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Special Report:

Kava and the Risk of Liver Toxicity: Past, Current, and Future

by Rolf Teschke, MD

A review of the recent research regarding the safety of kava (*Piper methysticum* G. Forster)

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Kava and the Risk of Liver Toxicity: Past, Current, and Future Aspects

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Editor's Note: In the process of reviewing the literature for the AHPA Report*, I found numerous recent papers on the topic of kava and liver toxicity. Instead of trying to cover them individually I asked the primary author of most of the articles to consider writing a guest article for AHPA. We are proud to feature that article here. –Steven Dentali, PhD, Chief Science Officer*

Kava refers to both the South Pacific herb (*Piper methysticum* G. Forster) and the products prepared from its rhizomes and roots that contain the psychoactive kavalactones (1). Due to their tranquilizing, sedative, and anxiolytic properties, kava is widely used all over the world for recreational and medicinal purposes. In the South Pacific, traditional aqueous kava extracts are part of the social and ceremonial life whereas in Western countries kava extracts are used as anxiolytic drugs, kava dietary supplements, and as recreational drinks (1-3). Various clinical trials have shown efficacy of kava for treatment of patients with anxiety disorders (2), but a current overarching concern with kava is the rare occurrence of hepatotoxicity (4) and the need to determine causation (5).

This review presents some highlights of the kava mystery related to the observed adverse reaction of rare toxic liver injury after kava use in a few susceptible patients. An approach is also made to promote future strategies for safe human kava use and improvement of kava quality standards.

Historical Facts

For centuries, kava has attracted the interest of physicians, pharmacologists, botanists, and agriculturists, and the obtained results of their studies have been summarized in excellent reviews (6,7). In the past, major efforts have been undertaken to identify those kava varieties, called also cultivars, which are most safe for human use (8,9). Early pioneering work has established the chemotyping of kava plants (6,10-13) that contain 18 kavalactones, but only the six major kavalactones are used to define a particular kava chemotype. They are: 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 High Performance Liquid Chromatography (HPLC) column (3): 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 more than 200 variant strains or cultivars (9), categorized as noble cultivars, medicinal cultivars, Two-Day cultivars, and the wild species *Piper wichmannii* C.DC, an ancestor of the domesticated kava *Piper methysticum* (14,15). Moreover, the chemotype may vary between roots, rhizomes, and basal stems (8,13). The multiplicity of kava cultivars used for medicinal purposes is the consequence of fragmentary standards of regulatory agencies and manufacturers (14-18) and rarely allowed causality attribution to a single kava cultivar (9). Therefore, it is apparent that any clinical or experimental kava-related study and each kava product should provide the chemotype of the involved kava cultivar.

In 2003, the opinion was expressed that in the South Pacific islands, consumption of aqueous kava extracts had a long tradition of safe usage to include lack of liver injury (19,20), even when higher amounts were consumed daily over many years (19). In the same year, however, case reports appeared showing toxic liver disease in two patients originating from New Caledonia due to kava use in the form of the traditional aqueous beverages derived from an unknown kava cultivar (21), possibly a non-drink Two-Day cultivar (8), with subsequent confirmed causality evaluation (4,22,23). In these two cases, there were increased levels of two liver values commonly known as transaminases, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) (21). The transaminases were markedly elevated between 13 and 42 times the upper limit of the normal ranges, findings that are in line with severe liver-cell injury. This particular enzyme constellation (21) was quite different from the pattern of corresponding liver values reported in other publications after the use of traditional aqueous kava beverages (21,24-26). There were either no activity changes of ALT (24-26) and of AST (26), or there were only marginally elevated ALT and AST levels in a few heavy kava users (21). These results indicated little if any signs of clinically

Disclaimer

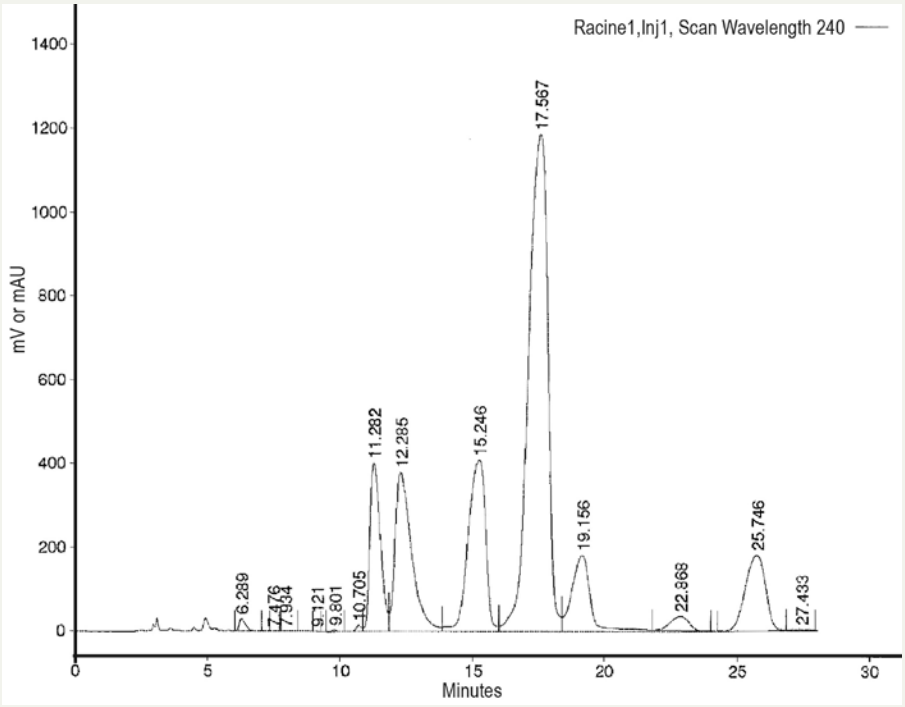
The views presented in this guest article are those of the author and do not necessarily reflect those of AHPA or its members. AHPA's current *Code of Ethics* expects members in good standing of the association that offer kava products for sale for internal use and that contain kava (*Piper methysticum*) to label such products so they bear the following or significantly similar statement:

