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Kava hepatotoxicity - a clinical review

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ABSTRACT

This review critically analyzes the clinical data of patients with suspected kava hepatotoxicity and suggests recommendations for minimizing risk. Kava is a plant (Piper methysticum) of the pepper family Piperaceae, and its rhizome is used for traditional aqueous extracts in the South Pacific Islands and for commercial ethanolic and acetonic medicinal products as anxiolytic herbs in Western countries. A regulatory ban for ethanolic and acetonic kava extracts was issued in 2002 for Germany on the basis of reports connecting liver disease with the use of kava, but the regulatory causality assessment was a matter of international discussions. Based on one positive reexposure test with the kava drug, it was indeed confirmed that kava is potentially hepatotoxic. In subsequent studies using a structured, quantitative and hepatotoxicity specific causality assessment method in 14 patients with liver disease described worldwide, causality for kava ± comedicated drugs and dietary supplements including herbal ones was highly probable (n = 1), probable (n = 4) or possible (n = 9) regarding aqueous extracts (n = 3), ethanolic extracts (n = 5), acetonic extracts (n = 4), and mixtures containing kava (n = 2). Risk factors included overdose, prolonged treatment, and comedication with synthetic drugs and dietary supplements comprizing herbal ones in most of the 14 patients. Hepatotoxicity occurred independently of the used solvent, suggesting poor kava raw material quality as additional causative factor. In conclusion, in a few individuals kava may be hepatotoxic due to overdose, prolonged treatment, comedication, and probably triggered by an unacceptable quality of the kava raw material; standardization is now required, minimizing thereby hepatotoxic risks.

Key words. Kava hepatotoxicity. Herbal hepatotoxicity. Drug induced liver injury. Herbs induced liver injury. Toxic liver disease. Liver injury.

INTRODUCTION

Herbal and drug hepatotoxicity represents a major clinical challenge regarding both assessment of the culprit[1-4] and therapeutic measures.[5] Similar to synthetic drugs, hepatotoxicity by herbs is an overall rare event in a few susceptible individuals.[6] However, it is well understood that frequency of herbal hepatotoxicity may increase due to improved awareness of possible hepatotoxic side effects by herbs and the growing herbal usage in Western countries. Herbs may be taken as a drug under regulatory control or as an unregulated dietary supplement including polyherbal mixtures.[3,6,7] These conditions complicate a sound causality assessment in patients with suspected herbal hepatotoxicity, especially when multimorbidity requires a polydrug therapeutical regime. Published case reports and spontaneous reports communicated to and from regulatory agencies may also lack a thorough, structured, quantitative and hepatotoxicity specific causality assessment approach, leading to doubtful causality associations between the used herb and the observed liver disease in some cases,[3,8] and herb identification may be another problem.[8] Considering these limitations, hepatotoxicity may be caused by a wide range of herbs such as Aloe vera,[9] Indian Ayurvedic herbs,[10] Atractylis gummifera, Callilepsis laureola, Camelia sinensis, Cascara sagrada, Chelidonium majus (Greater Celandine), Dai-Saiko To, Garcinia cambogia, Hydroxycut, Jin Bu Huan, Larrea divariatica (Chaparral), Mentha pulegium (Penny Royal), Morinda citrifolia (Noni), Paeonia sp., Paulinia cupana, Senna sp., Shou wu pian, Syo-Saiko-To, Teucrium po-

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lium (Germander), Valerian,[11] Boh-Gol-Zhee, Centella asiatica, pyrrolizidine alkaloids,[2] HerbaLife,[12] and kava.[13-18]

In an early case report published 1998, a positive reexposure test was described when the patient resumed her treatment with an ethanolic kava extract.[13] Based on this well documented case study, the property of kava as a potentially hepatotoxic herb was generally accepted.[14,15,19-21] However, due to confounding variables in cases with assumed kava hepatotoxicity following the use of ethanolic and acetonic kava extracts as well as kava-herbs mixtures, an international discussion emerged as to what extent kava may harm the liver.[14-30] There is now good evidence that under certain conditions kava may be hepatotoxic in a few susceptible patients,[13-21,30] but the hepatotoxic risk of kava use appears rather low provided kava treatments followed regulatory recommendations.[14,15,20,21] Furthermore, the issue appears to be more complex and challenging since some uncertainties exist as to what extent the use of traditional aqueous kava extracts may also be potentially hepatotoxic.[16,21,25,30]

The aim of this review is to evaluate the clinical data and courses of patients with kava hepatotoxicity. An approach will be made to elucidate the challenges and pitfalls of causality assessments used in this particular disease. Finally, issues of overdose, prolonged treatment, comedication, extraction procedures, and plant quality will be discussed.

DIAGNOSTIC CRITERIA OF KAVA HEPATOTOXICITY

All patients with primarily suspected hepatotoxicity by any drug or dietary supplement (DDS) including kava should undergo an assessment as to whether criteria of the diagnosis of hepatotoxicity as specific disease entity are indeed fulfilled.[3,31] In this context, drugs include synthetic and herbal drugs under regulatory control, and dietary supplements comprize also herbal dietary supplements which lack regulatory surveillance. DDS hepatotoxicity requires for its diagnosis values of alanine aminotransferase (ALT) and/or alkaline phosphatase (ALP) to be at least 2 N (N corresponds to the upper limit of the normal range), whereas the activities of aspartate aminotransferase (AST) and γ-glutamyltranspeptidase (γGT) are not considered in this context. For further assessment, differentiation of the hepatocellular, cholestatic or mixed form of hepatotoxicity caused by DDS is essential[31] by measurements of serum activities of ALT and ALP on the day the diagnosis of kava hepatotoxicity is suspected.[15] Each activity was expressed as a multiple of the upper limit of the normal range (N), and the ratio (R) of ALT: ALP was calculated. Liver injury is hepatocellular, when ALT > 2N alone or R ≥ 5; cholestatic, when there is an increase of ALP > 2N alone or when R ≤ 2; of the mixed type when ALT > 2N, ALP is increased and 2 < R < 5. Notably, for the regulatory cases with suspected kava hepatotoxicity virtually no initial data for ALT and ALP have been presented by the German regulatory agency BfArM[32] concerning the kava drug under its regulatory surveillance.[32,33] Therefore, the regulatory ban of kava use failed to include any information regarding a definition of suspected hepatotoxicity[32] and is consequently not founded on regulatory, clinical and scientific grounds.

