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Review article

Herbal hepatotoxicity by kava: Update on pipermethystine, flavokavain B, and mould hepatotoxins as primarily assumed culprits

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ABSTRACT

Herbal hepatotoxicity by the anxiolytic kava (*Piper methysticum* Forst. f.) emerged unexpectedly and was observed in a few patients worldwide. Liver injury occurred after the use of traditional aqueous kava extracts in the South Pacific region and of acetonic and ethanolic extracts in Western countries in rare cases, suggesting that the solvents used play no major causative role. In this review, we discuss actual pathogenetic issues of kava hepatotoxicity with special focus on developments regarding pipermethystine, flavokavain B, and mould hepatotoxins as possible culprits. There is abundant data of in vitro cytotoxicity including apoptosis by pipermethystine and flavokavain B added to the incubation media, yet evidence is lacking of in vivo hepatotoxicity in experimental animals under conditions similar to human kava use. Furthermore, in commercial Western kava extracts, pipermethystine was not detectable and flavokavain B was present as a natural compound in amounts much too low to cause experimental liver injury. There is concern, however, that due to high temperature and humidity in the South Pacific area, kava raw material might have been contaminated by mould hepatotoxins such as aflatoxins after harvest and during storage. Whether kava hepatotoxicity may be due to aflatoxicosis or other mould hepatotoxins, requires further studies.

1. Introduction

Initial uncertainty prevailed when in Europe cases of hepatotoxicity in temporal association with the use of acetonic and ethanolic extracts from the rhizomes of the anxiolytic herb kava (*Piper methysticum* Forst. f.) emerged [1,2]. These cases were perceived unexpected in view of the long tradition of safe kava use in the South Pacific Islands since some thousand years. Previously, the cases of assumed kava hepatotoxicity have been submitted to an ad hoc evaluation procedure with respect to causality for kava that was heavily debated [3–6], considering also that the assessment method employed for this analysis lacks liver specificity and accuracy [7]. The application of more sophisticated assessment tools with their structured, quantitative, and liver specific characteristics established causality for kava in a few patients with signs of toxic liver injury [8–11], and additional clinical aspects became evident [8,11]. In the past, there was speculation about kava hepatotoxicity not only regarding possible culprits [2,12–14] but also about both the predictable, intrinsic and the unpredictable, idiosyncratic typologies [1,8], requiring an update of new developments in the area of this special and exciting field of herbal hepatotoxicity.

In this review, we describe possible new culprits and the typology of kava hepatotoxicity that are at present under consideration and discussion, with the focus on the most recent and relevant causative agents. Amongst these are preferentially pipermethystine, flavokavain B, and mould hepatotoxins.

2. Kava function and metabolism

Rhizome and root extracts of kava exert psychoactive properties with special reference to anxiolysis, sedation, and relaxation [15]. These psychotropic effects are achieved from modulation of GABA activity via alteration of lipid membrane structure and sodium channel function, monoamine oxidase B inhibition, and noradrenaline and dopamine reuptake inhibition in the brain. Virtually all of the pharmacological activities can be attributed to the presence of six kavalactones as are kavain, dihydrokavain, methysticin, dihydromethysticin, yangonin, and desmethoxyyangonin. There is still some uncertainty as to what extent kavalactones are metabolized in the liver by lactone hydrolases and cytochrome P450 isoenzymes [3,6,14].

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3. Typology of kava hepatotoxicity

In cases of liver injury induced by conventional synthetic drugs, the classification of the prevailing type of injury is fairly well established [16–18]. Assignment is made either to the predictable, intrinsic, and dose dependent form that requires an overdose treatment regimen, is therefore rare under the commonly prescribed synthetic drugs, and typically represents the type found for instance in cases of paracetamol overdose; or to the unpredictable, idiosyncratic, and dose independent form with its immunologic and metabolic subgroups occurring in cases of liver injury caused by virtually all synthetic drugs used in therapeutic dosages [16]. In contrast, herbal hepatotoxicity is normally quite difficult to define regarding its typology, since herbs represent a combination of various constituents rather than one single compound as in synthetic drugs [19–21].