Caution: US FDA advises that a potential risk of rare, but severe, liver injury may be associated with kava-containing dietary supplements. Ask a healthcare professional before use if you have or have had liver problems, frequently use alcoholic beverages, or are taking any medication. Stop use and see a doctor if you develop symptoms that may signal liver problems (e.g., unexplained fatigue, abdominal pain, loss of appetite, fever, vomiting, dark urine, pale stools, yellow eyes or skin). Not for use by persons under 18 years of age, or by pregnant or breastfeeding women. Not for use with alcoholic beverages. Excessive use, or use with products that cause drowsiness, may impair your ability to operate a vehicle or dangerous equipment.

relevant liver-cell injury (4) in the study groups (21,24-26), as opposed to the two cases from New Caledonia with severe liver toxicity (21).

A clinical and scientific highlight was the unexpected observations stemming from five studies (21,24-27) that the use of traditional aqueous kava extracts derived from non-specified kava cultivars caused markedly increased levels of γ-glutamyltranspeptidase (γGT), another liver enzyme commonly used in routine liver-assessment conditions. Among these five reports, three were Australian studies involving Aborigines in Arnhem Land who consumed traditional aqueous kava extracts prepared with kava raw material imported from Pacific Islands (24,25,27). The fourth report studied inhabitants of New Caledonia who consumed traditional aqueous kava beverages prepared from plants imported from Vanuatu (21), and the fifth study provided data of a predominantly Tongan population of Hawaii, consuming traditional aqueous kava extracts prepared from plants of Hawaii (26). Considering these five studies with increased γGT levels (21,24-27), serum activities of another liver enzyme—the alkaline phosphatase (ALP)—were presented as increased (24-26), unchanged (21), or not evaluated (27). The observed increased levels of both γGT (21,24-27) and ALP (24-26) deserve further evaluation and are likely to be due to either malnutrition, alcohol, hepatic enzyme induction, enzyme adaptation, or cholestasis (4,5) in the investigated study groups (21,24-27). Since this particular enzyme constellation of increased γGT and ALP is not found in European cases of kava liver disease (4,28), the underlying mechanisms may be different.

Figure 1



Legend to Figure 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 minutes, corresponding to desmethoxyyangonin, dihydrokavain, yangonin, kavain, dihydromethysticin, and methysticin, respectively. Details are derived from a previous report (3).

There were no case reports of liver disease associated with the use of acetonic and ethanolic kava extracts as anxiolytic drugs in Western countries prior to 1998 when the first case of liver disease associated with the use of a non-specified kava cultivar was published (29). Consecutively, other case reports and spontaneous reports communicated to regulatory health agencies followed, but again lacking cultivar specifications (4,28,30-32). In 2002, these reports led to withdrawals of kava from various European countries (1,30,31); to a Food and Drug Administration (FDA) consumer advisory in the US (33,34); and to a practitioner alert, consumer advisory, and voluntary recall in Australia (19). Since 2005, aqueous

kava products are available again in Australia as Therapeutic Goods Administration (TGA) approved medicinal over-the-counter products (35,36).

Cases of primarily assumed liver disease caused by kava use (30) have been a matter of international discussions (31,32,37-41). Criticisms focused on the poor quality of the regulatory data presented (31,32,37,40), of it being highly selective (42), insufficiently evaluated (43), and with inappropriate causality-assessment methods used on an ad-hoc basis or with the unspecific liver scales of Naranjo and the World Health Organization (WHO) (44). Subsequent analysis using a structured, quantitative, and liver-specific assessment method established overall causality for kava in only a few patients (4,22,23,28). Surprisingly, liver injury observed in these few cases was causally related to the use of traditional aqueous kava extracts as well as to the use of acetonic and ethanolic kava drugs. The primary cause of the toxic event obviously resides with the crude material used to prepare the various kava extracts and may be attributed to poor quality (5), possibly caused also by mold hepatotoxins (45,46) rather than to any primary constituent of kava (Table 1) (1,47,48) as discussed in recent reviews (45,46).

The Pacific kava paradox—based on kava liver disease that was observed following the use of Western acetonic and ethanolic kava drugs but not of traditional aqueous kava extracts in the Pacific region (19,20)—was suggested in 2003. However, subsequent reports (4,22,23) and cases of the World Health Organization (WHO) (1) revealed that traditional aqueous kava extracts also used in New Caledonia, Australia, the US, and Germany may rarely exhibit potential hepatotoxic properties (49). The clinical characteristics were similar whether the hepatotoxic reactions were caused by aqueous, acetonic, or ethanolic kava extracts, and identical causality for kava was established for all cases and extract varieties (4,22,23). Since kava hepatotoxicity also occurred after the use of traditional aqueous kava extracts in the Pacific region, there is no basis to support the previously proposed Pacific kava paradox (49).

