

# German Kava Ban Lifted by Court: The Alleged Hepatotoxicity of Kava (*Piper methysticum*) as a Case of Ill-Defined Herbal Drug Identity, Lacking Quality Control, and Misguided Regulatory Politics

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## Key words

- *Piper methysticum*
- Piperaceae
- Kava
- efficacy
- hepatotoxicity
- risk-benefit-relation
- drug quality

## Abstract

▼ Kava, the rhizome and roots of *Piper methysticum*, are one of the most important social pillars of Melanesian societies. They have been used for more than 1000 years in social gatherings for the preparation of beverages with relaxing effects. During the colonial period, extract preparations found their way into Western medicinal systems, with experience especially concerning the treatment of situational anxiety dating back more than 100 years. It therefore came as a surprise when the safety of kava was suddenly questioned based on the observation of a series of case reports of liver toxicity in 1999 and 2000. These case reports ultimately led to a ban of kava products in Europe

– a ban that has been contested because of the poor evidence of risks related to kava. Only recently, two German administrative courts decided that the decision of the regulatory authority to ban kava as a measure to ensure consumer safety was inappropriate and even associated with an increased risk due to the higher risk inherent to the therapeutic alternatives. This ruling can be considered as final for at least the German market, as no further appeal has been pursued by the regulatory authorities. However, in order to prevent further misunderstandings, especially in other markets, the current situation calls for a comprehensive presentation of the cardinal facts and misconceptions concerning kava and related drug quality issues.

## Court Decision in Favour of Kava after 13 Years of Quarrel

▼ Until the year 2002, extracts of the rhizome and roots of the Melanesian plant kava [*Piper methysticum* G. Forst. (Piperaceae)] were marketed in Germany and other countries in the form of medicinal products licensed for the treatment of situational anxiety. After receiving a series of case reports concerning alleged liver toxicity, the German regulatory authority BfArM (Bundesinstitut für Arzneimittel und Medizinprodukte; Federal Institute for Drugs and Medical Devices) decided in the summer of 2002 to cancel all drug registrations for all medicinal products containing kava by a simple administration decision, with the exception of homeopathic dilutions of 4D (1 : 10 000) or higher. Formally, the benefit-risk ratio was declared negative. Other regulators outside Germany soon followed this decision. The consequences of this ban were felt worldwide and led to an economic disaster in many South Pacific states. Within Europe, the kava ban deprived physicians of an effective and comparatively safe

medication, creating a “therapeutic gap nobody wished for” [1].

BfArM's decision was internationally interpreted as a decision to protect the consumer from potential adverse effects. Consequently, the toxicity issue was rigorously debated by international scientists. Many experts questioned the causality of the case reports of liver toxicity. Consequently, numerous comments, reviews, and original papers were published both prior to and soon after the kava ban [2–14].

However, there seems to be a major misunderstanding in the international perception of the major issues causing a shift of the benefit-risk balance towards a negative outcome: Whereas the international debate was always focused on the risk side, the German authority had in fact based the withdrawal of marketing authorisation primarily on a denial of clinical efficacy [15, 16].

A most recent development demands a reexamination of the entire state of affairs concerning this psychoactive botanical drug. After more than a decade of a de facto “ban” of all kava-containing medicinal preparations, the German administra-

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tive court of Cologne ruled in the first week of June 2014 that the available data do not support the alleged hepatotoxicity, and that the ban was not justified merely based on the perception of an inconclusive efficacy [15,16]. The court consequently ruled the de facto “ban” illegal, thus technically restoring the German marketing authorisations to the status of 2002. This court ruling was confirmed in the appeal at the German upper administrative court of Münster on February 25, 2015. This ruling can be considered final, as no further appeal has been pursued by the regulatory authorities. It therefore can be expected to have a major impact on the international situation of kava.