CAUSALITY ASSESSMENT METHODS

In the case reports and spontaneous reports of patients with regulatory suspected kava hepatotoxicity, the causality for kava was primarily evaluated on an ad-hoc basis.[32] This approach was also used in other studies[13,14,19,20] despite its known high rate of missed diagnoses unrelated to the use of the investigated synthetic drugs[3,31] and herbs.[8,34-37] Certainly, various causality methods are available and have been discussed in the past.[3,21,38-43] Causality assessment was perceived as not well established in the regulatory cases,[44] and ad-hoc causality assessments are generally considered as inadequate methods for causality evaluation in patients with suspected kava hepatotoxicity.[17,21] In particular, the regulatory assessment of cases from Germany (n = 20) and Switzerland (n = 6) with assumed hepatotoxicity by kava using the ad-hoc approach for causality evaluation[32] is not acceptable on scientific grounds.[15-17,21] In a subsequent regulatory assessment, detailed appraisal of the WHO and the Naranjo scale has been presented, but it remained unclear whether one or both of these assessment methods have actually been applied to the 26 regulatory cases of assumed kava hepatotoxicity.[43] It rather appears that this was not the case; intermediate causality degrees such as possible/probable have been described and attributed to some patients, but intermediate classifications are not considered by the scale of WHO or Naranjo. The two latter scales are also hepatotoxicity unspecific assessment methods and should not be applied in cases of suspected hepatotoxicity by DDS[38,39] including kava.[32] Similarly, the WHO scale used for the causality assessment of he-

patotoxicity with kava products by the WHO[30] should no longer be used for a causality assessment of suspected toxic liver disease by DDS due to lack of hepatotoxicity specificity; it may be replaced by a structured, quantitative and hepatotoxicity specific causality assessment method commonly used by hepatologists in a similar context[3,31,40] and by EMA (European Medicines Agency, formerly EMEA) as outlined previously.[34,35]

The scale of CIOMS (Council for International Organizations of Medical Sciences)[40,41] or the maintest as its updated scale[3,31] represents a well validated structured, quantitative and hepatotoxicity specific causality assessment method and was employed for evaluation of suspected kava hepatotoxicity in a total of 31 cases[15-18] but not in other cases.[13,14,19,20,30,32,43] Using a structured causality assessment method, item by item may be evaluated and published;[15-18] this approach facilitates both transparency provided by the regulatory agencies and appropriate evaluation through the scientific community. Within the frame of a structured evaluation, a positive reexposure test is considered as a surrogate marker and gold standard for the diagnosis of DDS hepatotoxicity.[41] Although a positive rechallenge test supports DDS etiology, the sensitivity is not 100%.[3,41] For causality assessments in cases of suspected DDS hepatotoxicity, additional methods such as the pre-test for a quick evaluation and the post-test for exclusion of various differential diagnoses are available and useful.[3,31]

CASE SERIES

A total of 9 case series are worthy of discussion,[14,19,20,30,45-49] in addition to the 13 case reports to be analyzed subsequently.[13,47,50-61] In a comprehensive study of a case series published in Australia, heavy use of traditional aqueous kava extracts was associated with greatly increased serum activities of γGT and a concomitant decrease of bilirubin, but values for ALT, AST or ALP have not been published.[45] In another Australian report of traditional aqueous kava extracts, serum γGT and ALP activities were increased with normal values of ALT and bilirubin and lack of AST data presentation.[46] Similar results were obtained in a predominantly Tongan population in Hawaii with increased serum activities for γGT and ALP and unchanged ALT and AST values.[48] Further, a case series from New Caledonia showed in heavy users of traditional aqueous kava extracts high serum γGT activities in most cases and marginally elevated ALT and AST activities in only a few ones, whereas ALP values have not been communicated.[47] Considering the commonly normal or only slightly increased serum activities of ALT and AST,[46-48] in none of these case series evidence is provided for signs of striking and clinically relevant hepatocellular injury in the reported cases; this is in clear contrast to high ALT and AST values observed in some other patients who used ethanolic or acetonic kava extracts[15-21] or aqueous ones.[16,47] However, the laboratory constellation of increased γGT[45-48] and ALP[46,48] deserves further pathogenetic and clinical evaluation regarding possible malnutrition due to hypocaloric diets, alcohol, hepatic enzyme induction, enzyme adaptation, or cholestasis as discussed previously[16] on the basis of experimental data.[47,62-64] Indeed, the rare possibility exists and cannot be excluded with certainty at present that increased values of γGT and ALP[45-48] may already signify incipient but still subclinical hepatic injury of the cholestatic type; this form with high values of γGT and ALP is observed in some cases with pronounced drug induced liver injury.[42] At any rate, these four case series with populations originating from Australia,[45,46] New Caledonia[47] and Tonga,[48] are not suitable for further causality assessment on a quantitative basis due to lack of individual case details required for a thorough analysis.

There are five other case series of patients with primarily suspected kava hepatotoxicity.[14,19,20,30,49] Three studies reached the conclusion that there was little evidence for liver disease in causal relationship to kava use.[14,19,20] The fourth study[49] has been criticized and judged of little value because of the reporting of wrong data, age of patients, gender, and concomitant treatments.[30] Similarly, the causality assessment method used in this report[49] was considered not appropriate, lacking also an item by item analysis and important case details usually required for a sound causality evaluation.[18] Various data presented in the criticized study[49] could not be corroborated with results published by others.[13,18-20] The claim that other possible etiologies of hepatitis were ruled out in all patients[49] is also difficult to reconcile in view of various pre- or coexisting and kava independent liver diseases established by thorough analysis.[15] All four studies mentioned above[14,19,20,49] included also published case reports and spontaneous reports with regulatory attributed causality for kava,[32] and only these reports among others were further analyzed for quantitative causality assessment.[15-18] In addition, there was a compilation of 93 cases with kava hepatotoxicity primarily assu-

med by others and described by the WHO, but the notification was explicitly added that an intensive clinical examination of each individual report was not intended.[30] In general, the WHO cases were poorly documented, and most of the reports were considered incomplete to one degree or another; for instance, in 63% of the cases tests for acute viral infections were not mentioned. Nevertheless, eight of the cases were coded as having a probable association between kava use and liver disease.

CASE REPORTS

A total of 13 case reports of patients with primarily suspected kava hepatotoxicity have been published,[13,47,50-61] mostly as full length publications with two reports in abstract or short version form.[53,54] Case reports published as full length papers referred to patients originating from Germany (n = 5),[13,52,55,59,60] Switzerland (n = 2),[56,57] Spain (n = 1),[58] Australia (n = 1),[50] New Caledonia (n = 2),[47] and the United States (n = 1).[51] The cases have been analyzed in detail[15-21] with the exception of one case from Spain[58] and two cases from Germany.[59-61] In the Spanish report, kava extracts of unidentified brands with unknown applied solvents and possible other herbal ingredients have been used.[58]There were also daily overdoses of 750 mg kavalactones[58] which were with more than six times far beyond the regulatory recommendation of 60-120 mg daily for not longer than 3 months.[32,33] Since the kava containing products were taken for three months, this equates to a cumulative dose of 67.5 g.[58] The latter value is far beyond the allowed amount of 10.8 g[15] and suggestive of chronic intoxication due to massive overdose by a factor of 6.25. Early symptoms appeared within 2 weeks of treatment, suggesting an already ongoing liver disease such as a veno-occlusive disease (VOD). Histological changes were described as centrolubular hemorrhagic liver cell necrosis and other alterations which were considered compatible with VOD,[58] a thrombotic disease of the hepatic veins commonly observed after the use of teas and herbs containing pyrrolizidine alkaloids.[2] Compatible with the VOD diagnosis is the described prolonged dechallenge period of four months and raising serum activities of γGT and ALP even one month after cessation of the kava extracts. Due to lack of detailed information also regarding individual parameters, it is unclear whether hepatitis A was indeed assessed and to what extent and which individual other forms of hepatitis were excluded.[58] In the one report from Germany,[59] synthetic D-kavain was used rather than a claimed herbal kava extract,[60] and in the other German case, signs of liver disease appeared only three weeks after the end of short term use of traditional aqueous kava extracts,[61] lacking thereby a clear temporal association.