Table 1

Compounds Detected in Kava Roots Extracted with Water and Various Organic Solvents

Compounds	Detection in various extracts obtained with			
	Water	Acetone	Ethanol	Others
1. 10-Methoxyyangonin	+	-	-	-
2. Hydroxykavain	-	-	-	+
3. Dihydro-5,6-dehydrokavain	+	+	+	+
4. 7,8-Dihydrokavain	+	+	+	+
5. 7,8-Dihydroyangonin	-	+	-	+
6. Kavain	+	+	+	+
7. 7,8-Dihydro-5-hydroxykavain	-	+	-	+
8. 5,6-Dihydroyangonin	-	+	-	+
9. 11-Hydroxy-12-methoxydihydrokavain	-	+	-	+
10. 11-Methoxyyangonin	-	+	-	+
11. Desmethoxyyangonin	+	+	+	+
12. 5,6,7,8-Tetrahydroyangonin	+	+	+	+
13. Methysticin	-	+	-	+
14. Dihydromethysticin	+	+	+	+
15. 11,12-Dimethoxydihydrokavain	-	-	-	+
16. Yangonin	+	+	+	+
17. 11-Methoxy-12-hydroxydehydrokavain	-	-	-	+
18. 11-Hydroxyyangonin	+	+	-	+
19. 5,6-Dehydromethysticin	-	+	-	+
Non-kavalactones				
1. Flavokavain A	-	-	-	+
2. Flavokavain B	+	+	-/+	+
3. Flavokavain C	-	-	-	+
4. Cinnamic acid bornyl ester	+	+	+	+
5. 5,7-Dimethoxyflavanone	-	+	+	+
6. 2,5,8-Trimethyl-1-naphthol	-	-	-	+
7. 5-Methyl-1-phenylhexen-3-yn-5-ol	-	-	-	+
8. 8,11-Octadecadienoic acid-methyl ester	+	+	+	+
9. Pinostrobin chalcone	+	+	+	+
10. 5-hydroxy-4´-7-Dimethoxyflavanone	+	+	+	+
11. 5,7(OH)$_2$-4´-one-6,8-dimethylflavone	+	+	-	+
12. Cupric acid	?	?	+	?
13. Pipermethystine	?	?	+	?
14. Glutathione	+	-	-	-
15. Chromic acid	?	?	?	?
16. Aflatoxins of Aspergillus varieties	?	?	?	?
17. Hepatotoxic mycotoxins of other fungus var. and other mould hepatotoxins	?	?	?	?

The data in Table 1 are primarily derived from two reports, mainly from the study of Xuan et al., 2008 (47), but also from the compilation presented by the World Health Organization, 2007 (1). The following details of the assessed kava roots and the used solvents have been communicated: extraction of medium water, acetone, 95% ethanol, and others as are chloroform, methanol, and hexane, but no details regarding chemotype and part of roots (47); extraction of medium 95% ethanol, and dried, probably unpeeled roots of undeclared chemotype (1). Data for flavokavain B are also derived from the reports of Zhou et al., 2010 (48). Details of the table are derived from a previous report (45).

Table 2

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

Table 2 presents an alphabetical order of noble kava cultivars in Vanuatu with their place of origin according to the Republic of Vanuatu Kava Act No. 7 of 2002 (14) and Food Standards Australia New Zealand Technical Report, 2005 (15) with their chemotypes assessed in their roots as reported previously (45). 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 of Lebot and Lévesque, 1996 (10), Lebot et al., 1997 (6), and Siméoni and Lebot, 2002 (12), substantiated by recent reports of Lebot, 2006 (8) and Lasme et al., 2008 (13). As far as a cultivar keeps its chemotype fingerprint 42 … or 24 … , then it is a "noble" cultivar. Other requirements are that there are no parts exposed to light in the raw material, it is organically grown, all the parts are well identified and separated, it is sufficiently old (5 yrs. for export), and the village or origin is known (traceability) (14). Details of the table are derived from a previous report (45).

The Current Situation

Based on current knowledge, the clinical characteristic of kava-related liver disease is now fairly well described (4,5,28) and documented as possessing features similar to those observed in toxic liver disease due to the use of other herbs, dietary supplements, and synthetic drugs (4,5,46). Herbal hepatotoxicity is normally quite difficult to define regarding its typology, since herbs represent a combination of various ingredients rather than one single compound as with synthetic drugs (50-52). In cases of kava liver disease, assignment was made either to the predictable, intrinsic, and a dose-dependent form that requires an overdose-treatment regimen and is therefore basically preventable, or to the unpredictable, idiosyncratic, and a dose-independent form associated with a metabolic subgroup that therefore is not preventable (5,46). Contributing causative factors are overdoses, prolonged kava use, and co-medication with other herbs and synthetic drugs (5,6). Yet questions still remain that relate to poor kava quality including adulteration, misidentification, impurities, and mold hepatotoxins (1,3,5,9,15,18,45,46,49).

Good evidence is now available that the kava problem was not limited to the kava pharmaceutical markets in Germany and Switzerland (22,28,30,32) but may have also extended to the kava dietary supplement markets with polyherbal kava mixtures such as in the Unites States (22,23,53), Australia (22,23,54), and the traditional kava markets such as New Caledonia in the South Pacific Islands (21-23).