### Kava Tangled in a Regulatory Vicious Circle

As already mentioned, the German kava ban, which was followed by similar bans of other regulatory authorities, was not merely based on the possibility of severe adverse effects, but primarily on the supposed lack of appropriate clinical studies by “most recent GCP standards” demonstrating efficacy. The emphasis on “most recent GCP standards” is extremely important as the studies performed with kava in the two decades before the ban do self-evidently not fulfil the most recent standards, as the standards were defined years after the “well-established use” of kava was accepted and marketing authorisations for kava had been granted.

In the context of the kava safety debate, BfArM had rejected all evidence of efficacy not conforming to recent standards, and therefore found the licensed medicinal products non-efficacious. It is important to stress the fact that this denial of efficacy did not relate to kava as such and its pharmacological effects. It exclusively related to the specific herbal medicinal products on the German market and their licensed indications. And with BfArM declaring kava not to be efficacious, any possible risk, even a minor one, automatically shifts the benefit to risk ratio to the negative side, thus justifying the regulatory decision to ban kava.

With the kava ban being based on a perceived lack of clinical studies by “most recent GCP standards”, the whole problem could have been easily overcome by a new clinical trial, as in fact proposed to BfArM by the companies that had kava preparations on the market. However, here the snake bites its own tail: BfArM would not authorize such a study to be carried out because of safety concerns [15,16]!

BfArM treated kava extract preparations as completely unknown new entities for which there is no experience at all. This formal approach simply refers to regulatory ICH guidelines applicable to marketing authorisations of newly developed active pharmaceutical ingredients, and does not take the previous clinical and pharmacovigilance experience into account. This approach works like a checklist: The next phase of drug development depends on the full presentation of data of the previous phase. For new entities, it means the creation of a full new set of product-specific preclinical data before clinical exposure may occur, and even then only stepwise and very carefully incrementing the exposure, going from healthy volunteers to patients, and including pharmacokinetic and dose-finding studies. It also means that the true issue in the case of kava, i.e., the assessment of clinical safety, can be delayed to infinity on formal grounds.

Again, it is important to keep in mind that this procedure refers to specific medicinal products, not to kava as such. New publications such as the clinical trials published in the past years by the group of Sarris are extremely important for the field of kava re-

search [17–21], but are unfortunately disregarded in the regulatory process because the water extract and its dose scheme used in the trials does not correspond to the ethanol extracts previously authorised in German kava herbal medicinal products. Thus, BfArM calls for reinventing the wheel – the multimillion investment involved is, as the authority keeps saying, not their problem. Unfortunately it is the problem of the patients as well as of the South Pacific nations and many small farmers facing economic disaster caused by German regulatory legalism. The resulting economic damage can be estimated to amount to approximately 3 billion US\$ for the small Pacific nation of Samoa alone.

### The Court Case

During the process of the drug safety protocol (officially called “Stufenplanverfahren” in German, “graduated plan procedure”), i.e., the evaluation of the safety of kava products formerly authorised as medicinal products in Germany, the marketing authorisation holders filed extensive dossiers to demonstrate the inappropriateness of the total withdrawal of marketing authorisations by the regulatory authority. In parallel, there were several visits of representatives of the South Pacific kava producing countries to the German Ministry of Health with the aim of clarifying the situation, but no progress could be achieved. Legal options could not be taken until BfArM issued a final decision, which only happened in 2012, and even then only after pressure for inactivity was made through a legal complaint by the marketing authorisation holders [15].

After the issuing of the final decision by BfArM, the way to court was open. The situation finally culminated in a lawsuit of the former marketing authorisation holders against BfArM at the administrative court of Cologne, where all data and arguments were once again thoroughly examined. A detailed analysis of the original documentations of the reports presented by BfArM as a justification for the ban clearly demonstrated that the assessment by BfArM was not performed properly. Several cases were reported as duplicates, but still counted as individual cases, thereby inflating the number of reported cases of liver damages [7,22]. The regulatory assessment was made through an *ad hoc* approach, a method likely to produce different results if applied by different assessors, which was the case with kava when the assessments of the very same cases by BfArM, the European Medicines Agency, and independent scientists [23–28] were compared (● Table 1).

