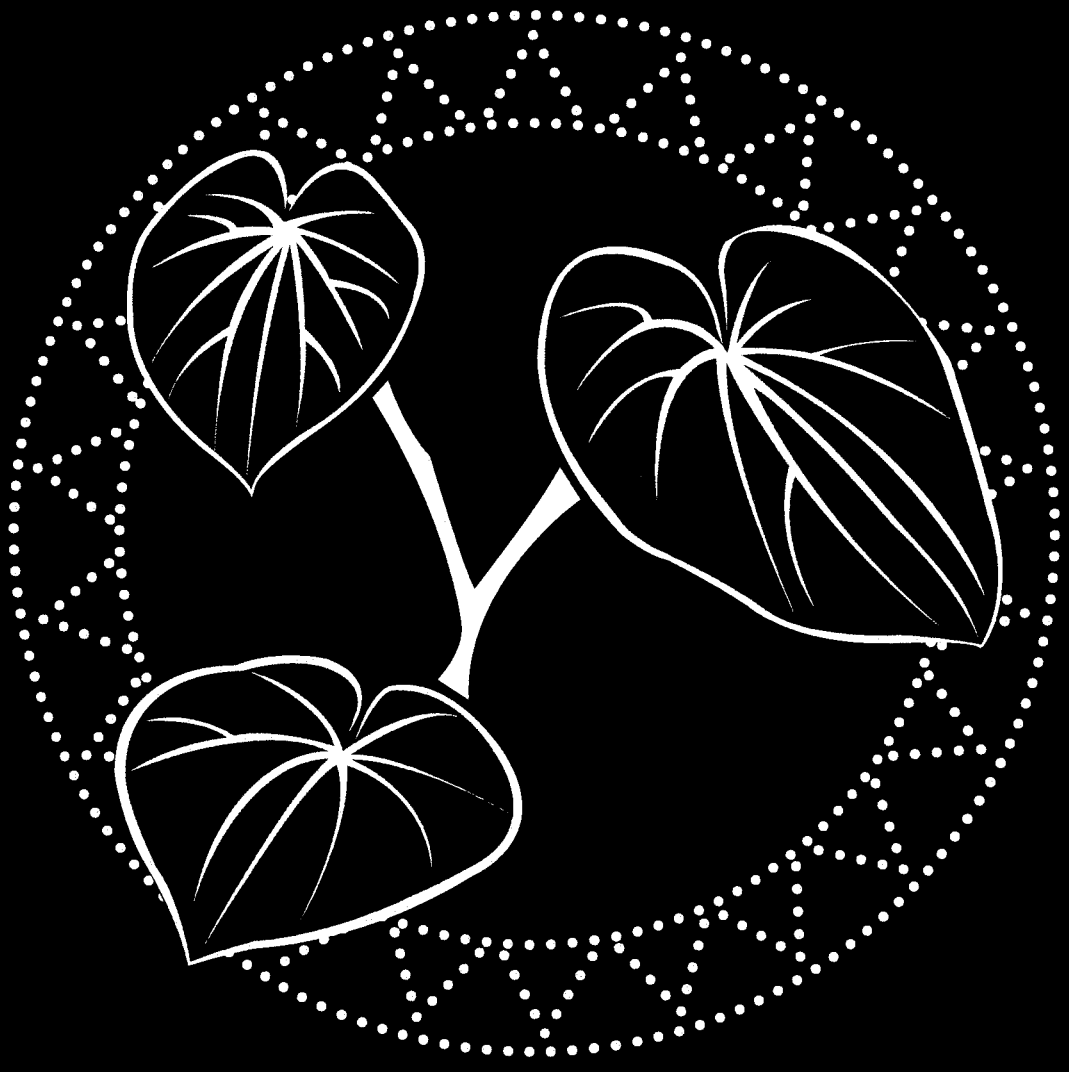
World Health Organization

Assessment of the risk of hepatotoxicity with kava products



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Executive Summary

Opinion on key question

1. Evidence from our review of case reports suggests that kava lactones in any type of product may rarely cause hepatic adverse reactions because of kava-drug interactions, excessive alcohol intake, metabolic or immune mediated idiosyncrasy, excessive dose or pre-existing liver disease.
2. In addition to this background incidence, products made from acetonic and ethanolic extracts appear to be hepatotoxic on rare occasions, seemingly from non-kava lactone constituents. The incidence is unknown, but is more significant than the background effect in '1'.

General overview

There has been international concern over the association of kava products and serious hepatotoxicity. Regulatory action banning these products in Europe has been controversial. The objective of this report is to investigate the possibility of hepatotoxicity with kava.

This report is written in four major sections:

I Description of kava
IIA Safety information –literature review
IIB Safety information –analysis of case reports
III Regulatory issues
IV Conclusions and recommendations

The first 3 sections are written as stand-alone documents with their own references. In addition there is:

- A summary of findings
- A summary of recommendations
- A bibliography.

I Description of kava

- The known pharmacologically active components are a group of kava lactones.
- The types of preparation are water 'extracts' (the traditionally prepared microsuspensions in water and 'teas' prepared from powdered kava root), organic extracts (ethanolic and acetonic) and synthetic. These different products are not chemically equivalent. Products prepared from the organic extracts have been those principally used in Europe and North America in pill or capsule form.
- The raw materials for the preparation of these products come from a variety of sources without adequate quality control and without sufficient standardization of selection of plant varieties or cultivars or plant parts.

IIA Safety information –literature review

- Clinical trials of kava have not revealed any hepatotoxicity.
- Most experimental studies have not shown that kava has a tendency to have a toxic effect on the liver.
- Most clinical reviews of case reports cast doubt on a causal association between kava products and liver problems. The cases have come to regulatory authorities as spontaneous reports. There have been no epidemiological studies and the incidence is not known.

IIB Safety information –review of case reports

1. Findings from case reports
   - This was undertaken using standard pharmacovigilance and pharmacoepidemiological methods.
   - 93 case reports were identified with the possibility of a small number of duplications.
   - There were seven patients who died and 14 patients had liver transplants.
   - As is usual in pharmacovigilance, most of the reports were incomplete to one degree or another.
   - Eight of the cases were coded as having a 'probable' association, meaning that essential information was present for a standard assessment, that a close association between the use of kava and the liver problem was established, that the patients recovered on withdrawal of kava and that no other plausible cause for the liver problems could be identified.
   - 53 cases were classified as having a 'possible' relationship meaning that a causal association was plausible, but that there were insufficient data for a full assessment, or there were other potential causes of liver damage.
   - Most of the other case reports were unassessable because of lack of information.
   - There were five cases with a positive rechallenge.
   - With the use of sales volume figures converted to a defined daily dose, rates of hepatic events were estimated for acetonic and ethanolic extracts and synthetic products. Patients taking acetonic and ethanolic extracts had a higher rate of liver problems than patients taking synthetic products. These differences were independent of age, gender, dose, duration of treatment, concomitant therapy and/or alcohol use and are unlikely to be confounded by other disease states.
2. Conclusions from review of case reports
   - The relationship (causality) ratings provide a significant concern of a cause and effect relationship between kava products and hepatotoxicity. A non-random effect is indicated by a higher rate for the organic extracts than for synthetic products.
   - Chemicals other than kava lactones might be responsible for hepatotoxicity with the organic extracts.
   - Kava products have a strong propensity for kava-drug interactions.
   - Risk factors for hepatic reactions appear to be the use of organic extracts, heavy alcohol intake, pre-existing liver disease, genetic polymorphisms of cytochrome P450 enzymes and excessive dose. Also, co-medication with other potentially hepatotoxic drugs and potentially interacting drugs, particularly other anxiolytics, antipsychotics and anti-thrombotics, might lead to harm.

Recommendations

1. Further research into kava products is necessary, in particular to identify and gain information about the toxicology of the non-kava lactone constituents. This needs to include any differences between root and rhizome.
2. Should any kava product be considered for approval by regulatory authorities, the following should be important considerations:
   2.1. Post-marketing surveillance and research.
   2.1.1. A risk management plan should be drawn up early in the approval process. This plan would include suggestions for pharmacoepidemiological studies, in particular cohort event monitoring, preferably with international collaboration. These studies should be undertaken on all products, including synthetic and water based. Reliance should not be placed on spontaneous reporting alone for post-marketing surveillance.
   2.1.2. Pharmacogenetic studies should be undertaken to determine differences in cytochrome P450 metabolic enzyme activity and any relationship to hepatotoxicity. This could be undertaken using case control studies, ideally nested case control studies of cohorts of users of kava from cohort event monitoring studies.
   2.1.3. Products from water based suspensions and further synthetic preparations should be developed and tested in clinical trials and consideration given to using these in preference to acetonic and ethanolic extracts.
   2.2. Conditions of use
   2.2.1. It would seem advisable that all kava products prepared as pharmaceuticals be available on prescription only in order to better monitor their use and apply necessary controls.
   2.2.2. Kava should not be used in patients with liver disease or a history of such, or in patients who take excessive alcohol.
   2.2.3. Warnings should be made available about the extensive risk of interactions with other drugs or herbal preparations. In particular, kava should not be used with antipsychotics, other anxiolytics or antithrombotics because of the risk of interactions which could include effects on the liver.
   2.3. Standards
   2.3.1. A pharmacopoeial standard for kava should be created. This should address the issues of quality, plant parts, dosage and methods of preparation. The findings of this review indicate that:
   2.3.2. Only the root or rhizome of *Piper methysticum* G Forst should be used for preparation of medicinal kava. No other species and no aerial parts should be used. Agreement should be reached on the appropriate cultivar(s).
   2.3.3. Adequate quality control measures standardized across the producing countries with agreed standard operating procedures, should be instituted for growth, harvesting and processing of the raw kava root or rhizome.

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Preamble

Terms of reference from WHO

SAFETY OF KAVA: Terms of Reference for Inquiry Committee

In October 2004, the WHO Advisory Committee on Safety of Medicinal Products (ACSoMP) considered the safety issues underlying the contemporary use of kava. The Committee was particularly concerned about the case reports of hepatotoxicity associated with the ingestion of kava.

The Committee resolved to commission an inquiry of three experts to assess all available published and unpublished evidence related to this safety issue. The three members were selected by the WHO secretariat and the Chair of the ACSoMP. The Chair of the inquiry was a member of ACSoMP.

The principal focus of the inquiry was on the safety of kava and addresses issues related to the following areas:

Kava species:

1. How many species of kava exist?
2. Which of these species are used commercially?
3. Examine the pharmacological properties of kava pyrones, kava lactones and any other substances in kava.

Preparations:

1. How was kava prepared traditionally?
2. How are current preparations prepared with a focus on aqueous, ethanol, and acetone extractions?
3. How are these preparations standardized?
4. Analysis of evidence supporting efficacy for each method of preparation/formulation.

Regulation:

1. How were kava products registered /regulated in countries (ie, what category did they come under: as medical products / nutraceuticals / dietary supplements etc)?
2. What was the basis for registering these products?

Hepatotoxicity with kava

1. Analysis of adverse reaction reports from the WHO global database, regulatory databases and any databases maintained by manufacturers that are related to hepatotoxicity of kava.
2. Synopsis of all other kava- related ADRs from the above mentioned databases.
3. Analysis of evidence from all safety studies, published and unpublished, related to the hepatotoxicity of kava.

Product Withdrawal, Ban, Restrictions

1. Identify those countries that have taken regulatory action and describe the basis for their action.
2. Identify those countries where no action has been taken.

Outcome

The resulting report was critically reviewed by all the members of the ACSoMP. The conclusions and recommendations are supported by the majority of the members. The UK member of the Committee supported some but not all the recommendations.

Introduction

The Committee appointed to handle this enquiry has done its best to gather evidence and opinion from as many sources as possible and examine them in an impartial manner, but admits that in spite of best efforts there will be unintentional gaps in some relevant issues, due in part to the extensive expertise required involving so many different fields of scientific endeavour, including hepatology, pharmacology, pharmacogenetics, pharmaceutical science, toxicology, safety of modern pharmaceutical medicines and of herbal medicinal products, botanical science, pharmacoepidemiology, clinical trials and experimental studies.

The report is written in four major sections:

I Description of kava
IIASafety information –literature review
IIB Safety information –analysis of case reports
III Regulatory issues
IV Conclusions and recommendations

The first three sections are written as stand-alone documents with their own references. In addition there is:

- A summary of findings
- A summary of recommendations
- A compilation of resources.

While there is some overlap and minor duplication between some sections, this has been retained for the sake of completeness of each individual section. Where overlap occurs, it has been written in a different context by a different author.

Background

From the 1990s cases of severe hepatic toxicity in people using kava-containing products were reported in Europe and in the United States of America. By the end of 2002 the German Federal Institute for Drugs and Medical Devices (BfArM) had collected 40 case reports, six of which involved liver transplants and there were three fatalities. This led to various worldwide regulatory measures, including a ban on kava-containing products in Europe. These restrictions became controversial with claims that the evidence for hepatotoxicity was weak and that the bans put in place unnecessarily harmed the economies of the Pacific Island kava-producing nations and denied patients an effective treatment for anxiety which, it was also claimed, was safer than other current pharmaceutical treatments. The issue was reviewed in WHO Pharmaceuticals Newsletter, No. 5, 2003: p. 8-9.

The current review of the alleged hepatotoxic effects of medicinal kava products undertaken by this expert committee was requested by the Quality Assurance and Safety of Medicines, Medicines Policy and Standards, World Health Organization on the advice of its Advisory Committee on Safety of Medicinal Products. This followed a Pacific European Kava Stakeholders meeting organized by the Centre for Development Enterprise (CDE), an EU-ACP (African, Caribbean, and Pacific states) organization, PRO INVEST Management and Phytopharm Consulting and was attended by representatives of international organizations such as the Pacific Islands Forum Secretariat (PIFS), World Health Organization (WHO), European Commission (EC), Technical Centre for Agricultural and Rural Cooperation ACP-EU (CTA) and the Commonwealth Secretariat (COMSEC). It included ambassadors of Pacific countries (Fiji, Samoa, Vanuatu), companies, institutions and others with an interest in kava as a traditional medicinal product. Phytopharm Consulting presented a summary of their in-depth investigation into EU Member States' market restrictions on kava products and the impact of such a restriction on the South Pacific Island countries such as Fiji, Samoa and Vanuatu. At this meeting WHO was asked if it could help in the re-analysis of the adverse reaction reports.

The issue is complex with a variety of extracts and products used of varying potency, many in combination with other herbal medicines. Many other factors come into play including pre-existing liver disease, alcohol use, use in combination with hepatotoxic drugs, potential kava-drug and kava-herb interactions. In addition, the lack of knowledge of any hepatotoxicity associated with thousands of years of traditionally prepared and traditionally used kava water 'extracts' and the use of kava preparations in different ethnic groups with different genetic characteristics, adds to the difficulty in assessment. There is also a lack of good epidemiological data.

Methodology of the report

This report followed a search strategy common to systematic reviews. The focus of the report is kava safety and particularly hepatotoxicity in humans based on analysis of individual case reports, observational studies and clinical trials whatever the type of kava preparation, dosing and indication.

Members of the Committee conducted analyses of relevant literature independently. However, the ability to interpret non-English language publications was limited. Individuals whose backgrounds are in general aspects of evaluating science, not necessarily focused specifically on kava, conducted the development and review of this report. However, consultants with relevant expertise provided significant additional assistance. The foreign language literature was included when it was deemed important in order to be comprehensive.

While this report aimed to be comprehensive some pertinent information that could be of importance in evaluating kava risk of illness or injury may have not been included particularly if available in languages other than English or German.

This report does not represent an authoritative statement regarding the safety of all kava preparations available.

Information included in other available comprehensive 'official' reports: The complete German Commission Monographs, HerbMed Database, Natural Standard Database, German Federal Office for Medicines and Medicinal Products (1990), Report of National Centres' Meeting WHO Drug Monitoring Programme (Stoller 2001), US Centers for Disease Control and Prevention, (USA 2002, 2003), Marketed Health Products Directorate/Health Canada report (Canada 2002), German Federal Institute for Drugs and Medical Devices (2002), Kava Report by Phytopharm Consulting (2003), Society for Medicinal Plant Research (2003), International Kava Executive Council Report (2004), US Food and Drug Administration (2005), 'Edward's Report' (2005), Traditional Medicines Evaluation Committee (European Herbal Practitioners Association 2005) and Therapeutic Goods Administration Fact Sheet (Australia 2005), has not been presented in detail.

The report follows the format described in the report, *Dietary Supplements: A Framework for Evaluating Safety (IOM/NRC, 2004)* and WHO Terms of Reference (p. viii).

Identification of available published documents

The search strategy included electronic searches, personal communications, bibliographies from secondary references, WHO databases and hand searches. The searches were updated to March 2005. No restrictions regarding language or quality of publications were imposed but only English articles were evaluated. When necessary translation of relevant German articles was requested.

Electronic searches were conducted using the following databases: MEDLINE (1966-2005), ToxLine5 (ToxLine Core and ToxLine Special) EMBASE (1980–2005), AGRICOLA (1979–2005), NAPRALERT, The Cochrane Library and EBM (Evidence Based Medicine) AMED (British Library), HerbMed, Natural Standard Database, IBIDS, International Pharmaceutical Abstracts and Conference Proceedings.

MEDLINE is a bibliographic database offered by the National Center for Biotechonology Information (National Library of Medicine and the National Institutes of Health) **PubMed or MedLine** provides access to over 12 million journal citations in the biomedical and life science literature. The citations range from 1966 to the present. In 2005, PubMed contains 15,000,000 biomedical journal citations. More information is available at http://www.ncbi.nlm.nih.gov/

ToxLine is a bibliographic database offered by the National Library of Medicine. ToxLine contains more than 3 million bibliographic citations covering the biochemical, pharmacological, physiological, and toxicological effects of drugs and other chemicals. It makes extensive use of CAS Registry Numbers. ToxLine Core includes the biomedical journal literature in toxicology available through MedLine. ToxLine Special complements the Core with citations from an assortment of specialized journals and other sources.

EMBASE is a bibliographic database offered by Elsevier Science. **EMBASE**, the Excerpta Medica database, is a bibliographic database covering the worldwide literature on biomedical and pharmaceutical fields, produced by Elsevier B.V. EMBASE citations range from 1974 to the present and include citations from more than 4,600 journals from about 70 countries and more than 10,461,188 records. More information is available at http://www.embase.com/

AGRICOLA is a bibliographic database offered by the National Agricultural Library. AGRICOLA provides access to over 12 million journal citations in the agriculture literature. The citations cover many aspects of agriculture and allied disciplines, including animal and veterinary sciences, entomology, plant sciences, aquaculture and fisheries, food and human nutrition, and many other topics. The database began in 1970 but contains older citations. AGRICOLA contains citations from 850 agricultural journals. More information is available at http://agricola.nal.usda.gov/

NAPRALERT (NAtural PRoducts ALERT) contains bibliographic and factual data on natural products, including information on the pharmacology, biological activity, taxonomic distribution, chemistry of plant, microbial, and animal (including marine) extracts as well as ethnomedicine use record, is a bibliographic and relational database offered by the University of Illinois at Chicago. NAPRALERT contains records from 1650 to the present. Approximately 50% of the file is from systematic survey of the literature from 1975 to the present. NAPRALERT contains more than 165,000 journal citations published in over 16,000 journals from around the world. More information is available at http://www.cas.org/ONLINE/DBSS/napralertss.html

The Cochrane Library consists of a regularly updated collection of evidence-based medicine databases, including The Cochrane Database of Systematic Reviews, The Database

of Abstracts of Reviews of Effects, The Cochrane Controlled Trials Register, The Cochrane Methodology Register, The NHS Economic Evaluation Database Health Technology Assessment Database and Cochrane Database of Methodology Reviews (CDMR). It is published four times a year. More information is available at: http://www.cochrane.org/reviews/clibintro.htm

EBM (Evidence Based Medicine) is a collection of databases with publications from 1993-present) with an emphasis on those about finding and evaluating clinically relevant patient management literature. More information is available at: http://www.medlib.iupui.edu/ebm/home.html#dbs

AMED (Allied and Complementary Medicine Database) is a bibliographic database produced by the Health Care Information Service of the British Library. It covers a selection of journals in three separate subject areas: several professions allied to medicine, complementary medicine and palliative care. All records have basic bibliographic information and many articles published from 1995 onwards have abstracts. AMED covers relevant references to articles from around 596 journals. The scope of coverage is mainly European with the majority of titles in English. More information is available at: http://www.bl.uk/collections/health/amed.html

HerbMed is an interactive, electronic herbal database and provides hyperlinked access to the scientific data underlying the use of herbs for health. It is an impartial, evidence-based information resource provided by the non-profit Alternative Medicine Foundation, Inc. More information is available at: http://www.herbmed.org/

Natural Standard Database is produced by Natural Standard, an international research collaboration that aggregates and synthesizes data on complementary and alternative therapies. The information is created by consensus using a comprehensive methodology and reproducible grading scales. More information is available at: http://www.naturalstandard.com/

IBIDS (The International Bibliographic Information on Dietary Supplements database) provides access to bibliographic citations and abstracts from published, international, and scientific literature on dietary supplements. More information is available at: http://dietary-supplements.info.nih.gov/Health_Information/IBIDS.aspx

Researchers in the field of complementary and alternative medicine (CAM), members of the International Kava Council, experts in the subject, and journal editors were consulted for access to additional references or ongoing research. A separate electronic search on MEDLINE and EMBASE was conducted for publications describing randomized, double-blind, placebo-controlled trials of kava extract for anxiety, and also in U.S. Patent and Trademark Office. http://www.uspto.gov/. and Special Nutritional Adverse Event Monitoring System (SN/AEMS).

Search terms

The search terms that were used were kava, kawa, kavain and *Piper methysticum*.

Selection criteria

Literature was collected if the document provided specific information about adverse events of kava, particularly hepatotoxicity. Standardized inclusion/exclusion criteria were utilized for selection.

Identification of case reports

Main sources

1. WHO Collaborating Centre for International Drug Monitoring (*the* Uppsala Monitoring Centre) database.
2. Gruenwald J, Mueller C, Skrabal J. Kava Report 2003: In-depth investigation into EU member states market restrictions on kava products. Phytopharm Consulting for Centre for the Development of Entreprise (CDE). 2003.
3. Medical literature.
4. FDA = U.S. Food and Drug Administration.
5. The national Brazilian Drug Monitoring Centre.
6. Medicines Control Agency, UK (now Medicines and Healthcare products Regulatory Agency).
7. German Federal Institute for Drugs and Medical Devices (BfArM). (This information was sourced from the Phytopharm document in English.)
8. Swiss Agency for therapeutic products (Swissmedic). (This information was sourced from the Phytopharm document.(2) in English)
9. Centers for Disease Control and Prevention, USA.
10. Commissioned reports.