At present, an abundance of information and proposals are now available regarding kava quality standardization (3,14-18,33-35,45,55,56) and legislation (14,33-35,56), which are prerequisite conditions to improve both the safety of kava consumers and the quality of kava raw material (1,3,45,55). Based on the Republic of Vanuatu Kava Act No. 7 of 2002, only noble kava cultivars are to be used as kava drugs or kava dietary supplements and they must meet various other quality specifications before export from Vanuatu (14). Names and the respective chemotypes of all noble kava cultivars in Vanuatu are available (Table 2) (6,8,10,12-15,45). This is useful information for local farmers, distributors, manufacturers, regulatory agencies, and physicians (3,45,55). Noble kava cultivars have a long tradition of safe use (3,6,9,13) and can easily be differentiated and identified by their characteristic chemotype (3,6,8,9,13) using standard methods that are described in detail (Table 3) (3,6,10,12,45,57). In addition to Vanuatu (3,13,14), noble kava cultivars also exist in other South Pacific islands that lack appropriate kava legislation (56), a problem at least for the present (45). According to the Vanuatu Kava Act, other kava cultivars such as medicinal cultivars, Two-Day cultivars, and Wichmannii varieties (14) are now prohibited for export (14).

Another kava quality standard pertains to the strict use of peeled subaerial rhizomes and roots (3,34,45,55). In the past, kava products occasionally contained aerial parts of kava plants (1,5,8,9,15,18,55) that contain the hepatotoxic compound pipermethystine (1). Aerial parts include in particular

Table 3

Standard Method to Assess Chemotype of Kava Cultivars

Analytical Approach
1. The kava plant to be assessed should have been dried for at least 2 weeks at 12% room humidity
2. Use of peeled plant organ: both rhizome and roots
3. Absolute ethanol as the solvent of primary choice
4. The previously described standard method of Siméoni and Lebot, 2002 (12) is the primary choice to assess the chemotype of kava cultivar

Other details are presented in additional references (6,10,45,57). Details of the table are derived from a previous report (45).

the lower stems (1,5), adventitious roots originating from the stems and extending into the soil (5,18), and upper, not uphilled parts of rhizomes (45). Of note, peeled and unpeeled kava rhizomes and roots are the form of kava raw material used for kava preparations in Australia (35), and peeled rhizomes were required by the German regulatory agency for kava drugs before the kava ban in 2002 (16,17).

Various recent reports advocate that kava products to be used as kava drugs or as kava dietary supplements should be water-based (1-3,34-36,55,58-60), as are the traditional kava beverages of the South Pacific islands (1). This specification has already been applied to medicinal kava products licensed by the Australian TGA (35) and was suggested (34) to be included in FDA's consumer advisory in the United States (33). The principles of these recommendations are based on the understanding going back to the safe form of aqueous kava extracts used traditionally for at least a millennium in the South Pacific region (1,3,19,20). There have been no regulatory reports or published case reports of liver injury associated with the use of medicinal aqueous kava products in the Australian market since their return in 2005 for the treatment of anxiety symptoms (35). Lack of liver toxicity was also evident in a short-term clinical trial with aqueous medicinal kava (1,36), but results of already planned long-term treatment are necessary to confirm these findings (60).

Presumably, the principles of Good Manufactural Practice (cGMP) are applied in the course of manufacturing kava dietary supplements in the United States (33) as well as in Australia for the preparation of medicinal kava products (35). There are, however, open questions whether and to what extent these principles have always been followed in the South Pacific islands (1,21). Shortcomings of kava quality related to adulteration, misidentification, and contamination were apparent (1,3,8,9,15,18, 45,55), and elimination of these problems is likely due to new legislation, regulatory guidance, and improved standards of processing and manufacturing.

Currently, there continues to be kava cultivation, harvest, consumption, and export in the South Pacific islands (56). Traditional aqueous kava beverages are consumed in the South Pacific islands for social and cultural purposes as usual (1,56). While kava legislation to ensure good kava quality is available for Vanuatu (14), it is lacking for the other South Pacific islands (56); and, this is reason for concern (45). The overall demand for kava raw material has decreased since 2002 (1,8,56) because of the European regulatory ban (30). Kava-producing countries of the South Pacific region export part of their kava raw material to regional countries such as Fiji, Kiribati, and New Caledonia (56). Kava is also sold in various amounts to countries such as the United States, Canada, Europe, China, Japan, New Zealand, and Australia (1,56), partly via the Internet (1). In the United States, kava is available as a kava dietary supplement (33,34). Medicinal aqueous kava extracts are available in Australia as over-the-counter medicine to be used for treatment of anxiety (2,35,36), with a limitation of 125 mg kavalactones per individual dosage and 250 mg kavalactones per day (35). Previous regulatory limits of 120 mg kavalactones per day were standard in Europe for acetonic and ethanolic kava drugs (16).

Future Requirements

Long-tem safety and efficacy will be tested to evaluate the risk/benefit ratio in new clinical trials with kava extracts for the treatment of anxiety disorders (1,45,60). The use of traditional aqueous extracts obtained from peeled rhizomes and peeled roots of a noble kava cultivar such as Borogu has been recommended for these studies (3,45,55,60). As a highlight, for the first time, recent short-term studies have shown efficacy and safety for aqueous kava extracts (36,59,62), which confirms previous reports from trials done with acetonic and ethanolic kava extracts (1,40,41,61). One of these new long-term studies has been started in Australia (60), where aqueous kava extracts are fully licensed (35), and hopefully other studies, including multi-center ones, will follow. To err on the side of caution and to ensure against liver injury, kava-consuming inhabitants of the kava-producing and -importing South Pacific islands should undergo clinical assessment of their liver function in relation to their consumption of kava cultivar, their daily kavalactone intake, and duration of kava use (45). Overall, the results of these new studies should facilitate further regulatory recommendations and decisions regarding kava use.