One further has to keep in mind that a case report is not yet proof of causality. Indeed, a detailed examination of the cases revealed a majority of reports that can be much more easily explained by known adverse effects of documented co-medications or alcohol abuse rather than by potential hepatotoxic effects of the kava preparations themselves. Finally, the application of a suitable method for assessing liver damage in clinical research like the CIOMS scale [28] reduced the number of cases to only three more or less adequately documented case reports of liver reactions possibly caused by kava [27] that remain without an obvious, more likely alternative explanation. Most notably, the number of these cases was so small, less than one case in one million monthly doses [11], that the most recent court ruling did not consider them to justify the abovementioned “ban”, especially as the chemically defined benzodiazepines, just as buspirone and selective serotonin reuptake inhibitors (SSRIs), potential clinical alternatives to kava preparations in the treatment of anxiety,

BfArM Case No.	BfArM	MCA	EMEA	Teschke et al. 2008 [24]
93 015 209*	Probable	Possible	Possible	Possible
94 006 568*	Probable	Possible	Possible	Unlikely
94 901 308*	Probable	Not assessable	Possible	Causality excluded
98 004 297*	Probable	Unlikely	Unlikely	Causality excluded
99 006 005	Probable	Not assessable	Possible	Causality excluded
99 006 200/01 004 110	Probable	Possible	Possible	Unlikely
00 005 994	Probable	Unlikely	Possible	Causality excluded
00 008 627	Probable	Possible	Possible	Causality excluded
01 003 950/01 003 951	Certain	Probable	Probable/Not assessable	Causality excluded
01 006 229	Probable	Not assessable	Probable	Causality excluded
01 006 939*	Probable		Not assessable	Probable
01 010 536	Probable		Not assessable	Possible
02 000 370	Probable		Not assessable	Causality excluded
02 001 414	Probable		Not assessable	Possible**
02 002 090/02 002 836	Probable		Not assessable	Possible
02 002 378	Probable		Possible	Causality excluded
02 003 010	Possible		Not assessable	Causality excluded
[29]	Certain	Probable	Probable	Certain***
[55]	Probable	Possible	Possible	Probable****
IKS 2000–3502*	Probable	Probable	Probable	Possible
IKS 2000–0014*	Probable	Probable	Probable	Causality excluded
IKS 1999–2596*		Possible	Possible	Possible
IKS 2000–2330*	Possible	Possible	Possible	Causality excluded

\* Case reports with acetone extract; \*\* Very poorly documented case; \*\*\* Case of idiosyncratic reaction (allergy to a component of the medicinal product); \*\*\*\* Up to 10-fold overdosed and with potentially causative co-medication

**Table 1** Causality assessments of the same kava case reports by different assessors. Assessments of authorities refer to documents issued during the drug safety protocol.

are also known to exert significant side effects that might well be more harmful for the patient than those expected from the use of the herbal drug, even in a worst case scenario [16].

The court therefore argued that the risk assessment of kava would have had to be performed in the context of its therapeutic environment. Generally speaking, even under the assumption of a very real risk for the patient, a drug must not be removed from the market if all possible replacements for it carry (or might potentially carry) an even higher risk. In this context, the court also ruled that the argument of BfArM that the major part of the clinical studies for kava were not performed according to the current guidelines for clinical studies, as the respective publications were published already before these guidelines, does apply to the chemically defined alternatives as well, and that therefore the risk of these therapeutic alternatives was unduly trivialised by BfArM.

On the clinical efficacy side, the court also argued that a company having a licensed drug on the market, with the regulating authority having accepted the clinical proofs of efficacy, is not obliged to continuously provide new evidence for the clinical efficacy of its product. The authority cannot withdraw its decision just because therapeutic guidelines may have changed at some later date. Therefore, clinical studies for the purpose of drug regulation stay valid once they have been accepted by the regulatory authorities in the process of obtaining the initial marketing authorisation.