Section I Description of kava preparations

General

Kava is the name used in the South Pacific Island countries to describe a local traditional drink which has been popular as a relaxing drink obtained from the root or rhizome of the plant botanically described as *Piper methysticum* G Forst of the plant family Piperaceae. This drink has been used for centuries without any reported ill-effects on the liver. The kava drink is made from the water extracts of the root or rhizome of *Piper methysticum* and over the years the plant too has been referred to as kava, especially in the western world. Why did kava become so important to the western world? This was because the European travellers of yester years who came to the South Pacific, found out that the Pacific Islanders were relaxing after a couple of bowls of the kava drink. Subsequently scientific research found out that the water extracts of kava had some pharmacologically active compounds which are now referred to as kava lactones. Kava lactones are also referred to as kava pyrones.

Kava lactones were analysed scientifically and were found to have interesting pharmacological activities such as central nervous system relaxing activity, anti-anxiety activity, and sedative activity. Because of these interesting biological activities of the kava lactones, European pharmaceutical industries extracted the biologically active ingredients and manufactured pills and capsules which subsequently became described as kava products using concentrated kava lactones extracted from the kava plant.

Composition and identified active substances of the kava root

The root stock of kava contains mainly carbohydrates (43%), fibre (20%), water (12%), protein (3.6%), simple sugars (3.2 %), trace minerals (3.2 %) and kava lactones (anything from about 4–22%, depending on the origin of the kava plant) (Lebot & Levesque 1989). Kava extracts became a commercial success due to these kava lactones. There are more than fifteen kava lactones but the most important biologically active components are kawain, yangonin, methysticin, dihydromethysticin, demethoxyyangonin, and dihydrokawain. The root also contains small amounts of pigments called flavokavins.

Many of the organic compounds mentioned above are not water soluble. In fact, about thirty organic compounds present in the root of kava (see Tables 1 & 2) do not dissolve in water but are freely soluble in 95% ethanol or acetone. These organic solvents were used by European pharmaceutical industries for extracting compounds from kava in their manufacture of the kava pills and capsules.

Table 1 gives a list of the water soluble and water insoluble compounds present in the kava root. Table 2 gives the names of the natural products present in the organic solvent extracts which are used to make kava pills/capsules.

A complete list of organic compounds isolated from kava are found in review papers on the subject (Lebot & Levesque 1989; Singh 2004).

Table 1 Natural products in typical kava root stock (100 g) (Lebot & Levesque 1989; Singh 2004).

Water Soluble Substances	
Glucose polymer similar to starch	43 g
Proteins (and peptides such as glutathione)	3.6 g
Simple sugars	3.2 g
Water Insoluble Substances	
Fibre	20 g
Trace minerals	3.2 g
Kava lactones, pigments and alkaloids	15 g

The stem peelings of kava also contain the biologically active kava lactones and became cheap raw materials for the production of kava pills and capsules by pharmaceutical industries in Europe in the late 1990s. Subsequent research showed the presence of alkaloids in the root and stem peelings. An alkaloid named as pipermethystine was one of the components of kava (see Table 2).

Table 2 Natural products soluble in organic solvents such as 95% ethanol—water

Kava lactones

(A typical 100 g of root stock would contain about 10-15 g of kava lactones; the percentage yield of kava lactones from roots can vary anything from about 4-22% depending on the origin of the root stock). The individual percentages of the kava lactones may also vary from sample to sample depending on the origin of the plant material. The names of the different kava lactones isolated and identified are given below (Singh 1999)

Kava lactones
11-Hydroxy-12-methoxydihydrokavain
7, 8-Dihydro-5-hydroxykavain
11, 12-Dimethoxydihydrokavain
Methysticin
Dihydromethysticin
Kavain7, 8-Dihydrokavain
5, 6-Dehydromethysticin
5, 6-Dehydrokavain
Yangonin
5, 6, 7, 8-Tetrahydroyangonin
5, 6-Dihydroyangonin
7, 8-Dihydroyangonin
10-Methoxyyangonin
11- Methoxyyangonin
11-Hydroxyyangonin
5-Hydrokavain
11-Methoxy-12-hydroxydehydrokavain
Others
Flavokavin A
Flavokavin B
Flavokavin C
Dihydrokavain-5-ol
Cuproic acid
Cinnamalketone
Methylenedioxy-3, 4-cinnamalketone
4-Oxononanoic acid
Benzoic acid
Phenyl acetic acid
Dihydrocinnamic acid
Cinnamic acid
Pipermethystine
1-(*meta*-methoxy cinnamoyl)pyrrolidine
1-Cinnamoylpyrrolidine

Pharmacological properties of kava extracts and kava natural products

The psychoactive potency of kava can vary considerably from weak to quite strong. Kava may induce sociability, feeling of peace, and harmony and, in large doses, induce sleep, or it may fail to produce relaxation but provoke nausea (Singh 1999). Kava drink initially produces a slight numbing of the tongue due to the presence of anaesthetic kava lactones in the extracts. After some more drinks, it relieves fatigue, reduces anxiety and produces a pleasant, cheerful and sociable attitude in the drinker (Singh & Blumenthal 1997). It is also claimed that a small amount of the kava drink relaxes the body, clears the mind and sharpens the mental faculties (Lebot 1997). Kava resin (the organic solvent extract of kava) has been demonstrated to have a weak sleep inducing action, paralyses the sensory nerves and initially stimulates and then paralyses the smooth muscles (Lebot 1997).

The water insoluble active substances become available to the drinker after emulsification, which may be by pounding or chewing. Kava extract was shown to have increased potency when activated by human saliva (Schubel 1924). This explains why kava drink prepared by pounding the root stock often has less physiological effect than that produced from finely chewed and emulsified root stock (Lebot 1998). Very heavy kava drinking may cause skin lesions and drying of the skin (Fackelmann 1992). The skin lesions disappear as soon as the drinker reduces the consumption of kava. It has been suggested that the kava pigments called flavokavin A and B may be the cause of the skin problems (Reichert 1997).

A variety of clinical effects of kava preparations has been claimed. Dihydromethysticin and dihydrokavain have been shown to be the active compounds which intensify the sleep-inducing effects (Hansel 1968). Dihydromethysticin and dihydrokavain have been found to be comparable to the drug dimethylaminophenazone in producing an analgesic effect in the drinker. In one study the analgesic effect was also shown to be stronger than aspirin but weaker than morphine (Hansel 1968). One of the kava lactones named as kavain produces local anaesthesia and its effect has been shown to be equal to that produced by cocaine. Kavain does not produce any toxicity in the tissues (Kretzchmar & Meyer 1969).

The local anaesthetic activity of the kava lactones was originally observed by Lewin (1886). Frater (1958) showed that a thin paste of kava powder when applied to the mucous membrane of the lip produced a slightly burning sensation and a feeling of numbness. With a pin prick test there was a slight impairment of feeling as compared with the rest of the lip. When some kava root was chewed for 15 minutes, however, the degree of anaesthesia was greater leading Frater to conclude that there was a definite local anaesthetic effect. Meyer and May (1964) tested for local analgesic effects and observed that all the kava lactones acted as local analgesics. Most of the kava lactones inhibited frog heart contraction (Meyer and May, 1964). These actions were compared with those of cocaine which showed a similar protection against ventricular fibrillation through its local anaesthetic effect.

Kava drinkers in the Pacific have experienced the anaesthetic activity of the drink on their tongues and the linings of the mouth for centuries. Considering this and the results of the published animal studies confirming the local anaesthetic activity of kava lactones, it could be concluded that kava does have anaesthetic activity. This has been further confirmed by the preparation of a novel topical anaesthetic from *Piper methysticum* (kava)—'Kavacaine' (Morse and Sharma, 2005).

Studies on kavain have shown bactericidal properties, especially against gonococcus, the specific pathogenic agent of gonorrhea, and against colon bacillus and blenorrhea (Steinmetz 1960). Dihydromethysticin completely inhibits the growth of *Aspergillus niger* (Shulgin 1973). The amoebicidal activity of yangonin is comparable to that of commercial drugs such as enterovioform, enteroquinol, clefamide, and furamidazole (Hansel 1968; Sotheeswaran 1987).

Dihydrokavain and dihydromethysticin inhibit muscular contractions and the effect of these kava lactones was shown to be comparable to those of synthetic products such as phenobarbital (Kretzchmar & Meyer, 1969). Dihydromethysticin is claimed to have a strong anticonvulsant action with the capability of inhibiting convulsions caused by strychnine in animals. It has been suggested that the anti-epileptic action of dihydromethysticin may be used to treat schizophrenia (Kretzchmar et al. 1970). Dihydromethysticin and dihydrokavain are muscular relaxants superior to substances normally used such as benzodiazepines (Kretzchmar et al. 1970). It has also been claimed that kava extracts provide protection against ischaemic brain damage (Blackhauss & Kreiglstein 1992). Preliminary results suggest that kava may have anti-cancer activity (Fujiki et al. 1998; Sotheeswaran et al. 2002).

The most widely studied potential therapeutic effect is for the treatment of anxiety. Table 3 summarizes the clinical trials with an assessment of their quality according to the Natural Standard validated grading rationale (Table 4).

Toxicity/side effects

Studies on animals only showed a low acute toxicity. The LD_{50} of kava resin given by intra peritoneal injection to mice, rats and rabbits ranged from 300 to 400 mg/kg. With oral administration, the LD_{50} in mice was 920 mg/kg for dihydrokavain and 1050 mg/kg for dihydromethysticin. Doses of 50 mg/kg of dihydromethysticin, administered three times a week for three months to rats, produced no evidence of chronic toxicity (Meyer, 1966).

In Fiji, a pilot study was performed in 2004 to evaluate the possible association of kava use (water extracts) and liver disease. Interestingly, the average number of kava bowls consumed in a lifetime for participants was 100,000. Despite this large number, no association was made between kava and liver disease. These findings did not provide any evidence that heavy use of traditionally prepared kava was associated with liver disease. It was concluded that kava cannot be linked to liver disease when taken in the traditional format, i.e. as water extracts in Pacific Island subjects (Malani 2005).

A recent report (Nerurkar 2004) stated that kava alkaloids may have contributed to and/or perpetuated hepatotoxicity in human hepatoma cells.

Table 3 Evidence table of studies of the use of kava for treatment of anxiety

(From http://www.naturalstandard.com/monographs)

N= number of subjects; ARR=Absolute Risk Reduction; NNT=Number needed to treat; NA= not applicable.

Condition	Study Design	Author Year	N	Statistically Significant?	Quality of Study	Magnitude of Benefit	ARR	NNT	Comments
Anxiety	Systematic review & meta-analysis	Pittler, 2000, 2002, 2003	11 trials	Yes	NA	Large	NA	NA	Pooled results reflect a significant reduction in mean anxiety scores (HAM-A).
Anxiety	Randomized controlled trial (RCT), double-blind	Malsch, 2001	40	Yes	5	Large	NA	NA	Well-conducted trial using WS 1490, up to 300 mg/day while tapering benzodiazepines.
Anxiety	RCT	Lehmann, 1996	58	Yes	5	Large	NA	NA	Well-conducted trial using WS 1490, 90 mg three times daily; validated scales used.
Anxiety	RCT	Kinzler, 1991	58	Yes	5	Large	NA	NA	Well-conducted trial using WS 1490, 300 mg/day; validated scales used.
Anxiety	RCT	Warnecke, 1991	40	Yes	5	Large	NA	NA	Well-conducted trial using WS 1490, 300 mg/day; validated scales used.
Anxiety	RCT	Singh, 1997	60	Yes	4	Large	NA	NA	Efficacy demonstrated for non-clinical anxiety.
Anxiety	Equivalence trial	Woelk, 1993	172	No	4	NA	NA	NA	WS 1490 300 mg/day found equivalent to two benzodiazepines. No placebo. No power calculation: sample size may be inadequate.
Anxiety	RCT	Volz, 1997	108	Yes	3	Medium	NA	NA	WS 1490 300 mg/day; validated scales used; poor description of methodology.
Anxiety (pre-operative)	RCT	Bhate, 1989	60	Yes	3	Large	NA	NA	60 mg kava extract given prior to surgery. Unequal gender ratio in treatment arms. Unclear measurement scales.
Anxiety (post-menopausal)	RCT	De Leo, 2000 & 2001	40	Yes	3	Medium	NA	NA	Benefit for post-menopausal anxiety when kava 100 mg/day combined with HRT.
Anxiety (peri-menopausal)	Randomized, controlled, open study	Cagnacci, 2003	68	Yes	2	Medium	NA	NA	Calcium vs. calcium plus kava 100 mg vs. calcium plus kava 200 mg.
Anxiety	RCT	Lehmann, 1989	52	Yes	3	Medium	NA	NA	Cavain 400 mg/day in 2 divided doses; poorly described methodology.
Anxiety	Equivalence trial	Lindenberg, 1990	38	No	2	None	NA	NA	Comparison with oxazepam, no placebo. No power calculation: sample size may be inadequate.
Anxiety	Case studies	Scherer, 1998	42	NA	NA	NA	NA	NA	100 mg kava extract/day over ~50 days improved anxiety (observational study).
Generalized anxiety disorder	Randomized, controlled, double-blind, multi-center comparison trial	Boerner, 2003	129	NA	5	NA	NA	NA	No difference observed between kava, buspirone, and opipramol after 8 weeks, although sample size may not be adequate to discern true differences. No placebo arm.
Generalized anxiety disorder	Randomized, placebo controlled, double-blind trial	Connor, 2002	37	No	4	None	NA	NA	No differences in HAMA after 4 weeks, although sample size may not be adequate to discern true differences.
Generalized anxiety disorder	Randomized, placebo controlled, double-blind trial	Gastpar, 2002	141	No	4	None	NA	NA	No differences in primary outcomes observed, although post hoc analysis revealed trends towards benefits of kava.
Anxiety disorder (associated with sleep disturbances)	Randomized, placebo controlled, double-blind trial	Lehrl, 2004	61	Yes	4	Small	NA	NA	Kava extract WS 1490 superior to placebo for improvement of sleep measures and HAMA.

Table 4 Natural Standard evidence-based validated grading rationale™

Grades reflect the level of available scientific evidence in support of the efficacy of a given therapy for a specific indication.

Expert opinion and folkloric precedent are not included in this assessment, and are reflected in a separate section of each monograph ('Strength of Expert Opinion and Historic/Folkloric Precedent').

Evidence of harm is considered separately; the below grades apply only to evidence of benefit.

Level of Evidence Grade	Criteria
A (Strong scientific evidence)	Statistically significant evidence of benefit from >2 properly randomized trials (RCTs), OR evidence from one properly conducted RCT AND one properly conducted meta-analysis, OR evidence from multiple RCTs with a clear majority of the properly conducted trials showing statistically significant evidence of benefit AND with supporting evidence in basic science, animal studies, or theory.
B (Good scientific evidence)	Statistically significant evidence of benefit from 1-2 properly randomized trials, OR evidence of benefit from ≥1 properly conducted meta-analysis OR evidence of benefit from >1 cohort/case-control/non-randomized trials AND with supporting evidence in basic science, animal studies, or theory.
C (Unclear or conflicting scientific evidence)	Evidence of benefit from ≥1 small RCT(s) without adequate size, power, statistical significance, or quality of design by objective criteria,* OR conflicting evidence from multiple RCTs without a clear majority of the properly conducted trials showing evidence of benefit or ineffectiveness, OR evidence of benefit from ≥1 cohort/case-control/non-randomized trials AND without supporting evidence in basic science, animal studies, or theory, OR evidence of efficacy only from basic science, animal studies, or theory.
D (Fair negative scientific evidence)	Statistically significant negative evidence (i.e., lack of evidence of benefit) from cohort/case-control/non-randomized trials, AND evidence in basic science, animal studies, or theory suggesting a lack of benefit.
F (Strong negative scientific evidence)	Statistically significant negative evidence (i.e. lack of evidence of benefit) from ≥1 properly randomized adequately powered trial(s) of high-quality design by objective criteria.*
Lack of evidence	Unable to evaluate efficacy due to lack of adequate available human data.

* Objective criteria are derived from validated instruments for evaluating study quality, including the 5-point scale developed by Jadad et al., in which a score below 4 is considered to indicate lesser quality methodologically (Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, McQuay HJ. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Controlled Clinical Trials 1996; 17[1]:1-12).

† Listed separately in monographs in the 'Historical or Theoretical Uses which Lack Sufficient Evidence' section.

Pharmacokinetic-pharmacodynamic considerations (Gruenwald 2002)

Despite the wide spectrum of pharmacological activities associated with the kava lactones and the number of compounds they represent, the present knowledge concerning them indicates that there are only slight differences in their mechanisms of action. Thus, the major differences distinguishing them appear to be in the pharmacokinetic properties of the individual compounds (Singh 2004) and, if the kava extract is involved, the relative proportions of the organic compounds present in the extract. Organic compounds when present in the resin or lipid soluble form, are readily absorbed by the gastrointestinal tract and are made bioavailable to the central nervous system. It is important to note that the pharmacological activities of aqueous extracts, when compared with resin obtained by extraction with organic solvents such as acetone or ethanol from the same kava raw material, are not equivalent. Experiments have shown that bioavailability increased in the order: pure compound, extract, and extract formulation. The data confirm that clinical data from one preparation or formulation cannot simply be transferred to other formulations without appropriate biopharmaceutical characterization (Biber et al. 2000).

In one of the studies on the neuropharmacological interactions of kava with CNS receptors, purified kava lactones and organic solvent extracts of kava were tested for their activity on GABA and benzodiazepine binding sites in rat and mouse brain membranes. The authors concluded that the neuroprotective activity exhibited by kava extract was probably by its constituents methysticin and dihydromethysticin (Backhauss & Krieglstein 1992).

A study with mice demonstrated the ability of kava components to potentiate sodium pentobarbital-induced sleeping time. Another study on male mice demonstrated that premedication with kava lactones dihydrokavain or dihydromethysticin prolonged and deepened sodium hexobarbital anaesthesia. In a study which looked at interaction with ethanol, kava extract greatly increased ethanol-induced hypnosis. Caffeine was found to shorten the duration of the analgesic effect of the kava lactone dihydromethysticin and dihydrokavain, but without affecting the peak effect (Bruggermann & Meyer 1963).

In a study of the metabolism of several kava lactones in male rats it was observed that about one-half of the 400 mg/kg dose of dihydrokavain administered was found in the urine in 48 hrs. About two-thirds of this was hydroxylated metabolites. The remaining one-third consisted of metabolites formed by the catabolism of the kava lactone and also included hippuric acid. The metabolites of the other kava lactones have also been characterized by analysing the urine samples from rats (Rasmussen et al. 1979).

Preparations and chemical differences of the extracts

Some South Pacific Island countries use fresh kava root or rhizome to prepare the traditional drink while others use dried and ground roots or rhizomes. For fresh preparations, the root is chewed by young females, who spit the juice into the kava bowl without swallowing it themselves. The juice is then mixed with water or coconut milk and further processed (Lebot et al. 1992). Though no chemical analysis of the kava drinks prepared this way has been performed, it is clear that the chemicals will be different from the normal kava preparations in which the drink is obtained as described below. The drinks prepared as described above are claimed to be more potent than the usual water extracts of kava root or rhizome.

In the South Pacific, most people drink only the water extracts of kava. This is obtained by adding water to kava roots which are finely ground and then filtered using cheese cloth. These water extracts have been shown to contain only

water soluble carbohydrates, proteins (see Table 1, and about 6-8 % organic compounds (Naiker et al. 2002).

The pharmaceutical industries were primarily interested in the organic solvent extracts of kava. Different companies used different solvents such as 95% ethanol or acetone to remove the organic compounds of interest to them. These compounds were essentially the kava lactones which had the required pharmacological activities required to market kava pills as anti-anxiety medication. The organic solvent extracts also contained small amounts of kava pigments and some alkaloids (Sotheeswaran 2004). This observation has been confirmed in another published study which showed that the chemical composition of organic solvent extracts (also referred to as secondary metabolites) of kava varies according to the extraction method (Nahrstedt et al. 2004).

Some marketed products, referred to as 'synthetic' (see section IIB), consist of a single kava lactone, L-kavain.

We should also note that though only one species of kava exists in the strictest sense, there are closely related species that are also called 'kava' by some traders or farmers. These are *Piper wichmanni, Piper aduncum* and *Piper auritum*. According to an official statement by the International Kava Executive Council, these species have been marketed as 'kava' in some South Pacific Islands and may have been used by the pharmaceutical industries in Europe to manufacture kava pills. Local people avoid using these *Piper* species to make their kava drink.

In conclusion, it is clear that water extracts as taken in the South Pacific, with hardly any serious kava-related hepatotoxicity reported, are chemically different from the 'kava' used to make kava pills in Europe and this difference could be responsible for the reported hepatotoxicity in some kava pill takers.

In addition to the related kava plants mentioned above, there are also many kava cultivars in the South Pacific. About 150 different cultivars are available and are used in the South Pacific Islands (Lebot & Levesque 1996b). The different cultivars are likely to have different percentages of kava lactones as evidenced in another study of the kava cultivars of Fiji (Sotheeswaran et al. 1988).

One kava variety, called 'Tudey' kava is cheap compared with the normal kava. It is called 'Tudey' kava because the pharmacological effect of drinking the water extract of this kava is claimed to last more than 24 hours (two days). It has been flooding the kava market since it is harvested after 1-2 years compared with the normal kava which is only harvested after 4-5 years. Though the 'Tudey' kava drink has hangover symptoms not experienced with the normal kava drink, according to in vitro experiments on liver cells, there has been no evidence that 'Tudey' kava might involve a risk of liver disorders (Gebhardt 2004).

There are three parts of the kava plant that are used to make the kava drink. They are *lewena, waka* and *civi civi*. The Fijian word *lewena* refers to the rhizome which is the kava part below the stem and above the root. *Waka* refers to the kava root and is the most expensive part of kava that is sold in the Fijian markets. When the chiefs in Fiji are visited *waka* are presented as traditional gifts. *Civi civi* (or kasa) refers to kava stem peelings which are not commonly used to prepare kava drink in Fiji. But it also contains the kava lactones which the kava pills contain. The German pharmaceutical industries preferred to buy *civi civi* to extract kava lactones to make kava pills. *Civi civi* was sold at almost one-tenth of the price of kava roots. It has now been shown that *civi civi* contains more alkaloids than the roots and it is suggested that this may be the cause of the liver toxicity problems associated with kava pills (Nerurkar, 2004; Ajuyah et al, 2004).

