Kava extracts: Safety and risks including rare hepatotoxicity

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Summary

Kava is a perennial shrub native to some islands of the South Pacific and has been cultivated for centuries to prepare a psychoactive beverage from its rhizoma by means of extraction. Subsequently, kava extracts are commonly used as herbal anxiolytic drugs also in many other countries all over the world including European ones and the USA. Toxicological and clinical studies have shown that kava extracts are virtually devoid of toxic effects with the exception of rare hepatotoxic side effects reported in few patients. When assessed primarily by the British regulatory authority MCA but also by us, a critical analysis of the suspected cases (n = 19) in Germany reveals that only in 1 single patient a very probable causal relationship could be established between kava treatment and the development of toxic liver disease due to a positive result of an unscheduled re-exposure test, whereas in another patient there might be a possible association. Out of the remaining 17 cases 12 patients were not yet assessable due to insufficient data and in 5 other cases a causal relationship was unlikely or could be excluded. The German regulatory authority might therefore well be advised to provide now additional information for those 12 patients with so far unsatisfactory data, facilitating a more appropriate assessment of causality. Nevertheless, in the meantime physicians and patients should continue to keep an eye on possible hepatotoxic side effects in the course of kava treatment, to stop the treatment already at first suspicion and to start with a careful diagnostic work up ruling out all other causes.

Key words: Kava extracts, hepatotoxicity, safety recommendation

Introduction

A cold water extract from the kava rhizoma has traditionally been used in religious ceremonies and at social events on the South Pacific Islands for hundreds of years (Hänsel and Woelk, 1994; Hoelzl et al. 1994; Loew, 2002; Loew and Gaus, 2002). The non-alcoholic drink is not only refreshing, relaxing and anxiolytic, it also decreases aggression and acts as a muscle relaxant drug without a negative influence on awareness or intellectual capacity. An aqueous extract is prepared by grinding the cleaned, peeled and chopped kava roots (approx. 30 g) and by extraction with cold water (approx. 300 ml). The traditional extract made from 10 g powdered crude drug and 100 ml water contains 71.6 mg kavapyrones, which represents a daily dose of 210 mg kavapyrones when 300 ml are drunken (Biber, 2001; Lazar, 1983). The quantities of
daily used kavapyrones in industrially produced ethanolic extracts (68.3 to 119.2 mg/day) and in acetonic extracts (68.3 mg/day) are much lower than in the traditional kava drink (Biber, 2001; Lazar, 1983; Hänsel and Lazar, 1985). Apart from natural variability, the distribution patterns of the individual kavapyrones in aqueous, ethanolic and acetonic extracts is virtually comparable (Hoelzl et al. 1994; Hänsel and Lazar, 1985).

In the past centuries there have been only few reports on side effects associated with kava drinks even with a relative high daily dose of kavapyrones (Hoelzl et al. 1994; Loew, 2002; Cox, 2002; Mathews et al. 1988). Similarly, a variety of experimental studies failed to show a significant potential of toxicity (Hänsel and Woelk, 1994; Hoelzl et al. 1994; Sorrentino, 1990; Gebhardt, 2001). In recent years, however, hepatotoxic side effects were suspected in patients treated with kava extracts (Loew, 2002; Loew and Gaus, 2002). The present report evaluates some experimental and clinical data concerning possible toxic effects associated with kava extracts including those of the liver.

Experimental studies on toxicology of kava extracts

The aim of pre-clinical toxicological investigations is to document or rule out toxic effects of a pharmaceutical preparation. The requirements are stipulated in national and international guidelines and include a wide spectrum of investigations, irrespective of whether the products are chemically-defined substances or plant extracts (Banz, 1995; Habs, 1998). Such data on the acute and chronic toxicity of acetic and ethanolic extracts have been collected in many studies (Hoelzl et al. 1994; Sorrentino et al. 1994) or are reviewed in several reports (Hänsel and Woelk, 1994; Hoelzl et al. 1994; Loew, 2002). Few examples are listed below.

