Phytomedicine 18 (2011) 96–103

Contents lists available at ScienceDirect

Phytomedicine

journal homepage: www.elsevier.de/phymed

Kava hepatotoxicity solution: A six-point plan for new kava standardization

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ARTICLE INFO

Keywords:
Kava
Piper methysticum
Kava hepatotoxicity
Herbal hepatotoxicity
Drug induced liver injury
Herbs induced liver injury
Kava regulation

ABSTRACT

Kava-induced liver injury has been demonstrated in a few patients worldwide and appears to be caused by inappropriate quality of the kava raw material. When cases of liver disease in connection with the use of kava emerged, this was an unexpected and challenging event considering the long tradition of safe kava use. In order to prevent kava hepatotoxicity in future, a set of quality specifications as standard is essential for the preparation not only of kava drugs and kava dietary supplements in the Western world but also for traditional kava drinks in the South Pacific Islands.

For all these purposes a uniform approach is required, using water based extracts from the peeled rhizomes and roots of a noble cultivar such as Borogu with at least 5 years of age at the time of harvest. Cultivated in Vanuatu for centuries, noble varieties (as defined in the Vanuatu Kava Act of December 2002) are well tolerated traditional cultivars with a good safety record. At present, Vanuatu kava legislation is inadequately enforced to meet quality issues for kava, and further efforts are required in Vanuatu, in addition to similar legislation in other kava producing South Pacific Islands. Future regulatory and commercial strategies should focus not only on the standardization of kava drugs, kava dietary supplements, and traditional kava extracts, but also on thorough surveillance during the manufacturing process to improve kava quality for safe human use. The efficacy of kava extracts to treat patients with anxiety disorders is well supported, but further clinical trials with aqueous kava extracts are necessary.

We thereby propose a six-point kava solution plan: (1) use of a noble kava cultivar such as Borogu, at least 5 years old at time of harvest, (2) use of peeled and dried rhizomes and roots, (3) aqueous extraction, (4) dosage recommendation of ≤250 mg kavalactones per day (for medicinal use), (5) systematic rigorous future research, and (6) a Pan Pacific quality control system enforced by strict policing.

In conclusion, at different levels of responsibility, new mandatory approaches are now required to implement quality specification for international acceptance of kava as a safe and effective anxiolytic herb.

Introduction

The efficacy of kava (*Piper methysticum* G. Forster) as an anxiolytic herb has clearly been shown for ethanolic and acetonic kava extracts (Pittler and Ernst 2003; Sarris and Kavanagh 2009) as well as water based ones (Sarris et al. 2009b). In the past, however, concerns have been expressed that toxic liver disease may have been caused in association with the use of kava as herbal remedy and dietary supplement in Western countries (Denham et al. 2002; Teschke et al. 2003, 2008b; Lebot 2006; Teschke and Wolff 2009) or as a traditional recreational beverage in the South Pacific region (Russmann et al. 2003; Teschke et al. 2008a, 2009). Kava hepatotoxicity became part of the growing group of herbal hepatotoxicity with major clinical and regulatory challenges, observed in a few patients with causalities for kava ± comedication (Teschke 2010a,b; Teschke et al. 2010). Its worldwide appearance in patients originating from European countries, the United States, Australia, and New Caledonia was unexpected (Denham et al. 2002; Teschke et al. 2008a, 2009), since kava has been used for centuries without overt toxic liver effects in the South Pacific Islands (Lebot et al. 1997; Denham et al. 2002; Currie and Clough 2003; Moulds and Malani 2003; Lasme et al. 2008). The international discussions centred on the question as to what extent kava may have been hepatotoxic due to poor kava quality (Schulze et al. 2003; Lebot 2006; Schmidt 2007; Teschke et al. 2008a; Sarris et al. 2009a; Teschke 2010b). Based on the worldwide interest and various uncertainties, inconsistencies and confounding variables associated with the reported cases of patients with kava hepatotoxicity, a thorough

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0944-7113/$ – see front matter © 2010 Published by Elsevier GmbH.
doi:10.1016/j.phymed.2010.10.002

WHO report addressing these issues was mandatory (WHO 2007). Specific points of concern included the use of inappropriate kava plants and plant parts, solvents, solubilizers, adulterations, and impurities (WHO 2007; Teschke 2010b).

The aim of this report is to discuss future requirements at the legislation, regulatory and commercial level in connection with kava-induced liver injury and to propose a six-point plan for standardization of kava drugs, kava dietary supplements, and traditional kava beverages for safe human use.

Kava: traditional and modern use

The term kava refers to the plant native to the South Pacific Islands and its products derived from its rhizome and roots such as traditional kava beverages, kava drugs, and kava dietary supplements (Lebot et al. 1997; Denham et al. 2002; WHO 2007).