Standardization / quality control of preparations

Prior to the ban imposed in 2001 on kava products, the pharmaceutical industries were mainly interested in the percentages of kava lactones in the plant material exported from the South Pacific. High Performance Liquid Chromatography (HPLC) methods were employed by kava exporters in the South Pacific to ascertain the percentages of kava lactones in the materials for export. The pharmaceutical industries re-tested the raw materials received and accepted them if the plant materials contained about 8% or more kava lactones.

The quality control methods available to the exporters of kava in the South Pacific or the importers of the plant materials for the extraction of kava products did not look for any other organic compounds (toxic or non-toxic) in the products prior to marketing. This lack of proper quality control measures resulted in the wrong parts of the plant or wrong extracts being used for the manufacture and sale of kava products such as kava pills and capsules.

Potential causes of hepatotoxicity in relation to differences in the chemical composition of the extracts.

There are several possible reasons why hepatotoxicity may occur with kava, such as dose, variety of kava, plant parts used, or type of extract. It is likely that the main problem is related to the chemical composition of the kava product taken. The great majority of cases of hepatotoxicity reported have been associated with kava products either in the form of tablets or pills and not the traditionally prepared water extract that is commonly drunk in the Pacific.

The problem therefore seems to lie mainly in the differences between the chemical composition of the organic solvent extracts used to make kava pills and the water extracts drunk in the Pacific. Table 1 lists the water soluble and water insoluble compounds reported in kava roots and Table 2 lists the organic compounds that are mainly not soluble in water but some of which may be found in the water extract as suspensions filtered through the cheese cloth used to filter the water extracts.

Now the question is, do we know if any of the water insoluble organic compounds can cause hepatotoxicity even rarely in kava pill users? Several research teams are currently working on this problem and as indicated, a group from Hawaii (Nerurkar et al. 2004) has suggested that the alkaloid, pipermethystine, may contribute to the rare but severe hepatotoxic reactions observed with some kava pill takers in Europe. Another group has reported that the organic solvent extracts used in the pills do not contain the water soluble peptide known as glutathione which is known to detoxify excess kava lactones in the liver and that excess kava lactones may cause hepatic stress (Denham et al. 2002). Glutathione is present in the water extract drunk in the Pacific.

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Section IIA Safety information: A literature review

Contents

Historical use

Kava has been traditionally used in certain South Pacific cultures both ceremonially and recreationally for hundreds of years. Europeans documented its use when they travelled to Polynesia in the eighteenth century (Norton 1998; Singh 1992; Spinella 2001). Kava is served to welcome village guests, to inaugurate new chiefs, and to bind communities together. Although specific kava rituals differ from place to place, the basic structure of the kava ceremony is surprisingly similar from island to island (Tavana al. 2003). Kava has a very long tradition of use as a tranquillizing ritual beverage and it is prepared from the root of the plant.

In addition to sedation or tranquillizing effects, kava has been used for its many claimed therapeutic properties including: diuretic, aphrodisiac, antidepressant, antidote for muscle spasms and cramping including menstrual cramps. Kava has also traditionally been used to treat migraine headache, venereal disease, gout, rheumatic conditions, colds, respiratory tract problems, wounds, chronic cystitis, weight reduction, muscle relaxation (Blumenthal 1998; Ernst 2002). In western societies, kava is used as an anxiolytic, muscle relaxant, mood enhancer, sedative or treatment for premenstrual syndrome. Kava lactones, the main ingredients in kava have been shown to affect a range of neurotransmitter systems and do have dose-dependent effects on the central nervous system, including antiepileptic, neuroprotective and local anaesthetic properties (Ang-Lee et al. 2001). Kava has had at least a 1500-year history of relatively safe use, with liver side effects never having arisen in the ethnopharmacological data (Loew & Gaus 2002).

Kava has been considered by many to be a safe and effective alternative to prescription medications for the treatment of anxiety (Pittler & Ernst 2000). A recent survey of web sites offering dietary supplements to the general public reported that 10% of products freely available to the public contain kava (Dennehy 2005).

To date at least 16 well-controlled double blind studies have shown that kava is effective at relieving anxiety. Moreover, in a meta-analysis of 11 high-quality clinical trials it was shown that unlike many conventional drugs used to treat general anxiety, kava is relatively free of side effects and is not addictive. The authors concluded that kava extract appears to be an effective symptomatic treatment option for anxiety and is relatively safe for short-term treatment (1 to 24 weeks) (Pittler & Ernst 2002; Cochrane Library 2005).

A number of recent controlled trials have shown that kava is also effective in stress-induced insomnia, mental stress (Cropley et al. 2002; Lehrl 2004; Wheatley 2001), and in enhancing cognitive performance (Thompson et al. 2004).

Kava adverse events

Estimates of the nature and scope of adverse drug reactions can mostly only be guessed, as in general the available data from 'case reports' would not be sufficient for interpretation. It is especially difficult to draw quantitative conclusions from the reported data in regard to morbidity, mortality or the underlying causes of adverse drug events, and attempts to extrapolate the available data to the general population would be invalid and perhaps misleading.

An adverse event rate from kava of 1 in 100 000 may possibly be recognized when the exposed population is very large, but would not be recognized in the Pacific, where the total population with heavy kava intake is probably less than 100 000 (it is unlikely to be more than 10% of the total population, which is little more than one million). More information on the total exposed population, both in the Pacific islands and in western countries, would be very useful in further exploring this issue.

Kava, especially water extracts, has been regarded as a safe remedy (Anke & Ramzam, 2004; Bilia et al. 2002; Blumenthal 2002; Ernst 2004; Stevinson et al. 2002). Organic kava extracts have been safely used under medical supervision for up to six months (Lehmann et al. 1996; Malsch & Kiesser 2001; Pittler & Ernst 2000; Volz & Kiesser 1997; Wheatley, 2001; Woelk et al. 1993). There are several reports and detailed reviews attesting to the safety of kava such as those from the European Commission, American Herbal Products Association, American Botanical Council, the Society for Medicinal Plant Research, International Kava Committee, Phytopharm Consulting, etc.

Based on the evidence of major trials and meta-analysis of trials up to 2002 authors have determined that reported adverse events related to kava are 'mild, transient and infrequent' (Pittler & Ernst 2002).

Reviews of adverse events observed in clinical trials and some observational studies have been published in the literature (Beaubrun & Gray 2000) and have been summarized in several internet databases such as 'Natural Standard Database', 'Natural Medicines Comprehensive Database' (www.naturaldatabase.com), and 'HerbMed Database'.

When kava has been taken in dosages ranging from 100 to 210 mg of kava pyrones daily, it has been associated with few adverse effects. Long-term use of kava, especially in high doses (400 mg of kava pyrones daily) has been associated with the development of flaky, dry, scaly skin and yellow discoloration of the skin, hair and nails (kava dermopathy) (Singh 1992; Wooltorton 2002) through an unknown mechanism (Schmidt & Boehncke 2000) but may relate to interference with cholesterol metabolism (Norton & Ruze 1994); the effect may be reversible upon cessation of the drug (Ernst 2002). In rare cases, kava may lead to allergic reactions, pupil dilation, blurred vision, disturbances of oculomotor equilibrium (Blumenthal 2002; Wheatley 2001). Other possible adverse effects include ataxia, hair loss, hearing loss and anorexia. It may also cause extrapyramidal side effects such as involuntary oral and lingual reflexes and twisting movements of the head and trunk, possibly due to dopamine antagonism (Bilia et al. 2002; Schelosky et al. 1995). A recent case report from Spain associates kava ingestion with severe parkinsonism in a 45 year-old woman (Meseguer et al. 2002) and a case control study of 83 indigenous Australians suggests that kava consumption is associated with ischaemic heart disease (IHD) and sudden cardiac deaths among, particularly, young Aboriginal sportsmen in this population (Clough et al. 2004). Kava may potentiate the effects of alcohol, benzodiazepines, and other sedative-hypnotic agents through additive effects (Spinella 2002). (See Natural Standard tables.)

Kava, unlike benzodiazepines, appears not to adversely affect cognitive function, mental acuity, or coordination, (Cairney et al. 2003; Heinze et al. 1994; Münte et al. 1993) although slight morning tiredness and reduced reactivity while driving as well as ataxia have been reported (Perez & Holmes 2005; Singh 1992). Commonly reported in more recent clinical trials are gastrointestinal complaints, abdominal pain and nausea.

There are two trials where clinically insignificant elevation of transaminases has been observed (Boerner et al. 2003; Connor & Davidson 2002) (see Safety Tables, Appendix 2). Liver function tests can be elevated after three to eight weeks of use, possibly followed by hepatomegaly (Escher et al. 2001). Kava can also exacerbate hepatitis in patients with a history of recurrent hepatitis. Abnormalities seem to resolve spontaneously after discontinuation of kava (Strahl et al. 1998). Most patients taking kava have not experienced such severe adverse effects and it is unclear which patients might be susceptible to adverse effects.

Heavy use of water extracts by Australian Aborigines and Pacific Islanders has been associated with dermopathy, increased levels of -glutamyl transferase and alkaline phosphatase, abnormally low body mass index (BMI), low blood lymphocytes, hematuria, macrocytic anaemia, ataxia, increased patellar reflexes, weight loss and hair loss, (Clough et al. 2003; Mathews & Riley 1988). These acute effects emerge at average consumption levels of from 310-440 g/week of kava powder (Clough 2003). 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 (Mathews & Riley 1988) and in the other, 45% of participants consumed alcohol (Clough et al. 2003).

On the other hand hepatic failure has never been observed with the traditionally prepared kava extract (however see case reports section IIA) but the controversy remains as to whether the population has been systematically evaluated and adverse effects reported (Currie & Clough 2003; Moulds & Malani 2003). In a recent Survey of Traditional Healers and Biomedical Practitioners in Native Populations in Savaii, Samoa, it was reported that Samoans were familiar with the effects of excessive kava use, especially sleepiness and dry skin, but no one reported major clinical signs of liver malfunction in association with kava drinking, such as yellowing of the eyes, brown urine, and changes in stool, even when asked specifically for signs of such symptoms (Tavana et al, 2003). Data from short-term post-marketing surveillance studies and clinical trials suggest that adverse events in general are rare, mild and reversible (Stevinson et al. 2002).

Summary of clinical case reports addressing hepatotoxicity

This report will focus on any new information available to the reviewers after 2002. A number of comprehensive reviews of the hepatotoxicity cases exist in the literature and will be mentioned throughout this section.

Isolated case reports of hepatotoxicity associated with ingestion of kava first started becoming known in the 1990s. Subsequently, news of possible European regulatory action began to surface as increased reports became available late in 2001 (Anke & Ramzam 2004; Blumenthal 2002; Clouatre 2004).

The majority of severe adverse effects associated particularly with liver toxicity are derived from the files of the BfArM in Germany (Clouatre 2004). Several authors have already undertaken an evaluation of these and other reports, with the most thorough and up-to-date likely being the work of Mathias Schmidt and Adolf Nahrstedt of the University of Münster. Originally published in the Deutsche Apotheker Zeitung in February 2002 (Schmidt & Nahrstedt 2002), a much-expanded version of this article is available on the Internet in an updated English translation under the title, 'Is kava really hepatotoxic?' (Schmidt 2003a).

In the 2003 review Schmidt analyses 82 hepatotoxicity cases from different sources [German health authorities (BfArM): 38 reports (excluding double entries), Swissmedic: 5 reports (excluding those also listed in the German case reports), US FDA: 21 reports, UK-MHRA: 4 reports, Health Canada: 3 reports, France (AFSSAPS): 2 reports, Australia TGA: 1 report, EMEA: 1 report (excluding those already mentioned in other categories), medical literature: 5 reports (excluding those already mentioned in other categories), unconfirmed German newspaper stories: 2 reports,]. The

author states that 20 cases are obviously not related to kava intake; in 21 case reports a potentially hepatotoxic concomitant treatment was identified. In seven cases there is considerable doubt concerning the causality of kava, whereas in 31 other cases the available data is too fragmentary for an assessment. That leaves only three cases where a likelihood of hepatotoxic effects by kava can be established, although in two of these three there were higher dosages and longer-term treatment than recommended. In only one of these case reports was kava taken according to the dosage recommendations of the German *Commission E Monograph* of no more than 120 mg kava lactones per day for three months or less. Therefore only one case remains. The authors also did a thorough analysis of the hepatotoxic potential of frequently used concomitant medications and a comparison of kava with other treatments for anxiety. They conclude, 'hepatotoxic effects of kava intake cannot generally be ruled out. However, in comparison with pharmaceutical treatments for stress and anxiety disorders, and in relation to drug intake related hepatotoxicity in general, the risk of adverse liver effects seems to be very low.'

A review of 36 cases of hepatitis in Germany concluded that kava was the certain or probable cause of the hepatitis in 24 of the cases, nine patients developed fulminant liver failure and eight of these patients required liver transplantation. Three patients died. In all other patients, a complete recovery was noticed after the withdrawal of kava. Hepatic necrosis or cholestatic hepatitis were noticed with both alcoholic and acetonic kava extract (Stickel et al. 2003). This review has been criticized and considered of little value because of reporting of wrong data, age of patients, gender, concomitant treatments and lack of liver test.

Three other valuable evaluations of case reports are those by Donald P. Waller (prepared for the American Herbal Products Association, February 15, 2002), one by Alison Denham prepared on behalf of the UK Traditional Medicines Evaluation Committee (a subcommittee of the European Herbal Practitioners Association) and one issued by the US Center for Disease Control also published in JAMA 2003. There is also the collection of cases from the pharmacovigilance database of the WHO dated January 31, 2000.

The analysis by American toxicologist/pharmacologist Donald Waller, of the College of Pharmacy at the University of Illinois at Chicago, of the approximately 30 hepatic adverse event reports (AERs) from Germany and 5 submitted to the FDA between May 1998 and September 2001 concluded that there is 'no clear evidence that the liver damage reported in the U.S. and Europe was caused by the consumption of kava'. In his report he presented two cases of excessive kava ingestion of up to 45,000 mg kava per day that did not present any liver toxicity. He also criticized the case reports from Germany and Switzerland as 'lacking in specific clinical and histological information' and recommended they be revised where possible to obtain further information. In addition, he stated that 'kava, when taken in appropriate doses for reasonable periods of time has no scientifically established potential for causing liver damage'. He also stated that toxicity can occur through a variety of mechanisms related to a production of the product or to altered sensitivity of populations of people previously unexposed to the phytochemicals in a particular plant product. Any pharmacologically active ingredient in a plant can interact with drugs, pre-existing conditions, or individual hypersensitivity (Waller 2002).

The *Morbidity and Mortality Weekly Report* issued by the US Centers for Disease Control (CDC) indicates that 11 patients using kava products have suffered liver failure and undergone subsequent liver transplants. This review includes the last two reports of liver failure from the United States. First, a 14 year-old girl who consumed for more than four months (Humberston, 2001, also published in 2003 in the same journal and by Campo, 2002). The authors state that the association is supported by four months of kava use, a negative work-up for alternative causes of liver failure, and histological changes in the liver (Humberston et al, 2003). Second, a 45 year-old women who consumed a kava-containing dietary supplement (CDC, 2002; web page, JAMA 2003).

Denham et al. reviewed thirty adverse events reported from Germany and Switzerland and initially submitted to the UK Medicines Control Agency (MCA) and Committee of Safety of Medicines (CSM) on January 11, 2002. The new version was completed in April 2002. This report argues that many of the case reports were duplicates and adverse events cited by the BfArM should not be attributed to kava. They also say that the BfArM document is deficient in other respects because it is unclear whether the term 'liver damage' refers to the results of a liver biopsy, or to the finding of raised alanine aminotransferase (ALT) blood levels that are interpreted as indicating damage to hepatocytes in hepatocellular disease. In addition, the report states that the properties of concentrated standardized kava extracts—as opposed to preparations that closely approximate those created for traditional use—contribute to causing adverse events.

These three expert reviews have concluded that kava being anecdotally linked to cases of liver dysfunction lacks adequate scientific evidence to confirm a causal relationship. Nevertheless, the authors conclude that kava products should be taken with caution in patients with liver disease and in those taking conventional drugs, and that any severe adverse event should be discussed with a physician and reported to the authorities.

Another independent analysis of 19 known cases from Germany was recently published in the peer-reviewed literature in 2003 (Teschke et al. 2003). The authors conclude that only two cases were probable kava-associated hepatotoxicities. In addition, 80% of these patients took kava overdoses and or self medicated kava for longer than three months. Most patients were taking concomitant medications with known hepatotoxicity. The authors also analyse discrepancies in the evaluations of cases made by regulatory agencies in Germany (BfArM) and UK (MCA). The authors advise nevertheless, that physicians and patients should be alert to possible hepatotoxic side effects in the course of kava treatment, stop the treatment at first suspicion and begin a careful diagnostic work up ruling out all other causes.

According to the reviewers several confounding factors have played a role in the association of kava and hepatotoxicity. Among these, the most common are: concomitant use of prescription medications, some of which are known or suspected to be hepatotoxic, ingestion of higher doses of kava,

sometimes up to 400 times more than the recommended dose; ethanolic vs acetonic extracts, idiosyncratic individual differences, erroneous association of kava in cases of pre-existing liver damage, current viral infections, and alcohol abuse. They also point out that duplicate reports and erroneous association of kava in cases of pre-existing liver damage have occurred (Blumenthal 2002).

The increase in the number of spontaneous reports up to 2002 may be due to increased awareness of the possible association of kava with liver disorder. In addition it may have been possible that the hepatotoxity problems were to some extent, a consequence of poor quality control caused by a rapid and extraordinary increase in the size of the market that by 1998 had a turnover of more than eight million US dollars in the United States of America (Murray 2000). In the South Pacific region the annual production of kava was estimated to be about 200 million US dollars (Gruenwald et al. 2002, 2003).

In summary, if all sources including unconfirmed newspaper reports are added, 96 reports of very different quality exist from 1990 to 2002. A total of nine patients who used kava products had liver failure and underwent subsequent liver transplantation; there were three deaths. The World Health Organization identified 28 cases of which there seems little doubt about causality in four.

On the one hand, this evidence argues strongly for a reappraisal of kava's safety. On the other, the quality of these reports has been challenged repeatedly because of duplicate or triplicate entries, missing indications and co-medication, wrong statements regarding dechallenge/rechallenge, abnormalities in reported laboratory testing, improbable temporal relationships between ingestion of the drug and the adverse event, the presence of pre-existing disease conditions etc. There appears to be either no consensus as to what standards of evaluation should be employed or, if such standards exist, they are difficult in practice even for experts to apply. This type of difficulty is more common than we would normally like to think (Kaplowitz 2001; Lucena et al. 2001; Juurlink et al. 2003).

Overview of original case reports 1990-2002 and regulatory action

Germany

The first cases of hepatotoxicity related to kava were presented to the Federal Institute for Drugs and Medical Devices (*Bundesinstitut für Arzneimittel und Medizinprodukte*, or BfArM) in Germany. Out of 105 spontaneous ADR-reports on kava, 24 were associated with impaired liver function or symptoms that could be linked to liver toxicity (including cases of cirrhosis, cholestatic hepatitis, and other types of hepatoxicity). Of the 24 cases, there was one fatality, three cases required liver transplant, and 18 cases were considered possibly or probably related to kava ingestion. Twelve patients were not yet assessable due to insufficient data and in five other cases a causal relationship was unlikely or could be excluded. Some authors recommended that the German regulatory authority provide additional information for those 12 patients with so far unsatisfactory data, facilitating a more appropriate assessment of causality (Teschke et al. 2003).

The German regulatory agency withdrew all kava-containing products from the market in June 14, 2002 just two weeks after switching kava products from 'OTC' to 'prescription' product. However the agency conceded that there were no scientifically based data regarding the mechanism of the kava hepatotoxicity. The histological picture of the explanted livers of patients was most compatible with a drug associated hepatotoxicity distinct from other liver disease or damage. An organ-specific hypersensitivity reaction was also considered. The causality was judged probable or possible in all cases. In one non-fatal case the causality was proven by a positive reaction (increase in liver enzyme concentrations) after re-exposure with a preparation containing kava only.

Switzerland

R. Stoller provided the results of a case series study involving 4 Swiss cases in which severe hepatic complications resulted from the use of an acetone extract of kava between 10 August 1999 and 20 February 2000. Of the 4 cases (2 severe hepatitis, 1 liver fibrosis, 1 severe liver injury), 3 were histologically confirmed, and one was a case of fulminant irreversible hepatitis requiring transplantation. In 3 of the cases, prothrombin time was increased. All 4 cases presented with jaundice (Stoller 2001).

Australia

On 15 August 2002 the Therapeutic Goods Administration (TGA) initiated a recall of all kava-containing products following the death of a woman associated with the use of kava-containing product. A voluntary recall of kava-containing medicines regulated by the TGA was initiated in conjunction with the complementary medicine industry. This resulted in all kava-containing medicines being removed from the market place. Consumers were advised to discontinue use of kava-containing medicines.

The TGA had placed a limit on the maximum amount of kava permitted per dosage form i.e., 125 mg kava lactones per tablet/capsule, a 3g limit of dried rhizome in tea bags, and all kava products must comply with a maximum daily dose of not more than 250 mg of kava lactones. Kava is now classified as a prohibited import under the Customs (Prohibited Imports) Regulations.

Canada

On 26 August 2002 a summary of 11 case reports associated with kava was submitted to Health Product Safety Information Division (HPSID) of Health Canada.

Four Canadian cases of liver toxicity associated with the use of kava-containing products were reported in response to a Public Advisory (issued 16 January 2002) in which health professionals were asked to report any cases of kava-related hepatotoxicity to HPSID. Two cases were considered serious.

United Kingdom

On 20 December 2001 the Medicines Control Agency (MCA) had one report of abnormal hepatic function associated with the use of kava in the UK. As of April 2002, the MCA received 3 reports of liver toxicity suspected of being related to kava consumption.

New Zealand

As of 16 January 2002 there were three ADR reports involving kava, none of which involved liver damage.

France

In France, two non-serious liver case reports were filed, both with questionable causality for kava. The French authorities suspended all registrations for drugs containing kava extract for the duration of one year, starting on 8 January 2001. However, there was no registered kava product in France, as kava is traded as a food supplement, which has officially not changed. The French authorities gave a recommendation not to sell kava, but it is still legal.

United States of America

Out of their 37 ADR reports involving kava, 10 were associated with liver problems. An update of the ADR reports received by the FDA (4 March 2002) revealed a total of 47 ADR reports received in association with kava, 20 of which were related to the liver.

It is important to note that most cases presented to the FDA were reported after general practitioners were asked to retrospectively screen their patient data for possible cases. The 'Dear Doctor' letter requested physicians to submit reports of cases of liver toxicity associated with the herb to the FDA's MedWatch system. The FDA letter was not intended as a public warning, but merely as a fact-finding measure.