In mice and rats, the LD$_{50}$ of a kava extract (acetone-water 11–20:1, standardised to 70% kavalactones) was of the order $>$1500 mg/kg BW after peroral application and $>$360 mg/kg BW after i.p. administration (Hoelzl et al. 1994). Acute reactions were dose dependent and expressed as a reduction in spontaneous motility, ataxia, sedation, lateral supine posture with reduced reflex reactions, unconsciousness and death due to respiratory paralysis. Repeated peroral administration of the same kava extract to Spraque-Dawley rats (20, 80 and 320 mg/kg BW) and beagles (8, 24 and 60 mg/kg BW) over 26 weeks failed to result in any substance-related deaths within the dose range investigated. With high doses, slight histopathological changes in liver tissues (centrilobular hypertrophy) and kidney (hyaline drops and epithelial pigmentation of the proximal tubules) were found in the rat. In the rat 10 mg/kg BW/day were tolerated without symptoms, and in the dogs 24 mg/kg BW/day were the no effect level (Hoelzl et al. 1994).

The mutagenicity of the same acetonic extract was investigated by means of the Ames test using Salmonella typhimurium TA98, TA100, TA1535, TA 1537 and TA1538, with and without metabolic activation (rat liver S9 mix) at dosages of up to 2.5 mg/plate (Hoelzl et al. 1994). The highest dose was toxic. The extract did not increase the numbers of revertants and showed no signs of mutagenicity. Furthermore, in the mouse the incidence of micronuclei-containing polychromatic erythrocytes in the micronucleus test was not increased after doses of 150, 300 and 600 mg/kg BW compared to solvent, in contrast to the positive control (cyclophosphamide 80 mg/kg BW).

An ethanolic kava extract was administered to rats in food (0.01% or 0.1%) over a period of 3 or 6 months (Sorrentino, 1990). In the three-months study no mortality, no weight changes and no haematological or blood chemical changes, particularly with regard to liver enzymes, occurred. The investigated organs were normal by macroscopic assessment and by organ weight. In individual liver lobes, slight oedematous swelling and lymphocytic infiltration in the portal and biliary areas were observed, and in the glomeruli of renal tissue leukocytic and lymphocytic infiltrations were registered in controls and treated cases (Sorrentino, 1990). Similarly, blood chemistry, laboratory values, and macroscopic and histological findings after the 8-months feeding programme with the same extract were normal (Sorrentino, 1990). The cytotoxicity of the ethanolic and acetonic extracts and of 6 kavapyrones were investigated in the MTT test (3-(4,5-dimethylthiazole-2-yl)-2,4-diphenyltetrazolium bromide) using rat hepatocytes and human HepG2 cells (Gebhardt, 2001). The extracts used showed no signs of hepatotoxicity in either of the tests systems. The EC$_{50}$ was $>$500 µg/ml in rat hepatocytes and could not be determined in human HepG2 cells. In contrast, the 6 kavapyrones showed a dose-dependent cytotoxicity in rat hepatocytes; this was less marked in HepG2 cells. Kavain was the most toxic in rat hepatocytes with an EC$_{50}$ value of 46 µg/ml. If it is assumed that 20% kavain is present in the whole extract, and complete resorption occurs, then a plasma concentration of 3.33 µl/ml can be calculated from a daily dose of 20 mg/kg kavain. This represents a 13.5-fold safety margin with regard to the EC$_{50}$. The safety margins for other kavapyrones are even greater (Gebhardt, 2001). It therefore appears that under normal experimental conditions kavapyrones are safe also with respect to the liver.
Assessment of safety and risk in patients under the treatment with kava extracts