Plant

Vanuatu is considered as the origin of the kava plant which belongs to the family of Piperaceae (Lebot et al. 1997). The physiological properties of kava have been demonstrated to result from the kavalactone content and the chemotype commonly assessed in plants of the same species with genetically defined phytochemical characteristics (Lebot and Lévesque 1996; Lebot et al. 1997; Lebot 2006; Lasme et al. 2008). Six major kavalactones account for approximately 96% of the lipid extract and have been shown to be pharmacologically active (Lebot 2006).

Traditional drink

Kava as the traditional water based drink is an integral part of religious, social, economic and political life in the South Pacific region for centuries and usually well tolerated, unless overdosage with prolonged use prevails (Lebot et al. 1997; Denham et al. 2002; Schmidt et al. 2005; WHO 2007; Lasme et al. 2008). There have been some early restrictions for its use in Australia (WHO 2007) and recent legal definitions for planting, harvesting and marketing kava plants in Vanuatu to be used as traditional kava drinks (Vanuatu Legislation 2002).

Herbal drug

Until 2002 when the ban for kava-based products was issued, ethanolic and acetonic kava extracts had been sold as regulatory approved drugs in pharmacies without prescription in Germany and Switzerland; in the latter country they have also been available in drug stores since 1998 (Teschke et al. 2008a,b). Similarly, in other countries such as Austria, Belgium, Brazil, Canada, Ireland, Portugal, and the United Kingdom, kava-based products under regulatory control have previously been available either as drugs (Schmidt et al. 2005; WHO 2007), or as dietary supplements (WHO 2007). Regulatory approval for kava drugs was restricted to treatment for anxiety.

Dietary supplement

It is unclear to what extent kava was used as unregulated dietary supplement in Germany and Switzerland, since only one single report from Germany presented the case of a patient who treated herself with a powdered kava rhizome (Weise et al. 2002). In both and other countries, there was lack of regulatory approval for the use of kava dietary supplements (WHO 2007).

Classification of kava cultivars

In December 2002, the Vanuatu government passed the Kava Act No. 7 (Vanuatu Legislation 2002; Food Standards Australia New Zealand 2005) which identifies and categorizes different cultivars into noble cultivars, medicinal cultivars, Two Days cultivars, and Wichmannii varieties.

Noble cultivars

A long history of commonly safe use as a traditional social beverage and lack of liver injury has been attributed to kava (Denham et al. 2002; Currie and Clough 2003; Moulds and Malani 2003; Schmidt et al. 2005), especially to the noble varieties (Lebot et al. 1997).

Medicinal cultivars

Medicinal varieties are considered having a long and proven history of beneficial properties amongst traditional Pacific herbalists for a variety of specific therapeutic effects, although not primarily for recreational use (Food Standards Australia New Zealand, 2005). They have been used exclusively for medicinal products and dietary supplements, suggesting their causative role for liver toxicity observed in patients who used these extracts.

Two Days cultivars

Two Days kava cultivars ("Tu Dei" kavas, two days intoxication) have occasionally been used for kava drugs (Schmidt 2007) and are now banned as an export commodity (Vanuatu Legislation 2002; Food Standards Australia New Zealand 2005). Strong psychotropic effects occur with these cultivars, and they usually cause side effects such as nausea due to high amounts of the kavalactone dihydromethysticin (Lebot et al. 1997).

Wichmannii cultivars

"Wichmannii" varieties (*Piper wichmannii* is the wild species ancestor of the domesticated kava, *P. methysticum*) are now also banned for export (Vanuatu Legislation 2002; Food Standards Australia New Zealand 2005). These varieties usually elicit strong physiological effects and are not used in daily consumption in the Pacific Islands (Lebot et al. 1997).

Kava prior to the ban

Standardization

Prior to the regulatory ban of kava in 2002 for Western countries, there was lack of standardization of kava to be used as traditional beverage in South Pacific Islands (WHO 2007), although side effects due to prolonged kava use at high dosage were known in Pacific Islanders and Australian Aborigines for a long time (Mathews et al. 1988; Clough et al. 2003; Russmann et al. 2003; WHO 2007; Brown et al. 2007; Teschke 2010a). However, the risk of liver damage was directly related to the amount of kava consumed that was up to 700 mg a day in one study, and in another report 45% of the participants consumed alcohol (WHO 2007), considering alcohol as common risk factor (Li and Ramzan 2010). As observed in Western countries, toxic liver injury also after use of traditional water based kava drinks was rare (Teschke et al. 2008a). Inappropriate or lacking standardization prior to the kava ban in 2002 was evident for the use of traditional kava drinks at various levels. There was lack of regulatory standards in the South Pacific Islands, a concern expressed 2001 by the Secretariat of the Pacific Community

Table 1
Regulatory shortcomings regarding kava prior to the kava ban.