Other countries

Up to 2002 there were no toxicity case reports presented to regulatory agencies in Spain, Japan, Brazil or Ireland. These agencies have suspended registration of kava products. The majority of countries around the world have released advisories cautioning about the use of kava-containing products.

New cases

Several new case reports of liver toxicity have been published in the literature since 2002. Two cases of hepatitis have been recently associated with ingesting traditionally prepared kava extracts for 4-5 weeks (Russman et al. 2003). One case of icteric hepatitis in Spain was published in letter form (Bujanda et al. 2002). Reports of two cases of hepatitis from Switzerland were associated with kava use and a consequent survey of 27 heavy kava drinkers in New Caledonia showed elevated gamma glutamyl transferase in 23/27 and minimally elevated transaminases in 8/27. The authors conclude that not only commercially available, but also traditionally prepared kava extracts may rarely cause liver injury (Russmann et al. 2003). In Australia a case of acute liver failure and death in a 56 year-old woman was associated with the use of a preparation containing kava and passionflower (*Passiflora incarnata*) (Gow et al. 2003). Two cases of hepatitis (one fulminating) were presented to the Brazil regulatory agency in 2003. These cases again are not proof of kava hepatotoxicity, but raise concern (Edwards 2005).

Personal communication with the Food and Drug Administration in the United States of America and the Marketed and Natural Health Products Directorate (Health Canada) in Canada confirmed that since 2002 no more cases of kava related hepatotoxicity have been reported to either agency. To the best of our knowledge there have not been any new reports from other countries, probably because kava products have been withdrawn from the market.

A recent evaluation of Dietary supplement (DS)-related adverse events (AEs) reported to the California Poison Control System. This indicated that the majority of these event were related to ephedra and very few to kava. Among 828 callers, 353 patients (74%) reported that the AE was related to products containing ephedra; other exposures frequently involved zinc, kava, creatine, and valerian but no details were provided. The majority of AEs were moderate and one was fatal (Dennehy et al. 2005b).

Summary of hepatotoxicity with kava

The mechanism of kava hepatotoxicity (if any) is not yet understood (Anke & Ramzan 2004; Ernst 2004; Mathews 2005). The significance of the information concerning kava's possible hepatoxicity prior to 1998 is unclear. The forms of kava used traditionally by Pacific Islanders and by some Aboriginal communities are not believed to be associated with the serious forms of liver damage observed in the case reports (TGA Fact Sheet 2005).

In addition, despite all the new information, hypotheses and theories, the mechanism of toxicity remains unknown and there are no clear predictors of toxicity, such as dosage or type of organic (acetone or ethanol) preparation, drug interactions etc, making the onset of damage unpredictable. No specific risk factors have been identified which may allow the safe use of kava under restricted conditions such as limiting the duration of treatment or its use in specific patient groups. Most experts believe that the available data point to an idiosyncratic-immunological genesis for the liver toxicity (Russmann et al, 2001; Schmidt 2003; Teschke 2003).

According to recent analyses kava can potentially produce liver toxicity but the incidence of those effects appears to be extremely low (Schmidt 2003; Edwards 2005; Miller 1998).

Experimental hepatotoxicological investigations showed no overt hepatotoxic reactions due to kava pyrones. A number of comprehensive reviews have been published in an attempt to explain the cause-effect relationship observed in the case reports but to date a clear mechanism to explain this purported hepatotoxicity has not been found.

A detailed analysis of the toxic liver effects of kava has been reviewed elsewhere (Anke & Ramzan 2004; Bauer et al. 2003; Clouatre 2004; Corrigan 2005; Gruenwald and Freder 2002; Hagemann, 2003; Health Canada, 2002; Stevinson et al. 2002; Singh 1992; Schmidt and Nahrstedt 2002; Schmidt 2003a,b; Simkins et al. 2005; Ulbricht et al. 2005). In addition, a number of experimental studies are available in the literature elucidating potential mechanisms of action (Frey 1991; Garrett et al. 2003; Gyllenhaal et al. 1999; Jamieson et al. 1989, Johnson et al. 2003; Jussofie et al. 1994, Boonen et al. 1998; Ma et al. 2004; Mathews et al. 2002, 2005; Nerurkar et al. 2004 a,b; Shinomiya et al. 2005; Singh, 2002, 2003; Smith 2001; Tarbah et al. 2003; Unger 1998, Unger et al. 2002; Weiss 2005, Whitton et al. 2003; Yuan et al. 2002; Zou et al. 2004, 2005). Mechanisms of toxicity have been presented and evaluated in a previous section of this report.

An immunologically mediated idiosyncratic mechanism or the chronic use of high doses of kava intake appear to be the most likely cause of kava toxicity. A direct toxic mechanism is much less likely (Schulze et al. 2001, 2003). Kava also has the potential for causing drug interactions through inhibition of P450 enzymes responsible for the metabolism of numerous pharmaceuticals (Mathews 2002, 2005). As several authors have noted, the range of hepatotoxic reactions found in the case reports is not compatible with the usual hepatotoxic reactions observed during adverse drug interactions. Many of these cases are disputed in terms of the causality between kava intake and liver toxicity; an analysis of the *in vitro, in vivo* and clinical data shows clearly that kava and its kava lactones are not predictable hepatotoxins (Corrigan 2005). Reports include necrosis, drug-induced hepatitis, and cholestatic hepatitis, that is, a pattern more indicative of a range of causes than of a single modality (Denham et al. 2002; Humberston et al. 2001). Such conclusions, if warranted, do not, however, mean that kava cannot be implicated in these cases.

The possibility that cytochrome CYP 2D6 deficiency might be a predisposing factor to hepatic complications associated with kava consumption has also been highlighted as being a potential risk factor particularly in two of the five Swiss reports This may make people especially susceptible to kava-induced liver injury because this abnormality might lead to a build-up of kava or one of its breakdown products to toxic levels (Anke et al. 2004; Russmann et al. 2001, 2003; Stoller 2001; Teschke et al. 2003). However, the type of testing needed to identify those for whom kava poses the greatest risk is not generally available.

The unclear relationship between kava use and necrotizing hepatitis has led to speculation that the disorder might represent a rare, idiosyncratic adverse reaction (Rotblatt & Ziment 2002). It has been speculated that individuals in poor health or with underlying liver diseases are more susceptible to liver damage if they take large amounts of kava. Enough crude evidence exists to suggest rather weakly that kava might interfere with liver function under certain conditions. Nevertheless, actual adverse events appeared to be limited to the chronic consumption of enormous amounts of the kava beverage that if extrapolated to the same dose in pill form is far in excess of any dosage that might be considered in Western practice (Chanwai 2000).

Whether kava is safe when taken in 'normal' doses is another question. A recent survey of German medical practices using the MediPlus database that has access to millions of prescriptions in the European Union revealed that kava prescriptions are seldom taken appropriately. Only 41% of the cases evaluated complied with the recommended daily dose. In 39% the drug was underdosed. In the majority of all cases (78% of the kava prescriptions that were written) the dose significantly exceeded the recommended intake. The authors conclude that the results may give an explanation why kava prescriptions are associated with a high incidence of adverse drug reactions (Schroder-Bernhardi and Dietlein 2001). A more detailed analysis of these data evaluating three kava products (trade names: Antares, Laitan and Kavasporal forte) revealed that in the case of a low-dosage recommendation (Antares and Laitan) there is a trend to over-dose in prescribing behaviour, which might increase the risk of undesirable adverse reactions. However, in the case of a higher dosage recommendation (Kavasporal forte) there is a tendency to under-dose. The authors suggest that this fact may explain the unexpected inefficacy of the therapy (Dietlein et al. 2003).

These findings raise the possibility that many of the reported cases of liver toxicity may have been due to excessive intake levels of kava. Almost 80% of the cases took kava pyrones in overdose (max 480 mg/day) and for a prolonged time of three months to two years (Teschke 2003). In few reports was the amount of kava used equal to or only slightly higher than the manufacturer's recommendation (Escher et al. 2001). Nevertheless, one cannot assume that the standard intake level of kava is safe for all individuals.

It is surprising that a side effect as serious as liver failure would not have been previously recognized during the hundreds, if not thousands, of years that kava has been used as a medicinal herb. Regarding the rarity (or possibly, absence) of cases linked with water extracts in its extensive traditional use authors have argued that this may be related to three possibilities (Edwards 2005).

- Under-reporting for traditional kava preparations in a situation where rare liver toxicity may go unnoticed;
- Toxic/allergenic material extracted in acetonic and ethanolic kava extracts but not in water extracts;
- Substandard kava (either 'Twoday' (Tudey) or including stem, leaf or bark material) exported for the manufacture of acetonic and ethanolic kava extracts during the 'Kava Boom'.

It has been pointed out that liver damage is likely to be the result of non-traditional production methods of commercially available kava supplements. The traditional kava beverage is essentially a water suspension and until recently large quantities of 10-15 times the recommended daily dose have been used without signs of liver damage (Whitton et al. 2003). See 'Type of Extract Paradigm' below.

Transient or fluctuating elevations in hepatic enzymes are commonly seen during therapy with a variety of drugs. A number of recent reviews address the issue of drug-induced hepatoxicity and it is clear that many different mechanisms play a role in the potential toxic effect of drugs and herbal medicines including kava. Factors affecting susceptibility to drug-induced injury include age, sex, concomitant use of other drugs, and genetic polymorphism in metabolic pathways involved in activation or disposition of therapeutic drugs as well as the products produced during metabolism that may be highly reactive and toxic (Maddrey 2005; Malani 2005; Pishvaian et al. 2004; Schiano 2003). These elevations in hepatic enzymes, often in the range of two to three-fold, are typically self-limited, often resolve with continuing therapy, and do not usually require discontinuation of the drug. GGT, in particular, is often elevated in the absence of any significant liver damage and thus is not very useful as a screening test. In addition, most of the categories of liver injury do not lead to hepatic failure (Foster B, Health Canada 2004). The measurement of transaminases in the relatively small number of patients involved in clinical trials may allow the detection of a signal that a drug will cause significant hepatotoxicity and should be encouraged in future kava clinical trials.

The determination of cause of hepatotoxicity is confounded by the presence of other drugs, the primary disorder under therapy and other disease states. Determination of the contribution of these confounders to hepatic injury is critical in the evaluation of possible drug-induced hepatic injury. Alcohol use is a significant confounding factor with respect to the risk of and severity of drug-induced hepatotoxicity. Other confounding factors may include concurrent infection, concurrent therapy with drugs, herbal medications or biologicals (with the potential for drug interactions, notably if one agent induces or inhibits the activity of key metabolic pathways) and compliance (Foster, Health Canada, 2004; Schiano 2003). Safety concerns and potential kava interactions with drugs and other herbs have been recently reviewed. The authors suggest that because some kava lactones possess pharmacological effects, such as blockade of GABA receptors and sodium and calcium ion channels, that these effects may lead to pharmacodynamic interactions with other substances which possess similar pharmacological properties. However, currently there is very little evidence to substantiate actual pharmacokinetic and/or pharmacodynamic interaction between drugs and kava (Singh 2005).

Causality issues

The association between kava and liver disease is surprising, disturbing and controversial. The 1998 edition of the German *Commission E Monographs*, considered to be an authoritative source on herbal medicines, does not mention liver disease or any other serious side effects in its discussion of kava (Blumenthal 1998).

It should be noted that individual cases such as those available do not prove cause and effect. Even where other known causes of liver damage (such as alcohol abuse and viral infections) were ruled out, it is possible that the use of kava by these individuals was a coincidence, rather than the cause of the problem. In addition, in several cases, drugs with potential hepatotoxicity such as: fluoxetine, paroxetine, acetylsalicylic acid, oral contraceptives, celecoxib, omeprazole and others may have been potential confounders.

Other authors have been more emphatic about the lack of association between kava ingestion and severe hepatotoxicity. 'Hence we could say that the medical reports are nowhere near a conclusive body of evidence that kava capsules might have caused acute or sub-acute liver toxicity in European kava pill consumers' (Schmidt 2003).

A direct causal relationship with kava use has been difficult to establish in the majority of the cases, and there is insufficient evidence to implicate kava as the responsible agent. Nevertheless, until further research clarifies any causality, kava should be used with caution.

The type of extract paradigm

The preparations of extracts may play a role in the development of toxicity. Alcohol (standardized to 30% kava lactones) and acetone (standardized to 70% kava lactones) extracts of kava have been linked to liver toxicity, however, water extracts (average content of 210 mg of kava lactones) have not (see exception in IIA). One reason for the cases of suspected liver toxicity in Europe could be that the extracts of kava used in the South Pacific and in Europe and USA were different. It is conceivable that different methods of preparation (alcohol, water or acetonic extraction) yield different kava alkaloids (Currie & Clough 2003; Moulds & Malani 2003). Acetonic and ethanolic extracts were implicated in several of the most serious cases. Water preparations of kava, on the other hand have been taken for centuries in the South Pacific with no recognition of definite liver problems associated with normal kava intake but this also has been argued (Russmann et al. 2003). Nevertheless, recent studies in rats found that the aqueous extract of kava does not affect liver function tests (Singh & Devkota 2003).

The part of the plant used to prepare the extracts as well as the wrong cultivar and the wrong kind of raw material (stem peelings instead of the roots) may contribute to the production of an extract with different constituents. There is a higher yield of kava lactones in the stem peelings, but also a number of phytochemical compounds not present in the roots. Kava preparations made with this kind of raw material are not comparable to kava as prepared from the root or rhizome. There are now a number of recent studies showing that the use of the aerial parts is potentially dangerous. Authors have stated that this was the type of kava that produced the most severe adverse effects observed in the European cases (Edwards 2005; Nerurkar et al. 2004 (see also Section I).

There have been cases where batch variations have been identified in particular products. There is also the possibility of unknown adulterants and contaminants (Thomsen et al. 2004). This assertion has not been proven scientifically. Some have suggested that the acetone solvent used to make the leading kava product may be the culprit.

Whitton et al. (Whitton et al. 2003) recently presented another theory concerning the difference between traditional kava preparations and commercially used products. They found that aqueous extracts contain glutathione, which has the potential to react with the kava lactones to provide protection against hepatotoxicity especially when detoxification pathways are saturated (Anke & Ramzan 2004; Whitton et al. 2003).

It is important to emphasize that until more toxicological studies are conducted, no one can suggest that differences in products have any toxicological significance.

Kava clinical trials

In general, randomized controlled trials (RCTs) are not designed or powered to pick up adverse reactions. Nor are they long enough to detect long-term adverse effects. This is particularly true when adverse reactions are rare or uncommon. Regarding serious liver toxicity the number of patients usually involved in Phase III clinical trials is typically too small to detect hepatic necrosis that occurs with an incidence of 1/10 000 and even too small to provide high assurance against risk with an incidence of 1/1000 or less [ICH-E-1]. However, although most of the data have never been published, it appears that most, if not all, drugs that cause hepatic necrosis also cause an asymptomatic, but significant (>5 fold), elevation of transaminases in a larger fraction of the population treated, which can be detected in typical Phase III trials. Therefore, any drug that is found to cause a significant incidence of elevated

transaminases relative to control, must undergo additional investigations into the mechanisms involved (Foster B, Health Canada, 2004). It has been stated, however that smaller elevations should not be seen as forerunners of more severe liver damage. In addition, many plant products do not seem to lead to toxic effects in everyone taking them, and they commonly lack a strict dose-dependency curve.

Clinical studies of kava extracts generally have suffered from the same shortcomings found in many other trials of natural products. Small sample size, short periods of treatment (usually 4–8 weeks and up to 24 weeks), lack of information about type and dose of extract used, ill-defined patient population, lack of adverse event reporting, etc. (Abadi et al. 2001; Gessner & Cnota 1994; Herberg 1991, 1993, 1997; Lehmann et al. 1996; Möller & Heuberger 1989; Saletu et al. 1989; Scherer 1998; Siegers et al. 1992). To some extent, these failings have been corrected in most recent trials. For this reason the following section will address mainly trials conducted in the past five years.

Systematic reviews, reports and general information about trials previous to 2000 have been published elsewhere (Brown 2001; Loew & Gaus 2002; Pittler & Ernst, 2000, 2002; Schmidt 2003).

A number of recent reviews evaluating the beneficial effects of kava in insomnia and anxiety conclude that kava seems to be effective in these indications but due to the 'reported' (but not confirmed) hepatotoxic effects kava should be administered with caution and following physicians recommendations about dose and duration of the treatment (Ulbricht 2005; Brown 2005; Wheatley 2005). Two reviews include information about other commonly used psychotropic herbal preparations (Wheatley 2005; Simkins 2005).

Safety results in clinical trials

The direct toxicity model as opposed to a model of the potentiation of the toxicity of other drugs is the model commonly reflected in the safety data of clinical trials. It has been stated that under the restricted conditions of these trials, kava extracts appear to be quite safe particularly in trials of 4 to 24 weeks duration. Similarly, very short-term trials of high kava lactone intake have not demonstrated toxicity: 300–600 mg per day acetone extract for one week (Johnson et al. 1991), 600 mg per day acetone extract for one week (Heinze et al. 1994; Münte et al. 1993), or 240 mg per day alcohol extract for two weeks (Herberg 1996).

The limitations of these clinical trials with regard to establishing safety are much the same as with establishing efficacy (Ernst 2002). A further limitation with regard to establishing safety is that these trials can only very poorly predict the fate of kava extracts in real world settings where patients ingest multiple drugs, alcohol and other compounds, often for extremely extended periods of time, and perhaps while taking many times the indicated dose for kava and/or one or more of these compounds.

The two meta-analyses on clinical trials on the acetone-based kava extract from Germany do not mention liver toxicity as one of the adverse effects, concluding that kava appears to be a safe and effective remedy for anxiety (Pittler & Ernst 2002). It should be noted, however, that most clinical studies in this meta-analysis utilized WS 1490 (W. Schwabe) as the active form of kava. This preparation is standardized to contain 70% kava lactones (Stoller 2001) while the majority of marketed kava products contain 30% kava lactones. As a result of these chemical and manufacturing differences, the generalizability of these trials is limited and may not be applicable to other kava-containing products.

Another review listed nine double-blinded, randomized controlled trials, involving 808 patients, and stated that kava was significantly superior to placebo for treating symptoms associated with anxiety. No liver toxicity was observed. These trials used a range of products standardized on 15–70% kava lactones, providing a daily dosage of 60–210 mg per day of kava lactones (Loew & Gaus 2002).

Stevinson and associates conducted a systematic review of case reports (from the spontaneous reporting schemes of the WHO, national drug safety bodies and ten manufacturers of kava preparations), short-term post-marketing surveillance studies and clinical trials of kava. Two post-marketing surveillance studies based on spontaneous reporting did not identify liver toxicity among a total of 7,978 patients taking 150 to 240 mg kava extract daily for approximately six weeks (Stevinson et al. 2002). The authors conclude that 'In the controlled clinical studies and post-marketing surveillance studies, subjective and objective organ-related adverse drug reactions were rarely or very rarely documented'. There is also a lack of hepatotoxicity reports in four post-marketing surveillance studies of kava or kava lactone involving 11,695 patients (Hoffman 1996; Siegers 1992; Spree & Croy 1992; Unger 1998). (These reports are in German and are reviewed in Schmidt 2003).

In view of the current scientific knowledge, the condemnation of kava extracts appears to be unwarrantable. German physicians now recommend kava as an herbal anxiolytic at a dose of 120–210 mg kavapyrone/day. The length of medication should be limited to 1–2 months, and liver enzymes should be checked before and during kava medication (Teschke, 2003).

In recent studies an attempt has been made to evaluate the effect of kava preparations in the liver and safety parameters including determination of liver enzymes, have been reported. In general, authors have concluded that kava is relatively safe. In none of these studies was there evidence of liver toxicity or other serious adverse events. Tables below provide a detailed summary of the most commonly observed adverse events observed in recent RCTs. In general over 500 patients have been enrolled in recent clinical studies and over 6,500 in open studies. Kava appears to be well tolerated by most users with most adverse events being rare, mild and reversible in about 2.3% of patients (Corrigan 2005). Between 2000 and 2005 a total of 15 clinical trials were identified with one trial done via Internet (Jacobs et al. 2005) not included in the tables because the trial's major objective was to evaluate the feasibility of conducting Internet-based RCTs and tested a combination of kava and valerian. Four were done with acetonic extracts and eight with ethanolic extracts. The majority of adverse events observed were unrelated to the kava treatment. Boerner et al. reported a slight increase in transaminases, which was also observed in the reference group (Boerner et al. 2003). Gastric complaints were observed in two studies (Cagnacci et al.

2003, Mittmann et al. 2000). Six trials included evaluation of liver function parameters. None of the studies, involving more than 180 patients receiving 55 to 210 mg of kava lactones for four weeks to six months, showed clinically relevant change in liver enzymes (Boerner et al. 2003; Connor & Davidson 2002; Gastpar & Klimm 2003; Geier & Konstantinowicz 2004; Lehrl 2004; Mittmann 2000).

Of the 14 trials recent trials in the tables, two were single dose studies, one was a two dose study, two were of two weeks' duration, and only three exceeded five weeks (eight weeks, three months and six months). The total number of patients involved was 395 and only 265 were involved in the six trials that assessed liver function. These studies combined would be inadequate to exclude hepatotoxicity.