Experimental hepatotoxicological investigations showed no overt hepatotoxic reactions due to kavapyrones, whereas casuistries with assumed mild to severe hepatotoxicity including liver transplantation and lethal outcome have been published for the past few years (Stoller, 2000; Strahl et al. 1998; Kraft et al. 2001; Brauer et al. 2001; Saß et al. 2001; Escher et al. 2001; Russmann et al. 2001). These reports resulted in the immediate withdrawal of the marketing (BfArM, 2002), leading to criticism not only in Germany (Loew, 2002; Schmidt and Nahrstedt, 2002; Teschke, 2002; Ernst, 2002) but also abroad (Cox, 2002; Waller, 2002; FDA, 2002). The ethno-botanist Cox (Cox, 2002) has rejected the criticism of the South Sea drug kava according to which it is supposed to cause liver damage. His research work in the South Pacific, where the crude drug is consumed regularly, has shown no higher incidence of liver disease. According to Mathews et al. (1988) increases of γ-glutamyltranspeptidase in Aborigines in Australia were only seen after high consumption of the kava drink. “There is no convincing evidence so far indicating direct kava toxicity to the liver when consumed according to traditional methods. … It is impossible to make any conclusion from the cases reported in Germany until more information is known about the details of individual cases”. The pharmacologist and toxicologist P. Waller, Illinois USA (Waller, 2002), criticised the case reports from Germany and Switzerland as “lacking in specific clinical and historical information” and recommended they be revised where possible to obtain further information. In addition, he stated that “kava, when taken in appropriate doses … has no scientifically established potential for causing liver damage”. But he warned that “any pharmacologically active agent can interact with drugs, pre-existing conditions and hypersensitivity reactions, possibly affecting the substance toxicity”. In a notice in June 2002 of the FDA (FDA, 2002) it was stated that: “FDA has no current intentions to seek a recall or other regulatory action but would rather continue to approach kava from a science-driven perspective. This means a continued study to the AER’s and continued discussion with industry … FDA is initiating in vitro studies to better understand metabolism of key kava components and possible relationship of the AER’s”. Stevinson et al. (Stevinson et al. 2002) analysed in a recent report the AER’s of kava preparations in detail and concluded: “Data from short-term post-marketing surveillance studies and clinical trials suggest that adverse events are in general rare, mild and reversible … it is concluded that when taken as short-term monotherapy at recommended doses, kava extracts appear to be well tolerated by most users. Serious events have been reported, and further research is required to determine the nature and frequency of such events”. Ernst (Ernst, 2002) is of the opinion that kava extracts are under-estimated regarding their efficacy and over-estimated regarding their risks.

The discrepancy between the evaluation and the decision of the German regulatory authority BfArM (Bundesinstitut für Arzneimittel und Medizinprodukte) and the opinion of the scientific community (Loew, 2002; Cox, 2002; Schmidt and Nahrstedt, 2002; Teschke, 2002; Waller, 2002; FDA, 2002; Stevinson et al. 2002; Ernst, 2002; Kommission E, 2002) was the reason for subjecting the suspected cases of liver damage reported to a critical assessment with regard to causality.

Clinical evaluation and causality assessment of suspected kava hepatotoxicity

The German regulatory authority BfArM came to the conclusion that in 19 patients (Table 1) there may be an association between kava treatment and the development of toxic liver disease, and the causality was defined to be either possible (n = 3), possible/probable (n = 2), probable (n = 12) or very probable (n = 2) (BfArM, 2002). On the contrary, the Medicines Control Agency (MCA) in London (MCA, 2002) concluded the causality in these 19 patients being not probable (n = 2), not assessable (n = 5), possible (n = 9) and probable (n = 3) (Table 1). Thus, the impact of causality was considered to be much weaker by MCA (MCA, 2002) compared to BfArM (BfArM, 2002), although the data provided were identical.