Items
1. Lack of standardization of the best kava cultivar(s) to be used for kava drugs
2. Absent standardization of minimum age of kava plant at the time of harvest
3. Absent declaration of the type of solvents and solubilizers to be used for kava drugs
4. Failure of standardization of the analytical method to quantify kavalactones in extracts
5. Undefined percentage content of individual kavalactones desired for kava extracts
6. Lack of prescription advice for kava drugs
7. Inappropriate surveillance at the level of farmers and manufacturers

For details see text and respective references.

in its report of Pacific kava, designed as a producer's guide (SPC 2001). As late as 2002, the Vanuatu government issued a Kava Act (Vanuatu Legislation 2002) which received approval by the Vanuatu Parliament only 6 years later following an amendment to this law. Finally, only in 2005 some food standards have been published (Food Standards Australia New Zealand 2005).

In Western countries such as Germany, a set of quality specifications for kava drugs has been developed as regulatory standards in the years before the ban was issued. The standards have been compiled by experts of the Germany regulatory agency in the German kava monograph (Commission E 1990) and were supplemented later on in the official German drug codex (DAC 1998). To summarize these previous standards, the ingredients of the kava extracts had to be derived from the peeled and dried rhizome (i.e. not exposed to light) of the kava plant, maximum daily use was 120 mg kavalactones for no longer than 3 months, and indications for kava extracts were anxiety, tension, and restlessness. Pregnancy, breastfeeding, and endogen depression were listed as contraindications.

Cultivar and chemotypes

Prior to the ban, efforts were not evident to clearly define the best kava cultivar(s) to be used. In Western countries and in the South Pacific Islands, neither regulators nor manufacturers or producers resolved this issue (Teschke et al. 2008a). As a result, they did not consider that the various cultivars may differ in their specific positive and negative effects, including those with possible hepatotoxic ones (Lebot 2006; Schmidt 2007; Lasme et al. 2008).

There have been various regulatory shortcomings regarding kava (Table 1). Kava is not a unique plant, and therefore represents a regulatory challenge. The regulatory kava monograph (Commission E 1990) and the official German Drug Codex (DAC 1998) did not allude to the existence of various kava cultivars and has never considered the abundance of kava strains as a regulatory safety issue before the kava ban. Uncertainties of the quality regarding the kava cultivars have been a matter of early and major concern (SPC 2001; Denham et al. 2002; Schmidt et al. 2005; Schmidt 2007; Lebot 2006; Teschke et al. 2008a,b). The possibility was not ruled out that the hepatotoxicity problems were, at least to some extent, a consequence of poor quality control caused by an extraordinary increase in the size of the kava market (WHO 2007). Concern has also been expressed that substandard kava cultivars such as Tu dei may have been exported (Lebot 2006; WHO 2007), and this was substantiated by analytical assessment for two retain samples from Germany (Schmidt 2007). The lack of product standardization and selection of kava cultivars of the best chemotype and kavalactone content has been recognized also by the Pacific Community (SPC 2001). In particular, there is no established physical or chemical quality specification for kava exported for pharmaceutical products.

Eighteen kavalactones have been isolated from kava extracts, but only the six major kavalactones are used to define a particular kava chemotype (Lebot et al. 1997; Lebot 2006; Schmidt 2007; WHO 2007): kavain (K), dihydrokavain (DHK), methysticin (M), dihydromethysticin (DHM), yangonin (Y), and desmethoxyyangonin (DMY). The individual kava chemotype may be established by a system of kavalactone signatures, attributing to each lactone a number in the sequence of its elution from the HPLC (high performance liquid chromatography) column (Fig. 1): DMY corresponds to 1; DHK to 2; Y to 3; K to 4, DHM to 5; and M to 6. When the figures are sorted in the sequence of decreasing quantities of individual lactones in the sample, a signature is formed by this method of chemotype coding. Based upon this assessment, it became evident that kava exists in form of more than 200 variant strains, commonly called cultivars. Moreover, the chemotype may vary between roots, rhizomes, and basal stems (Lebot 2006; Lasme et al. 2008). The multiplicity of kava cultivars used for medicinal purposes is the consequence of fragmentary standards of regulatory agencies and manufacturers (Commission E 1990; DAC 1998; SPC 2001; Vanuatu Legislation 2002; Food Standards Australia New Zealand 2005) and rarely allows causality attribution to a single kava cultivar (Schmidt 2007).