A further rationale the court gave for its pro-kava decision was that pure speculation on the potential danger of a drug does not constitute a “probable cause”, which in the sense of the law would justify the removal of a drug from the market by the authority. The regulating authority therefore cannot act on mere suspicion, but has the obligation to provide evidence for both the alleged dangers and the causal relationship with the suspected medication. The court ruled that BfArM had not conclusively proven the causal relationship between kava preparations and the alleged liver damage. Therefore, the risk to benefit ratio

could not be negative, and the ban of kava in Germany was thus illegal.

### Possible Theories Concerning the Perceived Liver Damage



The analysis of the case reports by Teschke had revealed only very few case reports with a relatively high probability of having been caused by kava, among them one report with a proven allergic reaction to the product [29], and thus a type of reaction which must be assessed apart from the issue of typically dose-dependent toxic reactions. Although the number of cases seems insignificant when compared with the known exposure data (450 million daily doses in ten years according to IMS data), the observed cases still demand a pharmacological explanation. Thus, over the past twelve years, several theories have been published, which, all in all, can be summed up in five major lines of thought:

- The “*human genetic variability theory*”: According to this school of thought, kava preparations are completely harmless to the general population. However, there is a small subgroup of the European Caucasian population lacking the metabolizing liver enzyme cytochrome P450 subtype 2D6 (CYP 2D6), as observed in one case report [30]. This mutation might lead to an unusual metabolic pattern in these patients, resulting in the transformation of the normally harmless constituents of kava into toxic metabolites in the liver. This theory suffers from the fact that this would be a typical dose-dependent toxicity. With approximately 7–9% of Caucasians being CYP 2D6-deficient, a much higher number of case reports would be expected not only in Germany, but in all Caucasian populations. This was quite obviously not the case; the observations were almost exclusively restricted to Germany and Switzerland, with the latter country using kava products of German origin.

- ▶ The “*metabolic toxification theory*” assumes a toxification of kava constituents through the formation of electrophilic quinoid metabolites, as demonstrated *in vitro* in hepatic microsomes [31,32]. Whereas both hypotheses could provide an explanation for liver toxicity in the presence of other drugs (interactions at the metabolic level), this type of reaction would, according to the authors, only occur with elevated exposures to kavalactones. With traditional kava drinking in the South Pacific, the kavalactone exposure by far exceeds the exposure with the German kava extract products. The maximum daily dose of German medicinal kava products was 120 mg kavalactones, whereas a single coconut shell of kava would provide > 210 mg [33], calculated with a method for which the results would have to be multiplied by 1.7 to be comparable to the level of modern HPLC methods [34]. Accordingly, Olsen et al. (2011) admit that “there remains no undisputable reason for the increased prevalence of kava-induced hepatotoxicity in Western countries” [32], the fact notwithstanding that such an increased prevalence has not been demonstrated.
- ▶ The “*organic solvent theory*”: In traditional kava use of the Pacific Islands, kava is always extracted with water. In contrast, the German medicinal products contained kava extracts prepared with ethanol-water mixtures, and one product contained an acetone extract. Organic solvents are used to achieve a better extractability of the kavalactones as the major active constituent fraction of kava rhizomes and roots. The “organic solvent theory” holds that kava may contain non-water-soluble hepatotoxic compounds that are not contained in the traditional aqueous extract, but enriched in the European preparations. This difference might explain why the traditional aqueous kava preparations are considered a safer option than the European organic extracts [35]. However, one must bear in mind that ethanol extracts of kava roots and rhizomes have been in use in Germany for more than 100 years, and were already mentioned for the first time by Lewin in 1886 [36], with no reports on relevant safety issues until the year 1999, when the first case reports of liver toxicity were published in Switzerland with a German-produced product. A recent focus of the debate is flavokavin B, which has been shown to be liver toxic in mice in relatively high doses [37], although others could not confirm this finding [38]. The organic solvent hypothesis has been largely ignored [26,27], but there may still be a relationship between the phytochemical composition of kava preparations and the quality of the herbal material.
- ▶ The “*wrong plant part theory*” assumes that European extract manufacturers used wrong plant parts such as leaves or stems. These plant parts may contain the alkaloid pipermethystine with liver-toxic properties [39,40]. However, an analysis of the European kava extracts clearly showed the absence of pipermethystine in the German kava extract preparations [41]. The hypothesis of using inappropriate plant parts and/or inappropriate protection against secondary contamination by mould toxins can still not be fully excluded, as it partly mirrors the current trading habits [42–45].
- ▶ The “*adulteration theory*”: Again, one should not ignore that kava rhizome and root extracts prepared with ethanol/water mixtures have a history of safe use in Germany dating back to at least 1886. Prior to the mid-1990 s, there was not a single report of liver toxicity from anywhere in the world. The question imposes itself: Might there have been a change of kava raw material quality with a potential impact on kava safety – a change, which might be considered an adulteration? There is increas-