Other novel strategies will be developed to minimize hepatotoxic risks due to the use of kava products. Some proposals have been made in the past (1,8,9,22,32,50,58), and new ones are presently emerging in the course of additional analyses (3,45,55,60). Future safety requirements for kava will have to take into account previous traditional experience (6) including farming practices (6,18) and manufacturer expertise (1,15). Kava is an effective anxiolytic herb (1,36,40,41,61) with a high potential for worldwide use (60). However, a prerequisite will be good-quality kava raw material created by following Good Agricultural Practices (GAP) for kava cultivation, farming, and harvesting followed by manufacturing sites operating under cGMP (3,45,55). Updates to previous kava quality-standardization approaches (14-18) are necessary, and ethnobotanical studies associated with local expertise and surveillance are required to achieve good quality of kava raw material (45).

Key issues for the future also include appropriate kava legislation in order to assure good kava quality standards (3,45,55). An update of the Vanuatu Kava Act (14) is required to make the kava standards for local and export use the same. Pan-Pacific kava legislation should be the primary aim with the involvement of all kava-producing South Pacific islands (3,45,55,56), using an updated version of the Vanuatu Kava Act (14) as a basis (3).

Novel experimental studies are required to elucidate theoretical pathogenetic mechanism(s) underlying reported kava-associated adverse events (45) in face of the

present uncertainty of their culprit(s) (5,45,46). Available data of numerous reports recently summarized suggests that causation appears to be multifactorial (45), which presents a particular challenge for agrobotanists, botanists, toxicologists, pharmacologists, farmers, and manufacturers. Most importantly, however, there is so far no clear evidence for a causative role of kavalactones (5) or non-kavalactone constituents such as pipermethystine (45,46,63) and flavokavain B (45,46) identified from kava (Table 1) (1,45). Therefore, additional studies should address enzymatic, analytical, and toxicological issues, using aqueous, acetonic, and ethanolic kava extracts (45). These extracts should be derived from different plant parts such as peeled and unpeeled rhizomes and roots, and their peelings, from both noble and non-noble kava cultivars with clear identification of their chemotypes. Suggestions for new research activities have also been made with respect to enzymatic degradation of kavalactones. Concomitantly, more research should be conducted on the bioavailability of kavalactones and non-kavalactones derived from aqueous kava extracts.

Early theories of kava-associated hepatotoxicity focused on the possibility that raw material could have been contaminated by oil, fertilizers, pesticides, nematodes, bacteria, fungi, and specific plant diseases such as kava dieback (18). However, in the past, virtually none of these possible causes have been explicitly evaluated in detail (1,5). Future identification of possible hepatotoxic kava constituents is desired (45,46,49). Recently, inquiries center on the question of whether kava hepatotoxicity might have been caused by the use of moldy kava raw material (45,46,49). Post-harvest storage of kava material is the major constraint in the warm, humid climate of the Pacific islands (18). In Vanuatu and Pohnpei (Micronesia), where kava is always consumed fresh, the raw material has a maximum shelf life of three to four weeks (45). However, the storage conditions are so poor that mold may develop rapidly on the roots only one week after harvest. In Pacific countries such as Fiji, Tonga, and Samoa, where the beverage is prepared from dried raw material, the parts can be stored for a longer period, but mold is still a problem. When dried kava was exported in bags and containers to Europe, mold sometimes developed in the bags, and if proper inspection did not occur before grinding and extraction, it is likely that hepatotoxins, including aflatoxins, could be present. In fact, a moldy taste of the beverage served in local kava bars of Nouméa (New Caledonia) has been recognized as a problem (Lebot, personal field observation) (45).

There are few data about kava contamination by bacteria (18,46,64) and *Aspergillus* species producing mycotoxins such as ochratoxin A (45,46,64) and aflatoxins (45,46,65), which may be represented as the sum of aflatoxin B_1, B_2, G_1, and G_2 (45). In three aqueous extracts prepared from the internal part of

the kava rhizome (minimizing soil contamination) various bacteria species were isolated: *Bacillus, Cellulomonas, Enterococcus, Pectobacterium, and Staphylococcus.* The conclusion was reached that the *Bacillus cereus* group and *Staphylococcus* species may produce toxins and cause foodborne illness (64). At present, however, we urgently need bacteriological studies using peeled rhizomes and roots, as well as their peelings, derived from moldy kava plants, and this would possibly provide evidence for additional bacteria species in sufficient quantities to elicit hepatotoxicity (45).

Of greater concern than bacteria are mycotoxin contaminants (45,46,65,66). Kava roots obtained from a botanical supplier were found to contain ochratoxin A at a level of 10.3 ng/g. Corrected for about 50 percent recovery obtained with the analytical, the actual concentration of ochratoxin was likely closer to 20 ng/g (66). In other studies, kava has been found to be contaminated with least 0.5 ng/g (65) of aflatoxins that are known human liver toxins (67-69). Other mycotoxins are likely to have similar hepatotoxicity potency, and an overall assessment has to include examinations of moldy kava plant rhizomes and roots with their peelings considered separately. It is presently unclear whether peeled rhizomes and roots are to be preferred over the unpeeled parts. An approach evaluating potential aflatoxin contamination would represent the first step in clarifying whether reported kava hepatotoxicity could be due to aflatoxicosis, similar to epidemic toxic hepatitis caused by food contaminated with aflatoxins that has been reported from India and Kenya (67-69). If causally related to aflatoxins or other mold-created hepatotoxins, kava hepatotoxicity may be regarded as a preventable disease both in the Pacific region and in Western countries with respect to both traditional aqueous and solvent-based kava extracts.

