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Kava hepatotoxicity: Comparison of aqueous, ethanolic, acetonic kava extracts and kava–herbs mixtures

Rolf Teschke*, Alexander Genthner, Albrecht Wolff

Department of Internal Medicine II, Division of Gastroenterology and Hepatology, Klinikum Hanau, Teaching Hospital of the Johann Wolfgang Goethe-University of Frankfurt/Main, Leimenstraße 20, D-63450 Hanau, Germany

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ABSTRACT

Ethnopharmacological relevance: Ethanolic and acetonic kava extracts have previously been causally related to rare hepatotoxicity observed in patients from Germany and Switzerland, but causality assessment was not performed in cases of patients having taken the traditional aqueous kava extracts of South Pacific islands or kava–herbs mixtures.
Aim of the study: To study the possible hepatotoxicity of aqueous kava extracts of the South Pacific Islands.
Materials and methods: Causality of hepatotoxicity by aqueous kava extracts and kava–herbs mixtures was assessed, using the updated score of the quantitative CIOMS (Council for the International Organizations of Medical Sciences).
Results: Causality was established in five patients from New Caledonia, Australia, the United States and Germany for aqueous kava extracts and kava–herbs mixtures. A comparison with 9 patients from Germany and Switzerland with established causality of hepatotoxicity by ethanolic and acetonic kava extracts reveals that the clinical picture in all 14 patients is similar, independently whether aqueous, ethanolic and acetonic kava extracts or kava–herbs mixtures were used.
Conclusions: Kava hepatotoxicity occurs also with traditional aqueous kava extracts of the South Pacific islands and thereby independently from ethanol or acetone as chemical solvents, suggesting that the toxicity is linked to the kava plant itself with a possibly low quality of the used kava cultivar or kava plant part rather than to chemical solvents.

1. Introduction

The consumption of traditional aqueous kava extracts derived from the rhizomes of the perennial shrub (*Piper methysticum* Forster, black pepper family Piperaceae) has been described for more than 200 years in South Pacific islands (Lebot et al., 1997). Based on an archaeological study of characteristic drinking bowls, however, it has been proposed that kava was first domesticated in Polynesia more than 2000 years ago (Denham et al., 2002). The term kava refers to both the kava plant and the various kava extracts (Denham et al., 2002; Stevinson et al., 2002). The most commonly used synonyms are kawa, ava, and awa, apart from at least 40 other vernacular variants (Lebot et al., 1997). The name kava kava, however, was applied to a related plant (*Piper excelsum*) (Singh, 1992) or to an unrelated one (*Muscari latifolium*) (Lebot et al., 1997). Traditional aqueous kava extracts are beverages and have to be differentiated from ethanolic and acetonic kava extracts sold as capsules or tablets to be used as herbal remedies. The raw material of the different extracts consists of fresh or dried kava rhizomes. The extracts are prepared by grinding and soaking the rhizomes, and as solvents either water, ethanol, or acetone are used, depending on the final use (Singh, 1992; Lebot et al., 1997; Denham et al., 2002). Kava extracts contain various kavapyrones, also called kavalactones, with psychoactive properties. The most important kavapyrones are kavain, methysticin, yangonin, and dihydrokawain, causing alterations of cerebral functions involving various mechanisms such as GABA binding, inhibition of noradrenaline uptake, and binding to sodium ion channel receptor sites (Block et al., 2004).

Traditional aqueous kava extracts were used in the South Pacific islands mainly for ceremonial reasons (Lebot et al., 1997; Denham et al., 2002). Occasions included welcome ceremonies of visiting parties, family feasts, and important community activities, apart from informal kava drinking on a social basis (Singh, 1992; Lebot et al., 1997). The consumption of aqueous kava extracts was commonly well tolerated in the absence of major side effects (Denham et al., 2002; Currie and Clough, 2003; Moulds and Malani, 2003), with increased serum activities of y-glutamyl transpeptidase (Mathews et al., 1988; Clough et al., 2003; Russmann et al., 2003), alkaline phosphatase (Clough et al., 2003) and alanine aminotransferase (Russmann et al., 2003) observed in some

* Corresponding author. Tel.: +49 6181 2964200; fax: +49 6181 2964211.
E-mail address: rolf.teschke@klinikum-hanau.de (R. Teschke).

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patients. In Western countries kava was mainly used as ethanolic or acetonic rather than aqueous extracts for treatment of anxiety disorders (Stevinson et al., 2002; Pittler and Ernst, 2003; Ernst, 2004), and discussions emerged regarding their possible hepatotoxic properties (BfArM, 2002; Loew and Franz, 2003; Schulze et al., 2003; Stickel et al., 2003; Teschke et al., 2003; Block et al., 2004; Clouatre, 2004; Schmidt et al., 2005; Schmidt, 2007; Teschke et al., 2008a,c).

