an *ad hoc* basis is obviously not the appropriate approach for evaluation of whether a chemical drug, herbal remedy or dietary supplement may have caused a hepatotoxic reaction in a given patient (4, 22). For instance, when treating physicians report cases of liver diseases, assumed to be related to treatment with chemical drugs on an *ad hoc* basis, to the World

Health Organization (WHO), causality of these cases included in the WHO database could not be re-evaluated (25). Similarly, the European Medicines Agency (EMEA) dismissed causality in 38 of 42 cases of spontaneous liver disease assumed by others before to be causally associated with black cohosh in *ad hoc* assessments (26). Causality for the remaining four patients was also dismissed when item by item scoring of the quantitative CIOMS scale was used (27). There have also been problems with *ad hoc* causality assessment of cases of suspected kava hepatotoxicity (5–14, 28–31) presented to the German regulatory agency (16). Causality re-evaluations by both the EMEA and the British Medicines Control Agency yielded quite different results despite identical data for each individual patient (12, 13, 17, 18). Therefore, a systematic diagnostic approach is obviously required.

It is of note that problems in causality assessment have also been reported (32–35) for adverse effects other than hepatotoxicity. In particular, no systematic decisional algorithms gave results in agreement with those of *ad hoc* causality assessment, because of confounding factors which compromised the sensitivity and specificity of the former methods (32). Moreover, without operational procedures, agreement between experts was low (33, 34). For general adverse drug reactions, decisional causality algorithms are sensitive but they have poor specificity (35).

Certainly, the main problem in causality assessment of potential drug-induced liver injury relates to the treating physicians (4). They should collect all the necessary data for causality assessment by the quantitative CIOMS scale for submission to the appropriate regulatory agency and the drug manufacturer concerned. The individual data in the CIOMS scale should be presented in the regulatory database, and then made available to both healthcare providers and the scientific community. Regulatory transparency is mandatory for drug safety.

In conclusion, the CIOMS scale is the preferred tool for causality assessment of liver disease possibly caused by kava. Grades of causality for potential kava hepatotoxicity were much lower when evaluated by methods such as MV or CIOMS than by regulatory *ad hoc* judgements for the 26 patients considered. Regulatory *ad hoc* causality assessments appear to be inadequate and lack transparency. We suggest that the initial step in causality assessment should begin with the application of the quantitative CIOMS scale using data provided by the treating physicians, who are responsible for reporting the individual CIOMS data item by item to their respective national regulatory agencies for further evaluation. The itemized CIOMS data should be in drug-regulatory agency databases and should be publicly available to all.

DISCLOSURE

No conflicts of interest exist.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Table S1. Quantitative causality assessment of 26 patients with suspected kava-induced liver disease using the MV scale. In section 4 (exclusion of alternative causes), the symbol (−) denotes a negative result whereas (+) denotes a positive result. Total points: <6 = causality excluded; 6–9 = causality unlikely; 10–13 = causality possible; 14–17 = causality probable; >17 = causality highly probable.

Table S2. Quantitative causality assessment for co-medication using the MV scale for 26 patients

with suspected kava-induced liver disease and assured to be so by regulatory agencies. In section 4 (exclusion of alternative causes), the symbol (–) denotes a negative result whereas (+) denotes a positive result. Total points: <6 = causality excluded; 6–9 = causality unlikely; 10–13 = causality possible; 14–17 = causality probable; >17 = causality highly probable.

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