Plant part

According to the official producer's guide for Pacific kava, edited by the Secretariat of the Pacific Community in Suva, Fiji Islands, there are six products from the kava plant considered for planting, the local market, and exports: stems, basal stems, chips of the rhizome, peelings of the rhizome, roots, and residues (SPC 2001). Stems are defined as plant parts more than 20 cm above the rhizome, used only as planting material; basal stems represent the first 20 cm of the stem just above the rhizome; chips of the rhizome are made from the peeled rhizome or the lower stems to be used for drinking; peelings of the rhizomes include also the peelings of the basal stems, previously used for export to pharmaceutical manufacturers and for drinking; roots without specification of use; residues consisting of mixed small pieces of the other commercial parts, used for drinking. It is of note that products declared as rhizomes may also contain basal stems and thereby aerial plant parts. Therefore, inappropriate product declaration might have been a problem for European countries requesting rhizomes alone but not combined with basal stems.

The quality of the best parts of the kava plant to be chosen was a matter of another debate (SPC 2001; Schmidt et al. 2005; Lebot 2006; WHO 2007; Teschke et al. 2008a,b). For clinical trials, analytical studies, and experimental investigations a variety of kava plant parts have been used and evaluated in detail (Table 2). Kava extracts to be used in Germany as kava drugs should have been prepared from dried rhizome chips of the kava plant according to the German regulatory agency (Commission E 1990), and the rhizome should be peeled as communicated by the official German drug codex (DAC 1998). In some European countries, however, kava preparations have often been manufactured from the root peelings or kava stumps excluding the aerial peelings (Schmidt et al. 2005). In the South Pacific the kava roots are often peeled; the peelings potentially exported, and the peeled roots used to prepare the traditional aqueous extract for their own consumption. These observations led to the conclusion that kava preparations made from the whole peeled root, as used traditionally, could be less likely to cause hepatotoxicity (Schmidt et al. 2005); this favourable statement should also apply to the rhizome, the preferred regulatory plant part (Commission E 1990; DAC 1998).

Readily available information suggests the previous use of aerial parts (SPC 2001; Dragull et al. 2003; Lebot 2006; WHO 2007; Teschke et al. 2008a,b) such as stems (SPC 2001; Dragull et al. 2003;

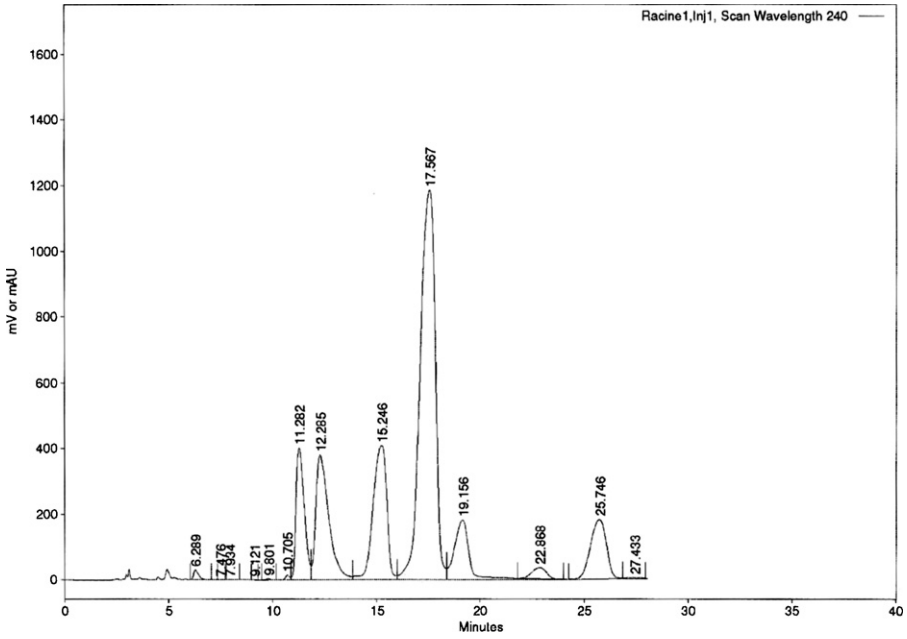

Fig. 1. HPLC chromatogram of the noble cultivar Borogu. There are six major peaks with retention times of 11.28, 12.28, 15.25, 17.57, 19.57, and 25.75 min, corresponding to desmethoxyyangonin, dihydrokavain, yangonin, kavain, dihydromethysticin, and methysticin, respectively.