With a quantitative causality assessment of CIOMS (Council for the International Organizations of Medical Sciences) (Danan and Bénichou, 1993), both a temporal and causal relationship of hepatotoxicity could be established for ethanolic and acetonic kava extracts ± co-medicated drugs in a recent study of patients from Germany and Switzerland, resulting in a detailed description of the characteristics of kava hepatotoxicity in this selected group (Teschke et al., 2008a). Since the latter report was confined to patients assessed before by the German and Swiss regulatory agencies (BfArM, 2002), other cases world wide from New Caledonia (Russmann et al., 2003), Australia (Gow et al., 2003), the United States (Humberston et al., 2003) and Germany (Weise et al., 2002) were not evaluated by the same analytical approach. Similarly, in the previous study only patients have been included who used ethanolic or acetonic kava extracts (Teschke et al., 2008a), whereas aqueous kava extracts and kava–herbs mixtures were not assessed.

In the present study using the quantitative CIOMS scale in its updated form, causality of the observed liver diseases could be confirmed for kava ± co-medication in further cases from all over the world. Moreover, hepatotoxicity occurred not only in connection with ethanolic and acetonic but also in addition with aqueous kava extracts as well as with kava–herbs mixtures. Since kava hepatotoxicity emerged also with traditional aqueous kava extracts, obtained in New Caledonia from South Pacific islands and in Germany, it is suggested that kava raw material of low quality may play a more important role for the pathogenesis than the chemical extraction medium. Finally, the clinical characteristics of kava hepatotoxicity were found to be similar in all evaluated countries world wide and independently from the mode of kava preparation.

2. Patients and methods

Quantitative causality assessment was applied in the present study to five patients with suspected hepatotoxicity by the use of traditional aqueous kava extracts and kava–herbs mixtures. Their characteristics were compared with those of nine patients from Germany and Switzerland with verified kava hepatotoxicity after use of ethanolic and acetonic kava extracts (Teschke et al., 2008a,c). In the latter studies the same method of quantitative causality assessment has been used as in the present analysis. The cases of the study patients were sufficiently documented, two originated from New Caledonia (Russmann et al., 2003), and one each from Australia (Gow et al., 2003), the United States (Humberston et al., 2003), and Germany (Weise et al., 2002).

The temporal as well as the causal association has been assessed with the quantitative criteria of CIOMS (Council for International Organizations of Medical Sciences) (Danan and Bénichou, 1993) used in its updated variety as main-test (Teschke et al., 2008b). The CIOMS system was derived from an international concensus meeting of experts who defined various parameters such as time to onset, course of improvement of laboratory data, risk factors, concomitant drugs, search for nondrug causes, previous information on hepatotoxicity of the drug, and response to readministration. It provides with each of these parameters a range of scores. The total score is then computed and may be divided into ranges that represent the causality as being highly probable, probable, possible, unlikely or excluded. The updated CIOMS scale was also used for causality assessment regarding all co-medicated drugs in temporal association with the observed liver disease, and only the single co-medication with the highest score was included in the analysis; provided the usage consisted of two or more drugs and/or dietary supplements. The CIOMS scale has been well validated (Bénichou et al., 1993) and is commonly accepted (Kaplowitz, 2001; Lucena et al., 2001; Lewis, 2002; Andrade et al., 2004, 2005; Teschke et al., 2008a,b; Teschke and Schwarzenboeck, 2009). It consists of two parts; one is available for the hepatocellular and the other one for the cholestatic (±hepatocellular) type of acute toxic liver disease (Danan and Bénichou, 1993). Differentiation by laboratory tests is therefore requisite for evaluation. Serum activities of alanine aminotransferase (ALT) and alkaline phosphatase (ALP) are measured on the day drug-induced hepatotoxicity is suspected. Each activity is expressed as a multiple of the upper limit of the normal range (N), and the ratio (R) of ALT:ALP is calculated. Liver injury is (1) hepatocellular, when ALT >2N alone or $R \geq 5$, (2) cholestatic, when there is an increase of ALP >2N alone or when $R \leq 2$, and (3) of the mixed type, when ALT >2N, ALP is increased and $2 < R < 5$. In all five cases high values for ALT were reported being in the range of 14–110 multiples of the upper limit of the normal range, and for ALP the corresponding values were 1.5 and 1.9 in two patients and not reported in the three others. Based on these laboratory data, it has been assumed that the patients of the present study exhibited a hepatocellular liver injury rather than a cholestatic or a mixed type one, and the appropriate CIOMS scale was used.