ing evidence that this was, in fact, the case [43,44,46]. The “adulteration theory” combines aspects from the aforementioned hypotheses, especially the “wrong plant part theory”. It also requires an additional introduction into the ethnobotanical background of kava.

### A Short Ethnobotanical Excursion into the History of Kava



The sudden occurrence of eight rather well-documented case reports of liver adverse effects in the context of the intake of acetone extracts of kava in Switzerland in 1999 and 2000 raised the alarm ultimately leading to the international kava bans following the German regulatory decision of 2002. As already mentioned, liver toxicity was completely unknown prior to these events, and strangely remained largely restricted to the German manufactured products. The question was therefore whether there had been a change in kava rhizome and root quality exported from the South Pacific producing countries around this time?

As a matter of fact, there was a “kava boom” in the mid-1990 s, with new markets rapidly evolving, such as the United States [44]. Until then, kava was typically produced by small scale cultivation in the backyards of small farmers. Kava remained in the ground for approximately five years to reach sufficient maturity, and was then sold on the markets or to professional wholesalers. The one dramatic change introduced in the mid-1990 s was the introduction of a German-controlled systematic cultivation of kava as a measure to cope with the increasing costs of the material obtained from non-systematic collections. The cultivar planted on these plantations is called “Palisi” and belongs to the so-called “two-day kava” cultivars (see below) of *P. methysticum* that display high yields of kavalactones and a good biomass already after one year of growing.

However, from an ethnobotanic point of view, this was a poor choice: Ethnobotanical studies in the countries of the central-western Pacific reveal that the development of kava over many centuries resulted in a large variety of at least 120–150 different cultivars of the species *P. methysticum* [47,48]. These cultivars can be attributed to eight major groups with very similar phytochemical properties. The development started with the fertile species *Piper wichmannii* C.DC. from Papua New Guinea, the roots of which were originally used for catching fish, and are deemed unsuitable for human consumption. In the absence of intoxicating drugs, mushrooms, or alcohol, the South Pacific peoples, at some point in history, started breeding *P. wichmannii* into the socially important plant *P. methysticum*, a sterile form that can only be multiplied by vegetative propagation. The oldest cultivars are, however, still very close or identical to *P. wichmannii*. Such cultivars are usually used for ceremonial or medicinal purposes (unrelated to anxiety), but not for daily kava drinking.

In Vanuatu, the archipelago with the highest number of different kava cultivars within the South Pacific, a differentiation is made between so-called “two-day kava” and “noble kava”. The former is to be avoided in kava drinking because it causes a hangover and flashbacks for two days following consumption. The so-called “noble” kava types are all closely related with respect to the kavalactone composition. The best cultivars show a relatively high content of kavain, and, in relation, low contents of dihydromethysticin, yangonin, and desmethoxyyangonin, i.e., of the more lipophilic kavalactones. The hypothesis is that these highly lipo-



philic kavalactones undergo enterohepatic cycling, thus causing flashbacks and a hangover [49].

Until the “two-day kava” cultivar Palisi was systematically planted for the production of acetone extracts, the export of two-day cultivars was not an issue in Vanuatu or in other Pacific kava-producing nations. Thus, the introduction of two-day kava into German kava products clearly constitutes a novelty and a sudden change in plant drug quality, a fact communicated early to BfArM, but never taken seriously, albeit the sudden occurrence of case reports in Switzerland was exclusively related to this particular acetone extract [7]. Only after the public warning of BfArM against kava were case reports with ethanol extracts collected. However, almost all of them were very poorly documented, and in most cases there were indications of other, non-kava related causes.