Safety tables–Summary of Adverse Effects in Clinical Trials

1. Table 1a Kava Extract LI150 (Ethanolic extract)
2. Table 1b Kava Extract (Extract uncertain)
3. Table 1c Kava Extract Naturel Bradel (Extract uncertain)
4. Table 2a Kava Extract LI150 (Ethanolic extract)
5. Table 2b Kava Extract LI150 (Ethanolic extract)
6. Table 2c Ethanolic extract
7. Table 2d Extract WS1490 (Acetonic extract)
8. Table 2e Extract WS1490 (Acetonic extract)
9. Table 2f Extract WS1490 (Acetonic extract)
10. Table 2g Extract WS1490 (Acetonic extract)
11. Table 2h (Ethanolic extract)
12. Table 2i Kavosporal forte (Ethanolic extract)
13. Table 2j (Ethanolic extract)
14. Table 2k (Ethanolic extract)

Table 1a Summary of adverse effects in clinical trials:

kava extract LI150 (ethanolic extract)

Study Design	Subjects/participants	Parameters monitored	Extract/placebo/Reference	Adverse effects and related findings
Boerner RJ et al., 2003 Randomized, reference-controlled, double blind Multicentre ***Institution:*** Ludwig-Maximilians-University, Germany ***Objective*** To assess efficacy and safety of kava extract	**Condition:** Outpatients with Generalized Anxiety Disorder Intention –to-treat; ***Age:*** 25-65 yrs 107 females, 20 males N=129	• Efficacy rating scales • Adverse events • Concomitant therapies • Vital signs/Physical exam • Clinical laboratory blood test Tests were conducted at weeks 0, 2, 4, 8. Follow up without treatment at week 9.	**Kava Extract:** ***Type:*** Kava extract LI150 standardized to a content of 30% kavapyrones ***Dose:*** 400 mg capsules/day ***Route:*** Oral ***Duration:*** 8 weeks + 1 week follow-up ***Number of subjects:*** 43 **Reference group:** ***Number of subjects:*** 86 (84 entered the trial) 43 assigned to 10 mg Buspiron 43 assigned to 100 mg Opipramol	**Kava Group:** ***Adverse effects:*** 4 subjects withdrew due to adverse effects. 27 treatment emergent adverse events, only 1 rated to be 'probably' related to medication. Slight increases of transaminases above upper limit in 2 of the 43 subjects (one had already displayed values slightly above normal at baseline) One subject suffered from panic attack requiring stationary treatment. No significant hepatotoxic reactions were reported in about 330 treatment weeks in this trial **Reference group:** ***Adverse effects:*** 1 subject withdrew due to adverse effects. 30 treatment emergent adverse events, only 4 rated to be 'probably' related to medication Slight increases of transaminases above upper limit in 5 of the 84 subjects (4 had already displayed values slightly above normal at baseline). Only one GGT increase was rated to be of clinical relevance (opipramol).

This study was published in English.

Table 1b Summary of adverse effects in clinical trials:

kava extract (extract type uncertain)

Study Design	Subjects/participants	Parameters monitored	Extract/placebo/Reference	Adverse effects and related findings
De Leo et al., 2001 Randomized ***Institution:*** University of Siena, Italy ***Objective:*** To evaluate the efficacy of combining kava extract with hormone replacement therapy	**Condition:** Women in physiological or surgical menopause with DSM IV for generalized anxiety. ***All subjects received 50 ug/ day (TTS, 17B estradiol) with or without progestogen*** N = 40	• Symptoms defined by the Hamilton Anxiety Scale (HAMA) Tests were conducted before and after 3 and 6 months	**Kava Extract:** ***Type:*** 55% kavain ***Dose:*** 100 mg capsules/day ***Route:*** Oral ***Duration:*** 6 months ***Number of subjects:*** 24 **Placebo group:** ***Number of subjects:*** 16	**Kava Group:** ***Adverse effects:*** None reported **Placebo group:** ***Adverse effects:*** None reported

This study was published in English.

Table 1c Summary of adverse effects in clinical trials:

kava extract Naturel Bradel (extract type uncertain)

Study Design	Subjects/participants	Parameters monitored	Extract/placebo/Reference	Adverse effects and related findings
Cagnacci A et al., 2003 Randomized prospective open ***Institution:*** University of Modena, Italy ***Objective:*** Investigate the efficacy of kava on mood perimenopausal women	***Condition:*** Perimenopausal women. ***All subjects received 1g/day of calcium during study*** ***Ages:*** 47-53 yrs N = 80	• Anxiety • Depression • Climacteric symptoms Subjective side effects evaluated after 1 and 3 months. Biochemical evaluations were performed in those presenting side effects	**Kava Extract:** ***Type:*** 55% kavaina ***Dose (group 1):*** 100 mg capsules/day ***Dose (group 2):*** 200 mg capsules/day ***Route:*** Oral ***Duration:*** 3 months **Treatment group 1:** ***Number of subjects:*** 20 **Treatment group 2:** ***Number of subjects:*** 20 **Reference control group:** ***Number of subjects:*** 40	**Kava Group:** ***Adverse effects:*** Nausea and gastric pain observed in 6 subjects, causing 2 out of the 6 to withdraw from study. Biochemical evaluation did not show any alteration, including those parameters documenting liver toxicity. **Reference group:** ***Adverse effects:*** Nausea and gastric pain observed in one subject.

This study was published in English.

Table 2a Summary of adverse effects in clinical trials:
kava extract LI150 (ethanolic extract)

Study Design	Subjects/participants	Parameters monitored	Extract/placebo/Reference	Adverse effects and related findings
Cairney et al., 2003 Controlled experiment (open study) ***Institution:*** Mental Health Research Institute of Victoria, Australia ***Objective:*** Investigate cognitive and saccade function of kava intoxicated subjects.	***Condition:*** Indigenous kava users ***Ages:*** 25-57 yrs 4 females, 24 males N=28	• Blood for analysis of lymphocytes and liver enzymes • Glutamyl transferase (GGT) and alkaline phosphatase (ALP) • Body mass index (BMI) • Physical examination • Behavioural characteristics • Saccade and cognitive tests Tests were conducted 8 hours after trial.	**Kava Extract:** ***Type:*** Kava LI150 ***Dose:*** 205 g of kava powder (approx. 150 times clinical doses). ***Average of 16.4g/h*** ***Route:*** Oral (drink) ***Duration:*** 14.4 hrs ***Number of subjects:*** 11 **Control group:** ***Number of subjects:*** 17	**Kava Group:** ***Adverse effects:*** Ataxia, tremors, sedation, disorientation, and blepharospasm. Elevated GGT and ALP levels were not accompanied by elevated aminotransferase (ALT) levels **Control group:** ***Adverse effects:*** Tremors, and blepharospasm.

This study was published in English.

Table 2b Summary of adverse effects in clinical trials:
kava extract LI150 (ethanolic extract)

Study Design	Subjects/participants	Parameters monitored	Extract/placebo/Reference	Adverse effects and related findings
Cropley M et al., 2002 Randomized, controlled experiment ***Institution:*** University of Surrey, UK ***Objective:*** Investigate whether kava or valerian could moderate the effects of psychological stress induced under laboratory conditions.	***Condition:*** Healthy volunteer students ***Ages:*** 18-30 yrs 30 females, 24 males N=54	• Blood pressure • Heart rate • Behavioral performace Tests were conducted at beginning and end of trial.	**Kava Extract:** ***Type:*** Kava LI150 ***Dose:***120 mg capsules/day ***Route:*** Oral ***Duration:*** I week ***Number of subjects:*** 18 **Valerian group:** ***Type:*** Valerian LI156 ***Dose:***2 x 600 mg capsules/day ***Route:*** Oral ***Duration:*** I week ***Number of subjects:*** 18 **Placebo group:** ***Number of subjects:*** 18	**Kava Group:** ***Adverse effects:*** None reported **Control/Reference group:** ***Adverse effects:*** None reported **Placebo Group:** ***Adverse effects:*** None reported

This study was published in English.

Table 2c Summary of adverse effects in clinical trials:
(ethanolic extract)

Study Design	Subjects/participants	Parameters monitored	Extract/placebo/Reference	Adverse effects and related findings
Connor et al., 2002 Randomized, double-blinded, placebo-controlled ***Institution:*** Duke University, USA ***Objective:*** To assess the efficacy and safety of a botanical anxiolytic, kava, in treating generalized anxiety disorder	***Condition:*** Outpatients with DSM-IV GAD ***Ages:*** 31 –75 yrs 31 females, 6 males N=38	• Efficacy assessments (HAMA, HADS, and SARA) • Vital signs • Laboratory and ECG assessments • Medication side effects • Withdrawal symptoms Tests were conducted weekly	**Kava Extract:** ***Type:*** KavaPure standardized to 70 mg kava lactones ***Dose 1:*** 2x70 mg capsules/day ***Dose 2:*** 2x140 mg capsules/day ***Route:*** Oral ***Duration:*** 1 week of dose 1 followed by 3 weeks of dose 2 ***Number of subjects:*** 19 **Placebo group:** ***Number of subjects:*** 18	**Kava Group:** ***Adverse effects:*** No evidence of withdrawal or sexual side effects **Placebo Group:** ***Adverse effects:*** No evidence of withdrawal or sexual side effects

This study was published in English.
A more detailed safety report is available in Connor et al. 2001

Table 2d Summary of adverse effects in clinical trials:

Extract WS 1490 (acetonic extract)

Study Design	Subjects/participants	Parameters monitored	Extract/placebo/Reference	Adverse effects and related findings
Gastpar et al., 2003 Randomized, placebo-controlled, double-blind Multicentre, parallel-group ***Institution:*** Rheinische Kliniken, Germany ***Objective:*** To investigate the efficacy of kava	***Condition:*** Outpatients with neurotic anxiety Intention –to-treat; 105 females, 36 males N=141	• Clinical laboratory blood test: blood cell counts, Hgb, liver function tests, bilirubinn, creatinine, glucose, cholesterol, electrolytes, calcium, PT • Urinalysis Tests were conducted at the beginning and end of the trial	**Kava Extract:** ***Type:*** WS 1490 acetonic monoextract from dried root standardized to 70% kava lactones ***Dose:*** 3 x 50 mg capsules/day ***Route:*** Oral ***Duration:*** 4 weeks + 2 weeks observation ***Number of subjects:*** 71 (62 entered the trial) **Placebo group:** ***Number of subjects:*** 70 (65 entered the trial)	**Kava Group:** ***Adverse effects:*** 2 subjects withdrew due to adverse effects assessed to be unrelated to the treatment. Tiredness. **Placebo Group:** ***Adverse effects:*** 4 subjects withdrew due to adverse effects assessed to be unrelated to the treatment.

This study was published in English.

Table 2e Summary of adverse effects in clinical trials:

Extract WS1490 (acetonic extract)

Study Design	Subjects/participants	Parameters monitored	Extract/placebo/Reference	Adverse effects and related findings
Geier FP et al., 2004 Randomized, placebo-controlled, double-blind outpatient ***Institution:*** Geriatric Hospital Elbroich, Germany ***Objective:*** Obtain information on dosage range and efficacy of kava	***Condition:*** Outpatients with non-psychotic anxiety Intention to treat; ***Ages:*** 51-90 yrs. 39 females, 11 males N=50	• Anxiety, tension, personality, well-being using HAMA, EAAS, KEPS, EWL 60-S, CGI • Severity of illness, recovery, therapeutic efficacy • Laboratory tests (Hgb Hcto total blood count, enzyme values, ALT, AST, GGT, alkaline phosphatase, total billirubin, cholesterol, and glucose) daily blood pressure, and heart rate measurements • Documenting all adverse events up to two weeks after termination of treatment phase Tests were conducted at the beginning and end of the trial	**Kava Extract:** ***Type:*** WS 1490 acetonic monoextract from dried root standardized to 70% kava lactones. ***Dose:*** 3 x 50 mg capsules/day ***Route:*** Oral ***Duration:*** 4 weeks + 2 weeks observation ***Number of subjects:*** 25 **Placebo group:** ***Number of subjects:*** 25	**Kava Group:** ***Adverse effects:*** None observed due to study medication. Two subjects withdrew due to adverse events unrelated to study medication (Pleuro pneumonia and pulmonary fibrosis). **Placebo Group:** ***Adverse effects:*** 1 subject withdrew due to adverse events on day three (nausea, retching, restlessness and sleeplessness).

This study was published in English.

Table 2f Summary of adverse effects in clinical trials:

Extract WS 1490 (acetonic extract)

Study Design	Subjects/participants	Parameters monitored	Extract/placebo/Reference	Adverse effects and related findings
Lehrl S., 2004 Prospective, randomized, placebo controlled, double-blind, 2 Parallel groups ***Institution:*** University of Erlangen-Nuremberg, Germany ***Objective:*** To investigate the efficacy and safety of kava	***Condition:*** Outpatients with neurotic anxiety Intention to treat; ***Ages:*** 24-72 yrs. 33 females, 28 males N=61	• Sleep, anxiety, well-being using SF-B, HAMA, Bf-S, CGI • Erythrocyte, sedimentation rate, erythrocyte count, hematocrit, hemoglobin, leukocyte count, thrombocyte count, ALT, g-GT and creatinine. • Urinalysis • Adverse events inquiry Tests were conducted at the beginning and after 2 and 4 weeks of the trial.	**Kava Extract:** ***Type:*** WS 1490 acetonic monoextract from dried root standardized to 70% kava lactones. ***Dose:*** 2 x 100 mg capsule/day ***Route:*** Oral ***Duration:*** 4 weeks ***Number of subjects:*** 34 **Placebo group:** ***Number of subjects:*** 27 (23 entered the trial)	**Kava Group:** ***Adverse effects:*** None observed and no drug-related changes in clinical or laboratory parameters or vital signs. **Placebo Group:** ***Adverse effects:*** Gastrointestinal complaints and nausea in one subject

This study was published in English.

Table 2g Summary of adverse effects in clinical trials:

Extract WS1490 (acetonic extract)

Study Design	Subjects/participants	Parameters monitored	Extract/placebo/Reference	Adverse effects and related findings
Malsch et al., 2001 Randomized, placebo controlled, double blind 2 parallel groups ***Institution:*** Ochsenzoll General Hospital, Germany ***Objective:*** To assess the efficacy of kava	***Condition:*** Outpatients with non-psychotic anxiety and pre-treatment with benzodiazepines. Intention –to-treat; ***Ages:*** 21-75 yrs. 15 females, 25 males N=40	• Scores of the Hamilton Anxiety Scale (HAMA) • Scores of the Bf-S (subjective well-being scale) • Erlangen Anxiety and Aggression Scale (EAAS) • Clinical laboratory tests • Urinalysis Tests were conducted at the beginning and end of the trial. Benzodiazepine withdrawal symptoms were assessed during treatment.	**Kava Extract:** ***Type:*** 70% kava lactones ***Dose:*** 3x2 50 mg capsules/day ***Route:*** Oral ***Duration:*** 5 weeks + 3 week follow-up 1 week of gradually increased daily dose from 50 mg to 300 mg, continued by 4 weeks of 300 mg dose Simultaneously, benzodiazepine was tampered off during the first 2 week, resulting in 3 weeks of pure kava. ***Number of subjects:*** 20 (17 who entered the trial) **Placebo group:** ***Number of subjects:*** 20 (19 who entered the trial)	**Kava Group:** ***Adverse effects:*** No subjects withdrew due to adverse effects. Symptoms due to withdrawal of benzodiazepine were observed in 5 subjects. No serious adverse events occurred during trial. **Placebo Group:** ***Adverse effects:*** No subjects withdrew due to adverse effects. Symptoms due to withdrawal of benzodiazepine were observed in 10 subjects. No serious adverse events occurred during trial.

This study was published in English.

Table 2h Summary of adverse effects in clinical trials
(ethanolic extract)

Study Design	Subjects/participants	Parameters monitored	Extract/placebo/Reference	Adverse effects and related findings
Mittmann et al., 2000 Randomized, unblinded, diazepam controlled	***Condition:*** Women for whom a vaginal hysterectomy was planned. N=53	• Extent of anxiety • Quality of medication-induced sedation • Blood pressure • Pulse frequency • Blood oxygen saturation values Tests were conducted before and after application as well as during and after the operation.	**Kava Extract:** ***Type:*** Kavasedon capsules extract from root stock standardized to 50 mg kava lactones per capsule ***Dose:*** 2 x 50mg capsules evening before operation and 2x50mg capsules 60 min. before operation ***Route:*** Oral ***Number of subjects:*** 26 **Reference group:** ***Number of subjects:*** 27	**Kava Group:** ***Adverse effects:*** 5 subjects nausea and vomiting, could not be attributed to the medication. **Reference Group:** ***Adverse effects:*** 5 subjects nausea and vomiting, could not be attributed to the medication.

This study was published in German wtih an English abstract.

Table 2i Summary of adverse effects in clinical trials:
Kavosporal Forte (ethanolic extract)

Study Design	Subjects/participants	Parameters monitored	Extract/placebo/Reference	Adverse effects and related findings
Neuhaus et al., 2000 Prospective, randomized, placebo controlled, double-blind, parallel group study.	***Condition:*** Women with anxiety concerning suspected breast cancer Intention to treat; N=20	• State trait anxiety scale (self rating) • 60 item characteristic word list (self rating) • State trait anxiety inventory (observed rated) Tests were conducted before the tissue samples were taken, and after 3 and 7 days	**Kava Extract:** ***Type:*** dry extract from root stock standardized to 47.5 to 52.5 kavapyrones ***Dose:*** 3 x 150 mg capsules/day ***Route:*** Oral ***Duration:*** 7 days ***Number of subjects:*** 10 **Placebo group:** ***Number of subjects:*** 10	**Kava Group:** ***Adverse effects:*** None observed. **Placebo Group:** ***Adverse effects:*** None observed.

This study was published in German wtih an English abstract.

Table 2j Summary of adverse effects in clinical trials
(ethanolic extract)

Study Design	Subjects/participants	Parameters monitored	Extract/placebo/Reference	Adverse effects and related findings
Thompson et al., 2004 Double-blinded, randomized, placebo-controlled. ***Institution:*** University of Hertfordshire, UK. ***Objective:*** To investigate the effects on emotional reactivity and cognitive performance.	***Condition:*** Healthy volunteers ***Ages:*** 18-53 yrs. 11 females, 9 males N=20	• State-trait-cheerfulness-inventory for mood changes Administered before and 50 minutes after intake. • Sperling partial report and Sternberg item recognition task for cognitive performance Administered 60 min. after intake.	**Kava Extract:** ***Type:*** standardized to 30% kavapyrones ***Dose:*** 2 x 150 mg capsules ***Route:*** Oral ***Duration:*** 1 dose of medication ***Number of subjects:*** 10 **Placebo group:** ***Number of subjects:*** 10	**Kava Group:** ***Adverse effects:*** None observed. **Placebo Group:** ***Adverse effects:*** None observed.

This study was published in English.

Table 2k Summary of adverse effects in clinical trials
(ethanolic extract)

Study Design	Subjects/participants	Parameters monitored	Extract/placebo/Reference	Adverse effects and related findings
Watkins et al., 2004 Double-blinded, randomized, placebo-controlled ***Institution:*** Duke University, USA ***Objective:*** To examine whether kava produces improvement in vagal control	***Condition:*** Outpatients with DSM-IV generalized anxiety disorder N=13	• Baroreflex control of heart rate (BRC) • Blood pressure • Respiratory sinus arrhythmia (RSA) Tests were conducted 1 day before, and 4 weeks after treatment.	**Kava Extract:** ***Type:*** standardized to 30% kava lactones ***Dose:*** 280 mg capsule/day ***Route:*** Oral ***Duration:*** 4 weeks ***Number of subjects:*** 6 **Placebo group:** ***Number of subjects:*** 7	**Kava Group:** ***Adverse effects:*** None observed. **Placebo Group:** ***Adverse effects:*** None observed.

This study was published in English, abstract was available.

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Section IIB Case reports of hepatotoxicity

Case reports of hepatotoxicity with kava

Data on case reports of hepatotoxicity with kava are presented along with related topics in 16 tables as follows:

1. Basic pharmacovigilance data
2. Additional data
3. Types of hepatic events
4. Histological changes
5. Concomitant potentially hepatotoxic medicines
6. Concomitant therapy not suspect
7. Patient outcome
8. Reports with a probable relationship
9. Reports with a possible relationship showing concomitant medicines
10. Reports with rechallenge information
11. Reports with an outcome of liver transplant
12. Reports with an outcome of death
13. Potential kava-drug interactions: alphabetical listing
14. Potential kava-drug interactions: listing by ATC code
15. Potential kava-drug interactions: listing in ATC groups
16. Reports not included with those of hepatotoxicity.

Sources

A detailed key to these tables is included. The key gives the sources referred to in the tables of case reports. Additional sources were as follows:

1. Centers for Disease Control and Prevention. Hepatic toxicity possibly associated with kava-containing products – United States of America, Germany, and Switzerland, 1999-2002. Morbidity and Mortality Weekly Report (MMWR). 2002;51:(47):1065-1067.
2. Schmidt M (2003) Is kava really hepatotoxic? An analysis of the known data on adverse effects of kava preparations on the liver. Universität Münster; 2003. Available from: http://www.uni-muenster.de/Chemie.pb/Kava/kavaframe.html.
3. Traditional Medicines Evaluation Committee. Response to concerns about *Piper methysticum* Forst. f., Kava. Traditional Medicines Evaluation Committee (TMEC), a subcommittee of the European Herbal Practitioners Association. 2002 Jan 11.
4. Waller DP. Report on kava and liver damage. American Herbal Products Association, Silver Spring, Maryland. 2002 Feb 15.

Data for many of the case reports was obtained from more than one source. There were inconsistencies in detail (e.g. age) from the different sources. Several authors have undertaken follow-up studies and generally, the latest data in the follow-up studies was used where differences existed. Great care has been taken to try to avoid duplications, but with the inconsistencies and incompleteness of data that might otherwise help match cases from different sources, it is likely that some duplications persist in those presented. In particular, Stickel et al. stated that they presented 27 cases from BfArM. We have been unable to match four of these cases with the BfArM data obtained from other sources and so there is potential for duplication here. In addition, two of the WHO cases from Germany could not be matched elsewhere.

Numbers

93 case reports are recorded (Tables 1 and 2). There are six case reports commonly included in reviews which are excluded from this report because the event details are too non-specific (table 16). Event descriptions used were: 'gall bladder pain', 'pain right hypochondrium', 'GT increased', 'faeces discoloured'. In the absence of other features, these are not indicative of liver disease. There was also a report of hepatic enzymes increased, but these had been increased prior to the consumption of kava and in the absence of any indication of subsequent change it does not qualify as a new event. These reports seem irrelevant and their inclusion may skew analyses.

Gender and age

Gender: Females 73 (79%); Males 20 (21%).

Age was given in 84 patients; mean 45.2 years; range 14-81 years; SD 13.38 years.

The preponderance of women might reflect the distribution of the population using kava. The mean ages for acetone (n=13) and ethanol (n=29) extracts and synthetic products (n=3) was 46.3, 45.8 and 46.1 years respectively. The mean for water extracts was 43.4 years. There were no statistically significant differences in mean ages and nor were there any statistically significant differences in gender distribution between extracts.

Products and extracts

Products: Of the kava products specifically named, the following were recorded most frequently: Laitan 14, Antares 8, Kava Ratiopharm 8, Kavatino 3.

Extracts: In 54 (58%) of the cases the type of extract could be identified. These were: ethanol 32 (59%), acetone 14 (26%), water 5 (9%), synthetic 4 (7%). The count of these is 55, but one patient was taking both synthetic and ethanol products. In an additional case (No. 1) the product is called 'Kava kava rhizoma' with no indication of the kind of extract available. One possibility is that it was the powdered rhizome used for making tea and in that case the product taken would have been a water based preparation. The dose quoted is very high for organic extracts and more like that of a water extract.