SPONTANEOUS REPORTS

Various spontaneous reports of patients with suspected kava hepatotoxicity have been presented to national regulatory agencies such as those of European countries,[30,32,43] Australia, Canada, and the United States.[43] In several studies the conclusion was reached that the German regulatory data presentation of most spontaneous cases of kava hepatotoxicity was selective,[3,17] and commonly of poor quality.[3,14,15,17,19-23,26,44] The latter qualification was also recognized in the WHO report[30] and is generally realized for other cases with suspected DDS hepatotoxicity.[3,4,8,34-37] As expected, most of the regulatory presented spontaneous reports could only be partially or not assessed at all, and causality for kava was unlikely, excluded or unassessable in many cases.[14,15,17-21,26,30,32] Similarly, there was little concordance of judgements when the high graded causality assignments of suspected kava hepatotoxicity proposed by the German BfArM[32] were further analyzed and found to be at best low graded by the former British MCA (Medicines Control Agency),[14,17,20] EMA,[17,20] or the WHO.[30] It is of note that 18 cases of spontaneous reports of patients originating from Germany and presented by the German regulatory health agency BfArM[32] were re-analyzed by the WHO report.[30] Among the 18 cases from Germany, the regulatory health agency attributed causalities for kava as highly probable (n = 1), probable (n = 11), and possible/probable (n = 2),[41] whereas the WHO report coded a probable causality as the highest grade for only one single case.[30] The causality categories and definitions of the WHO Collaborating Centre for International Drug Monitoring were used presumably by both the WHO report[30] and BfArM,[43] suggesting specific problems of the two assessor groups of experts with their causality assessments. These shortcomings support the view that the hepatotoxicity unspecific causality assessment method of the WHO scale is not suitable in this particular context since diverging results were obtained with identical cases. It also appears that spontaneous reports presented to and assessed by regulatory agencies failed to significantly contribute to the overall assessment of causality for kava in patients with suspected hepatotoxicity.

CHARACTERISTICS OF THE STUDY CASES WITH PRIMARILY SUSPECTED KAVA HEPATOTOXICITY

In a total of 31 patients with liver disease in primarily suspected causal relation to kava, causality assessment was considered feasible due to sufficient information in most cases (Table 1).[15,16,21] The ages of the 31 patients ranged from 14 to 81 years, and there were 28 females and 3 males. The activities of ALT and AST were usually greater than 5 N (upper limit of the normal range) and often fairly high, reaching values up to 3121 U/L (Table 1);[15,16] also, due to missed diagnosis, low values (ALT 115 U/L, AST 53 U/L) have been reported (case 26, Table 1). The initial ratio of ALT: AST was usually greater than 1. Serum γGT and ALP activities were, in general, normal or slightly elevated.[14] In all assessable cases there was an increased ratio of ALT: ALP greater than or equal to 5 when serum activities were expressed as a multiple of N. These results are compatible with hepatocellular liver disease and not with cholestatic or mixed type. Neither cytopenia nor eosinophilia in the differential blood count was commonly observed.

In 18 of 31 patients, alternative diagnoses were documented (Table 1):[14,15] genuine AIH, PBC, or overlap syndrome (case 2); HSV hepatitis (case 3); LKM positive AIH and pancreatitis (case 4); genuine AIH under treatment with cortisone (case 5); liver disease of unknown etiology (case 6); genuine SMA positive AIH, EBV AIH, EBV hepatitis, possibly also VZV hepatitis (case 7); questionable liver disease of unknown etiology (case 8); questionable liver disease of unknown etiology (case 9); liver disease of unknown etiology, possibly related to comedication (case 10); PBC (case 11); liver disease probably related to kava, cholecystitis, cholangitis or myelodysplastic syndrome (case 12); preexisting cryptogenic liver cirrhosis (case 14); liver disease of unknown etiology, possibly related to kava or pancreatitis (case 15); suspected preexisting hepatobiliary disease of unknown etiology (case 17); PBC, preexisting liver cirrhosis of unknown etiology, pancreatitis (case 18); EBV hepatitis (case 22); liver cirrhosis due to genuine AIH, PBC, or overlap syndrome (case 24); hyperthyroid hepatopathy (case 25); non-alcoholic steatohepatitis (case 26); and genuine AIH (case 29). It is of note that alternative diagnoses are quite often recognized when thorough causality assessments have been done in primarily suspected DDS hepatotoxicity.[3,31,34-37]

The clinical course was severe in eleven out of 31 patients and included death (n = 1), death after liver transplant (LTX) (n = 3), and LTX with good outcome (n = 7) (Table 1).[15,16] Confounding variables such as daily kava overdose, prolonged treatment and comedication were apparent in various patients (Table 1).[15,16,21] In 28 out of 31 cases, both daily dose of kavalactones and the duration of treatment were known (Tables 1 and 2).[15,16] When use of ethanolic and acetonic kava extracts was considered, only five out of evaluable 24 patients, corresponding to 21%, adhered to the regulatory recommendations regarding both the daily dose of kavalactones up to120 mg and the duration of treatment up to 3 months, whereas the other 19 patients (79%) did not so (Table 1).[15,16] With regard to kava-herbs mixtures, both patients used a daily overdose of 180 and 200 mg kavalactones for three and four months, respectively. Information of comedication could be assessed in 30 of 31 cases and was declared in 26 patients, equating to 87% (Table 1).[15,16] Furthermore, a detailed case analysis of the 26 patients with primarily suspected kava hepatotoxicity due to the use of ethanolic and acetonic kava extracts revealed that information regarding the indication for kava treatment was lacking in 5 patients (cases 4, 9, 10, 13, 17); in the remaining group of 21 patients, depression was included in the list of treatment indications for 10 patients (cases 1, 2, 5, 6, 8, 12, 14, 18, 20, 24), equating to 48%. Depressive disorders have been explicitly declared by the regulators as contraindication;[33] provided the patients adhered to the regulatory recommendation regarding depression as contraindication for kava treatment, the respective risk for kava hepatotoxic could have been diminuated almost by half.

In 23 out of 31 patients (Table 1), liver histology was available, showing a wide range of histological findings.[15,16] These include not only necrosis alone (cases 5,7,11,21) and combined with hepatitis (cases 17,19,29,30,31), hepatitis and intrahepatic cholestasis (cases 20 and 22), hepatitis and bile duct proliferation (case1), hepatitis, intrahepatic cholestasis, and bile duct proliferation (case 3), intrahepatic cholestasis (case 8), or hepatitis, intrahepatic cholestasis and cholangitis (case 12), but also other changes were found such as toxic hepatopathy with hepatic atrophy (case 4), piecemeal necrosis (case 24), lobular hepatitis (case 10), ballooning liver cells (case 26), intrahepatic cholestasis and fibrosis (case 18), and intrahepatic cholestasis with signs of hypersensitivity (case 2). Hepatic eosinophilia was also reported (case 21).

Table 1: Clinical data of all patients (n = 31) with primarily suspected liver disease in assumed association with the treatment by kava extracts.