In reported cases of hepatotoxicity by the anxiolytic kava, additional shortcomings in the course of assessing the respective cases were evident. These include the possibility of misidentification of plants, cultivar variation, inappropriate plant parts, adulteration, contamination, and confounding variables such as prolonged treatment duration, daily overdose, comedication with other herbs, dietary supplements and synthetic drugs, alcohol use, and preexisting liver disease [8,11]. Assignment of kava hepatotoxicity to one of the prevailing types of injury known from synthetic drugs was challenging, not only due to the various confounding variables [8,11,22] and to the numerous constituents of kava extracts [23–25], but also with respect to the low number of affected patients [8,11].

In 14 cases of toxic liver injury, causality has been established for kava ± comedication [11]. Normal daily doses of kavalactones were reported in 4 patients and daily overdoses in 8 cases, whereas assessment regarding daily overdose was not possible in the 2 patients who used traditional aqueous kava extracts. Comedication was described in 9 patients. In none of the 14 patients were there clinical or laboratory signs of hypersensitivity which could have been attributed to the use of kava. The question arose as to whether kava hepatotoxicity represents a predictable, intrinsic, dose-dependent, and therefore preventable disease, since it is causally related primarily to daily overdose; or it may reflect an unpredictable, idiosyncratic, and dose unrelated disease either of the immunologic or the metabolic type, occurring with normal daily dosages and thus lacking these preventive characteristics [8,11,14,22].

3.1. Unpredictable, idiosyncratic type

A positive reexposure test is the most commonly accepted hallmark for the diagnosis of toxic liver injury of the unpredictable, idiosyncratic type [16,26]. To both of its subgroups, the immunologic and the metabolic varieties, is this test applicable [16]. Adherence to the strict criteria to evaluate the reexposure test as well as treatment with recommended daily doses is mandatory [16,26], equating to a daily dose of kavalactones in the therapeutic range of ≤120 mg [8].

Based on the positive result of a reexposure test with an ethanolic kava extract and considering other characteristic features of the clinical course of one single patient [27], this case of kava hepatotoxicity was attributable to the unpredictable, idiosyncratic, and dose independent type of injury [8,11]. Its metabolic subgroup fits best to the characteristics of the case: the latency period of the first hepatotoxic event was six months of treatment with 60 mg kavalactones, associated with the use of an oral contraceptive (desogestrol, ethinylestradiol), paroxetine, and St. John's Wort; with two weeks, the latency period of the reexposure with kavalactones alone in the absence of any comedication was considerably shorter [27]. The data not only of this special case but also of 3 additional cases with established kava hepatotoxicity [11] are compatible with various characteristics of the metabolic type of the idiosyncratic reaction as are a variable duration of exposure of one week up to 12 months, the absence of clinical features of hypersensitivity such as rash, fever, and eosinophilia, the delayed response to rechallenge of many days or weeks, and a weak dose dependency in susceptible humans [16]. This metabolic form of the unpredictable, idiosyncratic type of injury found in a few patients with kava-induced liver injury is based on a metabolic aberration in unusually susceptible humans.

Conversely, the immunologic form of the idiosyncratic type of kava-induced liver injury was not seen in any of the patients with established kava hepatotoxicity after the use of kava taken at normal daily doses of kavalactones [8,11]. In particular, immunologic idiosyncrasy such as duration of exposure for 1–5 weeks, features of hypersensitivity, or prompt response to rechallenge after one or two doses [16] was lacking [8,11].

3.2. Predictable, intrinsic type

In 8 out of 14 patients with established kava hepatotoxicity was there a daily overdose of kavalactones documented, considering 120 mg kavalactones as maximum daily dose [11]. Using daily overdose as a criterion [16], kava hepatotoxicity might be attributed in these 8 patients to the predictable, intrinsic type of liver injury [11]. For further assessment of the underlying typology, the clinical data of these 8 patients were submitted to additional analyses regarding typical features of and requirements for the predictable, intrinsic type of hepatotoxicity, as are clear dose dependency and often short as well as relatively consistent latency period [16]. However, none of these 2 criteria mentioned before are met by the group of the 8 patients, considering published data of the individual cases [11]. In addition, the predictable type of hepatotoxicity is generally caused by agents that are intrinsically toxic through their molecule to which most persons are susceptible, resulting in a high incidence in humans (depending on dosage) [16], a criterion not compatible with the rarity of cases reported worldwide [8,11,22]. Finally and most importantly, kava hepatotoxicity should be reproducible in experimental studies, but evidence for experimental reproducibility is lacking [4,14,23,28]. Therefore, typical criteria in support for the classical predictable, intrinsic type of liver injury are lacking in these 8 patients with kava hepatotoxicity under consideration, requiring further assessment.