Avoiding the use of two-day kava is a recommendation clearly based on ethnobotanic experience. However, the differences in the kavalactone composition could only serve for the differentiation between “noble” and “two-day” kava cultivars, but they would not explain the occurrence of liver toxicity. Kavalactones have been tested in assays, but have never been found toxic [44]. The obvious question would be whether anything is known about other constituents.

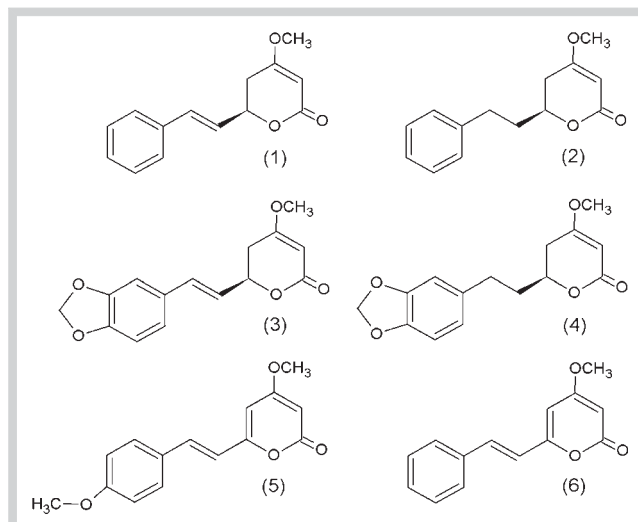
### Phytochemistry of Kava Cultivars

The well-documented anxiolytic effect of kava preparations can mainly be attributed to the fractions of the kavalactones (● Fig. 1; for the absolute configurations see [50]). Another fraction of phenolic kava compounds are the flavokavins (● Fig. 2). Among these, pure flavokavin B [37] and further flavokavins [51] were found to be potentially liver toxic in mice, whereas dihydromethysticin was shown to be nontoxic. Toxicity seems to be triggered only at relatively high concentrations, too high to be of relevance with the use of noble kava or its corresponding extract preparations [42].

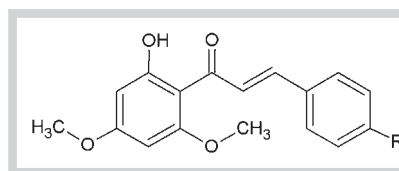
However, newly published data demonstrate differences in the flavokavin content of different kava cultivars (● Fig. 3): Lebot et al. showed a flavokavin B to kavalactones ratio of 0.39 in two-day kavas, and of 0.09 in noble kavas, based on the HPTLC analysis of samples of 72 different cultivars [52]. Similar findings were presented in 2012 in the High Level Conference on Kava in Port Vila, Vanuatu [44, 53] with a limited set of five representative cultivars based on an HPLC analysis: two noble cultivars (Borogu and Kelai), two two-day cultivars (Palisi and Bir Fok), and one *P. wichmannii* type (Sinibo) (● Fig. 3).

Based on the analyses of this still ongoing project, flavokavin B could be used as a marker for the determination of kava quality. From a practical point of view, a limitation of flavokavin B content to 2 mg/g of dried material would be sufficient to assure the use of noble kava and thus the possibility to lean on traditional safety experience.

Results from a currently ongoing research program in the South Pacific so far confirm these findings. Roots and peeled stumps of noble kava varieties usually contain less than 1 mg/g of flavokavin B in the dry matter, whereas the bark (“peelings”) frequently contains higher quantities than 2 mg/g in noble varieties, mostly exceeding 5 mg/g in non-noble varieties, especially in plant parts exposed to sunlight (unpublished data). These findings corroborate the traditional use of roots and peeled rhizome stumps only,



**Fig. 1** Major kavalactones in kava rhizomes and roots: (1) (+)-kavain, (2) (+)-dihydrokavain, (3) (+)-methysticin, (4) (+)-dihydromethysticin, (5) yangonin, (6) desmethoxyyangonin.