	Patient identification	Specific information for each individual patient	Source
01	BfArM 93015209 38 years Female	Acetonic kava extract (210 mg/d, 3.5 m) for depressive neurosis and anxiety. Daily kava overdose, prolonged kava treatment. Oral contraceptive, Diazepam and L-Thyroxine as CD. ALT 2305 U/L, AST 1048 U/L, and ALP 307 U/L. Exclusion of hepatitis A, B, C, CMV, EBV, but not of HSV or VZV. 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. Favourable outcome. Causality possible for kava and possible for CD. Diagnosis: Liver disease of unknown etiology, possibly related to kava and CD.	14, 15, 17- 20, 32
02	BfArM 94006568 68 years Female	Acetonic kava extract (210 mg/, 24 m) for depressive disorder. Daily kava overdose, prolonged kava treatment. St. John's wort and Aluminium hydroxide as CD. ALT 596 U/L, AST 617 U/L, and ALP 210 U/L. Exclusion of hepatitis A, B, C, CMV, EBV, but not of HSV or VZV. Increased ANA and AMA titres. Ultrasonography data not presented. ALT normalisation documented after 3 months. Kava unrelated causality due to recurrent increase of ALT despite kava cessation Favourable outcome. Causality unlikely for kava and excluded for CD. Diagnosis: Genuine AIH, PBC or overlap syndrome.	14, 15, 17- 20, 32
03	BfArM 94901308 50 years Female	Acetonic kava extract (210 mg/d, 1.5 m) for unknown indication. Daily kava overdose. Furosemide, Atenolol, and Terfenadine as CD. Known Terfenadine overdose with up to 300 mg daily (allowed maximal 120 mg). ALT 950 U/L, AST 1045 U/L, and ALP 315 U/L. ALT normalisation not documented after 2 months. Kava unrelated cause due to recurrent increase of ALT. Complete exclusion diagnostic work-up, but HSV-IgM positive. Cessation of initial steroid treatment at time when HSV hepatitis was diagnosed. Favourable outcome. Causality excluded for kava and excluded for CD. Diagnosis: HSV-hepatitis.	14, 15, 17- 20, 32
04	BfArM 98004297 81 years Female	Ethanolic kava extract (120 mg/d, 10 m) for anxiety and restlessness. Prolonged kava treatment. Hydrochlorothiazide and Crataegus extract as CD. No ultrasound results. No exclusion of hepatitis A and C, CMV, EBV, HSV, and VZV, but LKM positive. Recurrent ALT increase despite kava cessation, suggesting kava independent cause. No further ALT follow up due to early death. Chronic pancreatitis at autopsy. Lethal outcome. Causality excluded for kava and excluded for CD. Diagnosis: LKM positive AIH and pancreatitis.	14, 15, 17- 20, 32
05	BfArM 99006005 33 years Female	Ethanolic kava extract (180 mg/d, 4 m) for depression. Daily kava overdose, prolonged kava treatment. Cisapride as CD. ALT maximal 1000 U/L, AST 700 U/L, and ALP 400 U/L. 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. Course of ALT under cortisone therapy for AIH fails to represent the natural enzyme course, therefore not assessable. Genuine AIH suggested by reporting physician without information of specific antibodies. Favourable outcome. Causality excluded for kava and excluded for CD. Diagnosis: Genuine AIH under treatment with cortisone.	14,15 17-20-32
06	BfArM 99006200 35 years Female	Ethanolic kava extract (120 mg/d, 3 m) for depression. St. John's wort as CD. Possible treatment also with acetaminophen. ALT 964 U/L, AST 721 U/L, and ALP 135 U/L. Data for exclusion of non kava causes not available. Exact ALT course and date of normalisation not reported. Multiple sclerosis as comorbidity. Poorly documented case. Favourable outcome. Causality unlikely for kava and excluded for CD. Diagnosis: Liver disease of unknown etiology.	14, 15, 17- 20, 32

07	BfArM 00005994 Saß et al. (53) 50 years Female	Ethanolic kava extract (60 mg/d, 7 m) for stress. Prolonged kava treatment. Estrogens, gestagens, Metformin, Glimepiride, and St. John's wort as CD. ALT and AST, each around 1000 U/L. Exclusion of hepatitis A, B, C, CMV, EBV, HSV, biliary obstruction, alcoholism. Positive titres for EBV-IgM, ANA, SMA and significant increases of VZV-IgG. Cortisone treatment. ALT course not assessable due to LTX. Favourable outcome after LTX. Causality excluded for kava and excluded for CD. Diagnosis: Genuine SMA positive AIH, EBV-AIH, EBV hepatitis, possibly also VZV hepatitis.	14, 15, 17- 20, 32, 53
08	BfArM 00008627 Brauer et al. (54) 23 years Female	Ethanolic kava extract (240 mg/d, 4 mo) for depression, nervosity and anxiety. Daily kava overdose, prolonged duration of kava treatment. Rizatriptan and oral contraceptive as CD. ALT 519 U/L, ALP 216 U/L, AST not recorded. Kava unrelated cause due to recurrent increase of ALT during kava discontinuation. Further ALT course not assessable due to LTX and lethality. Exclusion of hepatitis A, B, C, biliary obstruction, alcoholism, Wilson's disease. No exclusion of EBV, HSV and VZV, positive titre for CMV-IgM. Lethal outcome. Causality excluded for kava and excluded for CD. Diagnosis: CMV hepatitis.	14, 15, 17-20, 32, 54
09	BfArM 01003950 48 years Female	No data available. Undeclared indication. Unassessable case. Unclear case, not suitable as index case for a possible subsequent re-administration (see case 10, identical patient). ALT, AST, and ALP not recorded. Favourable outcome. Causality excluded for kava and not assessable for CD. Diagnosis: Questionable liver disease of unknown etiology.	14, 15, 17- 20, 32
10	BfArM 01003951 56 years Female	Ethanolic kava extract for undeclared indication, no further details available. Daily dose of kava and duration of treatment unknown. L-Thyroxine, Estradiol, Omeprazole, and Losartan as CD. Various other co-medicated dietary supplements. ALT 299 U/L, AST 106 U/L, ALP normal. Course of ALT not evaluable. ALT values before questionable kava re-administration not presented. Hepatitis B and C, CMV, EBV, and HSV excluded, but not Hepatitis A and VZV. Normal titre of ANA, other autoimmune parameters not assessed. Treatment with cortisone for unknown reason. This case and the former one (identical patient) is unsuitable for assessment as a positive rechallenge test. Favourable outcome. Causality unlikely for kava and possible for CD. Diagnosis: Liver disease of unknown etiology, possibly related to CD.	14, 15, 17- 20, 32
11	BfArM 01006229 32 years Male	Ethanolic kava extract (240 mg/d, 3 m) for restlessness. Daily kava overdose. Valerian extract as CD. ALP 2222 U/L, AST 2319 U/L, ALP 520 U/L. Exclusion of hepatitis A, B, C, CMV, biliary obstruction. EBV, HSV, and VZV not excluded. Recurrent ALT increase during kava cessation, suggesting kava independent cause. Adipositas. Increased AMA titres. Cortisone treatment for unknown indication. LTX (2x). Favourable outcome after LTX (2x). Causality excluded for kava and excluded for CD. Diagnosis: PBC.	14, 15, 17- 20, 32
12	BfArM 01006939 36 years Male	Acetonic kava extract (70 mg/d, 1.5 m) for depression. No CD. ALT 2341 U/L, AST 2425 U/L, and ALP 530 U/L. Exclusion of hepatitis A, B, C, E, CMV, EBV, alcoholism, bile duct obstruction and negative results for ANA, AMA, LKM, p-ANCA, SLA, SMA.HSV and VZV not excluded. ALT normalisation not documented after 2 months. Thickening of wall of gallbladder, suspected cholecystolithiasis, liver histology also with cholangitis and bile duct proliferation. Hepato-splenomegaly, increased MCV and pancytopenia (anemia, leucopenia, thrombocytopenia). Favourable outcome. Causality probable for kava. Diagnosis: Liver disease probably related to kava, cholecystitis, cholangitis or myelodysplastic syndrome as possible alternative diagnosis.	14, 15, 17- 20, 32
13	BfArM 01010536 45 years Female	Ethanolic kava extract (45 mg/d, 4 m) for undeclared indication. Prolonged duration of kava treatment. Cynara scolymus extract as CD. ALT 1000 U/L, AST 700 U/L, and ALP 360 U/L. Exclusion of hepatitis A, B, C, bile duct obstruction, alcoholism. CMV, EBV, HSV and VZV not excluded. Autoimmune parameters and ALT course not described in detail. Favourable outcome. Causality possible for kava and unlikely for CD. Diagnosis: Liver disease of unknown etiology, possibly related to kava.	14, 15, 17- 20, 32