3. Results

3.1. Causality assessment

In the group of the study patients (Table 1) causality assessment was achieved applying the quantitative CIOMS scores (Table 2). With this approach the question was to be answered whether the observed liver diseases were causally related to the intake of kava, co-medicated synthetic drugs, herbal remedies or dietary supplements. All patients reached a total score ranging from 3 to 8 points for kava ± co-medication, corresponding to a possible or probable causality (Tables 2 and 3). These data substantiate that the hepatotoxic property of kava is independent whether it was used as aqueous kava extracts in New Caledonia (cases 1 and 2), as kava–herbs mixtures in Australia and the United States (cases 3 and 4), or as aqueous kava extract in Germany (case 5). It is also obvious that patients from various countries all over the world are involved.

3.2. Specific characteristics of the study patients

Details of the study patients with toxic liver disease and a possible or probable causality related to the use of kava ± co-medication are given in Table 1. All patients were females. One of these was only 14 years old, and the age of the others ranged from 55 to 59 years. With the exception of 1 patient, the other patients took up to 3 co-medicated synthetic drugs or up to 20 co-medicated herbal remedies and dietary supplements. At least in 1 patient (case 1) the extent of co-medication suggests major co-morbidity.

The indication was anxiety for use of kava-herbs extracts in two patients (cases 3 and 4) and not explicitly declared in the remaining three patients with the assumption that the two patients from New Caledonia took the traditional aqueous kava extracts most probably under ceremonial conditions.

Results of liver histology were available in three patients with liver cell necrosis alone (case 4) or in combination with toxic hepatitis (cases 3 and 5).

Table 1
Clinical data of all patients ($n = 5$) with suspected liver disease in association with the use of traditional aqueous kava extracts and kava–herbs mixtures. For patient 04, the list of co-medication includes also information gathered by Schmidt et al. (2005). LTX denotes liver transplantation.

Patient	Identification	Age (years)	Sex	Kava extract/ mixture	Duration of use (months)	Kavapyrones (mg/d)	Kavapyrones cumulative (g)	Co-medication	Outcome (f = favourable, d = died)	Possible risk factors			
										Cumulative dose	Prolonged use	Daily overdose	Co-medication
01	New Caledonia: Russmann et al. (2003)	59	f	Aqueous	1.0	?	?	Lisinopril, phenobarbital, fenofibrate	f	?	–	?	+
02	New Caledonia: Russmann et al. (2003)	55	f	Aqueous	1.25	2.571	90.000	–	f	?	–	?	–
03	Australia: Gow et al. (2003)	56	f	Mixture	3	180	16.2	*Passiflora incarnata*, *Scutellaria lateriflora* (declared, but not identified); vitamins (unspecified); mineral supplements (unspecified)	LTX d	+	–	+	+
04	USA: Humberston et al. (2003)	14	f	Mixture	4	200	24.0	Ibuprofen, St. John's wort, Siberian ginseng root, chamomile, peppermint leaves, cinnamon, lemmon grass, ginger root, licorice root, roasted chicory root, catnip leaves, natural flavours including natural lemmon ones, Tilia estrella flowers, valerian root, spermint leaves, hawthorn berries, orange blossoms, magnesium, vitamin B_6, vitamin B_{12}, vitamin C	LTX	+	+	+	+
05	Germany: Weise et al. (2002)	34	f	Aqueous/ powdered, ethanolic before	3	120	10.8	L-Thyroxine, potassium iodine	f	–	–	–	+

Table 2
Quantitative causality assessment for kava using the updated CIOMS scale for all patients ($n = 5$) with suspected liver disease in association with the use of traditional aqueous kava extracts and kava–herbs mixtures. Details of the patients are given in Table 1. Total points: ≤0 = causality excluded; 1–2 = causality unlikely; 3–5 = causality possible; 6–8 = causality probable; >8 = causality highly probable.