Nerurkar et al. 2004; Lebot 2006) and leaves (Dragull et al. 2003) of the kava plant in the manufacturing process prior to the kava ban; these raw materials might have been taken instead of the usual rhizome. More specifically, according to the WHO report German pharmaceutical industries preferred to buy kava stem peelings to extract kavalactones to make kava drugs; kava stem peelings were sold at almost one-tenth of the price of kava roots (WHO 2007). It was also argued that commercial crude drug material that may have been adulterated by stem peelings and leaves, could possibly introduce the alkaloid pipermethystine into the commercial drugs (Dragull et al. 2003; Lebot 2006; WHO 2007), but recent analytical studies showed the absence of pipermethystine, at least in a series of retained samples of finished kava products from the German market (Lechtenberg et al. 2008). Nevertheless, uncertainty remains that the quality of commercial kava extracts may have varied from one batch to the other, and quality control of kava raw products was possibly not stringent enough. Uncertainty also exists regarding use of adventitious roots, originating from the stems and extending directly into the soil; they develop quite easily and are considered as valuable due to their high kavalactone content (SPC 2001). Undoubtedly, adventitious roots are aerial plant parts, not recommended for human use.

Extraction media and solubilizers

Prior to the kava ban, ethanol, acetone, and water have preferentially been used as media for kava extracts, but there was no regulatory statement which medium may be superior (Commission E 1990; DAC 1998). There was also no regulatory definition of the desired percentage of the kavalactones in the extracts. Various solubilizers such as macrogol, craspovidon, mentha oil, methyl acryl acid polymer and polysorbate polyols have been included in the extracts; all of them lack a regulatory recommendation of the best one to be used (Teschke et al. 2008a).

Daily dosage and duration of use

Prior to the ban, the daily dose was limited to 60–120 mg kavalactones according to the German kava monograph (Commission E 1990), but this statement has been subject of some specific considerations (Schmidt 2007; Teschke et al. 2008a). The previous regulatory recommendation for the maximum dose of 120 mg kavalactones is not sufficiently qualified since the analytical method for quantification has not been described (Commission E 1990); but it appears that TLC (thin layer chro-

Table 2
Compilation of kava plant parts used as raw material for various purposes.

Kava plant part
1. Rhizomes/syn. rootstocks (SPC 2001; Loew and Franz 2003; Dragull et al. 2003; Ernst 2004; Food Standards Australia New Zealand 2005; Weiss et al. 2006; Teschke et al. 2008b)
2. Rhizomes, fresh (WHO 2007)
3. Rhizomes, dried (Weise et al. 2002; Dragull et al. 2003; WHO 2007)
4. Rhizome roots (Brown et al. 2007)
5. Roots (SPC 2001; Dragull et al. 2003; Moulds and Malani 2003; Nerurkar et al. 2004; Lebot 2006; Brown et al. 2007)
6. Roots, fresh (Denham et al. 2002; Loew and Franz 2003; Currie and Clough 2003; WHO 2007)
7. Roots, dried (Denham et al. 2002; Currie and Clough 2003; Moulds and Malani 2003; Schmidt et al. 2005; Weiss et al. 2006; WHO 2007; Brown et al. 2007)
8. Roots, decorticated (Loew and Franz 2003)
9. Root barks, fresh and dried (Denham et al. 2002)
10. Roots, adventitious (SPC 2001)
11. Stems, including lower ones (SPC 2001; Currie and Clough 2003; Lebot 2006)
12. Stem peelings (SPC 2001; Dragull et al. 2003; Lebot 2006)
13. Stumps, including peelings (Ernst 2004, 2007; Lebot 2006)
14. Leaves (Dragull et al. 2003; Ernst 2004)

A variety of kava plant parts have been used and evaluated for clinical trials, analytical studies, and experimental investigations.

Table 3
Proposals for future strategies.

Recommendations
1. Vanuatu legislation regarding the preferred noble cultivar(s) such as Borogu
2. Additional legislation of peeled rhizome and roots to be used for water based kava extracts
3. Corresponding legislation also in other countries of the South Pacific Islands
4. Regulatory definition of noble cultivar such as Borogu and use of its peeled rhizomes and roots
5. Regulatory standardization of quantitative method for kavalactones in the extract
6. Limitation of kava use to water based extracts
7. Regulatory definition of daily dose and duration of use
8. Mandatory prescription guidance for kava drugs to minimize risks
9. Regulatory surveillance of cultivators, harvesters, farmers, and manufacturers

For details see text and respective references.

matography) was used (Loew and Franz 2003). As there are major quantitative differences, for instance, between TLC and HPLC (high performance liquid chromatography), accuracy is lacking (Schmidt 2007). Therefore, a dose of 120 mg kavalactones assayed by TLC corresponds to 170 mg quantified by HPLC. German drug companies were not obliged to note the used method to quantify kavalactones in their drugs, and it remained unclear whether 120 mg kavalactones in their products reflect assessment by TLC or HPLC. On a clinical basis, most patients with verified kava hepatotoxicity used a daily overdose of kavalactones (Teschke et al. 2008a,b, 2009).