Prerequisite for assessment of the predictable, intrinsic type of injury in the 8 cases with established kava hepatotoxicity after the use of overdosed kavalactones is the uniformity of the kava products used and their qualities, criteria that have not been fulfilled [11,14]. There is clear evidence that kava extracts are prepared quite differently, and discussions emerged about poor quality of kava products [12–14,23,25] related to the plant itself [14,29–33] and possibly caused by mould hepatotoxins as contaminants [25]. Consequently, a few batches of poor quality kava extracts might have been sufficient to cause in a limited number of individuals dose dependent hepatotoxic reactions of the predictable, intrinsic type, basically preventable through appropriate measures. It seems appropriate to evaluate and identify possible culprits of toxic liver injury associated with the use of various kava extracts.

4. General considerations of possible culprits

In the past, a wealth of possible culprits for kava hepatotoxicity was under consideration and discussion [3–6,12–14,33]. Amongst these were areas such as ethnic origin prone to liver injury predisposition; hepatic glutathione depletion; cyclooxygenase inhibition; P-glycoprotein alterations; genetic enzyme deficiencies; interactions at the level of hepatic microsomal cytochrome

Table 1
Pipermethystine and flavokavain B content in ethanolic extracts derived from roots of various kava cultivars.

Chemical compound	Ava La'au of Samoa	Palisi	Commercial extract	Unknown cultivar
Pipermethystine (mg/g dry weight)	Not detectable	Not detectable	Not detectable	Not assessed
Flavokavain B (mg/g dry weight)	0.35	3.52	1.09	32.3
Kavalactones (mg/g dry weight)	78.28	66.09	71.14	548.8
Flavokavain B (mg/120 mg kavalactones)	0.54	6.39	1.83	7.06

The data are derived from the following sources: Ava La'au, a noble cultivar of Samoa [28]; Two-Day cultivar Palisi, a non-noble cultivar of Vanuatu, and a commercial kava extract (spissum) without further classified kava cultivar(s) (Personal communication by Dr. Hermann Kurth, Finzelberg Corp., Andernach, Germany); unknown kava cultivar obtained from Pure World; Naturex, South Hackensack, NJ, USA [44]. The amounts of flavokavain B are expressed as mg per 120 mg kavalactones, the maximum amount for daily human use in Germany and Switzerland before the ban [25].

P450 between kavalactones, drugs, and alcohol; comedication; non-compliance of regulatory treatment standard; solvents and solubilizers used for kava extract preparation; existence of one or more toxic constituents within or outside the kavalactone group or of toxic metabolites; and quality of the kava raw material regarding cultivar and used plant part, misidentification, adulteration, and impurities.

At present, of special interest as possible culprits for kava hepatotoxicity are pipermethystine and flavokavain B as constituents of the kava plant and mould hepatotoxins as suspected contaminants of the kava raw material.

5. Pipermethystine

Within the past few years, there was considerable interest in pipermethystine as a possible culprit of kava hepatotoxicity [14,34–42]. The piperidine alkaloid pipermethystine, one of the non-kavalactones present in the kava plant, induces in vitro liver cell death via GSH depletion and modulation of MAPK and NF-κB signalling pathways [37]. These and other in vitro studies have all been carried out with human hepatoma HepG2 cells [37,40] and human normal liver cells line L-02 [37]; pipermethystine has been added to the cell media, and this led to the appearance of cytotoxicity associated with apoptosis [37,40]. Already in 2003, pipermethystine was the first compound considered to be potentially toxic and responsible for the rare cases of liver injury observed in association with the use of kava in Western countries [34]. This led to the assumption that acetonic and ethanolic extracts of kava may contain pipermethystine as a toxic alkaloid, not bioavailable in water extracts [23]. Theoretically, pipermethystine could primarily be present in the kava rhizomes and roots and be liberated from these plant parts by acetone and ethanol but not by water; alternatively, acetonic and ethanolic extracts of kava rhizomes and roots could have been adulterated by other plant parts containing pipermethystine.