Hepatocellular injury	Possible score	Patients 1	2	3	4	5
1. Time to onset from the beginning of the drug						
5–90 days	+2	2	2	2		2
<5 or >90 days	+1				1	
2. Time to onset from cessation of the drug						
≤15 days	+1	1	1	1	1	1
3. Course of ALT after cessation of the drug						
Decrease ≥50% within 8 days	+3					
Decrease ≥50% within 30 days	+2			2		
No information	0	0	0		0	0
Decrease ≥50% after the 30th day	0					
Decrease <50% after the 30th day or recurrent increase	−2					
4. Risk factor ethanol						
Yes	+1					
No	0	0	0	0	0	0
5. Risk factor age						
≥55 years	+1	1	1	1		
<55 years	0				0	0
6. Concomitant drug(s)						
None or no information	0		0			
Concomitant drug with incompatible time to onset	0					
Concomitant drug with compatible or suggestive time to onset	−1			−1		−1
Concomitant drug known as hepatotoxin and with compatible or suggestive time to onset	−2	−2			−2	
Concomitant drug with evidence for its role in this case (positive rechallenge or validated test)	−3					
7. Search for nondrug causes						
Group I (6 causes)						
Anti-HAV-IgM		–		–	–	–
Anti-HBc-IgM/HBV-DNA		–	–	–	–	–
Anti-HCV-IgM/HCV-RNA		–		–	–	–
Biliary obstruction (ultrasonography)		–	–	–	–	–
Alcoholism (AST/ALT ≥2)		–	–	–	–	–
Acute recent hypotension history (particularly if underlying heart disease)		–	–	–	–	–
Group II						
Complications of underlying disease(s)		–	–	–	–	–
Clinical and/or biological context suggesting infection by PCR and						
CMV (Anti-CMV-IgM)				–		
EBV (Anti-EBV-IgM)				–		
HSV (Anti-HSV-IgM)						
Evaluation of groups I and II						
All causes – groups I and II – reasonable ruled out	+2					
The six causes of group I ruled out	+1	1		1	1	1
Five or four causes of group I ruled out	0		0			
Less than four causes of group I ruled out	−2					
No drug cause highly probable	−3					
8. Previous information on hepatotoxicity of the drug						
Reaction labelled in the product characteristics	+2	2	2	2	2	2
Reaction published but unlabelled	+1					
Reaction unknown	0					
9. Response to readministration						
Doubling of ALT with the drug alone	+3					
Doubling of ALT with the drug(s) already given at the time of first reaction	+1					
Increase of ALT but less than *N* in the same conditions as for the first administration	−2					
Other situations	0					
Total points		5	6	8	3	5

3.3. Kava extracts and mixtures

The two patients from New Caledonia used a traditional aqueous kava extract obtained from Vanuata, a South Pacific island, for 1.0 and 1.25 months (cases 1 and 2) (Table 1). Whereas the daily consumption of kavapyrones was unknown in the first patient, the second one took 18 g kavapyrones weekly corresponding to 2.6 g daily, yielding a cumulative dose of 90 g.

Kava mixtures were used by two patients (cases 3 and 4) (Table 1). They have taken a daily overdose of 180 and 200 mg

Table 3
Causality assessment with the CIOMS scale. Comparison kava and co-medicated drug(s) including other herbal remedies, dietary supplements and co-medicated chemical drugs.

Patient	CIOMS scores		CIOMS causality	
	Kava	Co-medicated drug(s)	Kava	Co-medicated drug(s)
1	5	4	Possible	Possible
2	6		Probable	
3	8	3	Probable	Possible
4	3	4	Possible	Possible
5	5	3	Possible	Possible

kavapyrones for 3 and 4 months, respectively. The former patient used kava contained in a mixture with other herbs such as *Passiflora incarnata* and an unknown herb listed as *Scutellaria laterifolia* but not identified as such, whereas the latter one took a mixture consisting of kava, St. Johns's wort, Siberian ginseng root, chamomile, peppermint leaves, cinnamon, lemmon grass, ginger root, licorice root, roasted chicory root, catnip leaves, natural flavours including natural lemmon ones, Tilia estrella flowers, valerian root, spermint leaves, hawthorn berries, orange blossoms, magnesium, vitamin B_6, vitamin B_{12}, vitamin C. Co-medication consisted also of ibuprofen.

The fifth patient used two different kava extracts at a daily dose of 120 mg kavapyrones for a total of 3 months (case 5) (Table 1). Initially she took an ethanolic extract and later on an aqueous extract based on powdered kava.

3.4. Characteristics of kava hepatotoxicity

All patients of the present study showed a causal relationship between the observed liver disease and the use of kava ± co-medication (Tables 2 and 3). Some typical features of kava hepatotoxicity were evident: (1) kava hepatotoxicity may be caused by the use of aqueous kava extracts and kava–herbs mixtures; (2) it may occur after a treatment for 1–4 months and daily doses of 120–200 mg kavapyrones (kava–herbs mixture) or 120 mg to 2.6 g kava-pyrones (aqueous kava extract); (3) co-medication was a risk factor for the development of kava hepatotoxicity; (4) intake of kava–herbs mixtures with high daily kava doses ± prolonged consumption may be associated with the risk of life-threatening acute liver failure requiring liver transplantation; (5) kava hepatotoxicity may exhibit high serum activities of ALT compared to ALP and is characterized upon liver biopsy by liver cell necrosis alone or combined with toxic hepatitis; (6) all patients were females and (7) causality was probable or possible for kava ± co-medication in all five patients.