14	BfArM 02000370 50 years Female	Ethanolic kava extract (240 mg/d, 3.5 m) for depression. Daily kava overdose, prolonged duration of kava treatment. Oral contraceptive and Cyclandelat as CD. ALT, AST, and ALP not recorded. Virtually no data available. ALT course not documented. Exclusion of non kava causes incompletely documented. Infection and autoimmune disease excluded without further details. Report from pharmacist, not from treating physician who denied a possible causality for kava. Cryptogenic liver cirrhosis diagnosed in spring 1998, start with kava treatment 20.2.1998. Case not assessable. Favourable outcome. Causality excluded for kava and excluded for CD. Diagnosis: Pre-existing cryptogenic liver cirrhosis.	14, 15, 17- 20, 32
15	BfArM 02001414 46 years Female	Ethanolic kava extract (360 mg/d, 1 m) for restlessness and exhaustion. Daily kava overdose. No CD. ALT 1442 U/L, AST 683 U/L, and ALP 325 U/L. Course of ALT poorly and normalisation not documented. Exclusion of hepatitis A, B, C mentioned, but no details documented. CMV, EBV, HSV, and ZVZV not excluded. Chronic epigastric pain with increased lipase and decreasing under i. v. infusion therapy, increased GGT and ALP. Ultrasound data not reported. Favourable outcome. Causality possible for kava. Diagnosis: Liver disease of unknown etiology, possibly related to kava or pancreatitis..	14, 15, 17- 20, 32
16	BfArM 02002090 26 years Female	Ethanolic kava extract (50 mg/d, 0.25 m) for stress. Sulfasalazine, Diclofenac, Progesterone, Omeprazole, Butylscopolaminium-bromide as CD. ALT 572 U/L, AST 220 U/L, and ALP 163 U/L. ALT course poorly documented. Exclusion of hepatitis A, B, C, CMV, and EBV mentioned but specific data not documented AMA, SLA/LP, and LKM with negative results, but ANA not reported. Known Bechterew´s disease and adipositas as co-morbidity. Favourable outcome. Causality possible for kava and unlikely for CD. Diagnosis: Liver disease of unknown etiology, possibly related to kava.	14, 15, 17- 20, 32
17	BfArM 02002378 61 years Female	Ethanolic kava extract (120 mg/d, 3 m) for undeclared indication.. Omeprazole, Hymecromon, Ginkgo biloba extract as CD. ALT, AST, and ALP not recorded. The use of Hymecromon suggests pre-existing hepato-biliary disease. Virtually no data available. Case is not assessable. Lethal course after LTX. Causality excluded for kava and excluded for CD. Diagnosis: Suspected pre-existing hepato-biliary disease of unknown etiology.	14, 15, 17- 20, 32
18	BfArM 02003010 48 years Female	Ethanolic kava extract (860 mg/d, 6 m) for depression. Daily kava overdose, prolonged duration of kava treatment. Silymarin, Rheumeda (homeopathic preparation), Gelum (mineral supplement), and Polilevo (amino acid complex) as CD. ALT 620 U/L, AST 712 U/L, and ALP 400 U/L. Well documented case with all necessary details. Recurrent ALT increase during kava discontinuation suggests kava independent cause. Increased AMA titres, lipase, and y-globulins. Edematous pancreatitis shown by ultrasound examination. Reported data of cirrhosis and fatty liver. Known regular alcohol consumption. Favourable outcome after LTX. Causality excluded for kava and excluded for CD. Diagnosis: PBC, pre-existing liver cirrhosis of unknown cause and pancreatitis.	14, 15, 17- 20, 32
19	BfArM (NN) Strahl et al. (13) 39 years Female	Ethanolic kava extract (60 mg/d, 6 m) for anxiety. Prolonged duration of kava treatment. Oral contraceptive, Paroxetine, and St. John's wort as CD. ALT 600 U/L, AST 400 U/L, ALP 183 U/L.Well documented case with exclusion of all relevant kava independent cause. Cytochrome P450 2D6 deficiency. Positive re-challenge test, thereby highly probable causality Favourable outcome. Causality highly probable for kava and excluded for CD. Diagnosis: Liver disease with highly probable relation to kava.	13-15, 17- 20, 32, 57
20	BfArM (NN) Kraft et al. (55) 60 years Female	Ethanolic kava extract (1200 mg/d, 12 m) for depression. Daily kava overdose, prolonged duration of kava treatment. Etilefrine and Piretanide as CD. ALT >1000 U/L, AST >1000 U/L, ALP >500 U/L. Well documented case. Negative results for AMA and LMA, data for ANA not available. Exclusion of non kava causes fairly well reported, except results of ultrasound examination. Adipositas (BMI 31.8 kg/m^2) as comorbidity. Favourable outcome after LTX. Causality probable for kava and probable for CD. Diagnosis: Liver disease with probable relation to kava and CD.	14, 15, 17- 20, 32, 55