There is only one single well documented case report (Table 1, patient 19) showing a clear association between kava intake and the development of hepatotoxicity by the observation of a recurrent increase of transaminase activities following reexposure with a kava extract as a monotherapy (Strahl et al. 1998). However, in this particular patient there have been various predisposing factors which may have triggered the kava hepatotoxicity before the onset upon reexposure. The predisposing factors include an oral contraceptive (Table 1) which by itself may exhibit the rare potency of hepatotoxicity (Zimmerman, 1999). Another predisposing factor of the observed kava hepatotoxicity upon reexposure may be assumed to be the previous long treatment with paroxetine (Table 1) (Strahl et al. 1998) which not only has potentially hepatotoxic properties by itself but is also a substrate and inhibitor of the isoenzyme cytochrome P450 2D6 (Michalets, 1998), thereby influencing metabolic functions associated
with cytochrome P450 2D6. Interestingly, this particular patient (Table 1, patient no 19) (Strahl et al. 1998) does have a hepatic microsomal cytochrome P450 2D6 deficiency on a genetic basis as shown later (Russmann et al. 2001). Finally, the same patient had a previous treatment with St. John’s wort (Table 1, patient no 19) (Strahl et al. 1998), which is known as an enzyme inducer of various forms of cytochrome P450 isoenzymes including 1A2 and 3A4. The possibility of the development of kava hepatotoxicity triggered by this enzyme induction cannot be ruled out. It therefore appears that kava hepatotoxicity evoked upon reexposure might have been caused at least partially by various conditions including pre-treatment with the oral contraceptive or with paroxetine, genetic cytochrome P450 2D6 deficiency and St. John’s wort. Nevertheless, despite the various predisposing factors a causality assessment of very probable is warranted between kava treatment and the observed hepatotoxicity.

In another patient (patient 9, identical with patient 10) a positive reexposure test was assumed by both BfArM (BfArM 2002) and MCA (MCA 2002): – not probable; 0 not assessable; + possible; ++ probable; +++ very probable; LTX – liver transplantation; Ci – cirrhosis of the liver.