4. Discussion

In the present study cases reported from New Caledonia, Australia, the United States and Germany with assumed kava hepatotoxicity following the use of aqueous kava extracts and kava–herbs mixtures (Table 1) were subjected to causality assessment applying the updated quantitative CIOMS criteria (Table 2). Causality of the observed liver disease could be established in all patients for kava ± co-medicated herbs, dietary supplements and synthetic drugs (Tables 2 and 3). With the quantitative CIOMS criteria, causality was previously established in nine patients from Germany and Switzerland after treatment with ethanolic and acetonic kava extracts (Teschke et al., 2008a,c). When the results of the latter studies were combined with the data of the present analysis with 5 patients, kava hepatotoxicity may fairly well be characterized with these 14 patients observed world wide in connection with the use of various kava extracts and mixtures (Table 4).

It appears that inhabitants from countries all over the world including New Caledonia may be susceptible for kava hepatotoxicity as shown in the present study (Tables 1–3) and reported previously from Germany and Switzerland (Teschke et al., 2008a,c). Of major concern is the hepatotoxic potency of aqueous kava extracts in the two patients from New Caledonia and in one patient from Germany (Tables 1–3) (Weise et al., 2002; Russmann et al., 2003), substantiating that the use of traditional aqueous extracts has risks similar to those by the treatment with ethanolic and acetonic kava extracts reported from Germany and Switzerland (Teschke et al., 2008a,c). This raises the question to what extent the quality of the kava raw material may be a major contributing factor for the toxicity rather than the used chemical extraction medium.

The quality of kava depends on several major conditions and on their complex combinations (Lebot and Levesque, 1996; Denham et al., 2002; Loew and Franz, 2003; Lebot, 2006; Schmidt, 2007; Lechtenberg et al., 2008). They include the chemotype and thus the

Table 4
Summary of characteristics of all 14 patients with hepatotoxicity in established 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 ($n=2$)
Age (years)	34–59	26–60	36–50	14–56
Female gender	3/3	5/5	2/4	2/2
Kavapyrones (mg/d)	120–2.571	45–1.200	70–280	180–200
Duration (months)	1.0–1.25	0.25–12	1.5–3	3–4
Co-medication	2/3	4/5	2/4	2/2
Daily kava overdose	n.a.	2/5	3/4	2/2
Prolonged kava use	0/3	3/5	1/4	1/2
Favourable outcome (±LTX)	3/3	5/5	4/4	1/2
Lethal outcome (±LTX)	0/3	0/5	0/4	1/2
Requirement for LTX	0/3	1/5	1/4	2/2
Established causality for kava alone	1/3	3/5	2/4	0/2
Established causality for kava ± co-medication	2/3	2/5	2/4	2/2
Possible causality for kava ± co-medication	2/3	3/5	3/4	1/2
Probable causality for kava ± co-medication	1/3	1/5	1/4	1/2
Highly probable causality for kava ± co-medication	0/3	1/5	0/4	0/2

The individual data of patients who used the traditional aqueous kava extracts or kava–herbs mixtures are given in Tables 1–3, and those who used ethanolic and acetonic kava extracts have been published before (Teschke et al., 2008a,c). LTX denotes liver transplantation, n.a. not assessable.

internal proportion of the six major kavapyrones, the total kavapyrone content, the plant part used for kava preparation, the method of preparation, and the use of fresh or dry plant material. Multiple different kava cultivars exist which are planted, harvested, traded and consumed (Lebot and Levesque, 1996; Lebot, 2006; Schmidt, 2007). These cultivars are characterized by their specific chemotype and differ regarding their positive and negative effects (Lebot, 2006; Schmidt, 2007). As it presently stands, there is uncertainty of the incriminated hepatotoxic agent(s) and the kava cultivar with the highest and lowest hepatotoxic risk. In Germany kava had drug status, and the national regulatory agency stated that the peeled rhizome of the kava plant should be used without reference to a particular kava cultivar (Kommission E of BGA, 1990). Due to lack of definition, any kava cultivars could have been used, even those of low quality with hepatotoxic potency. Moreover, the possibility exists that also parts other than the rhizome may have been used to satisfy the demand, especially at times when the kava market boomed at the end of the last decade (Lebot, 2006; Schmidt, 2007). At the same time, the first report of kava hepatotoxicity appeared in 1998 (Strahl et al., 1998), suggesting that kava quality might have been excellent before the kava boom started.

Non-adherence to the recommendations for kava use may be considered as another risk factor. According to the German regulatory agency, the daily use was limited to an equivalent of 60–120 mg kavapyrones for not longer than 3 months (Kommission E of BGA, 1990). Only a minority of the patients in Germany and Switzerland adhered to the recommendations (Teschke et al., 2003, 2008a,c). Applying these regulatory recommendations to the patients from Australia and the United States (cases 3 and 4) of the present study, there was daily overdose ± prolonged treatment (Table 1). A recommended upper limit regarding kavapyrones in the traditional aqueous kava extracts is not available, and information regarding therapeutic doses has not been published. One of the patients from New Caledonia used 18 g kavapyrones per week corresponding to 2.6 g per day (case 2), which is in the lower range of traditional aqueous kava consumption (9–130 g kavapyrones per week) (Russmann et al., 2003). Theoretically, kavapyrones derived from aqueous kava extracts may have a poor intestinal absorption, contrasting to acetonic and ethanolic kava extracts which have in their tablets or capsules also solubilizers such as macrogol. The amounts of kavapyrones in aqueous extracts are therefore not necessarily comparable with those of ethanolic or acetonic extracts regarding efficacy or toxicity.