Pipermethystine was found in aerial parts of kava plants [34] including leaves [34,36,39] and peelings of the lower stem [34,37], with negligible amounts detected in peeled stems [34]. In another study of stem peelings, however, pipermethystine was absent from all samples above the limit of quantification of 0.0045% [39]. Uncertainty also exists regarding 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 [38]. Undoubtedly, adventitious roots are aerial parts of the kava plants, not recommended thereby for human use as kava drugs, kava dietary supplements, or traditional kava drinks.

Regarding pipermethystine, however, there are no data available for adventitious roots.

The question was as to whether the primary raw material of kava rhizomes and roots may contain pipermethystine [23,35,36,39]. Early experiments suggested that in roots of a not further described kava cultivar small amounts of pipermethystine may be present, but because of its instability on standing and to most separation techniques, it had not previously been reported [35]. Reviewing in detail the natural products soluble in organic solvents such as 95% ethanol–water in roots of an undeclared kava cultivar, pipermethystine is a water-insoluble non-kavalactone substance, but quantitative results were not available [23]. The conclusion was reached that kava rhizomes and roots may contain the water insoluble pipermethystine extractable with organic solvents such as 95% ethanol. This was confirmed in further studies showing that pipemethystine can be extracted with 100% acetone or 100% methanol as solvents in trace amounts from kava roots derived from a greenhouse kava cultivar of an apparent chemotype with high amounts of methysticin [36], signifying a non-noble, non-drink kava cultivar [12,13]. With both solvent media, the amount of extracted pipermethystine was with 0.011% in the root extract approximately 100 times higher than in the leaf extract, reaching 1.34% (w:w) [36]. These high percentages of 95–100% of ethanol and acetone used for the extraction procedures in these experimental studies [23,36] are hardly comparable to those of 30% and 70% used for the preparation of kava medicinal extracts with ethanol and acetone, respectively [23]. Of note, in self-produced, non-commercial extracts derived from roots of two identified kava cultivars using 96% ethanol and 75% or 100% acetone as extraction media, pipermethystine was absent from all samples above the limit of quantification of 0.0045% [39].

Theoretically, commercial products of kava rhizomes and roots may contain pipermethystine because of adulteration with aerial kava plant parts, as proposed by several groups [23,34,40]. This uncertainty was based on reported details related to the manufacturing process of Western kava products; in particular, the use of aerial plant parts for commercial kava extracts was not uncommon and a matter of debate [8,12,23,34,37,38]. This kind of adulteration applied especially to stem peelings replacing the usual peeled rhizomes in the kava extract, an approach favoured by the low prices of kava stem peelings sold at almost one-tenth of the price of kava roots and rhizomes [23]. To study whether adulteration of Western kava extracts by stem peelings is a major issue, ethanolic and acetonic kava extracts have been assessed for pipermethystine (Table 1) [6,28,39]. It was not detected in a commercially available, in Germany registered kava product [28] and in a series of retained samples of finished kava products from the German market [39]. However, uncertainty still remains that the qualities of commercial kava extracts may have varied from one batch to the other, and poor quality such adulteration might have been escaped. Shortcomings include also the lack of analytical quality assessment of kava extracts taken by individuals with suspected kava hepatotoxicity in Western countries [8,11,14]. At least in Fiji, Tonga, and Hawaii, routine analyses of commercial kava root extracts have early been performed and showed no detectable pipermethystine in all samples using HPLC and GC [34].

As it presently stands, pipermethystine may cause cytotoxicity and apoptosis under in vitro conditions using liver cell assays [37,40], but other experimental studies show an absence of toxicity in therapeutic doses or even a hepatoprotective effect [41]. In particular, in vivo application of pipermethystine in high doses of 10 mg/kg/day to rats failed to result in any experimental liver injury

[42]. Considering these in vivo results in experimental animals combined with the obvious lack of pipermethystine as a constituent in commercial kava extracts, overall evidence for pipermethystine as culprit of human kava hepatotoxicity has not convincingly been presented.