21	IKS 2000-3502 Escher et al. (56) 50 years Male	Acetonic kava extract (280 mg/d, 2 m) for tensions. Daily overdose of kava. No CD. ALT max 3627 U/L, AST max 3360 U/L, ALP max 430 U/L. Asthenia as first symptom, continuation of kava treatment for one more week. Fever, rash. Occasional alcohol consumption. Exclusion of hepatitis A, B, C, and E, CMV, EBV, but not of HSV, VZV, AIH or Wilson's disease. Data of MCV, amylase and lipase not reported. ALT course not available. Exclusion of biliary obstruction.32, 56 Favourable outcome after LTX. Causality possible for kava. Diagnosis: Liver disease of unknown etiology, possibly related to kava.	15, 18, 20,
22	IKS 2000-0014 Russmann et al. (57) 33 years Female	Acetonic kava extract (210 mg/d, 1.5 m) for personal problems. Daily overdose of kava. Exsepta (homeopathic medication) as CD. ALT max 2430 U/L, AST max 2552 U/L, ALP max 299 U/L. Continuation of kava treatment for another week despite symptoms. Recurrent increase of ALT 16 days after kava cessation, in line with kava unrelated liver disease. Five months after kava cessation still slightly increased aminotransferases. Occasional alcohol consumption, 60 g alcohol the day before clinical symptoms. Increased titres of EBV-IgM with normal EBV-IgG, suggestive for EBV-hepatitis. Hepatitis A and C as well as CMV and HIV sufficiently excluded HBc-IgM, HEV, HSV and VZV not assessed. ANA, AMA, SMA, p-ANCA all negative. Cytochrome P450 2D6 deficiency. Lymphocyte transformation test reactive for kavalactones. Exclusion of biliary obstruction. Histology includes destruction of interlobular bile ducts, suggesting alternative diagnosis of bile duct destruction of unknown cause. Favourable outcome. Causality excluded for kava and excluded for CD. Diagnosis: EBV hepatitis.	15, 18, 20, 32, 57
23	IKS 1999-2596 46 years Female	Acetonic kava extract (140 mg/d, 3 m) for neurodystonia. Daily overdose of kava. Hydrochlorothiazide, Valsartan, and Propanolol as CD. ALT max 1900 U/L, AST max 2005 U/L, ALP not recorded. Poorly documented case. Course of ALT values not reported. Not further specified exclusion of hepatitis and EBV. Data of CMV, HSV, VZV and autoimmune parameters not reported. Improvement of laboratory values starting 13 days after cessation of all medications including kava. Not further declared exclusion of common drug unrelated causes. Normal ultrasound results. Favourable outcome. Causality possible for kava and possible for CD. Diagnosis: Liver disease of unknown etiology, possibly related to kava and CD.	15, 18, 20 32
24	IKS 2000-2330 59 years Female	Acetonic kava extract (70 mg/d, 2 m) for depression. Estradiol, Norethisterone acetate, and Celecoxib as CD. ALT max 989 U/L, AST max 754 U/L, ALP 354 U/L. Poorly documented case. Overweight. Insignificant alcohol consumption. MCV increased, possibly alcohol related. Course of ALT values not reported. Not further specified exclusion of acute hepatitis A, B, and C. Negative IgM titres for CMV and EBV. HSV and VZV not excluded. Positive titres for ANA and AMA (anti-M2 negative). Question regarding cortisone treatment. Liver cirrhosis, Child C with increased y-globulins. Exclusion of biliary obstruction. LTX only 7 months after kava cessation. Favourable outcome after LTX. Causality excluded for kava and excluded for CD. Diagnosis: Liver cirrhosis due to genuine AIH, PBC or overlap syndrome.	15, 18, 20, 32
25	IKS 2001-2046 39 years Female	Acetonic kava extract (140 mg/d, 0.3 m) for nervosity. Daily overdose of kava. No CD. ALT 100 U/L, AST 82 U/L, ALP 44 U/L (dates not listed). Poorly documented case. Denied alcohol consumption. Nervosity as indication for kava treatment. Kava medication August 2000 for 8-10 days. Increased liver values 2 months after kava cessation. At that time, diagnosis of hyperthyroidism (Basedow) and initiation of treatment with carbimazole, subsequent rapid regression of ALT to normal values within 1 week. Retrospective assessment includes nervosity in August 2000 due to hyperthyroidism, treatment by kava ineffective, cessation of kava, 2 months later diagnosis of hyperthyroidism with associated ALT increase, subsiding under thyrostatic therapy. Negative, not further specified hepatitis serology 11 months before increased ALT. Favourable outcome. Causality excluded for kava. Diagnosis: Hyperthyroid hepatopathy.	15, 18, 20, 32
26	IKS 2000-0219 56 years Female	Acetonic kava extract (70 mg/d, 1 m) for anxiety. St. John's wort and Silymarin as CD. ALT max 115 U/L, AST max 53 U/L, ALP 79 U/L.Adipositas as co-morbidity declared. Denied alcohol consumption. Poorly documented case. Increased liver values in January 2000 (ALT 115 U/L, AST 53 U/L), obviously not ascribed primarily to kava since no cessation was considered. Kava treatment from December 1999 until 8.9.2000. Not further specified negative results for hepatitis serology and autoimmune antibodies. Normal ultrasound results. Liver biopsy 9 months after initial ALT increase with ballooning liver cell degeneration without inflammation or necrosis. Normalization of ALT 3 months after kava cessation. Hypocaloric diet, reduction of body weight by 18 kg down to 52 kg in the 4 months preceding increased ALT values. Favourable outcome. Causality excluded for kava and excluded for CD. Diagnosis: Non-alcoholic steatohepatitis.	15, 18, 20, 32

27	Russmann et al. (47) 59 years Female	Aqueous kava extract (unknown daily dose, 1 m) for no medical indication. Use of traditional kava prepared with tap water and dried kava root imported from the islands of Vanuatu. Lisinopril, Phenobarbital and Fenofibrate as CD. Patient of Oceanian origin. ALT 568 U/L, AST 671 U/L, and ALP not recorded. Normalization of increased values of amino transferases three months after kava discontinuation. Negative serology for HBs antigen and antibodies against HBs, hepatitis A and hepatitis C. Positive titres for anti-HBc IgG. Titres for anti-nuclear and anti-DNA antibodies were 1:128 and 1:20, respectively. Dilatation of bile ducts excluded by abdominal ultrasound. Data of CMV, EBV, HSV, and VZV not presented. Favourable outcome: Causality possible for kava and possible for CD. Diagnosis: Liver disease possibly related to kava and CD.	16, 20, 47
28	Russmann et al. (47) 55 years Female	Aqueous kava extract (2.571 mg/d, 1.25 m) for no medical indication, used as traditional kava beverage. No CD. Patient of Oceanian origin. ALT 1666 U/L, AST 1569 U/L, and ALP not recorded. Normalization of initially increased amino transferases3 months after kava discontinuation. Hepatitis serology negative for anti-HBc IgM, hepatitis A IgG antibodies, and HBs antigen, and positive for anti-HBc and anti-HBs IgG antibodies. ANA 1:40. Negative antibodies against LKM and SMA. Dilatation of bile ducts excluded by abdominal ultrasound. Data of CMV, EBV, HSV and VZV not presented. Favourable outcome. Causality probable for kava. Diagnosis: Liver disease probably related to kava.	16, 20, 47
29	Gow et al. (50) 56 years Female	Kava mixture (180 mg/d, 3 m) for anxiety. Daily kava overdose. As CD there are the following ingredients of the mixture: Passiflora incarnate and Scutellaria lateriflora (declared, but not identified). Vitamins (unspecified) and mineral supplements (unspecified). ALT 4539 U/L, ALP 190 U/L, and AST not recorded. Known stable benign monoclonal gammopathy (IgG). Minimal alcohol consumption. Assays for acute hepatitis A, B, and C viruses, EBV and CMV were negative without presentation of details. Data of HSV and VZV not available. Normal values for serum copper and ceruloplasmin. Absence of Kayser-Fleischer rings. ANA 1:160, SMA negative. Small liver by abdominal Doppler ultrasound without further abnormalities. Lethal outcome after LTX. Causality probable for kava and possible for CD. Diagnosis: Liver disease probably related to kava and possibly to CD. Alternative genuine ANA positive AIH.	16, 20, 50
30	Humberston et al. (51) 14 years Female	Kava mixture (200 mg/d, 4 m) for anxiety. Daily kava overdose, prolonged kava treatment. As CD there are the following ingredients of the mixture: St. John's wort, Siberian ginseng root, chamomile, peppermint leaves, cinnamon, lemmon grass, ginger root, licorice root, roasted chicory root, catnip root, natural flavours including natural lemmon ones, Tilia estrella flowers, valerian root, spearmint leaves, hawthorn berries, orange blossoms, magnesium, vitamin $B_{6,}$ vitamin$_{12}$, vitamin C. Ibuprofen as CD. ALT > 4400 U/L, AST >3500 U/L, and ALP not recorded. In laboratory findings no infectious or autoimmune processes detected, but details not presented. Poorly documented case. Favourable outcome after LTX. Causality possible for kava and possible for CD. Diagnosis: Liver disease of unknown etiology, possibly related to kava and CD.	16, 20, 51
31	Weise et al. (52) 34 years Female	Aqueous powdered kava extract, ethanolic extract before (120 mg/d, 3 m) for undeclared indication. L-Thyroxine and potassium iodine as CD. ALT 884 U/L, AST 547 U/L, and ALP 319 U/L. Exclusion of hepatitis A-C, but CMV, EBV, HSV and VZV not evaluated. Negative results for ANA, AMA, and SMA. Favourable outcome. Causality possible for kava and possible for CD. Diagnosis: Liver disease possibly related to kava and CD.	16. 52