There is convincing evidence that kavapyrones inhibit in vitro virtually all isoenzymes of cytochrome P450, which are required for the metabolism of most exogenous compounds (Mathews et al., 2002; Anke and Ramzan, 2004; Singh, 2005). On the other hand, it has been reported that the total amount of hepatic cytochrome P450 is increased in experimental animals fed with kavapyrones (Russmann et al., 2003) but, in the absence of an experimental pair-feeding design to control for adequate dietary intake of nutrients by the kava group identical to the control group, the data are difficult to interpret. Increased hepatic contents of cytochrome P450 have been described solely with hypocaloric, carbohydrate restricted diets (Teschke et al., 1981), raising the question whether animals fed sedative kavapyrones may have a lower carbohydrate intake and hence increased hepatic levels of cytochrome P450 just on dietary grounds. This view is supported by the observation that at least in heavy kava consumers of an Aboriginal community in Australia a decreased body mass index reflecting malnutrition was reported (Mathews et al., 1988), but in face of these different experimental and clinical data the relevance of malnutrition remains to be established. Due to lack of supporting evidence, there is also uncertainty whether kavapyrones are metabolized by cytochrome P450 (Russmann et al., 2003) or more specifically by its isoenzyme 2D6 as claimed previously (Stickel et al., 2003; Singh, 2005).

Co-medication with synthetic drugs was considered as a risk factor in patients with kava hepatotoxicity (Teschke et al., 2008a,c), a finding confirmed in the present study (Tables 1 and 3). Co-medicated herbal remedies and dietary supplements may also be causally related to the observed hepatotoxicity, at least to a certain extent (Table 3), in line with previous results (Teschke et al., 2008a,c). In particular, the use of kava–herbs mixtures may be risky, as shown by one patient (case 4) who used as much as 20 co-medicated herbal and other dietary supplements (Table 1). With a combined use of kava and co-medication the question is open for discussion whether kavapyrones promote hepatotoxicity elicited by the co-medicated compounds or vice versa. Interactions at the site of hepatic microsomal cytochrome P450 are known for most exogenous compounds including synthetic drugs, kavapyrones and ingredients of St. John's wort (Mathews et al., 2002; Anke and Ramzan, 2004; Singh, 2005). These interactions are of potential clinical relevance, and a combination therapy should therefore be avoided. Urinary evaluation for chemical analysis may be helpful in cases of suspected side effects.

It is of note that the three patients (cases 1, 2 and 5) of the present study who used the traditional aqueous kava extracts (Table 1), all experienced high serum activities of ALT associated with a low value of y-glutamyl transpeptidase and alkaline phosphatase in one patient (case 5). Conversely, previous studies with high consumers of the traditional aqueous kava extracts showed increased activities mainly of y-glutamyl transpeptidase (Mathews et al., 1988; Clough et al., 2003; Russmann et al., 2003) and to a lesser degree also of alkaline phosphatase (Clough et al., 2003) and alanine aminotransfersase (Russmann et al., 2003). Raised y-glutamyl transpeptidase activities have been viewed as hepatotoxic effects of kava (Mathews et al., 1988), reversible liver function tests (Clough et al., 2003), a condition not necessarily implying subclinical liver toxicity (Moulds and Malani, 2003), or enzyme induction (Russmann et al., 2003). Experimental studies have shown that a hypocaloric, carbohydrate restricted diet increases hepatic activities of y-glutamyl transpeptidase (Teschke and Petrides, 1982), enzyme conditions commonly associated with corresponding enhanced serum activities (Teschke et al., 1983). Since kava use may cause a decrease of the body mass index along with malnutrition (Mathews et al., 1988), overt or even subclinical dietary impairment may be causally related to increased serum y-glutamyl transpeptidase activities in kava consumers by a mechanism involving hepatic enzyme induction. No valid explanations are presented for increased serum activities of alkaline phosphatase (Clough et al., 2003) and alanine aminotransferase (Russmann et al., 2003) in some patients, considering also that the latter enzyme was not increased in activity in another study (Clough et al., 2003).

Due to the regulatory ban of kava drugs in various countries (Schmidt et al., 2005), additional clinical assessments of hepatotoxicity by kava are presently not possible. Moreover, since open questions regarding the quality of the kava raw material still remain (Schmidt, 2007; Teschke et al., 2008a,c), additional clinical studies of kava hepatotoxicity are less promising at that time. As long as these confounding variables prevail, further efforts are not warranted.