6. Flavokavain B

The chalcone flavokavain B is a well established constituent of the kava plant [14,23–25,28,43,44] and belongs to the group of flavonoids with primarily hepatoprotective properties due to its radical scavenging actions [28,45]. As a non-kavalactone ingredient present in kava extracts, however, flavokavain B has been considered as a possible culprit for human kava hepatotoxicity [43,44]. In vitro studies have shown that flavokavain B as a constituent of methanolic extracts derived from roots of the Two-Day kava cultivar Isa is cytotoxic to human hepatoma HepG2 cells, and it was explicitly mentioned that its in vivo hepatotoxicity effects are yet to be elucidated [43]. Additional in vitro experiments revealed cytotoxicity not only in human HepG2 hepatoma cells but also in immortalized nontumor origin human liver cells, line L-02, following treatment with flavokavain B. This has been isolated and purified from ethanolic extracts of kava roots of a not further described kava cultivar that contained high amounts of flavokavain B [44] as for instance the Two-Day cultivar Isa [25]. When morphology of these L-02 cells exposed to flavokavain B was assessed, the cells showed loss of microvilli, cell rounding, and blebbing, suggesting that they were undergoing apoptosis. These cellular changes have been ascribed to GSH-sensitive oxidative stress through modulation of IKK/NF-κB and MAPK signalling pathways. It is obvious from these in vitro studies that kava cultivars have been used for assessment which are rich in flavokavain B and derived from problematic non-drink cultivars [43,44] such as Palisi [43] which does not belong to the favoured group of noble cultivars [13].

The amounts of flavokavain B found in kava extracts vary considerably, depending on the extraction medium and the cultivar used for analytic assessment (Table 1) [24,25,28,43,44]. In dried roots of a not further specified kava cultivar imported from Ronnie's Nakamal (Port Vila, Vanuatu), analysis by gas-chromatography–mass spectrometry (GC–MS) showed for flavokavain B peak areas (%) of 0.1 and 0.5 for aqueous and acetonic extracts, respectively; but in ethanolic extracts of this single study, flavokavain B has surprisingly not been detected [24].

In other studies, flavokavain B was present in ethanolic extracts of kava roots [23,24,28,43,44] with a ten-fold higher amount when the Two-Day cultivar Palisi was used compared to the Ava La'au variety of Samoa, a noble kava cultivar [25,28]. On a quantitative basis, ethanolic extracts derived from the roots of various kava cultivars including noble cultivars and Two-Day cultivars contained 0.35–32.3 mg flavokavain B/g dry weight, with corresponding figures of 66.1–548.8 mg kavalactones/g dry weight [25,28]. Based on these results, in ethanolic extracts 0.54–7.06 mg flavokavain B are found equating to 120 mg kavalactones [28], the maximum kavalactone dose recommended for daily human use [8,11,14,22]. Therefore, a previous German ethanolic kava extract with the maximum daily recommended amount of 120 mg kavalactones contained also 0.54–1.83 mg flavokavain B compared to 6.39–7.06 mg present in extracts derived from non-drink kava cultivars including Two-Day varieties [25]. The worst case scenario with 7.06 mg flavokavain B taken up in association with 120 mg kavalactones per day by a 70 kg individual would result in a daily uptake of 0.1 mg flavokavain B/kg body weight (Table 1). In experimental animals, however, modest signs of hepatotoxicity are observed with in vivo application of flavokavain B only at a daily dose of 25 mg per kg body weight [44], a value 250 times higher than the usual daily uptake of patients. Certainly, when amounts of flavokavain B are calculated and converted from animals to humans, additional evaluations might be useful discussing the normalization of body surface area (BSA) method [47]. It is also unclear whether the in vitro results obtained for flavokavain B with human hepatoma and normal liver cells [43,44] are principally transferable to patients with kava hepatotoxicity; keeping in mind that other studies with flavokavain B seem to show an absence of toxicity in therapeutic doses or even a hepatoprotective effect [6,28,41,46]. At present, however, these preliminary studies do not necessarily substantiate flavokavain B as the primary culprit for human kava hepatotoxicity, requiring additional assessments.