Some uncertainties remain regarding the safety of kava use with respect to various kava quality standards (70). Of particular interest is the use of aqueous versus organic solvents (1). Ethanolic extracts of kava are manufactured and distributed in New Zealand and in the United States. New Zealand kava manufacturers supply TGA-compliant aqueous liquid kava extracts as well as 90% ethanol/water extracted solid kava products and 60% ethanol/water liquid kava extracts, as reported in 2005 (71). The situation in the United States is similar as manufacturers are not restricted to aqueous-only extracts and are free to manufacture hydro-ethanolic (ethanol/water) extracted products. Labelling of kava products should provide information regarding kava cultivar, place of origin, and the used plant part and solvent.

It is apparent that we need more details on the multiple facets of kava production and use. Establishing certainty related to rare reports of kava-associated liver disease awaits a definitive answer for their final causality attribution(s). With the proposed research activities and qualifying measures, it is hoped that the safety of individuals consuming kava will substantially be improved.

Conclusions

Kava-related liver disease is a well-defined clinical entity that occurred in a few patients after the worldwide use of kava. Toxicity was associated with ingestion of traditional aqueous kava extracts, acetonic and ethanolic kava drugs, and kava dietary supplements in kava-herb mixtures. These adverse reactions emerged unexpectedly in face of the apparent safe traditional use of kava for thousands of years; these reactions were most probably a consequence of poor-quality raw kava material employed in the manufacture of a few kava extracts. Further clinical trials and experimental research is necessary to evaluate whether kava hepatotoxicity may be due to mold-produced hepatotoxins. To minimize hepatotoxic risks due to kava use, efforts have to be undertaken to improve kava quality standards and to establish strict regulations for kava cultivators, farmers, harvesters, manufacturers, and physicians treating patients for anxiety, tension, and restlessness. Thorough national regulatory measures and Pan-Pacific kava legislation are mandatory.