For the use of traditional kava beverages, there was no regulation regarding maximum length of usage (Food Standards Australia New Zealand 2005). Treatment duration no longer than 3 months was advised for kava drugs by the German regulatory agency (Commission E 1990), but prolonged treatment was usual (Teschke et al. 2003, 2008a,b; Schmidt et al. 2005; WHO 2007).

Future strategies for standardization

It was in the overall interest to further investigate any legitimate hypothesis concerning kava' toxicity in order to attempt either to exonerate some forms of kava, or to provide recommendations that will assure their safe use (Richardson and Henderson 2007). Recently, pathogenetic aspects of kava hepatotoxicity have been reviewed in detail (Teschke 2010b); strategies have now to be developed to minimize hepatotoxic risks of kava products (Table 3), with some proposals made in the past (Schmidt et al. 2005; Lebot 2006; Schmidt 2007; WHO 2007; Richardson and Henderson 2007; Teschke et al. 2008a). The kava problem was not limited to the kava pharmaceutical markets such as Germany and Switzerland (Schmidt et al. 2005; Teschke et al. 2008a,b), but is extended to the kava dietary supplement markets with polyherbal kava mixtures such as the Unites States and Australia, and also to the traditional kava markets like New Caledonia in the South Pacific Islands (Russmann et al. 2003; Teschke et al. 2008a, 2009; Schmidt 2007; WHO 2007). Therefore, an overall approach to standardization of kava extracts to be used as drugs, dietary supplements, and traditional drinks needs to now be mandatory.

There is an urgent need of standardization, primarily at both the legislation and regulatory level, followed at the commercial level. The WHO report criticized the lack of accepted standards for the growth of kava, collection practices, and supply of raw material for medicinal purposes (WHO 2007). There is also inadequate quality control in the selection of the appropriate plant parts of kava, in the collection of the appropriate plant parts and in the preparation and testing of the raw materials. Quality control should include analytical verification of the chemotype using HPLC (Lebot and Lévesque 1996; Lebot et al. 1997; Siméoni and Lebot 2002; Lasme et al. 2008) or the recently described method of near-infrared reflectance spectroscopy (NSIR) (Lasme et al. 2008); the NSIR system has been calibrated for the six major kavalactone content measurements. To meet safety concerns, all involved parties starting from the patient and general consumer down to the cultivator and farmer are well advised to contribute to the overall goal of improving the safety of kava use. We thereby propose a kava solution plan as outlined subsequently.

Six-point kava solution plan

There are several key elements of the proposed six-point kava solution plan: (1) use of a noble kava cultivar such as Borogu that is at least 5 years old at time of harvest, (2) use of peeled and dried rhizomes and roots, (3) aqueous extraction, (4) dosage recommendation of $\leq$250 mg kavalactones per day (for medicinal use), (5) systematic rigorous future research, and (6) a Pan Pacific quality control system enforced by strict policing.

(1) Noble cultivar

There is little clinical and experimental support to suggest medicinal kava cultivars as the variety of choice for kava drugs, kava dietary supplements, and traditional kava drinks since these varieties have previously been associated with toxic liver injury. But how is the ideal kava extract to be defined? Kava cultivars with a long history of safe use as a traditional social kava beverage in the South Pacific Islands should ideally be chosen. These criteria are basically met by a few noble cultivars (Lebot 2006; Schmidt 2007; Lasme et al. 2008), as classified by the Vanuatu Kava Act (Vanuatu Legislation 2002) and listed with all details subsequently (Food Standards Australia New Zealand 2005). Accordingly, good candidates in alphabetical order are primarily the listed noble kava cultivars (Table 4).

In the past, the chemotype of the preferred cultivar has not yet definitively been determined, but suggestions have been made (Schmidt 2007; WHO 2007; Food Standards Australia New Zealand 2005; Sarris et al. 2009b). It should be one with a high relative content of kavain (Lebot 2006; Schmidt 2007; Sarris et al. 2009b), considering also its advantageous lack of P450 inhibitory properties and preventing thereby possible interactions with drugs (Mathews et al. 2002); dihydrokavain may be necessary in amounts sufficient to mediate the anxiolytic properties of kava (Amorim et al. 2007); recommendations include also low amounts of methysticin (Mathews et al. 2002; Schmidt 2007), desmethoxyyangonin (Schmidt 2007), and eventually dihydromethysticin (Mathews et al. 2002). These criteria are not generally met by all previous medicinal cultivars used for German and Swiss kava drugs alleged to cause toxic liver disease; such as chemotypes 526431, 462531, 254631, and 246531 (Schmidt 2007). Possible candidates are cultivars with a chemotype signature of 423561 or 425361, with high amounts of kavain and dihydrokavain and low amounts of methysticin and desmethoxyyangonin.