The greater proportion of patients using ethanol extracts is likely to be due to their prevalence of use and not because of any greater toxic effect on the liver (see *Comparative risk of extracts* below).

Doses

In a few patients a range of doses was given. In these cases dose analyses were based on the mid-point of the range. Mean doses were calculated separately for acetone and ethanol extracts and dose values were only included if they were expressed as kava lactones. There were 13 such doses included in the acetone extract group and the mean dose was 142.7 mg/day; range 70-245 mg/day; SD 67.72 mg/day. There were 25 included in the ethanol extract group with a mean daily dose of 165.8 mg; range 30-840 mg/day; SD 162.30. The difference in means is not statistically significant (t-test: t=0.489, DF=36, P=0.6277). The doses for water extracts were very much higher. Kava lactones are not soluble in water and form a microsuspension with lower bioavailability than the acetone and ethanol extracts (see Section I, 'Pharmacokinetic–pharmacodynamic considerations'), hence the higher doses. Because of this higher dose, and lack of standardization of kava lactone content in water extracts, they are excluded from comparative dose analyses.

The recommended dose range of kava lactones for the treatment of anxiety has varied, but the most recent recommendations from German Commission E, taking into account efficacy and risk of hepatotoxicity, appear to be daily doses of 120-240 mg/day for up to eight weeks (Blumenthal, 2000; Gruenwald et al, 2003). In 1990, the German commission E had recommended 60-120 mg kava lactones for not more than 12 weeks. There were 40 reports where the kava lactone dose was given for acetone or ethanol extracts, or synthetic products. Of these, 5 (12.5%) exceeded the upper limit of the recommended dose, but one of these was only marginally above the limit (245 mg), leaving four (10%) with a daily dose greater than 245 mg/day. Further, 12 (30%) of the reported cases were using daily doses below the recommended lower limit (range 30-70 mg/day). Of the cases coded with a probable relationship (table 8), using ethanol or acetone extracts and with the dose specified as kava lactones (n=5), none exceeded the upper recommended limit of 240 mg/day. These results are not consistent with the claim that 80% of patients took kava in overdose (Teschke et al. 2003).

Duration to onset of the event

Only the WHO database, the Brazil reports and a few of the FDA reports provided appropriate dates for accurate assessment of this data element: date of first administration, date of onset of the event and date of withdrawal of the product. Most gave a period of administration in terms of weeks or months. In some cases withdrawal obviously took place several weeks after the onset of the event. Figures in Table 1 are bracketed when they appear to represent the total administration time and not specifically the time to onset of the event. For the purposes of calculation of statistics, all durations have been converted to days. The figures are inaccurate, but nevertheless useful.

74 (80%) of the reports provided information on duration. The mean for these cases was 111 days, SD 130, range 6-730 days. 80% fell within 135 days (4.5 months), while 90% fell within 195 days (6.5months). The median time to onset was 90 days. Taking cognizance of the current recommended duration of therapy of 8-12 weeks, only 46 (62%) of known durations were 90 days or less.

Without a comparator group of patients who did not suffer any hepatic events, no interpretation of these figures can be given to the effect of duration of therapy.

There were 14 reports with durations in those using acetone extracts and 23 for ethanol extracts. The means were 105 and 119 days respectively. The difference is not statistically significant (t-test: t=0.322, DF=35, P=0.749).

Hepatic events

Terminology

A variety of event terms was used in the reports, many being synonymous and frequently several event terms were used in individual case reports. From these, a single term was selected for each report that provided the most appropriate description and as far as possible terminology has been standardized to that of WHOART.

Hepatic events

Those reported are listed in Table 3. Both cholestatic and hepatocellular types of liver disorder were described, but with many of the reports it was not possible to determine the initial type of injury.

Histological details

These were available in summary form for 28 of the reports and are shown in Table 2 and more particularly in Table 4. Necrosis was described in 16 (57%) of the 28 cases, hepatocellular injury in 8 (29%), cholestatic injury in 7 (25%) and in a further 8 (28%) cases the abnormalities were described as toxic in appearance or typical of drug induced or chemical damage. Case 7 showed an autoimmune type hepatitis which was unchanged more than four months later following withdrawal of kava and recovery from the illness. This suggests the likelihood of pre-existing autoimmune disease.

Concomitant therapy

Table 1 lists the presence or absence of concomitant therapy or whether this was recorded. There was no reference ('NR') to other therapy in 21 (22.6%) of the reports. In 57 (61.3%) of the cases other therapy was in use ('Yes') which might have caused or contributed to hepatic abnormalities. In 8 (8.6%) cases other therapy was in use which is not suspected ('NS') of causing liver damage and in 7 (7.5%) it was stated that no other therapy or significant alcohol was in use ('No').

Table 2 shows for each case what other significant therapy or possibly significant alcohol intake was in use. Table 5 lists those medications used concurrently with kava, which could be suspected of causing or contributing to the hepatic event. The reference standard used for determining this has been the DrugDex evaluations published by Micromedex and the evaluations published by Natural Standard. Hepatotoxicity with some of the medicines listed must be very rare indeed, e.g. with penicillin V, one of the most widely used of all medicines. Over the period in which reports of hepatotoxicity with kava were identified there were no reports in the WHO worldwide database of hepatic necrosis, the commonest type of hepatic event diagnosed (histologically) with kava.

There were 19 of 31 (61.3%) reports in which ethanolic

extracts were associated with other suspect drugs and eight of 14 (57.1%) of reports with acetonic extracts. Comparing the two extract types, the relative risk (ethanolic v acetonic) of an extract being associated with another suspect drug was 1.07 (95% CI 0.63-1.28). This difference is not statistically significant.

Table 6 shows the products not suspected of being involved in the hepatic event.

Dechallenge

This important information was often missing. Dechallenge was not mentioned in 30 reports (32%) (Table 1). When dechallenge took place, there was usually the implication that all other therapy was withdrawn at the same time.

Outcome

Outcome information is shown in Table 7. The outcome was unknown or not stated for 19 (20.4%) of the cases. There are 14 (15%) liver transplants recorded and seven (7.5%) deaths. 53 patients (57%) were known to have recovered or were improved at the time of the report.

Relationship and causality

Establishing the strength of the relationship between administration of a medicine and a clinical event is the first step towards assessing causality. In general, most case reports or case series describe a relationship and the likelihood of a causal association is strengthened or established later from an aggregation of reports taking into consideration pharmacological and epidemiological factors in particular. This report follows the widely used causality categories / definitions of the WHO Collaborating Centre for International Drug Monitoring (*the* Uppsala Monitoring Centre, 2000).

None of the events reported were classified as certain. For this term to be applied there needs to be a plausible relationship time-wise with the administration of the product, recovery on withdrawal, the absence of confounding factors (eg concomitant medicines) and a positive rechallenge of the suspect drug alone. Clearly deaths cannot fit this category. It is also suggested that patients who had liver transplants cannot fit this category because there can be no rechallenge of the same organ.

Eight reports (8.6%) were classified as having a *probable relationship* (Table 8). For a 'probable' classification to apply there must be good information, which would include duration to onset of the event, recovery on withdrawal of the product (known outcome) and the absence of other potential causes of hepatotoxicity. If the time to onset of the event is well outside the usual compared with other cases in the series, or information on withdrawal or the outcome is not known, then the relationship should not be classified as probable. Reports with liver transplants have been excluded from this category because the organ did not recover on withdrawal of the kava product.

Table 9 lists 54 cases classified as *possible*. This grading may have been applied due to lack of information e.g. outcome, or to the concomitant use of other products, including alcohol, which had the potential to cause liver damage. As previously stated, it could be argued that some of the concomitant drugs listed would be highly unlikely to cause a hepatic reaction e.g. penicillin V. In addition it is impossible to interpret the significance of comments such as, 'regular alcohol' or 'moderate alcohol', but some doubt as to their potential effect exists and so the 'possible' classification was used.

It has been argued on a number of occasions that because a potential hepatotoxic product has been in use concomitantly with kava, the hepatic event would not be caused by kava (Schmidt 2003), but this is not true. It simply means that doubt exists. In addition there is considerable potential for the interaction of kava with a wide variety of medicines (Table 13).

There are 28 cases (30%) listed as *unassessable* (Rel 6, Table 1) because of lack of data.

Although there are uncertainties about many of the cases, there is good evidence of hepatotoxicity with kava, including *water-based 'extracts'*. There are five reports associated with water-based preparations, two of which are coded probable and three possible. Only two of these were prepared in the traditional manner.

Rechallenge

A positive rechallenge is a requirement for coding a drug-event relationship as 'certain' (or 'definite'). Table 10 lists the five case reports with rechallenge information. These cases are discussed in some detail because of the importance of this observation. All had recurrence of liver problems with rechallenge and all recovered on further withdrawal. However none of these five reports were coded as certain because other factors clouded the issue.

Four were coded as 'possible' (Nos. 26, 32, 33 & 80) and one as 'probable' (No. 19). Case 19 was coded probable because it was stated that rechallenge was with the kava product alone and although it is possible that the other drugs (paroxetine and Pramino—a COC) were involved in the development of the hepatic event, relapse of the event occurred with kava alone. In two of the 'possible' cases (Nos. 26, 32) it was stated that other potentially hepatotoxic drugs were used concurrently, but in neither case was it stated that rechallenge was with kava alone, although it would be reasonable to assume this. Case 26 had missing data (e.g. duration to onset) that further weakened the ability to assess the relationship. Cases 33 and 80 had no reference to the use of other drugs, but it cannot be assumed that none were being taken. Also, there was missing information in these two cases that further weakened the ability to assess the relationship. It should be understood that all five patients recovered on withdrawal of kava. This, of course, is a requirement before rechallenge is undertaken. In spite of the difficulties in assessment outlined, it remains significant that five patients relapsed on re-exposure to kava. Despite the unknown factors, this is an indication of a causal effect.

Four of the five were with ethanol extracts. In the fifth case the type of extract was unknown.

Differential diagnosis

The main principle of this review of case reports is to examine them collectively using pharmacovigilance and pharmacoepidemiological methods. An intensive clinical

examination of each individual report is not intended and such an approach is often inconclusive because of the usual uncertainties and deficiencies of information. It is seldom that unequivocal conclusions can be reached on individual cases and elements of doubt usually remain. Conclusions reached are usually on the grounds of probability and stronger conclusions on probability are likely to be made by examining the whole aggregation of reports.

This approach does not mean that clinical factors should be ignored. Indeed they are very important, but when diagnostic features are not clear-cut an overall perspective of the aggregated reports is likely to be more helpful. The two most important problems in differential diagnosis are the questions of alcohol and acute viral hepatitis.

There are 11 (12%) reports where *alcohol* is mentioned as a possible factor, but unfortunately, usually in vague terms which are difficult to interpret. Only one (No. 92) had a diagnosis of chronic alcoholic liver disease. Another patient (No. 34) had cirrhosis before exposure to kava and died with a histological diagnosis of 'toxic hepatopathy'. A hepatic reaction to kava is not excluded in these two patients, because excessive exposure to alcohol could be a risk factor for a hepatic reaction to kava. One other of these 11 patients (No. 47) received a liver transplant and had a histological diagnosis 'toxic-necrotic hepatitis'.

Many of the clinical and histological features of the kava reports cannot be distinguished from acute *viral hepatitis*. It is known that 32 (34%) of the patients were admitted to hospital. In 60 (65%) of the reports hospitalization was not referred to and only in one was it stated that the patient was not admitted. Kava was not known as a potential cause of liver toxicity and in most patients, it would have been implicated unexpectedly by a process of elimination of the commonly known diagnoses. Hospitalized patients in particular should have been thoroughly investigated and acute viral hepatitis ruled out as a cause before kava was considered seriously. With this reasoning it seems highly unlikely that kava would have been considered before the exclusion of acute viral causes. Consistent with this, in the reports of 34 (37%) patients in the series, it was stated that acute viral infection was excluded. In 59 (63%), tests for acute viral infection were not mentioned. In 14 of these the patients had been admitted to hospital and it is assumed that they would have had tests for viral infection. If this assumption is correct, acute viral infection could be excluded from 48 (52%) of patients. There is no information about hospitalization or virus infection for the other 45 patients. Not surprisingly, none of the reports referred to positive tests for acute viral hepatitis.

It is of interest to look at the more serious cases. It was stated in the report details for 10 of the 14 transplant patients that tests for acute viral hepatitis were negative. The other four patients had, of course, been hospitalized and it seems safe to assume that they were also negative. Of the seven deaths, four were said to be negative and the other three had been hospitalized.

Liver transplants

Tables 11A and 11B summarize 14 reports with liver transplant. Three of these patients died. In only half was the *type of extract* available: 6 ethanol and 1 acetone. The relative risk for ethanol was 2.7 (95% CI 0.359 to 20.442). This is not statistically significant. The age spread was 14-60 years. One case (Case No. 18) was an overdose and another suspect drug was present as well. Alcohol was mentioned in only one ('moderate alcohol' in case 47). One patient (No. 86) was taking no other therapy, in one there was no other suspect drug (No. 31) and in another there was no reference to concomitant therapy. Eleven of the 14 patients were taking other therapy that could potentially cause hepatic reactions.

Of the 14 patients who had liver transplants the relationship (causality) coded was 'possible' in 10 and 'unassessable' in four.

The mean *age* for transplant patients was 42.6 years and for non-transplant patients 45.7. The mean *duration to onset* was 114.5 days for transplant patients and 110.2 for those without transplants. Neither of these differences is statistically significant. The range for duration to onset was two weeks to one year. Six of the 11 patients with durations were exposed for three months or less with three of two months or less.

Dose was assessed in reports which expressed the dose as kava lactones and for patients where the extract was identified as acetone (n=1) or ethanol (n=4). The mean for transplant patients was 325.0 mg per day and for non-transplant patients 132.6 mg per day. This difference in means is statistically significant (t-test: t = -3.302, DF = 36, 95% CI -310.63 to -74.22, P = 0.0022). One of these cases (No.8) was an overdose. If this case is excluded, the mean dose for transplant patients falls to 196.25 mg and the difference in means is no longer statistically significant (P = 0.1201).

Age, duration to onset, or dose (excluding overdose) were not identified as risk factors for liver transplant when compared with non-transplant patients.

Outcomes of death

Table 12 shows details of the seven cases with a fatal outcome. Three of these appeared to be the result of complications from transplant surgery. All were taking other potentially hepatotoxic therapy as well as kava. There were four patients using ethanol extracts and the type of extract for the other three was unknown.

The *mean age* of patients who died was 46.3 years (range 22-81), while the mean for survivors was 45.1. The *mean dose* (n=4) (only ethanol extracts) for patients who died was 135 mg kava lactones per day (SD 75.50), while the mean dose of kava lactones (only ethanol extracts) for patients who survived was 165 mg per day (SD 173.36) (n=22). For the *duration to onset*, the mean was 126 days for patients who died and 109 days for survivors. There is no statistically significant difference between patients who died and the survivors for any of these factors.

Duration of exposure to kava for those who died ranged from 24 to 300 days. Four of the seven patients had a duration of three months or less. This does not seem to indicate that shorter periods of exposure are safer.

Liver injury leading to death was coded as having a 'possible' relationship in all seven cases, whether as a direct result of the hepatic event, or following transplant surgery.

Age, dose or duration of therapy were not identified as risk factors for death. No comparison was possible with patients who did not have hepatic events.

Interactions

Kava is said to induce or inhibit multiple cytochrome P450 enzymes which are important agents in the metabolism of many drugs (Matthews et al. 2002; Clouatre 2004; Denham et al. 2002). Under experimental conditions, inhibition of the following P450 enzymes has been observed: 1A2, 2C9, 2D6, 3A4, and 4A9/11. This provides considerable potential for kava-drug interactions to occur and 200 drugs or combinations have been listed as interacting suspects (DrugDex 2005). These are presented in Tables 13 and 14 along with the ATC codes for the medicines. Table 15 groups the ATC codes for the drugs involved in the clinically relevant categories more commonly represented. Antipsychotics, anxiolytics and antithrombotic drugs are the most significant in number. Four of the cases (Table 2: Nos. 5, 30, 58, 75) received concomitantly drugs listed as having the potential for interactions (phenobarbital, diclofenac, and warfarin). Interaction with diclofenac (Nos. 30 and 75) in particular, might have caused hepatic damage.

Idiosyncratic reactions

Six patients (Nos. 7, 32, 43, 54, 55 and 78) showed evidence of an immune mediated idiosyncratic response while two (Nos.19, 43) had evidence of an idiosyncratic metabolic reaction, being deficient in CYP 2D6 enzyme (poor metabolisers). Genetic polymorphisms may well play a part in susceptibility to liver damage by kava either directly or by interaction with drugs. Idiosyncratic reactions may be either metabolic and dose-related in type or immunologic.

Incidence

Incidence cannot be calculated without knowledge of the population at risk for the denominator and an accurate estimate for the numerator of the number of cases of hepatotoxicity that have occurred in association with kava products. Neither of these is known. An estimate has been made of the incidence based on daily doses from sales figures for the denominator and attributable reported events for the numerator. This was calculated as 0.008 cases per one million daily doses (Schmidt 2001). Clearly the incidence is very low, but this estimate is not plausible. Estimates of patient use from sales figures are inaccurate because of wastage, variations in dosage and differences in periods of administration. But more importantly, it is not appropriate to base the numerator on known reported events from spontaneous reporting. With Western type pharmaceuticals the spontaneous reporting rate of adverse events is estimated to be 5% and is likely to be less with drug-event associations that are unknown or events that are not serious. This may be why there are few reports of non-serious hepatic events with kava. It is also well known that the reporting rate for herbal medicines is much less than for pharmaceuticals. It is likely that considerably less than 1% of adverse events associated with herbal medicines are reported.

Comparative risk of extracts

Rates of hepatic events were estimated for acetonic and ethanolic extracts and synthetic products using German sales data for the denominators and German cases for the numerators. Patient numbers were not available for the calculation of rates. IMS figures for kava products sold in Germany for the years 1991-2001 were made available. These sales volume figures have been converted to the number of 120 mg dose equivalents (of kava lactones) sold and as such, have been used as the denominators. Unfortunately there was often no date of onset of the events available, but it could be determined that all of the cases included fell within this period. The earliest case report identified of suspected hepatotoxicity with kava was recorded in October 1990 (Table 1 case report 8) and this case was excluded from the risk calculations because it pre-dated the sales figures. There were no others identified prior to 1991. Nine cases were recorded in 2002, but except for one, it was obvious that the onset of the event occurred in 2001. The single exception was entered in June 2002, but treatment dates recorded were also in 2001. In respect of timing therefore, the cases and sales data match. Sales data were available for products derived from acetonic and ethanolic extracts and synthetic products only.

Comment on methodology

In the absence of data on patient numbers, the use of sales volume figures are an accepted method of estimating rates. Sales figures in the form of number of Defined Daily Doses (DDD), which have been developed by The WHO International Working Group for Drug Statistics Methodology, are a useful surrogate for patient numbers. There is no DDD for kava preparations, but a daily dose of 120 mg kava lactones was selected for our purposes.

The number of daily doses sold is likely to be a reasonable representation of patient numbers, but with reservations. They could only provide for reasonably accurate comparisons if patients took the different preparations for similar lengths of time. On a comparative basis, for equal sales volumes, longer periods of administration would result in smaller numbers of patients and conversely, shorter periods of exposure would result in larger numbers. Although there is no information on the comparative duration of exposure in relation to the different products in general, there is no statistically significant difference between the extracts for duration of exposure in the reports on hepatotoxicity.

Variations in doses used for different products could make comparisons inaccurate. In terms of doses used amongst the cases, there is no statistically significant difference between the two organic extracts, but the doses used for the synthetic products were higher at a significant level. If this was true of all users, an equivalent number of 120 mg doses would represent fewer patients for the synthetic products, which would in reality result in a smaller denominator for calculation of rates and the estimated rate would therefore be higher. This effect would result in a reduction of the difference between the organic extracts and synthetic products.

Three comparisons were made between the different products: (a) acetonic versus ethanolic extracts, (b) acetonic versus synthetic extracts and (c) ethanolic versus synthetic extracts. Cases were included regardless of the relationship (causality) assessment. The results are shown in the table:

Table: Comparison of risk of extracts of kava

Numerators are the number of German cases of hepatotoxicity reported associated with kava products. Denominators are the number of 120 mg dose equivalents of the relevant kava products sold in Germany from 1991-2001 (IMS data).

Acetonic extract	(Laitan)
Number of cases	13 cases from 69,285,876 doses
Ethanolic extracts	(Antares 7, Kava Ratiopharm 8, Kavacur 2, Kavain Harras Plus* 1, Kavasedon 1, Kavasporal Forte 1, Kavatino 3, Limbao 2, Maoni 2)
Number of cases	27 cases from 128,076,158 doses
Relative risk	(acetonic v ethanolic extracts) = **0.89**
95 % CI	= 0.46 to 1.73
Chi-square test	$\chi 2$=0.1192 df=1 P=0.7299

Acetonic extract	(Laitan)
Number of cases	13 cases from 69,285,876 doses
Synthetic	(Neuronika 2, Kavain Harras Plus* 1)
Number of cases	3 cases from 100,905,988 doses
Relative risk	(acetonic v synthetic extracts) = **6.31**
95 % CI	= 1.80 to 22.15
Chi-square test	$\chi 2$=10.8942 df=1 P=0.0010

Ethanolic extracts	(Antares 7, Kava Ratiopharm 8, Kavacur 2, Kavain Harras Plus* 1, Kavasedon 1, Kavasporal Forte 1, Kavatino 3, Limbao 2, Maoni 2)
Number of cases	27 cases from 128,076,158 doses
Synthetic	(Neuronika 2, Kavain Harras Plus* 1)
Number of cases	3 cases from 100,905,988 doses
Relative risk	(ethanol v synthetic extracts) = **7.09**
95 % CI	= 2.15 to 23.37
Chi-square test	$\chi 2$=14.1258 df=1 P<0.0002

*Each pill of Kavain Harras Plus contained 50 mg kava lactones consisting of 30 mg of synthetic origin and 20 mg derived from an ethanolic extract and so this case was included in both groups. The sales figures for the denominator were apportioned in a 30:20 ratio for the products that were of synthetic and ethanolic extract origin respectively.

Interpretation of results

a. There was no statistically significant difference in the relative risk of hepatotoxicity between products prepared from acetonic and ethanolic extracts.
b. Hepatotoxicity with the product prepared from an acetonic extract (Laitan) occurred at approximately six times the rate of that for synthetic products. This difference is statistically significant.
c. Hepatotoxicity with products prepared from ethanolic extracts occurred with a relative risk of approximately seven when compared with synthetic products. This difference is statistically significant.