In conclusion, rare hepatotoxicity is causally related to the use not only of ethanolic and acetonic kava extracts as shown previously but also of kava–herbs mixtures and traditional aqueous kava extracts. Causality regarding all kava preparations was ascertained employing the quantitative causality assessment with the updated CIOMS scores. Since toxicity occurs also with the traditional and original aqueous kava extracts of the South Pacific islands, the most probable pathogenetic factor is the low quality of kava regard-

ing cultivar(s) and/or used plant parts during the emerged kava boom.

Conflict of interest

No conflicts of interest exist.

References

Andrade, R.J., Camargo, R., Lucena, M.I., González-Grande, R., 2004. Causality assessment in drug-induced hepatotoxicity. Expert Opinion on Drug Safety 3, 329–344.

Andrade, R.J., Lucena, M.I., Fernández, M.C., Pelaez, G., Pachkoria, K., García-Ruiz, E., García-Muñoz, B., González-Grande, R., Pizarro, A., Durán, J.A., Jiménez, M., Rodrigo, L., Romero-Gomez, M., Navarro, J.A., Planas, R., Costa, L., Borras, A., Soler, A., Salmerón, J., Martin-Vivaldi, R., 2005. Drug-induced liver injury: an analysis of 461 incidences submitted to the Spanish registry over a 10-year period. Gastroenterology 129, 512–521.

Anke, J., Ramzan, I., 2004. Pharmacokinetic and pharmacodynamic drug interactions with kava (*Piper methysticum* Forst. f.). Journal of Ethnopharmacology 93, 153–160.

Bénichou, C., Danan, G., Flahault, A., 1993. Causality assessment of adverse reactions to drugs. II. An original model for validation of drug causality assessment methods: case reports with positive rechallenge. Journal of Clinical Epidemiology 46, 1331–1336.

BfArM (Bundesinstitut für Arzneimittel und Medizinprodukte, Bonn. Federal Institute for Drugs and Medicinal Products in Germany), 2002. http://www.bfarm.de/de/arzneimittel/am_sicher/stufenpl/Besch-kava-Final.pdf.

Block, K.I., Gyllenhaal, C., Mead, M.N., 2004. Safety and efficacy of herbal sedatives in cancer care. Integrative Cancer Therapies 3, 128–148.

Clouatre, D.L., 2004. Kava kava: examining new reports of toxicity. Toxicology Letters 150, 85–96.

Clough, A.R., Bailie, R.S., Currie, B., 2003. Liver function test abnormalities in users of aqueous kava extracts. Journal Toxicology/Clinical Toxicology 41, 821–829.

Currie, B.J., Clough, A.R., 2003. Kava hepatotoxicity with Western herbal products: does it occur with traditional kava use? Medical Journal of Australia 178, 421–422.

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

Denham, A., McIntyre, M., Whitehouse, J., 2002. Kava—the unfolding story: report on a work-in-progress. The Journal of Alternative and Complementary Medicine 8, 237–263.

Ernst, E., 2004. Kava update: a European perspective. New Zealand Medical Journal 117, U1143, PMID:15570327 [PubMed – indexed for MEDLINE].

Gow, P.J., Connelly, N.J., Hill, R.L., Crowley, P., Angus, P.W., 2003. Fatal fulminant hepatic failure induced by a natural therapy containing kava. Medical Journal of Australia 178, 442–443.

Humberston, C.L., Akhtar, J., Krenzelok, E.P., 2003. Acute hepatitis induced by kava kava. Journal of Toxicology/Clinical Toxicology 41, 109–113.

Kaplowitz, N., 2001. Causality assessment versus guilt-by-association in drug hepatotoxicity. Hepatology 33, 308–310.

Kommission E of BGA, 1990. Monographie Piperis methystici rhizoma (Kava-Kava-Wurzelstock). Bundesanzeiger Nr. 101. dated June 1, 1990.

Lebot, V., 2006. The quality of kava consumed in the South Pacific. HerbalGram 71, 34–37.

Lebot, V., Levesque, J., 1996. Genetic control of kavalactone chemotypes in *Piper methysticum* cultivars. Phytochemistry 43, 397–403.

Lebot, V., Merlin, M., Lindstrom, L., 1997. Kava, the Pacific elixir. Yale University Press, New Haven.

Lechtenberg, M., Quandt, B., Schmidt, M., Nahrstedt, A., 2008. Is the alkaloid pipermethystine connected with the claimed liver toxicity of kava products? Pharmazie 63, 71–74.

Lewis, J.H., 2002. Drug-induced liver disease. Current Opinion in Gastroenterology 18, 307–313.