References

1. World Health Organization. Assessments of the risk of hepatotoxicity with kava products. WHO Document Production Services: Geneva, Switzerland; 2007
2. Sarris J, LaPorte E, Schweitzer I. Kava: a comprehensive review of efficacy, safety, and psychopharmacology. Aust N Z J Psychiatry 2011; 45: 36-44
3. Teschke R, Sarris J, Lebot V. Kava hepatotoxicity solution: A six-point plan for new kava standardization. Phytomedicine 2011; 18: 96-103
4. Teschke R. Kava hepatotoxicity: a clinical review. Ann Hepatol 2010; 9: 251-265
5. Teschke R. Kava hepatotoxicity: pathogenetic aspects and prospective considerations. Liver Int 2010; 30: 1270-1279
6. Lebot V, Merlin M, Lindstrom L. Kava, the Pacific elixir. New Haven: Yale University Press; 1997
7. Singh YN, Blumenthal M. Kava: An overview. Distribution, mythology, botany, culture, chemistry, and pharmacology of the South Pacific's most revered herb. Herbal Gram 1997; 39: 33-55
8. Lebot V. The quality of kava consumed in the South Pacific. HerbalGram 2006; 71: 34-37
9. Schmidt M. Quality criteria for kava. HerbalGram 2007; 73: 45-49
10. Lebot V, Lévesque J. Genetic control of kavalactone chemotypes in *Piper methysticum* cultivars. Phytochemistry 1996; 43: 397-403.
11. Lebot V, Johnston E, Zheng QY, McKern D, McKenna D. Morphological, phytochemical and genetic variation in Hawaiian cultivars of 'Awa (Kava, *Piper methysticum,* Piperaceae). Economic Botany 1999; 53: 407-418
12. Siméoni P, Lebot V. Identification of factors determining kavalactone content in Kava (*Piper methysticum* Forst. F.). Biochem System Ecol 2002; 30: 413-424
13. Lasme P, Davrieux F, Montet D, Lebot V. Quantification of kavalactones and determination of kava (*Piper methysticum*) chemotypes using near-infrared reflectance spectroscopy for quality control in Vanuatu. J Agric Food Chem 2008; 56: 4976-4981
14. Vanuatu Legislation: Republic of Vanuatu Kava Act No. 7 of 2002. Available at: http://www.paclii.org/vu/legis/num_act/toc-K.html Accessed February 17, 2011
15. Food Standards Australia New Zealand. Kava. A human health risk assessment. Technical report Series No.30. 2005. Available at: http://www.foodstandards.gov.au/scienceandeducation/publications/technicalreportserie1338.cfm Accessed February 17, 2011
16. Commission E of BGA/BfArM, 1990. Monographie Piperis methystici rhizoma (Kava-Kava-Wurzelstock). Bundesanzeiger Nr. 101; dated June 1, 1990
17. DAC (Deutscher Arzneimittel-Codex). Kava-Kava-Wurzelstock: Piperis methystici rhizoma. Official monograph, 1998, Govi-Verlag, Eschborn (Germany)
18. SPC Report. Pacific kava: a producer's guide. Secretariat of the Pacific Community, 2001. Suva, Fiji Islands. ISBN 982-203-810-0
19. Currie BJ, Clough AR. Kava hepatotoxicity with Western herbal products: does it occur with traditional kava use? Med J Aust 2003; 178: 421-422
20. Moulds RFW, Malani J. Kava: herbal panacea or liver poison? Med J Aust 2003; 178: 451-453
21. Russmann S, Barguil Y, Cabalion P, Kritsanida M, Duhet D, Lauterburg BH. Hepatic injury due to traditional aqueous extracts of kava root in New Caledonia. Eur J Gastroenterol Hepatol 2003; 15: 1033-1036
22. Teschke, R, Schwarzenboeck A, Akinci A. Kava hepatotoxicity: a European view. New Zeal Med J 2008; 121: 1283. Available at: http://www.nzma.org.nz/journal/121-1283/3296/ Accessed February 17, 2011
23. Teschke R, Genthner A, Wolff A. Kava hepatotoxicity: Comparison of aqueous, ethanolic, acetonic kava extracts and kava-herbs mixtures. J Ethnopharmacol 2009; 123: 378-384
24. Clough AR, Bailie RS, Currie B. Liver function test abnormalities in users of aqueous kava extracts. J Toxicol Clin Toxicol 2003; 41: 821-829
25. Clough AR, Jacups SP, Wang Z, Burns CB, Bailie RS, Carney SJ, Collie A, Guyula T, McDonald SP, Currie BJ. Health effects of kava use in an eastern Arnhem Land community. Intern Med 2003; 33: 336-340
26. Brown AC, Onopa JO, Holck P, Kaufusi P, Kabasawa D, Craig WJ, Dragull K, Levine AM, Baker JD. Traditional kava beverage consumption and liver function tests in a predominantly Tongan population in Hawaii. Clin Toxicol 2007; 45: 549-556
27. Mathews JD, Riley MD, Fejo L, Munoz E, Milns NR, Gardner ID, Powers JR, Ganygulpa E, Gununuwawuy BJ. Effects of the heavy usage of kava on physical health: summary of a pilot survey in an aboriginal community. Med J Aust 1988; 148: 548-555
28. Teschke R, Schwarzenboeck A, Hennermann KH. Kava hepatotoxicity: a clinical survey and critical analysis of 26 suspected cases. Eur J Gastroenterol Hepatol 2008; 20: 1182-1193
29. Strahl S, Ehret V, Dahm HH, Maier KP. Necrotising hepatitis after taking herbal remedies. Dtsch Med Wschr 1998; 123: 1410-1414. (Article in German)
30. BfArM (Bundesinstitut für Arzneimittel und Medizinprodukte, Bonn. Federal Institute for Drugs and Medicinal Products in Germany). Rejection of Drug Risks, Step II. As related to: Kava-Kava (*Piper methysticum*)-containing, and kavain-containing drugs, including homeopathic preparations with a final concentration up to, and including D4. June 14, 2002. Available at: http://www.spc.int/cis/documents/02_0714_BfArM_Kava_Removal.pdf Accessed February 17, 2011
31. Teschke R, Gaus W, Loew D. Kava extracts: safety and risks including rare hepatotoxicity. Phytomedicine 2003; 10: 440-446
32. Schmidt M, Morgan M, Bone K, McMillan J. Kava: a risk-benefit assessment. In: Mills M, Bone K (Eds). The essential guide to herbal safety. Elsevier Churchill Livingstone, St. Louis (Missouri), 2005; 155-221
33. FDA (U.S. Food and Drug Administration): Consumer advisory: Kava-containing dietary supplements may be associated with severe liver injury. Issued March 25, 2002. Available at: http://www.fda.gov/Food/ResourcesForYou/Consumers/ucm085482.htm Accessed February 17, 2011
34. Teschke R, Schulze J. Risk of kava hepatotoxicity and the FDA consumer advisory. J Am Med Ass 2010; 304: 2174-2175
35. Therapeutic Goods Administration (TGA), Australian Government, Department of Health and Aging. Kava fact sheet, April 2005. Web page last updated September 20, 2010. Available at: http://www.tga.gov.au/cm/kavafs0504.htm Accessed February 17, 2011
36. Sarris J, Kavanagh DJ, Byrne G, Bone KM, Adams J, Deed G. The Kava Anxiety Depression Spectrum Study (KADSS): a randomized, placebo-controlled crossover trial using an aqueous extract of Piper methysticum. Psychopharmacol 2009b; 205: 399-407
37. Denham A, McIntyre M, Whitehouse J. Kava – the unfolding story: report on a work-in-progress. J Altern Complement Med 2002; 8: 237-263
38. Schulze J, Raasch W, Siegers CP. Toxicity of kava pyrones, drug safety and precautions- a case study. Phytomedicine 2003; 10, Suppl IV: 68-73
39. Clouatre DL. Kava kava: examining new reports of toxicity. Toxicol Lett 2004; 150: 85-96
40. Ulbricht C, Basch E, Boon H, Ernst E, Hammerness P, Sollars D, Tsourounis C. Safety review of kava (*Piper methysticum*) by the Natural Standard Research Collaboration. Exp Opin Drug Saf 2005; 4: 779-794