Basic data were obtained from various sources.[14-20] Regulatory information and ad-hoc causality assessment was presented by the database of the German regulatory agency (BfArM)[32] and the Swiss regulatory agency (formerly IKS).[32] With the scale of CIOMS (40) or the main-test as its updated scale,[3,31] causality assessment for kava and CD was achieved.[15,16] For ALP, AST, and ALP usually initial values are given. Regarding the section of specific information for each individual patient, 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.[54] For the kava extracts and mixtures, the consumed amount was given in mg kavalactones/d, and the duration of treatment was presented in month(s), m in short.

A detailed causality analysis of all 31 patients has been performed with the scale of the updated CIOMS in form of the main-test.[15,16,21] The studies were based on 26 regulatory cases from Germany (n = 20) and Switzerland (n = 6)[41] including published reports[13,53-58] with primarily assumed causality for kava by the regulators.[32] In addition, five published case reports[47,50-52] of patients originating from New Caledonia,[47] Australia,[50] the United States,[51] and Germany[52] with a possible or probable causality for kava alone or combined with comedicated DDS were included.[16] Due to insuffient data supply essential for a hepatotoxicity specific causality assessment, some cases of other reports[19,20,30] have not been considered in this analysis. In the overall group of 31 cases, a temporal association between emerging liver disease and kava use was not apparent in 4 patients (cases 9,10,17,25).[15,16] Causality for kava ± comedication was unlikely or excluded in 17 of 31 cases and evident in the remaining 14 patients (Table 1). It was highly probable for kava alone (n = 1), probable for kava alone (n = 2), probable for both kava and comedication (n = 1), probable for kava and possible for comedication (n = 1), possible for kava alone (n = 1), and possible for both kava and comedication (n = 8).[15,16,21] Kava has been used by these 14 patients as aqueous kava extracts (n=3), ethanolic kava extracts (n = 5), acetonic kava extracts (n = 4), and herbal mixtures containing also kava (n = 2), and some typical features became evident (Table 2).[15-18,21]

KAVA HEPATOTOXICITY AS A SPECIFIC DISEASE ENTITY

A total of 14 patients (cases 1,12,13,15,16,19-21,23,27-31) with liver disease showed a highly probable, probable, or possible causality for kava ± comedication (Table 1), with involvement of all kava products (Table 2). Only these 14 patients were used as basis for the characterization of kava hepatotoxicity as a specific read disease entity (Table 3), and the data of the present analysis were supplemented by various results of previous studies.[14-21] Of the 14 patients, twelve were females and two males which corresponded to a ratio of 6: 1, and the ages ranged from 14 to 60 years (Table 2). Their initial values for ALT, AST, and ALP were in the ranges of 568-4539 U/L, 220-3500 U/L, and 163-530 U/L, respectively (Table 1). Histology of the liver was available in eight of the 14 patients, showing liver cell necrosis and hepatitis (cases 1,12,19-21,29-30,31), combined with either bile duct proliferation (case 1) or intrahepatic cholestasis (case 20).

The indication for treatment with ethanolic and acetonic kava extracts was not declared in one (case 13) out of 9 patients, and depression was listed as indication in the documents of four patients (cases

Table 2. Summary of characteristics of all 14 patients with hepatotoxicity in highly probable, probable or possible causal relationship to the use of aqueous, ethanolic and acetonic kava extracts and kava-herbs mixtures.

Characteristics	Aqueous kava extracts (n = 3)	Ethanolic kava extracts (n = 5)	Acetonic kava extracts (n = 4)	Kava-herbs mixtures (n = 2)	All kava products (n = 14)
Age (years)	34 - 59	26 - 60	36 - 50	14 - 56	14-60
Female gender	3/3	5/5	2/4	2/2	12/14
Kavalactones (mg/d)	120 - 2.571	45 - 1.200	70 - 280	180--200	45-2.571
Duration (months)	1.0 - 1.25	0.25 - 12	1.5 - 3	3 - 4	0.25-12
Comedication	2/3	4/5	2/4	2/2	10/14
Daily kava overdose	n.a.	2/5	3/4	2/2	7/11
Prolonged kava use	0/3	3/5	1/4	1/2	5/14
Favorable outcome (± LTX)	3/3	5/5	4/4	1/2	13/14
Lethal outcome (± LTX)	0/3	0/5	0/4	1/2	1/14
Requirement for LTX	0/3	1/5	1/4	2/2	4/14
Highly probable causality for kava alone	0/3	1/5	0/4	0/2	1/14
Probable causality for kava alone	1/3	0/5	1/4	0/2	2/14
Probable causality for both kava and comedication	0/3	1/5	0/4	0/2	1/14
Probable causality for kava and possible for comedication	0/3	0/5	0/4	1/2	1/14
Possible causality for kava alone	0/3	3/5	1/4	0/2	4/14
Possible causality for both kava and comedication	2/3	0/5	2/4	1/2	5/14

The individual data of the 14 patients who used the various kava extracts or kava-herbs mixtures are given in Table 1, and other details of the cases have been published before (15,16,21). LTX denotes liver transplantation, n.a. not assessable.

Table 3. Typical features of kava hepatotoxicityγ.