Table 1. Clinical data of patients with suspected toxic liver injury under the treatment with kava extracts. The data are derived from databases of the BfArM (BfArM 2002) and of the involved pharmaceutical companies as well as from published reports for patients 7 (Saß et al., 2001), no 8 (Brauer et al., 2001), no 19 (Strahl et al., 1998) and no 20 (Kraft et al., 2001). Patient no 9 and 10 are identical with a not sufficiently documented reexposition test. The causality assessment was done by the BfArM (BfArM 2002) and the MCA (MCA 2002): – not probable; 0 not assessable; + possible; ++ probable; +++ very probable; LTX – liver transplantation; Ci – cirrhosis of the liver.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Duration of therapy (months)</th>
<th>Kava-pyrones (mg/d)</th>
<th>Comedication</th>
<th>Outcome</th>
<th>Causality assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>39</td>
<td>f</td>
<td>3</td>
<td>210</td>
<td>Oral contraceptive, Diazepam</td>
<td>good</td>
<td>++</td>
</tr>
<tr>
<td>2</td>
<td>69</td>
<td>f</td>
<td>24</td>
<td>up to 210</td>
<td>St. John’s wort, Maalox</td>
<td>good</td>
<td>+</td>
</tr>
<tr>
<td>3</td>
<td>50</td>
<td>f</td>
<td>1.5</td>
<td>210</td>
<td>Furosemide, Atenolol, Terfenadine</td>
<td>good</td>
<td>++</td>
</tr>
<tr>
<td>4</td>
<td>81</td>
<td>f</td>
<td>3</td>
<td>210</td>
<td>Hydrochlorothiazide</td>
<td>lethal</td>
<td>++</td>
</tr>
<tr>
<td>5</td>
<td>33</td>
<td>f</td>
<td>4</td>
<td>180</td>
<td>Cisapride</td>
<td>good</td>
<td>+</td>
</tr>
<tr>
<td>6</td>
<td>35</td>
<td>f</td>
<td>3</td>
<td>120</td>
<td>St. John’s wort</td>
<td>good</td>
<td>+</td>
</tr>
<tr>
<td>7</td>
<td>50</td>
<td>f</td>
<td>7</td>
<td>60</td>
<td>Estrogenes, Gestagenes, Metformin, Glimpirid</td>
<td>LTX</td>
<td>++</td>
</tr>
<tr>
<td>8</td>
<td>23</td>
<td>f</td>
<td>4</td>
<td>240</td>
<td>Rizatriptan, Oral contraceptive</td>
<td>LTX, lethal</td>
<td>+/++</td>
</tr>
<tr>
<td>9</td>
<td>56</td>
<td>f</td>
<td>?</td>
<td>?</td>
<td>good</td>
<td>good</td>
<td>?</td>
</tr>
<tr>
<td>10</td>
<td>56</td>
<td>f</td>
<td>?</td>
<td>?</td>
<td>L-Thyroxine, Estradiol, Lomprazol, Losartan</td>
<td>good</td>
<td>+++</td>
</tr>
<tr>
<td>11</td>
<td>32</td>
<td>m</td>
<td>3</td>
<td>240</td>
<td>Crataegus extract</td>
<td>Valeriana extract</td>
<td>LTX (2x)</td>
</tr>
<tr>
<td>12</td>
<td>36</td>
<td>m</td>
<td>1.5</td>
<td>70</td>
<td>–</td>
<td>good</td>
<td>++</td>
</tr>
<tr>
<td>13</td>
<td>45</td>
<td>f</td>
<td>Several</td>
<td>120</td>
<td>Cynara scolymus extract</td>
<td>good</td>
<td>+</td>
</tr>
<tr>
<td>14</td>
<td>50</td>
<td>f</td>
<td>3.5</td>
<td>240</td>
<td>Oral contraceptive, Cyclandelat</td>
<td>good/Ci</td>
<td>+</td>
</tr>
<tr>
<td>15</td>
<td>46</td>
<td>f</td>
<td>1</td>
<td>360</td>
<td>–</td>
<td>good</td>
<td>++</td>
</tr>
<tr>
<td>16</td>
<td>26</td>
<td>f</td>
<td>0.25</td>
<td></td>
<td>Sulfasaladiazine, Diclofenac Progesterone, Omeprazole, Butylscopalaminum bromide</td>
<td>good</td>
<td>+/++</td>
</tr>
<tr>
<td>17</td>
<td>61</td>
<td>f</td>
<td>3</td>
<td>120</td>
<td>Omeprazole Hymecromon Ginkgo biloba extract</td>
<td>LTX, lethal</td>
<td>++</td>
</tr>
<tr>
<td>18</td>
<td>40</td>
<td>f</td>
<td>6</td>
<td>–</td>
<td>Osteoporolesis</td>
<td>LTX</td>
<td>+</td>
</tr>
<tr>
<td>19</td>
<td>39</td>
<td>f</td>
<td>6</td>
<td>60</td>
<td>Oral contraceptive, Paroxetine, St. John’s wort</td>
<td>good</td>
<td>+++</td>
</tr>
<tr>
<td>20</td>
<td>60</td>
<td>f</td>
<td>12</td>
<td>480</td>
<td>Etilefrin, Piretanid</td>
<td>LTX</td>
<td>++</td>
</tr>
</tbody>
</table>
causal relationship being very probable and probable, respectively (Table 1). However, the data provided for the assumed kava hepatotoxicity both upon first kava administration (patient 9) and upon rechallenge (patient 10) are poorly or not at all documented. This applies for the extent of the elevated liver enzymes activities in the serum, the latency period, the employed kava extract, the exact course of the serum enzymes activities after withdrawal of the drug and the exclusion of other causes for the observed disease (patient 9) (BfArM, 2002). There is also the question on the improvement of the liver enzyme activity in the serum due to corticosteroid therapy (patient 10), a finding commonly observed and indicated in patients with chronic autoimmune hepatitis. It therefore appears that a causal relationship is not yet assessable mainly due to insufficient documentation.