Loew, D., Franz, G., 2003. Quality aspects of traditional and industrial kava-extracts. Phytomedicine 10, 610–612.

Lucena, M.I., Camargo, R., Andrade, R.J., Perez-Sanchez, C.J., Sanches de la Cuesta, F., 2001. Comparison of two clinical scales for causality assessment in hepatotoxicity. Hepatology 33, 123–130.

Mathews, J.D., Riley, M.D., Fejo, L., Munoz, E., Milns, N.R., Gardner, I.D., Powers, J.R., Ganygulpa, E., Gununuwawuy, B.J., 1988. Effects of the heavy usage of kava on physical health: summary of a pilot survey in an Aboriginal community. Medical Journal of Australia 148, 548–555.

Mathews, J.M., Etheridge, A.S., Black, S.R., 2002. Inhibition of human cytochrome P450 activities by kava extract and kavalactones. Drug Metabolism and Disposition 30, 1153–1157.

Moulds, R.F.W., Malani, J., 2003. Kava: herbal panacea or liver poison? Medical Journal of Australia 178, 451–453.

Pittler, M.H., Ernst, E., 2003. Kava extract for treating anxiety (Cochrane Review). In: Cochrane Library, Issue I. Update Software, Oxford.

Russmann, S., Barguil, Y., Cabalion, P., Kritsanida, M., Duhet, D., Lauterburg, B.H., 2003. Hepatic injury due to traditional aqueous extracts of kava root in New Caledonia. European Journal of Gastroenterology and Hepatology 15, 1033–1036.

Schmidt, M., 2007. Quality criteria for kava. HerbalGram 73, 45–49.

Schmidt, M., Morgan, M., Bone, K., McMillan, J., 2005. Kava: a risk-benefit assessment. In: Mills, M., Bone, K. (Eds.), The Essential Guide to Herbal Safety. Elsevier Churchill Livingstone, St. Louis (Missouri), pp. 155–221.

Schulze, J., Raasch, W., Siegers, C.P., 2003. Toxicity of kava pyrones, drug safety and precautions—a case study. Phytomedicine 10 (Suppl. IV), 68–73.

Singh, Y.H., 1992. Kava: an overview. Journal of Ethnopharmacology 37, 13–45.

Singh, Y.H., 2005. Potential for interaction of kava and St. John's wort with drugs. Journal of Ethnopharmacology 100, 108–113.

Stevinson, C., Huntley, A., Ernst, E., 2002. A systematic review of the safety of kava extract in the treatment of anxiety. Drug Safety 25, 251–261.

Stickel, F., Baumüller, H.M., Seitz, K., Vasilakis, D., Seitz, G., Seitz, H.K., Schuppan, D., 2003. Hepatitis induced by kava (*Piper methysticum* rhizoma). Journal of Hepatology 39, 62–67.

Strahl, S., Ehret, V., Dahm, H.H., Maier, K.P., 1998. Necrotising hepatitis after taking herbal remedies. Deutsche Medizinische Wochenschrift 123, 1410–1414 (Article in German).

Teschke, R., Gaus, W., Loew, D., 2003. Kava extracts: safety and risks including rare hepatotoxicity. Phytomedicine 10, 440–446.

Teschke, R., Moreno, F., Petrides, A.S., 1981. Hepatic microsomal ethanol oxidizing system (MEOS): respective roles of ethanol and carbohydrates for the enhanced activity after chronic alcohol consumption. Biochemical Pharmacology 30, 1745–1751.

Teschke, R., Neuefeind, M., Nishimura, M., Strohmeyer, G., 1983. Hepatic gamma-glutamyl-transferase activity in fatty liver: comparison with other liver enzymes in man and rats. Gut 24, 625–630.

Teschke, R., Petrides, A.S., 1982. Hepatic gamma-glutamyltransferase activity: its increase following chronic alcohol consumption and the role of carbohydrates. Biochemical Pharmacology 31, 3751–3756.

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

Teschke, R., Schwarzenboeck, A., Hennermann, K.H., 2008a. Kava hepatotoxicity: a clinical survey and critical analysis of 26 suspected cases. European Journal of Gastroenterology and Hepatolology 20, 1182–1193.

Teschke, R., Schwarzenboeck, A., Hennermann, K.H., 2008b. Causality assessment in hepatotoxicity by drugs and dietary supplements. British Journal of Clinical Pharmacology 66, 758–766.

Teschke, R., Schwarzenboeck, A., Akinci, A., 2008c. Kava hepatotoxicity: a European view. New Zealand Medical Journal 121, 90–98.

Weise, B., Wiese, M., Plötner, A., Ruf, B.R., 2002. Toxic hepatitis after intake of kava-kava. Verdauungskrankheiten 4, 166–169 (Article in German).