7. Mould hepatotoxins

Early concerns focused on the possibility that kava raw material could have partially been contaminated by oil, fertilizers, pesticides, nematodes, bacteria, fungi, and specific plant diseases such as kava dieback [38]. However, in the past virtually none of these possible causes has explicitly been evaluated in detail [14,23]. Recent considerations centre now on the question as to whether kava hepatotoxicity might have been caused by the use of mould kava raw material [25].

The major constraints occurring in the Pacific islands, where the weather is warm and humid, are the postharvest storage conditions of the kava plant parts [38]. In Vanuatu and Pohnpei (Micronesia) where kava is always consumed fresh, the raw material has a shelf life of three to four weeks maximum [25]. However, the storage conditions are partially so poor that moulds may develop rapidly on the roots one week after harvest. In Pacific countries like Fiji, Tonga, and Samoa where the beverage is prepared from dried raw material, the parts can be stored for a longer period, but moulds are also a problem. Finally, when the dried kava was exported in bags and containers to Europe, moulds 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. As an example, a mouldy taste of the beverage served in local kava bars of Nouméa (New Caledonia) has been recognized as a problem (Lebot, personal field observation).

There are few data about kava contamination by bacteria [48] and *Aspergillus* species producing mycotoxins like ochratoxin A [49] and aflatoxins [50]. In three aqueous extracts prepared from the internal part of the kava rhizome to minimize 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 [48]. At present, however, bacteriological studies using peeled rhrizomes and roots as well as their peelings derived from mould kava plants are lacking and urgently needed; possibly providing evidence for additional bacteria species in sufficient quantities to elicit hepatotoxicity [25].

Of more concerns are mycotoxins as contaminants [49,50]. Kava roots obtained from a botanical supplier were found to contain ochratoxin A at a level of 10.3 ng/g, and corrected for about 50% recovery the actual concentration was 20 ng/g [49]. In other studies kava was naturally contaminated with aflatoxins of at least 0.5 ng/g [50], compounds potentially toxic to the human liver [51–53]. Other fungi candidates have to be considered with similar hepatotoxicity potency, and overall assessment has to include parts of mould kava plants with preference of rhizomes and roots as peeled organs and their separate peelings. It is conceivable that the bark of kava rhizomes and roots contain higher amounts not only of bacteria but also of fungi, an important aspect since quantity is a major parameter for hepatotoxicity; another issue to be clarified is whether

peeled rhizomes and roots should be preferred for kava extracts rather the unpeeled parts. Considering these views, in initial studies with mould kava raw material the degree of aflatoxin contamination should be assessed [25]. This approach represents the first step to clarify whether kava hepatotoxicity may be due to aflatoxicosis, in analogy to epidemic toxic hepatitis caused by food contaminated with aflatoxins reported from India and Kenya [51–53]. If causally related to aflatoxins or other mould hepatotoxins, kava hepatotoxicity may be regarded as a preventable disease both in the Pacific region and in Western countries with respect to traditional aqueous kava extracts and solvent based ones.

8. Kava plant as raw material

The kava plants exist in form of multiple varieties called cultivars [53–58] which have been used in the past to prepare kava extracts [12,13,23,38]. To ensure uniformity of the kava raw material as basis for kava extracts, proposals have been made for clinical trials [31,32,59,60] and consumption as herbal dietary supplements [25,29–32]. These include the recommendation to prepare water based extracts from peeled roots and rhizomes of a noble kava cultivar such as Borogu with a long tradition of safe use for some thousand years in the South Pacific region [29–32]. Kava is an effective treatment modality of anxiety disorders [31,41,61], and safety must be ensured by prevention of mould hepatotoxin contamination [29,30,32] and other specific measures of quality control [12,13,25,29,30,32].

9. Concluding remarks

Kava hepatotoxicity represents primarily a rare herbal idiosyncratic liver injury of the metabolic form, but an additional intrinsic type due to aflatoxins or other hepatotoxins contaminating kava plants after harvest remains to be established. Despite vigorous research efforts, there is little evidence that in vitro cytotoxic compounds such as pipermethystine or flavokavain B may have caused human kava hepatotoxicity. Further research is necessary to evaluate as to whether kava hepatotoxicity may be due to aflatoxicosis or other mould hepatotoxins.

Conflicts of interest statement

No conflicts of interest exist.

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