Based on the opinion of local experts, the noble kava cultivar Borogu with the chemotype signature 423561 is now one of the preferred kava varieties (Lasme et al. 2008) and may easily be identified by a typical HPLC chromatogram (Fig. 1). According to the chemotype, Borogu has a high content of kavain and in order of decreasing amounts dihydrokavain, yangonin, dihydromethysticin, methysticin, and desmethoxyyangonin (Siméoni and Lebot 2002; Lasme et al. 2008); its chemotype is identical for both roots and rhizomes (Lasme et al. 2008), allowing the use of the two plant parts. Cultivated with a long tradition in Vanuatu (the area of origin of *Piper methysticum*), Borogu is well established for daily drinking

Table 4
Noble kava cultivars of Vanuatu.

Noble cultivar	Origin	Chemotype
Ahouia	Tanna	426531
Amon	Tanna	246513
Asiyai	Aneityum	246531
Bir Kar	Santo	246513
Bir Sul	Santo	246531
Biyai	Aneityum	426531
Borogoru	Maewo	425361
Borogu	Pentecost	423561
Gegusug	Gaua	246531
Ge vemea	Vanua Lava	245631
Ge wiswisket	Gaua	246513
Kelai	Epi	423516
Leay	Tanna	246351
Melomelo	Ambae	245361
Melmel	Pentecost	246531
Miela	Emae	426351
Naga miwok	Vanua Lava	246351
Olitao	Emae	245631
Palarasul	Santo	246531
Palasa	Santo	246531
Paliment	Emae	426351
Pia	Tanna	423516
Poivota	Santo	243561
Pualiu	Tongoa	246531
Puariki	Tongoa	423156
Sese	Pentecost	245631
Silese	Malekula	423651
Urukara	Santo	426531

Alphabetical order of noble kava cultivars in Vanuatu with their place of origin (Vanuatu Legislation 2002; Food Standards Australia New Zealand 2005) and their chemotype assessed in their roots. The numbers of the chemotypes correspond to the following kavalactones: 1, desmethoxyyangonin; 2, dihydrokavain; 3, yangonin; 4, kavain; 5, dihydromethysticin; and 6, methysticin. The data are based on original studies (Lebot and Lévesque 1996; Lebot et al. 1997; Siméoni and Lebot 2002) and substantiated by recent reports (Lebot 2006; Lasme et al. 2008). As far as a cultivar keeps its chemotype fingerprint 42... or 24..., then it is a "noble" cultivar. Other requirements are that (1) there are no parts exposed to light in the raw material, (2) it is organically grown, (3) all the parts are well identified and separated, (4) it is sufficiently old (5 years for export), (5) and the village or origin is known (traceability) (Vanuatu Legislation 2002).

without apparent side effects and is known for its rapid effect, thus a potential ideal candidate for future clinical studies. Regulatory kava standardization regarding the best noble kava cultivar(s) such as Borogu to be used for both traditional and medicinal purposes is mandatory, should kava enter the pharmaceutical market again.

(2) Peeled rhizomes and roots

The kava WHO Report differentiates the rhizome from the roots and clearly defines the rhizome as the kava part below the stem and above the roots (WHO 2007). At least for future kava drug manufacturing in Western countries, the rhizomes and underground roots (excluding the adventitious ones) may be used; they should be peeled and their chips be dried. At the local manufacturing level, however, uncertainties remain due to vague legislation.

The Vanuatu Kava Act No. 7 of 2002 describes some protection rules of kava for export which include kava drugs and kava dietary supplements (Vanuatu Legislation 2002). Excluded from export are stumps, shoots, growing buds, lateral branches, and other planting materials of kava, as well as fresh plant parts such as roots or stumps that could be used for propagation. Kava or kava products may only be exported when each of the following is clearly marked on it: name of the variety, island of origin, distinct organs of the kava, and the words "Original Vanuatu Kava". In essence, any part of the kava plant may be exported, as long as labeling conforms to the legislation. The labeling does not require the information whether the plant part is peeled or not; nor whether peelings are to be exported. This leads to the conclusion that neither the peeled rhizome nor the rhizome itself is a legislative issue in Vanuatu. Additional legislative efforts are therefore necessary to ensure that only peeled and dried rhizomes and roots are exported to be used for kava drugs and dietary supplements. Surprisingly, Vanuatu Kava legislation differentiates between kava quality requirements for local use and those for export. For example, minimum maturation time for the kava plant at harvest is 5 and 3 years for export purposes and for local markets, respectively. To circumvent possible mix-ups and associated quality problems of kava products considered for export, legislation for quality specifications should be identical for both the local and the international markets.