Characteristics
(1) The existence of kava hepatotoxicity as a specific disease entity has been verified by a positive reexposure test in one single patient;
(2) A probable causality for kava ± comedication in four out of 14 patients with liver disease creates concern regarding safety of patients and pharmacovigilance considerations;
(3) In nine patients and thus in the majority of cases, causality for kava ± comedication was graded as only possible and hence weak;
(4) Kava hepatotoxicity may be caused by traditional aqueous kava extracts, commercial ethanolic and acetonc kava extracts, and kava-herbs mixtures;
(5) Daily overdose of kavalactones and prolonged treatment are common phenomena in patients with kava hepatotoxicity and considered as risk factors;
(6) Synthetic or herbal drugs and dietary supplements including herbal ones are comedicated with kava in the majority of cases and considered as risk factors;
(7) Half of the patients used ethanolic or acetonic kava extracts for depression, a clear regulatory contraindication;
(8) The ages of the 14 patients ranged from 14 to 60 years, and the ratio of females: males was 6: 1;
(9) High serum activities are found for ALT but not for ALP, suggestive of a hepatocellular type of toxic liver injury in patients with kava hepatotoxicity;
(10) Histology showed predominantly liver cell necrosis and hepatitis;
(11) Clinical course was severe in three patients due to risk factors: daily overdose, prolonged treatment, comedication, and use of kava-herbs mixtures;
(12) Outcome was favourable in 13 of 14 patients, but three of these required LTX;
(13) Risk factors include comedication and non-adherence to regulatory treatment recommendations such as daily overdose and prolonged treatment, but not extraction media or solubilizers;
(14) Kava hepatotoxicity represents the predictable type of hepatotoxicity in those patients who might have used one of the few extracts containing inappropriate kava quality; in all other patients, kava hepatotoxicity represents the idiosyncratic reaction of the metabolic type.
(15) Due to lack of epidemiologic data, the incidence of kava hepatotoxicity cannot accurately be calculated but appears to be low.

The data are based on the cases of 14 patients with kava hepatotoxicity and a highly probable, probable or possible causality for kava ± comedication (Tables 1 and 2).[15,16,21]

1,12,15,20) of the remaining eight ones (Table 1). Therefore, half of the patients with kava hepatotoxicity were treated for depression as a disease which is contraindicated for kava treatment according to the regulatory statement.[33] It appears that kava hepatotoxicity might have been a preventable disease in half of the patients, provided regulatory recommendations were followed and treatment with kava would not have been initiated.

Considering all 14 cases (Tables 1 and 2), daily overdose (cases 1,15,16,20,21,23, 29,30), prolonged treatment (cases 1,13,19,20,30), or both together (cases 1,20,30) was not uncommon, excluding two patients (cases 27 and 28) who used a traditional aqueous kava extract in New Caledonia. They could not be assessed regarding maximal allowed daily dose and duration of usage due to lack of general recommendations or restrictions in the Pacific region. Toxic liver injury may occur following treatment of 1-4 months and daily doses of 120-200 mg kavalactones (ethanolic and acetonic kava extracts, herbs-kava mixtures) or after 1-2 months and a daily dose of 120 mg and 2.6 g kavalactones (aqueous kava extract). Hepatotoxicity was observed with all extraction media (Tables 1 and 2), supporting the view of poor quality of the kava raw material as contributory factor.[15,16,20,21,30,65] Comedication was described in nine of 14 patients (cases 1,13,16,19,20,23, 29-30,31). Therefore, confounding variables such as daily overdose, prolonged treatment, comedication, and poor kava quality have to be considered in the context of specific causality assignment.[14-23,30,65,66]

In ten out of the 14 patients, hepatotoxicity showed restoration after kava and drug cessation with a good clinical outcome (cases 1, 12, 13, 15, 16, 19, 23, 27, 28, 30, 31; Tables 1 and 2).[15,16] Three other patients (cases 20,21,30) required liver transplant (LTX) and survived, whereas a lethal course after LTX was described for another patient (case 29). The former patient (case 20) had a daily overdose of kavalactones, increased length of kava therapy, high cumulative dose of kavalactones, and comedication with probable causality for both kava and comedication; the second patient (case 21) had a daily overdose of kavalactones and an increased cumulative dose of kavalactones with a possible causa-

lity for kava; the third patient (case 30) used a herbs-kava mixture and comedication with ibuprofen, had a daily overdose and an increased cumulative dose of kavalactones as well as a prolonged treatment, and was coded with a possible causality for both kava and comedication; and the fourth patient (case 29) used a herbs-kava mixture, had a daily overdose and increased cumulative dose of kavalactones, and causality assessment was probable for kava and possible for comedication, but as alternative diagnosis genuine AIH has to be considered in this particular patient who experienced a lethal outcome in the course of LTX.

In one of the 14 patients, a positive reexposure test has been reported 3 months after the end of an initial treatment with an oral contraceptive, paroxetine, St. John's Wort, and an ethanolic kava extract (60 mg kavalactones/d) of 6 months duration (case 19, Table 1)[13] and thereby twice as long as recommended by the regulators.[33] Despite these shortcomings, this case reached a highly probable causality for kava upon quantitative, structured and hepatotoxiity specific causality assessment.[15] The positive reexposure test in this particular case clearly shows that kava has the potency of hepatotoxicity, and this is commonly acknowledged.[14,16-21] This highly probable causality for kava in one single patient (case 19, Table 1) in connection with a probable causality for kava ± co-medication in four other patients (cases 12,20,28,29) (Tables 1 and 2) creates concern on clinical grounds and pharmacovigilance considerations. On the other hand, in nine out of 14 cases and thereby in the majority of patients (cases 1,13,15,16,21,23,27,30,31) (Tables 1 and 2), causality of hepatotoxicity for kava ± comedication was graded as only possible and thus weak (Table 2).

RECOMMENDATIONS

The present results of kava hepatotoxicity (Table 3) are in line with characteristics described for cases of liver injury induced by chemical drugs and dietary supplements, including herbal ones.[1-6,42] Should kava as a drug return to the market, certain measures are requisite. There is an urgent need to adhere to treatment recommendations including regulatory indication, to avoid comedication, and to implement standards for good kava quality.

CONCLUDING REMARKS

Herbal hepatotoxicity by the use of aqueous, ethanolic and acetonic kava extracts and herbs-kava mixtures was verified in a few patients in connection with overdose, prolonged treatment and comedication, most probably also as a consequence of poor quality of the kava raw material contained in a few kava extracts. To minimize hepatotoxic risks due to kava use, efforts have to be undertaken to improve treatment modalities and to implement kava quality standards.

ABBREVIATIONS

- **AIH:** Autoimmune hepatitis.
- **ALP:** Alkaline phosphatase.
- **ALT:** Alanine aminotransferase.
- **AMA:** Antimitochondrial antibodies.
- **ANA:** Antinuclear antibodies.
- **BfArM:** Bundesinstitut für Arzneimittel und Medizinprodukte (German regulatory health agency).
- **BMI:** Body mass index.
- **CD:** Comedicated drug(s).
- **CIOMS:** Council for International Organizations of Medical Sciences.
- **CMV:** Cytomegalovirus.
- **EBV:** Epstein Barr virus.
- **γGT:** γ-glutamyltranspeptidase.
- **HAV:** Hepatitis A virus.
- **HBV:** Hepatitis B virus.
- **HCV:** Hepatitis C virus.
- **HEV:** Hepatitis E virus.
- **HIV:** Human immunodeficiency virus.
- **HSV:** Herpes simplex virus.
- **IKS:** Interkantonale Kontrollstelle Schweiz (Swiss regulatory agency).
- **IgM:** Immunglobulin M.
- **IgG:** Immunglobulin G.
- **LKM:** Liver kidney microsomal antibodies.
- **LTX:** Liver transplantation.
- **MCV:** ;Median cell volume.
- **p-ANCA:** Perinuclear antineutrophil cytoplasmic antibodies.
- **PBC:** Primary biliary cirrhosis.
- **SLA:** Soluble liver antigen.
- **SMA:** Smooth muscle antibodies.
- **VZV:** Varicella zoster virus.

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