In respect of the rate estimate for the synthetic products there is potential for reporting bias with a resulting underestimate compared with the organic extracts. The international 'scare' concerning kava and hepatotoxicity in 2001 resulted in increased reporting and occurred at a peak in the sales of products produced from acetonic and ethanolic extracts. However, sales of the main synthetic product (Neuronika) had dropped by almost 90% over the decade and were low at the time of the scare and associated increased reporting.

On the other hand, the mean dose of kava lactone in cases using the synthetic products was greater than that for products from acetonic or ethanolic extracts at a statistically significant level: compared with acetonic products $t = 8.170$, $DF = 13$, $P < 0001$; compared with ethanolic products $t = 2.703$, $DF = 27$, $P = 0.0117$. If there is a dose relationship for hepatic events, then these differences in mean doses should lead to an increased rate with the synthetic products. In these terms, the lower rate estimate for the synthetic products has increased significance.

There was no statistically significant difference in mean age between the users of the acetonic and ethanolic extracts or the synthetic products.

The differences in rates of hepatic events between patients who took the products derived from the organic extracts and those who took the synthetic products cannot be explained by differences in age, gender, dose or duration of therapy. Nor can they be explained by the concomitant use of other suspect drugs, including alcohol. There were no statistically significant differences in these parameters, (with the exception of dose). There is also no indication that patients using the organic extracts had a different pattern of background morbidity or diseases affecting the liver, or genetic differences, that might explain the difference in rate of the synthetic products, although numbers of the latter are small.

The differences in rates of hepatic events therefore reveal that hepatic problems associated with the use of the organic extracts are probably non-random and that some of the events at least, are due to the kava products used. Because doses of kava lactones used with the synthetic products were greater, it is reasonable to assume that the toxic effects are likely to be due to, or influenced by, components other than kava lactones in the extracts.

Although these results are subject to potential biases concerning dose and reporting rate, the lower rate estimate for synthetic products is plausible and is consistent with the proposition that hepatotoxicity related to the organic extracts is due to non-kava lactone chemicals extracted by the solvents.

The results do not allow any firm conclusions concerning the potential hepatotoxicity of the synthetic products, which are presumably without the additional chemicals that might be toxic to the liver in the organic extracts. The synthetic products appear safer than the organic extracts. There were no reports within the recommended dose range. Two of the three reports concerning synthetic products alone were coded as possible (see table). Synthetic products and water extracts might have an adverse effect on the liver through kava-drug (or kava-herb) interactions and genetic polymorphism.

Risk factors

Based on the number of daily doses sold as denominators, there appears to be a higher risk of hepatic events in patients taking acetonic and ethanolic extracts than with synthetic products.

Other possible risk factors for the development of hepatotoxicity with kava (age, gender, dose, duration of therapy) cannot be assessed because of the lack of a comparator group of kava-takers who did not develop hepatotoxicity. Age and

duration of therapy do not appear to increase the risk of liver transplant or death.

- Excessive dose of kava may possibly increase the risk of liver transplant and presumably, the risk of developing hepatotoxicity.
- There is no significant difference seen between the chemical extracts (acetone or ethanol) in the risk of developing hepatic failure requiring transplant. As there were no fatal cases recorded as using acetonic extracts, the comparative risk with ethanolic extracts cannot be calculated.
- Genetic polymorphism causing a deficiency of cytochrome P450 2D6 and/or other isoenzymes seems likely to increase risk.
- There is strong theoretical potential for kava-drug interactions to cause hepatic reactions.
- Alcohol was mentioned as a possible factor in 11 of the cases, and excessive use must be considered as a risk factor.

Summary of findings of review of case reports

1. 93 case reports of hepatotoxicity associated with the use of kava products have been compiled. There is the possibility of a small number of duplications.
2. The mean age was 45 years and 79% of the patients were women.
3. The type of extract used was given in 54 reports: ethanol 59%, acetone 26%, water 9%, synthetic 7%.
4. There appears to be a lesser risk of hepatic events in patients using synthetic products than in those using ethanolic or acetonic extracts.
5. The seemingly higher risk with the organic extracts was not related to age, gender, dose, duration of therapy or concomitant therapy and is unlikely to be related to intercurrent illness
6. An explanation for the apparent higher risk with the organic extracts seems likely to be due to the presence of chemicals other than kava lactones. Presumably such chemical constituents are not present in the synthetic products and are not significantly bioavailable in the water-based preparations.
7. There is evidence that idiosyncratic reactions occur, both metabolic and immunologic.
8. The mean duration to onset of liver problems was 111 days. 80% fell within 4.5 months.
9. Both cholestatic and hepatocellular liver injury were described. Hepatic necrosis was the most common lesion seen histologically.
10. There is considerable potential for kava-drug interactions. 61% of patients had concomitant therapy which may have caused or contributed to the hepatic event.
11. There were 14 liver transplants and seven deaths.
12. Of the 93 reports, eight were coded as having a probable causality and 53 as possible. 28 were unassessable.
13. Five of the patients had a positive rechallenge.
14. There were five reports involving water extracts. Three were coded with a causality of possible and two probable. Two were from traditionally prepared kava.
15. Of the hepatic events leading to the 14 transplants, 11 were coded as having a possible relationship and three as unassessable.
16. The events for all seven patients who died were coded as having a possible relationship.
17. 15 (16%) of the patients had either no other drug, or alcohol, or no other suspect therapy.
18. A causal relationship between products derived from acetonic and ethanolic extracts and liver toxicity seems likely.
19. Risk factors appear to be the use of organic extracts, concomitant therapy with potentially hepatotoxic drugs or other drugs with a potential for interaction with kava, pre-existing liver disease, alcohol and genetic polymorphism of the cytochrome P450 system causing enzyme deficiency.
20. The higher rate of toxicity with the organic extracts could be due to the use of incorrect plant parts or inappropriate cultivars.
21. There is a lack of accepted standards for the growth of kava, collection practices and supply of the raw material for medicinal purposes. There is also inadequate quality control in the selection of appropriate cultivars of *Piper methysticum* in the collection of the appropriate plant parts and in the preparation and testing of the raw materials.

Key to tables

Order The tables are sorted by type of extract.

No = reference number.

Age: in years.

Dose: in mg per day. The dose refers to the kava lactone content where possible, but sometimes to the product.

Dur = duration on therapy in days. Unbracketed numbers refer to the time to onset of the event. Bracketed numbers refer to the time on treatment without reference to the onset of the event.

OPS = other possible suspect drugs. This refers to concomitant therapy. NR = not recorded; NS = Other products were in use but not suspected as being culpable; No = It was reported that no other therapy was being given concomitantly; Yes = Other medications were in use which might have caused or contributed to hepatotoxicity.

Dech = dechallenge. X = no information given; Y = Yes, dechallenge occurred or there were strong reasons for assuming this; N = No, the product being continued for a significant period beyond the event.

Rech = rechallenge. X = no information given; N = no; R = rechallenge occurred with a recurrence of the problem; Neg = rechallenge occurred with a negative result.

Rel = relationship (causality). Grades are according to WHO definitions: 2 = probable; 3 = possible; 4= unlikely; 6 = unassessable.

Report Id = identifier used by the main source of information.

Other sources = Other sources from which information was gleaned.

Main sources

1. *BfArM* = German Federal Institute for Drugs and Medical Devices. (This information was sourced from the Phytopharm document.)

2. *Brazil* = The national Brazilian Drug Monitoring Centre
3. *Denham* = Denham A, McIntyre M, Whitehouse J. Kava—the unfolding story: report on a work-in-progress. The Journal of Alternative and Complementary Medicine 2002; 8(3):237-263.
4. *FDA* = USA Food and Drug Administration.
5. *IKS* = Swissmedic = Swiss Agency for therapeutic products.
6. *Literature*
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10. *WHO* = WHO Collaborating Centre (the Uppsala Monitoring Centre) database.
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Table 1 Case reports of hepatotoxicity with kava: Basic pharmacovigilance data

No	Sex	Age	Product	Extract	Dose	Dose Type	Dur	Hepatic event	OPS	Dech	Rech	Outcome	Rel
01	M	-	Kava-kava rhizoma	Water	900		-	Hepatic function abnormal	NR	X	X	Not recovered	6
02	F	37	Kava Gold	Water	750	kava lactones	(24)	Jaundice	NR	Y	X	Improving	3
03	F	27	Kava tea	Water	2400	kava lactones	(180)	Jaundice	NS	Y	N	Recovered	2
04	F	55	Kava traditional drink	Water	2571	kava lactones	35	Hepatocellular liver injury	No	Y	N	Recovered	2
05	F	59	Kava traditional drink	Water	-		28	Hepatocellular liver injury	Yes	Y	N	Recovered	3
06	F	39	Natures Way Celestial Kava tea	Water	-		180	Hepatitis	Yes	Y	Neg	Recovered	3
07	F	21	Kavain Harras plus	Synthetic+ Ethanol	400-500	kava lactones	(210)	Hepatitis	Yes	Y	N	Recovered	4
08	M	35	Neuronika	Synthetic	400	kava lactones	56	Hepatitis cholestatic	Yes	Y	N	Recovered	3
09	F	-	Kavain harras	Synthetic	-		-	Hepatitis	NR	X	X	Unknown	6
10	F	69	Neuronika	Synthetic	400	kava lactones	56	Hepatitis cholestatic	Yes	Y	X	Recovered	3
11	F	22	Antares	Ethanol	240	kava lactones	120	Hepatic necrosis	Yes	Y	N	Transplant, Died (6 months)	3
12	M	32	Antares	Ethanol	240	kava lactones	(75)	Hepatic necrosis	Yes	Y	N	Transplant	3
13	F	35	Antares	Ethanol	120	kava lactones	57	Hepatitis	Yes	Y	N	Recovered	3
14	F	37	Antares	Ethanol	120	kava lactones	-	Hepatitis	NR	X	X	Not recovered	6
15	F	46	Antares	Ethanol	240	kava lactones	(105)	Cirrhosis	Yes	Y	N	Recovered	3
16	F	46	Antares	Ethanol	360	kava lactones	(28)	Jaundice	NR	Y	N	Recovered	3
17	F	47	Antares	Ethanol	120	kava lactones	(30)	Hepatic function abnormal	Yes	N	N	Recovered	3
18	F	60	Antares	Ethanol	480-1200	kava lactones	(365)	Hepatic failure	Yes	Y	N	Transplant	3
19	F	39	Kava	Ethanol	60	kava lactones	194	Hepatic necrosis	Yes	Y	R	Recovered	2
20	F	-	Kava Ratiopharm	Ethanol	-		-	Hepatitis	Yes	X	X	Unknown	6
21	F	34	Kava ratiopharm	Ethanol	120	kava lactones	(90)	Hepatitis	NS	Y	N	Recovered	2
22	M	39	Kava Ratiopharm	Ethanol	120	kava lactones	210	Hepatitis	Yes	Y	X	Recovered	3
23	F	50	Kava Ratiopharm	Ethanol	60	kava lactones	(195)	Hepatic failure	Yes	Y	N	Transplant, Died [Stickel]	3
24	M	50	Kava Ratiopharm	Ethanol	120	kava lactones	(180)	Jaundice	NR	X	X	Unknown	6
25	F	52	Kava Ratiopharm	Ethanol	60	kava lactones	(105)	Hepatic function abnormal	NR	X	X	Unknown	6
26	F	56	Kava Ratiopharm	Ethanol	-		-	Hepatitis	Yes	Y	R	Recovered	3
27	F	61	Kava Ratiopharm	Ethanol	120	kava lactones	(90)	Hepatic failure	Yes	X	X	Died	3
28	F	32	Kavacur	Ethanol	240	kava lactones	(28)	Hepatitis	Yes	X	X	Unknown	6
29	M	45	Kavacur	Ethanol	120	kava lactones	(90)	Hepatitis cholestatic	NR	Y	X	Unknown	3
30	F	26	Kavasedon	Ethanol	50	kava lactones	6	Hepatitis	Yes	Y	N	Recovered	3
31	F	47	Kavasporal forte	Ethanol	-		-	Hepatic failure	NS	X	X	Transplant	6
32	F	33	Kavatino	Ethanol	180	kava lactones	(120)	Hepatitis toxic	Yes	Y	R	Recovered	3
33	F	62	Kavatino	Ethanol	60	kava lactones	-	Hepatocellular liver injury	NR	Y	R	Recovered	3
34	F	81	Kavatino	Ethanol	120	kava lactones	(300)	Hepatic failure	Yes	Y	N	Died	3
35	M	55	Kavosporal	Ethanol	30	kava lactones	(28)	Hepatitis cholestatic	Yes	Y	X	Recovered	6
36	F	41	Limbao	Ethanol	-		-	Hepatic failure	Yes	X	X	Transplant	6
37	F	59	Limbao	Ethanol	240	kava lactones	120	Hepatocellular liver injury	NS	Y	X	Recovered	2
38	F	-	Maoni	Ethanol	-		-	Hepatitis	NR	X	X	Unknown	6
39	F	45	Maoni	Ethanol	45	kava lactones	(120)	Hepatitis	NS	Y	N	Recovered	2
40	F	24	Maoni forte	Ethanol	120	kava lactones	(90)	Jaundice	NR	X	X	Unknown	6
41	F	72 / 75	Phyto-Geriatrikum	Ethanol	25	extract	(730)/ (180)	Hepatitis cholestatic	Yes	Y	X	Recovered	3
42	F	-	Laitan	Acetone	70	kava lactones	60	Hepatic failure	NR	Y	X	Unknown	3
43	F	33	Laitan	Acetone	210	kava lactones	(21)	Hepatitis cholestatic	NS	Y	N	Recovered	2
44	F	37	Laitan	Acetone	140	kava lactones	(60)	Hepatitis	Yes	Y	Neg	Recovered	3
45	F	39	Laitan	Acetone	210	kava lactones	106	Jaundice	Yes	Y	X	Recovered	3
46	F	46	Laitan	Acetone	140	kava lactones	(135)	Hepatocellular liver injury	Yes	Y	N	Recovered	3
47	M	50	Laitan	Acetone	210-280	kava lactones	30	Hepatitis toxic	Yes	Y	N	Transplant	3
48	M	50	Laitan	Acetone	140	kava lactones	120	Hepatic function abnormal	NR	Y	N	Recovered	4
49	F	57	Laitan	Acetone	100		30	Hepatitis	Yes	Y	X	Recovered	3

Table 1 Case reports of hepatotoxicity with kava: Basic pharmacovigilance data (continued)

No	Sex	Age	Product	Extract	Dose	Dose Type	Dur	Hepatic event	OPS	Dech	Rech	Outcome	Rel
50	F	59	Laitan	Acetone	70	kava lactones	(21)	Hepatocellular liver injury	Yes	Y	N	Recovered	3
51	M	36	Laitan 100	Acetone	70	kava lactones	46	Hepatic necrosis	NR	Y	N	Recovered	3
52	M	38	Laitan 100	Acetone	70	kava lactones	21	Hepatitis	Yes	Y	X	Recovered	3
53	M	39	Laitan 100	Acetone	70	kava lactones	14	Hepatocellular liver injury	No	Y	X	Recovered	3
54	F	50	Laitan 100	Acetone	210	kava lactones	75	Hepatitis	Yes	Y	X	Recovered	3
55	F	68	Laitan 100	Acetone	210	kava lactones	730	Hepatitis cholestatic	NS	Y	X	Recovered	3
56	F	45	Combination NOS		150	kava lactones	56	Hepatitis cholestatic	Yes	Y	X	Transplant	3
57	M	24	Hard Gainers 6		200	product (6 herbs)	24	Hepatic failure	Yes	Y	N	Died	3
58	F	70	Herbalife KB		180	kava lactones	-	Hepatic function abnormal	Yes	X	X	Unknown	6
59	M	72	Hi-Health		-		14	Liver injury	Yes	X	X	Unknown	6
60	F	-	Kava		120	kava lactones	(365)	Hepatic function abnormal	NR	X	X	Unknown	6
61	F	-	Kava		-		LT	Hepatic function abnormal	NR	X	X	Unknown	6
62	F	24	Kava		120	kava lactones	(150)	Hepatitis cholestatic	No	X	X	Recovered	6
63	F	28	Kava		-		-	Hepatic function abnormal	Yes	X	X	Not recovered	6
64	F	30	Kava		200		60	Hepatitis fulminant	Yes	Y	N	Died	3
65	M	33	Kava		100		(14)	Hepatic necrosis	Yes	X	X	Recovered	6
66	F	33	Kava		-		-	Jaundice	Yes	X	X	Transplant	6
67	F	34	Kava		120	kava lactones	(30)	Not described	No	X	X	Recovered	6
68	M	38	Kava		-		-	Hepatitis	NS	X	X	Unknown	6
69	F	39	Kava		-		(60)	Hepatic function abnormal	Yes	Y	N	Recovered	3
70	F	39	Kava		-		(60)	Hepatic function abnormal	Yes	Y	X	Recovered	3
71	M	40	Kava		-		90	Hepatic function abnormal	Yes	Y	X	Recovered	3
72	F	41	Kava		120	kava lactones	(300)	Not described	No	X	X	Recovered	6
73	F	43	Kava		-		14	Hepatic failure	Yes	X	X	Transplant	3
74	F	44	Kava		-		-	Hepatic function abnormal	Yes	Y	X	Unknown	6
75	F	44	Kava		200		119	Hepatitis fulminant	Yes	Y	N	Transplant	3
76	F	46	Kava		-		101	Hepatitis	NR	Y	N	Unknown	4
77	F	47	Kava				90	Hepatic function abnormal	NR	X	X	Unknown	6
78	F	49	Kava		120	kava lactones	(30)	Hepatic necrosis	Yes	X	X	Recovered	6
79	F	51	Kava		-		(120)	Hepatic function abnormal	Yes	Y	X	Recovered	3
80	F	51	Kava		-		(60)	Hepatic function abnormal	NR	Y	R	Recovered	3
81	F	53	Kava		-		-	Jaundice	Yes	Y	X	Recovered	3
82	M	55	Kava		750		90	Hepatitis	No	Y	N	Recovered	2
83	F	57	Kava		120		150	Hepatitis	Yes	X	X	Recovered	3
84	F	60	Kava		-		(90)	Hepatic failure	NR	X	X	Transplant	6
85	F	60	Kava		-		-	Hepatic function abnormal	Yes	Y	X	Recovered	3
86	F	14	Kava (2 products)		-		105	Hepatitis fulminant	No	Y	N	Transplant	3
87	F	56	Kava 1800 Plus		180	kava lactones	(90)	Hepatic failure	Yes	Y	N	Transplant, Died	3
88	F	-	Kava extract		450	extract	(60)	Hepatic function abnormal	Yes	Y	X	Recovered	3
89	M	63	Kava formula		300	product	(42)	Hepatocellular liver injury	Yes	Y	X	Improved	3
90	M	38	Kava Kava liquid extract		50	kava lactones	(14)	Hepatitis	NR	Y	X	Recovered	3
91	F	-	NutriZAC		30	kava lactones	(730)	Hepatic function abnormal	Yes	Y	X	Recovered	3
92	F	52	Puritan's Pride		-		-	Cirrhosis	Yes	X	X	Unknown	6
93	F	-	TruNature Kava		150-225	kava lactones	(90)	Hepatic function abnormal	Yes	Y	N	Improving	3

Table 2 Case reports of hepatotoxicity with kava: additional data

No	Report Id	Source	Other sources	Sex	Age	Concomitant	Comment	Histology
01	2821655	WHO		M	-	Not recorded		
02	14995	FDA	Phytopharm 2.4.21 (EMEA 60)	F	37	(Unknown herbals)		
03	15281	FDA	Phytopharm 2.5.4 (EMEA 55)	F	27	None suspect		
04	11.2	Literature (11)		F	55	None		
05	11.1	Literature (11)		F	59	Lisinopril, phenobarbital, fenofibrate	All drugs withdrawn. Other drugs restarted.	
06	15466	FDA	Phytopharm 2.6.21 (EMEA 58)	F	39	Tetracycline, alcohol		
07	3608	BfArM	WHO 8100484, Phytopharm 2.6.5 (EMEA 21)	F	21	Paracetamol, pantoprazole, MDMA		Autoimmune hepatitis un-changed after > 4 months
08	92901203	BfArM	Denham 2, Phytopharm 2.4.1 (EMEA 11)	M	35	'Regular alcohol'		
09	33	MCA		F	-	Not recorded		
10	90003882	BfArM	Denham 1, Phytopharm 2.6.1 (EMEA 10)	F	69	Bemetizid, pentoxifyllin		
11	8627	Literature (3)	WHO 2767171. Phytopharm 2.5.3 (EMEA 23), BfArM 8627	F	22	COC (Pramino)		Cholestatic hepatitis. Pronounced necrosis.
12	1006229	BfArM	WHO 2852999, Phytopharm 2.4.6 (EMEA 31), Denham 30	M	32	Valerian		Necrotising hepatitis
13	99006200	BfArM	BfArM 1004110, WHO 2851883, MCA 25	F	35	Paracetamol		
14	8032012	WHO		F	37	Not recorded		
15	2000370	BfArM	Phytopharm 2.4.9 (EMEA 39)	F	46	COC (Klimonorm)		
16	2001414	BfArM	Phytopharm 2.4.17 (EMEA 41)	F	46	Not recorded		
17	99005139	BfArM	WHO 2464986, Denham 24, Phytopharm 2.7.2 (EMEA 3)	F	47	Fish oil		
18	8	Literature (8)	Phytopharm 2.6.23 (EMEA 5), similar to case 85 (Weekly Magazine)	F	60	Piretanide	Overdose	Necrosis & intrahepatic cholestasis
19	5	Literature (5)	Phytopharm 2.2.1, Denham 10	F	39	Paroxetine, COC (Pramino)	Rechallenge of kava only. Poor metaboliser.	Acute necrotising hepatitis
20	1003951	BfArM	BfArM 1003950, Denham 28	F	-	Omeprazole, estradiol, losarten		
21	1003089	BfArM	WHO 2851368, MCA 25, Phytopharm 2.4.4 (EMEA 24), Denham 22	F	34	None suspect		
22	1008989	BfArM	WHO 2854406, Phytopharm 2.6.12 (EMEA 34)	M	39	Interferon-beta		
23	6	Literature (6)	Denham 20, Stickel, Phytopharm 2.6.6 (EMEA 22), BfArM 5994	F	50	COC (Gravistat), glimepiride, metformin		Necrosis liver cells
24	2003559	BfArM	Phytopharm 2.4.14 (EMEA 48)	M	50	Not recorded		
25	2002541	BfArM		F	52	Not recorded		
26	2851799	WHO		F	56	Esberitox, omeprazole		
27	2001135	BfArM	BfArM 2002378, Phytopharm 2.6.14 (EMEA 40)	F	61	Bemetizid, omeprazole		Necrotising hepatitis
28	2004364	BfArM	Phytopharm 2.4.15 (EMEA 49)	F	32	COC (Marvelon)		
29	1009681	BfArM	Phytopharm 2.4.7 (EMEA 35)	M	45	Not recorded		Cholestatic hepatitis
30	2002090	BfArM	BfArM 2002836, Phytopharm 2.6.16 (EMEA 45)	F	26	Diclofenac, sulfasalazine, MPA		
31	2003010	BfArM	Phytopharm 2.7.4 (EMEA 46)	F	47	None suspect		Drug-induced cell necrosis and fibrosis
32	99006005	BfArM	WHO 2598102, Phytopharm 2.6.4 (EMEA 20), Denham 14	F	33	Cisapride		
33	99003911	BfArM	Denham 13, Phytopharm 2.4.2 (EMEA 19)	F	62	Not recorded		
34	98004297	BfArM	Denham 9, Phytopharm 2.7.1 (EMEA 16)	F	81	Alcohol, hydrochlorothiazide, nitrendipin	Cirrhosis preceded kava	Toxic hepatopathy
35	1010222	BfArM	Phytopharm 2.6.13 (EMEA 36)	M	55	Glibenclamide		Cholestatic hepatitis
36	15320	FDA		F	41	COC (Diane)		