For patient 11 (Table 1) a probable association between kava and observed hepatotoxicity was suggested by both BfArM (BfArM, 2002) and MCA (MCA, 2002). However, there are obviously major pitfalls of the evaluation. Serum activities for ALT are recorded partially under the therapy with steroids for the time 8/8–8/21/2001 and not before (general practitioner) or thereafter waiting for the transplantation. Therefore, the time course of ALT could not fully be assessed and a second peak of ALT activity is indeed possible, rendering then a not probable causal relationship. Moreover, whereas cytomegalie infection was ruled out, this was not the case for Epstein-Barr or herpes simplex virus infection. Both of these infections are compatible with the clinical course of the acute liver failure. It is also not clear how and to what extent hepatic copper overload (M. Wilson) was excluded, a disease which is often overlooked as cause of acute liver failure. Similarly, a non-alcoholic steatohepatitis (NASH) as risk factor is not excluded (102 kg BW, 186 cm). Finally, there was a rechallenge with corticosteroids leading to a normalisation of serum liver enzyme activities. Thus, kava hepatotoxicity is not probable in this patient, at least according to the MCA assessment.

For patient 2 (Table 1) with a possible causal relationship between kava administration and hepatotoxicity (MCA, 2002), an assessment which merits further critical evaluation:

All these 9 patients had a comedication with up to 5 other chemically defined or herbal drugs most of these being potentially hepatotoxic or enzyme inducers.

**Patient 1**: Exact laboratory data and time course are not given. By histological assessment a viral hepatitis could not be excluded. The case is still insufficiently documented.

**Patient 2**: The latency period with 24 months was extremely long and not observed in other patients. The liver histology of a cholestatic type of liver disease is not commonly observed in other suspected cases. There is also no sufficient documentation to what extent other causes for the observed liver disease have been excluded. In particular, the laboratory data and their exact time course are not given, hepatitis serology was unspecifically documented, CMV was not excluded, a positive ANA titer was not further evaluated, and data on ultrasound examination of liver, gall bladder, bile ducts and pancreas as well as amylase and lipase values to rule out a pancreatitis were not given. The case is poorly documented.

**Patient 3**: The liver histology revealed a hepatitis of longer duration which is not compatible with a short duration of kava therapy of only 1.5 months. The symptoms before the development of jaundice were flu-like which are common to viral hepatitis A, EBV, CMV and hepatitis simplex, but data on IgM of these viral infections are not given. Moreover, there was a recurrent increase of serum transaminase activities upon cessation of kava therapy which speaks against a role of kava in the observed liver disease.

**Patient 5**: In this patient not further specified antibodies were found suggesting the beginning of an autoimmune hepatitis which was successfully treated with corticosteroids leading to a normalisation of serum liver enzyme activities. Thus, kava hepatotoxicity is not probable in this patient, at least according to the data presented so far.

**Patient 6**: There is no documentation on ultrasound data of the liver, gall bladder, bile ducts or pancreas. It is also unclear whether hepatitis A, B, C, D and E, EBV, CMV and herpes have been excluded. Finally, the exact time course of serum transaminases activities is not given. Therefore, the case is insufficiently documented.
Patient 7: There is no information whether or not and to what extent other causes of liver failure including non-alcoholic steatohepatitis (NASH) are excluded. The documentation is therefore not yet satisfactory for evaluation.

Patient 8: It is unclear whether an infection by EBV, CMV or herpes or other diseases of liver and alterations of the gall bladder or bile ducts are sufficiently being ruled out. There is also no time course of transaminase activities in the serum following drug withdrawal available making a conclusive assessment of causality all in all difficult.

Patient 17: Poorly documented, not yet assessable case.