41. Ernst E. A re-evaluation of kava (*Piper methysticum*). Br J Clin Pharmacol 2007; 64: 415-417
42. Teschke R, Wolff A. Kava hepatotoxicity: Regulatory data selection and causality assessment. Dig Liv Dis 2009; 41: 891-901
43. Teschke R, Fuchs J, Bahre R, Genthner A, Wolff A. Kava hepatotoxicity: comparative study of two structured quantitative methods for causality assessment. J Clin Pharm Ther 2010; 35: 545-563
44. Teschke R, Wolff A. Regulatory causality evaluation methods applied in kava hepatotoxicity: Are they appropriate? Reg Toxicol Pharmacol 2011; 59: 1-7
45. Teschke R, Qiu SX, Xuan TD, Lebot V. Kava and kava hepatotoxicity: requirements for novel experimental, ethnobotanical, and clinical studies based on a review of the evidence. Phytother Res 2011; in press
46. Teschke R, Qiu SX, Lebot V. Herbal hepatotoxicity by kava: update on pipermethystine, flavokavain B, and mould hepatotoxins as primarily assumed culprits. Dig Liv Dis 2011; in press
47. Xuan TD, Fukuta AA, Wie AC, Elzaawely AA, Khanh TD, Tawata S. Efficacy of extracting solvents to chemical compounds of kava (*Piper methysticum*) root. J Nat Med 2008; 62: 188-194
48. Zhou P, Gross S, Liu JH, Yu BY, Feng LL, Nolta J, Sharma V, Piwnica-Worms D, Qiu SX. Flavokawain B, the hepatotoxic constituent from kava root, induces GSH-sensitive oxidative stress trough modulation of IKK/NF-κB and MAPK signaling pathways. FASEB J 2010; 24: 4722-4732
49. Teschke R, Sarris J, Schweitzer I. Kava hepatotoxicity in traditional and modern use: The presumed Pacific kava paradox hypothesis revisited. Submitted for publication
50. Richardson WN, Henderson L. The safety of kava – a regulatory perspective. Br J Clin Pharmcol 2007; 64: 418-420
51. Teschke R, Bahre R. Severe hepatotoxicity by Indian Ayurvedic herbal products: A structured causality assessment. Ann Hepatol 2009; 8: 258-266
52. Navarro VJ. Herbal and dietary supplement hepatotoxicity. Semin Liver Dis 2009; 29: 373-382
53. Humberston CL, Akhtar J, Krenzelok EP. Acute hepatitis induced by kava kava. J Toxicol / Clin Toxicol 2003; 41: 109-113
54. Gow PJ, Connelly NJ, Hill RL, Crowley P, Angus PW. Fatal fulminant hepatic failure induced by a natural therapy containing kava. Med J Aust 2003; 178: 442-443
55. Teschke R, Sarris J, Glass X, Schulze J. Kava, the anxiolytic herb: back to basics to prevent liver injury? Br J Clin Pharmacol 2011; 71: 445-448
56. Codex alimentarius. Commission E. Discussion Paper on the Development of a Standard for Kava. JOINT FAO/WHO FOOD STANDARDS PROGRAMME, September 2010, eleventh session, CX/NASWP 10/11/8. Available at: *ftp://ftp.fao.org/codex/ccnaswp11/na11_08e.pdf* Accessed February 1, 2011
57. Lebot V, Lévesque J. The origin and distribution of kava (*Piper methysticum* Forst. F. Piperaceae): A phytochemical approach. Allertonia 1989; 5: 223-281
58. Sarris J, Adams J, Wardle JL. Time for a re-assessment of the use of kava in anxiety? Compl Ther Med 2009; 17: 121-122
59. Sarris J, Adams J, Kavanagh D. An explorative qualitative analysis of participants' experience of using kava versus placebo in an RCT. Aust J Med Herbalism 2010a; 22: 12-16
60. Sarris J, Teschke R, Stough C, Scholey A, Schweitzer I. Re-introduction of kava (*Piper methysticum*) to the EU: Is there a way forward? Planta Med 2011; 77: 107-110
61. Pittler M H, Ernst E. Kava extract for treating anxiety (Cochrane Review). Cochrane Database Syst Rev 2003; Issue 1: CD003383. Wiley Interscience. DOI: 10.1002/14651858
62. Sarris J, Kavanagh DJ. Kava and St. John's wort: Current evidence for use in mood and anxiety disorders. J Altern Complement Med 2009; 15: 827-836
63. Lechtenberg M, Quandt B, Schmidt M, Nahrstedt A. Is the alkaloid pipermethystine connected with the claimed liver toxicity of kava products? Pharmazie 2008; 63: 71-74
64. Kandukuru P, Huang AS, Dong J, Bittenbender HC, Li Y. Rapid identification of bacterial isolates from aqueous kava (*Piper methysticum*) extracts by polymerase chain reaction and DNA sequencing. Applied Microbiol 2009; 49: 764-768
65. Weaver CM, Trucksess MW. Determination of aflatoxins in botanical roots by a modification of AOAC Official Method 991.31: single-laboratory validation. J AOAC Int 2010; 93: 184-189
66. Trucksess M, Weaver C, Oles C, D'Ovidio K, Rader J. Determination of aflatoxins and ochratoxin A in ginseng and other botanical roots by immunoaffinity column cleanup and liquid chromatography with fluorescence detection. J AOAC Int 2006; 89: 624-630
67. Krishnamachari KA, Bhat RV, Nagarajan V, Tilak TB. Hepatitis due to aflatoxicosis. An outbreak in Western India. Lancet 1975; 7915: 1061-1063
68. Tandon HD, Tandon BN, Ramalingaswami V. Epidemic of toxic hepatitis in India of possible mycotoxic origin. Arch Pathol Lab Med 1978; 102: 372-376
69. Ngindu A, Johnson BK, Ngira JA, Nandwa H, Jansen AJ, Kaviti JN, Siongok TA. Outbreak of acute hepatitis caused by aflatoxin poisoning in Kenya. Lancet 1982; 319: 1346-1348
70. Teschke R, Lebot V. Kava Quality Standardization Code. Submitted for publication
71. Rasmussen, P. New Zealand Association of Medical Herbalists. Submission on proposed reclassification of kava as a prescription medicine – Medicines classification committee, June 2005. Available at: *http://nzamh.org.nz/downloads/kavamay05.pdf* Accessed: February 17, 2011