(3) Aqueous extraction

Since hepatotoxic reactions were observed with traditional aqueous kava extracts as well as ethanolic and acetonic extracts, the used solvents appear to play no major role for the observed hepatotoxicity (Teschke et al. 2008a; Teschke 2010b). However, to be on the safe side, aqueous kava extracts should be given preference rather than extracts prepared with chemical solvents. The Kava WHO Report has recommended the use of water based kava extracts for medicinal and recreational purposes in analogy to traditional aqueous kava beverages (WHO 2007). This proposal should commonly be followed, an initial study with aqueous kava extracts already showed preliminary results of safety and efficacy in treating patients with anxiety symptoms (Sarris et al. 2009b, 2010a).

(4) Daily dose and duration of treatment

With the introduction of water based kava extracts for kava drugs and dietary supplements, new regulatory challenges emerge regarding the daily dose of kavalactones to be recommended. Regarding ethanolic and acetonic kava extracts, the upper limit in Germany was 120 mg kavalactones per day before the kava ban (Commission E 1990), determined by TLC and not by HPLC (Loew and Franz 2003). In Australia the maximum daily dose of kavalactones allowed for registered aqueous kava extracts to treat anxiety disorders is limited to 250 mg, quantified by HPLC (Sarris et al. 2009b). This value is considerably lower than the use of 2500 mg kavalactones ingested with traditional water based kava beverages per day in the South Pacific Islands; under these conditions hepatotoxic side effects occurred (Russmann et al. 2003; Teschke et al. 2009). Thus, an appropriate safety range is necessary to be on the side of caution. Some uncertainties pertain to the duration of treatment with aqueous kava extracts which was 4 weeks and thus only short term (Sarris et al. 2009b). At present, therefore, defined standards for daily dose of kavalactones and duration of therapy are lacking and have to be established.

(5) Future research

It is well recognized that further clinical trials with aqueous kava extracts are necessary to firmly establish water based kava extracts as effective and safe therapy options for anxiety disorders (Sarris et al. 2010b). The raw material for the aqueous extracts should be derived from peeled and dried rhizomes and underground roots (i.e. non adventitious) of a noble kava cultivar such as Borogu (Lasme et al. 2008), matured for at least 5 years (Vanuatu Legislation 2002). These clinical studies should determine efficacy, possible side effects including hepatotoxic ones, and the maximum of both daily dose of kavalactones and duration of therapy (Sarris et al. 2010b). Safety data derived from clinical studies with water based kava extracts may easily be transferred to traditional used aqueous kava extracts, provided the set of quality specifications such as the noble kava cultivar and the use of peeled rhizomes and roots are identical for both conditions. For clarification of the

discrepancies aroused by allegedly hepatotoxic reactions of some kava preparations, additional studies have to be performed with the new cultivar preparations in comparison with the former kava extracts. These studies should comprise chemical standardization and molecular biological investigations inclusive genomic studies. Attention should be paid to pipermethystine (WHO 2007) and flavokavain B (Zhou et al. 2010) as possible culprits for kava hepatotoxicity (Teschke 2010b). There is also the urgent need to prove or disprove aflatoxin contamination of the kava raw material as a possible mechanism for the observed liver toxicity in a few patients.

(6) Legislation, regulatory standards, and commercial surveillance

Strict standards for safe use of aqueous kava extracts as herbal drugs, dietary supplements and traditional drinks have to be established by legislation in the South Pacific Islands and by regulatory agencies of countries involved in the cultivation and farming of kava plants as well in the production and distribution of kava extracts. New legal and regulatory approaches including strict commercial surveillance are mandatory since traditional aqueous kava extracts may not necessarily be devoid of side effects. Kava has the potential of reconsideration as an approved herbal drug for effective and safe treatment of anxiety, but further steps are now required.

Conclusions

Based on the experience with hepatotoxic side effects due to the use of aqueous, ethanolic, and acetonic kava extracts, as well as herbs–kava mixtures in a few patients, efforts have to be undertaken to improve kava quality. Suggestions have been made to use water based extracts of peeled rhizomes and roots derived from a noble kava cultivar such as Borogu planted at least 5 years before harvest. This set of quality specifications should be used as standard not only for kava drugs and kava dietary supplements in Western countries but also for the traditional kava drinks in the South Pacific Islands. In addition, there is an urgent need to establish strict legal and regulatory surveillance of kava cultivators, farmers, harvesters, and manufacturers. Further clinical trials with aqueous kava extracts are necessary to confirm efficacy and lack of side effects in patients with anxiety disorders. Provided these studies are promising, a return of kava to Western countries is feasible. It is intended that the six-point kava solution plan we propose will advance the research, development and supply of kava globally and eventually lead to the return of kava to restricted markets.

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