**Fig. 2** Flavokavins in *P. methysticum*.  
Flavokavin A R = OCH<sub>3</sub>;  
flavokavin B R = H.

and the avoidance of non-peeled materials and sun-exposed plant parts.

Such unsuitable plant parts, especially peelings of two-day kava, are unfortunately still sold by certain traders in Vanuatu and Fiji (in the latter case, with re-exported material from Vanuatu). Vanuatu has officially banned exports of two-day kava through the Vanuatu kava act, but does not have the means to control the quality of the exports. Furthermore, this law unfortunately makes an exception from this prohibition of exporting two-day kava plant materials when the client specifically demands such a quality – a loophole in the legislation extensively used by some traders. The other kava-producing South Pacific nations, i.e., Fiji, Samoa, and Tonga, do not have two-day varieties. This situation calls for better quality control of kava materials imported for the manufacturing of medicinal products. New regional standards for the identification of kava raw materials suitable for kava drinking are currently being proposed to Codex Alimentarius. It would seem wise to adopt these standards for the identification of kava root and rhizome materials intended for the use in kava extracts in medicinal products.

### Conclusions and Future Prospects

The current state of ethnopharmacological and phytochemical research still does not confirm a causal relationship between the consumption of kava preparations and the occurrence of adverse liver reactions. With the assumption of the (albeit very rare) existence of such a type of reaction, manufacturers should seek guidance for the quality of plant material known to be safe through centuries of traditional experience. The problem of pos-



**Fig. 3** Typical morphology of kava cultivars found on the island of Santo, Vanuatu. (Color figure available online only.)

sible hepatotoxicity of kava preparations was potentially caused by ill-defined herbal drug identity, a lack of appropriate quality control, and misguided regulatory politics.

Thus, in order to re-establish “noble” kava to its rightful place as an essential anxiolytic drug in the European market, its botanical and phytochemical differentiation from the “non-noble” kava varieties has to be established by pharmacopoeial regulations. This should be a minor problem, as there are already several plant drugs where the pharmacopoeia does already differentiate between closely related and easily misidentified species (e.g., *Illicium verum* vs. *Illicium anisatum*). With the circumstantial evidence supporting a raw drug identity/quality issue at the base of the problem of hepatotoxicity, the definition of appropriate quality standards should, in any case, be helpful.

There is, however, not much time to act on the problem of drug identity of pharmaceutically suitable kava varieties. In the past 10 years, kava exports from the South Pacific islands have again multiplied, reaching the same level as at the time before the kava ban in 2001. The United States have especially evolved as a kava market, with currently more than 90 kava bars serving kava of frequently highly doubtful quality. Similarly, the market of New Caledonia has shifted to the import of large quantities of two-day kava roots and (mainly) peelings from Vanuatu, with the argument that the higher kavalactone concentrations and, at the same time, relatively low costs allow for the production of more kava drinks at lesser expenses. If the flavokavins or other as yet non-identified constituents of non-noble kava are truly responsible for liver toxicity, this could be playing with fire. There are already isolated reports of liver toxicity related to kava use from New Caledonia – cases that are now discussed in the context of potential mould-related toxicity [54], but even this aspect would have to be part of quality specifications.

With the revocation of the German kava “ban” by the Administrative Court of Cologne and the Upper Administrative Court of Münster, a major hurdle for a constructive discussion and a potential comeback of kava has been overcome. Therefore, now is the time to act to prevent the problem of kava-related hepatotoxicity from reoccurring by introducing appropriate regulatory standards concerning its drug quality and, even more so, drug identity.

### Conflict of Interest

▼  
M.S. gave scientific consulting to the marketing authorisation holders of the German kava extract products in the course of the drug safety protocol and the court cases. He also received re-

search grants from the EU and the Pacific countries for studying quality issues of kava in the South Pacific and preparing a standard for noble kava. This publication has not been supported by any grants.

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