Patient 20: With 12 months the latency period is extremely long and with daily dosages of 480 mg kavapyrones there is an extreme overdose. Many but not all possible causes for liver failure are excluded. The evaluation regarding causality is somewhat complicated due to possible pre- and coexisting diseases (Kraft et al. 2001). In the past history there was a pulmonary embolism requiring cardio-pulmonary resuscitation 11 years ago, raising the question whether pulmonary embolism occurred again resulting in a shock liver. Moreover, the patient took from time to time etilefrin which is indicated in hypotonic circulatory dysregulation with arterial hypotonic values, without compensatory tachycardia. The medication included also piretanid as a diuretic drug for recurrent edema which might be due to underlying cardio-pulmonary disease such as a coronary heart disease. In addition, a low arterial blood pressure of only 100/50 mm Hg is mentioned. The possibility is therefore not excluded that the progressive liver failure might be due to insufficient oxygen supply by arterial hypotension and/or liver congestion due to right heart failure. It also remains to be established whether a non-alcoholic steatohepatitis (NASH) may be contributory since the patient had an excessive overweight (90 kg at 168 cm, BMI 31.8 kg/m²). Under these conditions a causality assessment might be evaluated only with possible in the present stage.

Taking together the assessment of the MCA (Table 1) (MCA, 2002) and the critical evaluation of the patients’ data as shown above, then it appears that out of 19 patients with suspected kava hepatotoxicity only 1 patient may have a very probable association between kava treatment and the development of toxic liver injury. From the remaining 18 patients causality was possible in 1 patient, not definitively assessable in as much as 12 patients due to insufficient data, and not probable or excluded in 5 patients. It remains to be established, however, whether additional data of the 12 patients with a so far not assessable association may result in a higher frequency of possible or probable causal associations. Further approaches for assessment of causality in these patients are urgently needed.

### Concluding remarks

The kava story is exciting and has nevertheless some pitfalls, but what can we learn from it? First, when drug induced hepatotoxicity is suspected, try to get all information about the case including liver values (ALT, AP) to evaluate the time of onset of the reaction and the complete course. Second, assess risk factors such as alcohol and age. Third, evaluate coadministration with other drugs. Fourth, research vigorously for non drug causes. Finally, try to get more information on possible hepatotoxicity of the drug and find out whether an unwanted readministration has been done and what the results are. When you have completed your job, a causality assessment between drug therapy and liver disease may be possible or not.

What did happen to kava? Kava hepatotoxicity was not observed (or not sufficiently searched for?) in consumers of the kava drink on the islands of the South Pacific in the past centuries. It also could not be demonstrated in experimental studies with kava extracts in the last decades, and it was not observed in premarketing and clinical studies in patients treated with kavapyrones as the main constituents of the extracts within the last 1–2 decades in Europe and the USA. Since few years, however, hepatotoxicity was suspected under the treatment with kava extracts, and there was mostly a temporal (!) relationship only between kava intake and the appearance of overt liver disease rather than a clear causal association, leading to a questionable evaluation and unacceptable consequences.

Reviewing the 19 cases with suspected kava hepatotoxicity, there is only one single patient with a very probable and another one with a possible causal relationship between kava intake and hepatotoxicity. Thus, kava hepatotoxicity is a fact and no phantasy, but it is also a very rare event similar to the potentially hepatotoxic properties of many other commonly used chemically defined drugs and of some other herbal medicinal preparations.

In all other patients assessment of causality was hampered to a smaller part by overlooking other causes for the observed liver disease and to a greater part just by the fact that documentation was mostly incomplete, at least in the present stage of evaluation. Interestingly, the MCA was also not able to assess various cases due to incomplete data supply.

Despite these uncertainties the German regulatory authority BfArM has classified the causal relationship with very probable, probable or possible in all patients and has subsequently revoked kava extracts from the German market. It is now in the responsibility of BfArM to provide additional data of the patients cases to the scientific community to further strengthen or dismiss a causal relationship of the suspected kava hepato-
toxicity in the respective patients, and external expertise including the ones of the expert commission of the BfArM should be heard.

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