Table 2 Case reports of hepatotoxicity with kava: additional data (continued)

No	Report Id	Source	Other sources	Sex	Age	Concomitant	Comment	Histology
37	2223603	WHO	BfArM 99500453, Denham 11, Phytopharm 2.4.3 (EMEA 17)	F	59	None suspect		
38	38	MCA		F	-	Not recorded		
39	1010536	BfArM	Phytopharm 2.4.8 (EMEA 37)	F	45	None suspect		
40	2002732	BfArM	Phytopharm 2.4.11 (EMEA 44), similar to case 64 (Stickel 27)	F	24	Not recorded		
41	97002825	BfArM	BfArM 97003551 Denham 7	F	72 / 75	Vitamin A	Combination product	
42	8030171	WHO	BfArM 2005178	F	-	Not recorded		
43	4	Literature (4)	Denham 16, Phytopharm 2.3.1 (EMEA 7), WHO 2639336, IKS 2000-0014	F	33	None suspect	Poor metaboliser	Drug-induced hepatitis
44	99062501	BfArM	Denham 12, Phytopharm 2.6.11 (EMEA 18)	F	37	Diclofenac, COC (Microdiol)		
45	93015209	BfArM	WHO 1384768, Denham 4, Phytopharm 2.6.3 (EMEA 12); similar to case 72	F	39	COC (Gravistat)	All meds withdrawn	Cholestatic hepatitis
46	1999.2596	IKS	Denham 15, Phytopharm 2.6.9 (EMEA 6)	F	46	Hydrochlorothiazide, valsartan		
47	9	Literature (9)	Denham 18, Phytopharm 2.3.2 (EMEA 9), WHO 2458938, IKS 2000-3502	M	50	'Moderate alcohol' (BfArM, Denham 18)	Paracetamol just before transplant.	Toxic-necrotic hepatitis
48	2003278	BfArM	WHO 8028354, Phytopharm 2.4.13 (EMEA 47)	M	50	Not recorded	Onset 1m after stopping	
49	2607228	WHO		F	57	Silybum	Withdrawn 8m after reaction began	
50	2000.2330	IKS	Denham 17, Phytopharm 2.6.10 (EMEA 8)	F	59	Celecoxib		
51	1006939	BfArM	WHO 2762468, Phytopharm 2.4.12 (EMEA 33)	M	36	Not recorded		Necrotising hepatitis
52	1001228	BfArM	BfArM 1001924 / 8, Denh 26, WHO 8019808	M	38	Penicillin V, 'regular alcohol' (Stickel 12)		Necrotising hepatitis
53	2850853	WHO	Denham 27	M	39	None		Cholestatic hepatitis
54	1482277	WHO	BfArM 94901308, Denham 6, Phytopharm 2.6.2 (EMEA 14)	F	50	Terfenadine, furosemide	Abnormal LFTs before kava.	Drug induced hepatitis
55	1536454	WHO	BfArM 94006568, Denham 5	F	68	None suspect		Toxic-cholestatic liver damage
56	15035	FDA	FDA 15274, Phytopharm 2.6.18 (EMEA 53)	F	45	Rabeprazole		Subfulminant hepatic necrosis
57	11444	FDA		M	24	Chromium piccolinate, vanadyl sulphate		
58	10257	FDA		F	70	Lisinopril, warfarin		
59	15556	FDA		M	72	Valerian	Hepatitis C	
60	44	MCA		F	-	Not recorded		
61	65.1	Canada (EMEA id)	Phytopharm 2.4.28 (EMEA 65)	F	-	Not recorded		
62	27	Stickel	Similar to case 40. (BfArM 2002732)	F	24	None		
63	8206938	WHO		F	28	Fluoxetine		
64	2003422	Brazil		F	30	Passiflora		
65	29	Stickel		M	33	'Regular alcohol'		Necrotising hepatitis
66	14810	FDA	Phytopharm 2.7.7 (EMEA 52)	F	33	COC (LoEstrin), chemotherapy		
67	15	Stickel		F	34	None		
68	15317	FDA	Phytopharm 2.7.8 (EMEA 56)	M	38	None suspect	Binge use	
69	64	France (EMEA id)	Phytopharm 2.4.29 (EMEA 64), MCA 65	F	39	Yes (drug not stated)		
70	65	MCA	Similar to case 45 (BfArM 93015209)	F	39	Unspecified possibly hepatotoxic drugs		
71	1	MCA	Phytopharm 2.7.12 (EMEA 1)	M	40	Alcohol		
72	25	Stickel		F	41	None		
73	275	Press report	Phytopharm 2.7.5	F	43	Beta blocker, anaesthetic		

Table 2 Case reports of hepatotoxicity with kava: additional data (continued)

No	Report Id	Source	Other sources	Sex	Age	Concomitant	Comment	Histology
74	14723	FDA	Phytopharm 2.6.17 (EMEA 51)	F	44	Celecoxib, citalopram		
75	1939507	Brazil		F	44	Diclofenac, famotidine		Toxic hepatitis
76	2380373	WHO		F	46	Not recorded	Onset > 1 yr after stopping	
77	47	MCA		F	47	Not recorded		
78	28	Stickel		F	49	'Regular alcohol'		Necrotising hepatitis
79	14951	FDA	Phytopharm 2.4.20 (EMEA 59)	F	51	Omega-3		
80	15267	FDA	Phytopharm 2.4.25 (EMEA 62)	F	51	Not recorded		
81	8119572	WHO	Canada, Phytopharm 2.5.5 (EMEA 66)	F	53	Alcohol		
82	10	Literature (10)		M	55	None		Haemorrhagic necrosis
83	14	Stickel		F	57	Candesartan, oestrogen		Lobular hepatitis
84	2001	Weekly Magazine	Phytopharm 2.4.18; similar to case 18 (literature (8)/ Phytopharm 2.6.23)	F	60	Not recorded		
85	14538	FDA	Phytopharm 1.6.19 (EMEA 50)	F	60	Capecitabine, chaparral	Secondaries in liver? Chemo restarted & OK	
86	3	Literature (1, 2)	Phytopharm 2.4.31	F	14	None		Hepatocellular necrosis / chemical hepatitis
87	7	Literature (7), TGA		F	56	Passiflora incarnata		Severe acute hepatitis, massive necrosis.
88	2	MCA		F	-	Alcohol, fluoxetine		
89	15319	FDA	Phytopharm 2.7.9 (EMEA 57)	M	63	Enalapril, hydrochlorothiazide	History of hepatitis C	
90	67	Canada (EMEA id)	Phytopharm 2.4.27 (EMEA 67)	M	38	Not recorded		
91	15250	FDA	Phytopharm 2.4.23 (EMEA 54)	F	-	Multivitamins, 'moderate alcohol'	Phytopharm records as male	
92	13198	FDA		F	52	>60 herbs, alcohol		Chronic alcoholic liver disease
93	15252	FDA	Phytopharm 2.4.24 (EMEA 61)	F	-	Dexatrim Green Tea		

Table 3 Hepatic events reported in association with kava

Hepatic event	Count	%
Hepatitis	22	23.7
Hepatitis cholestatic	9	9.7
Hepatitis fulminant	3	3.2
Hepatitis toxic	2	2.2
Hepatic failure	11	11.8
Hepatic necrosis	6	6.5
Jaundice	9	9.7
Hepatocellular liver injury	8	8.6
Liver injury	1	1.1
Hepatic function abnormal	18	19.4
Cirrhosis	2	2.2
Not described	2	2.2
Total	93	100.3

Table 4 Case reports of hepatotoxicity with kava: histological data

No	Histology	Hepatic event	Outcome
19	Acute necrotising hepatitis	Hepatic necrosis	Recovered
07	Autoimmune hepatitis un-changed after > 4 months	Hepatitis	Recovered
45	Cholestatic hepatitis	Jaundice	Recovered
35	Cholestatic hepatitis	Hepatitis cholestatic	Recovered
53	Cholestatic hepatitis	Hepatocellular liver injury	Recovered
29	Cholestatic hepatitis	Hepatitis cholestatic	Unknown
11	Cholestatic hepatitis. Pronounced necrosis.	Hepatic necrosis	Liver transplant, Died (6 months)
92	Chronic alcoholic liver disease	Cirrhosis	Unknown
54	Drug induced hepatitis	Hepatitis	Recovered
31	Drug-induced cell necrosis and fibrosis	Hepatic failure	Liver transplant
43	Drug-induced hepatitis	Hepatitis cholestatic	Recovered
82	Haemorrhagic necrosis	Hepatitis	Recovered
86	Hepatocellular necrosis / chemical hepatitis	Hepatitis fulminant	Liver transplant
83	Lobular hepatitis	Hepatitis	Recovered
18	Necrosis & intrahepatic cholestasis	Hepatic failure	Liver transplant
23	Necrosis liver cells	Hepatic failure	Liver transplant, Died [Stickel]
12	Necrotising hepatitis	Hepatic necrosis	Liver transplant
27	Necrotising hepatitis	Hepatic failure	Died
51	Necrotising hepatitis	Hepatic necrosis	Recovered
52	Necrotising hepatitis	Hepatitis	Recovered
65	Necrotising hepatitis	Hepatic necrosis	Recovered
78	Necrotising hepatitis	Hepatic necrosis	Recovered
87	Severe acute hepatitis, massive necrosis.	Hepatic failure	Liver transplant, Died
56	Subfulminant hepatic necrosis	Hepatitis cholestatic	Liver transplant
75	Toxic hepatitis	Hepatitis fulminant	Liver transplant
34	Toxic hepatopathy	Hepatic failure	Died
55	Toxic-cholestatic liver damage	Hepatitis cholestatic	Recovered
47	Toxic-necrotic hepatitis	Hepatitis toxic	Liver transplant

Table 5 Case reports of hepatotoxicity with kava: significant concomitant medicines

No	Sex	Age	Rel	OPS	Concomitant
05	F	59	3	Yes	Lisinopril, phenobarbital, fenofibrate
06	F	39	3	Yes	Tetracycline, alcohol
07	F	21	4	Yes	Paracetamol, pantoprazole, MDMA
08	M	35	3	Yes	'Regular alcohol'
10	F	69	3	Yes	Bemetizid, pentoxifyllin
11	F	22	3	Yes	COC (Pramino)
12	M	32	3	Yes	Valerian
13	F	35	3	Yes	Paracetamol
15	F	46	3	Yes	COC (Klimonorm)
17	F	47	3	Yes	Fish oil
18	F	60	3	Yes	Piretanide
19	F	39	2	Yes	Paroxetine, COC (Pramino)
20	F	-	6	Yes	Omeprazole, estradiol, losarten
22	M	39	3	Yes	Interferon-beta
23	F	50	3	Yes	COC (Gravistat), glimepiride, metformin
26	F	56	3	Yes	Esberitox, omeprazole
27	F	61	3	Yes	Bemetizid, omeprazole
28	F	32	6	Yes	COC (Marvelon)
30	F	26	3	Yes	Diclofenac, sulfasalazine, MPA
32	F	33	3	Yes	Cisapride
34	F	81	3	Yes	Alcohol, hydrochlorothiazide, nitrendipin
35	M	55	6	Yes	Glibenclamide
36	F	41	6	Yes	COC (Diane)
41	F	72 / 75	3	Yes	Vitamin A
44	F	37	4	Yes	Diclofenac, COC (Microdiol)
45	F	39	3	Yes	COC (Gravistat)
46	F	46	3	Yes	Hydrochlorothiazide, valsartan
47	M	50	3	Yes	'Moderate alcohol' (BfArM, Denham 18)
49	F	57	3	Yes	Silybum
50	F	59	3	Yes	Celecoxib
52	M	38	3	Yes	Penicillin V, 'regular alcohol' (Stickel 12)
54	F	50	3	Yes	Terfenadine, furosemide
56	F	45	3	Yes	Rabeprazole
57	M	24	3	Yes	Chromium piccolinate, vanadyl sulphate
58	F	70	6	Yes	Lisinopril, warfarin
59	M	72	6	Yes	Valerian
63	F	28	6	Yes	Fluoxetine
64	F	30	3	Yes	Passiflora
65	M	33	6	Yes	'Regular alcohol'
66	F	33	6	Yes	COC (LoEstrin), chemotherapy
69	F	39	3	Yes	Yes (drug not stated)
70	F	39	3	Yes	Unspecified possibly hepatotoxic drugs
71	M	40	3	Yes	Alcohol
73	F	43	3	Yes	Beta blocker, anaesthetic
74	F	44	6	Yes	Celecoxib, citalopram
75	F	44	3	Yes	Diclofenac, famotidine
78	F	49	6	Yes	'Regular alcohol'
79	F	51	3	Yes	Omega-3
81	F	53	3	Yes	Alcohol
83	F	57	3	Yes	Candesartan, oestrogen
85	F	60	3	Yes	Capecitabine, chaparral
87	F	56	3	Yes	Passiflora incarnata
88	F	-	3	Yes	Fluoxetine
89	M	63	3	Yes	Enalapril, hydrochlorothiazide
91	F	-	3	Yes	Multivitamins, 'moderate alcohol'
92	F	52	6	Yes	>60 herbs, alcohol
93	F	-	3	Yes	Dexatrim Green Tea

Table 6 Case reports of hepatotoxicity with kava: concomitant therapy not suspect

No	Sex	Age	Hepatic event	Outcome	Rel	OPS	Products not suspect
03	F	27	Jaundice	Recovered	2	NS	Psyllium, vitamins B6 & E, St John's Wort, phytoestrogen mix (Mex yam, black cohosh, dong quai)
21	F	34	Hepatitis	Recovered	2	NS	Jodthyrox (Levothyroxine, potassium iodide)
31	F	47	Hepatic failure	Transplant	6	NS	Sylmarin, Polilevo (arginine, ornithine, citrullin), Gelum (mineral supplement), Rheumeda (antirheumatic homeopathic preparation).
37	F	59	Hepatocellular damage	Recovered	2	NS	Buscopan
39	F	45	Hepatitis	Recovered	2	NS	Artichoke extract (taken occasionally)
43	F	33	Cholestatic hepatitis	Recovered	2	NS	Exepta (homeopathic combination product)
55	F	68	Hepatitis cholestatic	Recovered	3	NS	St John's Wort, Maaloxan (magnesium and aluminium hydroxide)
68	M	38	Hepatitis	Unknown	6	NS	St John's Wort

Table 7 Case reports of hepatotoxicity with kava: summary of outcomes

Outcome	Count	%
Died	7	7.5
Transplant	14	15.1
Recovered	50	53.8
Improved	3	3.2
Not recovered	4	4.3
Unknown	19	20.4

Table 8 Case reports of hepatotoxicity with kava: cases with 'probable' relationships

No	Sex	Age	Product	Extract	Dose	DoseType	Dur	Hepatic event	OPS	Dech	Rech	Outcome	Rel
03	F	27	Kava tea	Water	2400	kava lactones	(180)	Jaundice	NS	Y	N	Recovered	2
04	F	55	Kava traditional drink	Water	2571	kava lactones	35	Hepatocellular liver injury	No	Y	N	Recovered	2
19	F	39	Kava	Ethanol	60	kava lactones	194	Hepatic necrosis	Yes	Y	R	Recovered	2
21	F	34	Kava ratiopharm	Ethanol	120	kava lactones	(90)	Hepatitis	NS	Y	N	Recovered	2
37	F	59	Limbao	Ethanol	240	kava lactones	120	Hepatocellular liver injury	NS	Y	X	Recovered	2
39	F	45	Maoni	Ethanol	45	kava lactones	(120)	Hepatitis	NS	Y	N	Recovered	2
43	F	33	Laitan	Acetone	210	kava lactones	(21)	Hepatitis cholestatic	NS	Y	N	Recovered	2
82	M	55	Kava		750		90	Hepatitis	No	Y	N	Recovered	2

No	Report Id	Source	Other sources	Sex	Age	Concomitant	Comment	Histology
03	15281	FDA	Phytopharm 2.5.4 (EMEA 55)	F	27	None suspect		
04	11.2	Literature (11)		F	55	None		
19	5	Literature (5)	Phytopharm 2.2.1, Denham 10	F	39	Paroxetine, COC (Pramino)	Rechallenge of kava only. Poor metaboliser.	Acute necrotising hepatitis
21	1003089	BfArM	WHO 2851368, MCA 25, Phytopharm 2.4.4 (EMEA 24), Denham 22	F	34	None suspect		
37	2223603	WHO	BfArM 99500453, Denham 11, Phytopharm 2.4.3 (EMEA 17)	F	59	None suspect		
39	1010536	BfArM	Phytopharm 2.4.8 (EMEA 37)	F	45	None suspect		
43	4	Literature (4)	Denham 16, Phytopharm 2.3.1 (EMEA 7), WHO 2639336, IKS 2000-0014	F	33	None suspect	Poor metaboliser	Drug-induced hepatitis
82	10	Literature (10)		M	55	None		Haemorrhagic necrosis

Table 9 Case reports of hepatotoxicity with kava: 'possible' relationships showing concomitant therapy

No	Sex	Age	Dur	Dech	Rech	Concomitant	Outcome
02	F	37	(24)	Y	X	(Unknown herbals)	Improving
05	F	59	28	Y	N	Lisinopril, phenobarbital, fenofibrate	Recovered
06	F	39	180	Y	X	Tetracycline, alcohol	Recovered
08	M	35	56	Y	N	'Regular alcohol'	Recovered
10	F	69	56	Y	X	Bemetizid, pentoxifyllin	Recovered
11	F	22	120	Y	N	COC (Pramino)	Transplant, Died (6 months)
12	M	32	(75)	Y	N	Valerian	Transplant
13	F	35	57	Y	N	Paracetamol	Recovered
15	F	46	(105)	Y	N	COC (Klimonorm)	Recovered
16	F	46	(28)	Y	N	Not recorded	Recovered
17	F	47	(30)	N	N	Fish oil	Recovered
18	F	60	(365)	Y	N	Piretanide	Transplant
22	M	39	210	Y	X	Interferon-beta	Recovered
23	F	50	(195)	Y	N	COC (Gravistat), glimepiride, metformin	Transplant, Died
26	F	56	-	Y	R	Esberitox, omeprazole	Recovered
27	F	61	(90)	X	X	Bemetizid, omeprazole	Died
29	M	45	(90)	Y	X	Not recorded	Unknown
30	F	26	6	Y	N	Diclofenac, sulfasalazine, MPA	Recovered
32	F	33	(120)	Y	R	Cisapride	Recovered
33	F	62	-	Y	R	Not recorded	Recovered
34	F	81	(300)	Y	N	Alcohol, hydrochlorothiazide, nitrendipin	Died
41	F	72 / 75	(730)/ (180)	Y	X	Vitamin A	Recovered
42	F	-	60	Y	X	Not recorded	Unknown
44	F	37	(60)	Y	Neg	Diclofenac, COC (Microdiol)	Recovered
45	F	39	106	Y	X	COC (Gravistat)	Recovered
46	F	46	(135)	Y	N	Hydrochlorothiazide, valsartan	Recovered
47	M	50	30	Y	N	'Moderate alcohol' (BfArM, Denham 18)	Transplant
49	F	57	30	Y	X	Silybum	Recovered
50	F	59	(21)	Y	N	Celecoxib	Recovered
51	M	36	46	Y	N	Not recorded	Recovered
52	M	38	21	Y	X	Penicillin V, 'regular alcohol' (Stickel 12)	Recovered
53	M	39	14	Y	X	None	Recovered
54	F	50	75	Y	X	Terfenadine, furosemide	Recovered
55	F	68	730	Y	X	None suspect	Recovered
56	F	45	56	Y	X	Rabeprazole	Transplant
57	M	24	24	Y	N	Chromium piccolinate, vanadyl sulphate	Died
64	F	30	60	Y	N	Passiflora	Died
69	F	39	(60)	Y	N	Yes (drug not stated)	Recovered
70	F	39	(60)	Y	X	Unspecified possibly hepatotoxic drugs	Recovered
71	M	40	90	Y	X	Alcohol	Recovered
73	F	43	14	X	X	Beta blocker, anaesthetic	Transplant
75	F	44	119	Y	N	Diclofenac, famotidine	Transplant
79	F	51	(120)	Y	X	Omega-3	Recovered
80	F	51	(60)	Y	R	Not recorded	Recovered
81	F	53	-	Y	X	Alcohol	Recovered
83	F	57	150	X	X	Candesartan, oestrogen	Recovered
85	F	60	-	Y	X	Capecitabine, chaparral	Recovered
86	F	14	105	Y	N	None	Transplant
87	F	56	(90)	Y	N	Passiflora incarnata	Transplant, Died
88	F	-	(60)	X	X	Fluoxetine	Not recovered
89	M	63	(42)	Y	X	Enalapril, hydrochlorothiazide	Improved
90	M	38	(14)	Y	X	Not recorded	Recovered
91	F	-	(730)	Y	X	Multivitamins, 'moderate alcohol'	Recovered
93	F	-	(90)	Y	N	Dexatrim Green Tea	Improving

Table 10 Case reports of hepatotoxicity with kava: reports with positive rechallenge

No	Sex	Age	Product	Extract	Dose	DoseType	Dur	Hepatic event	OPS	Dech	Rech	Outcome	Rel
19	F	39	Kava	Ethanol	60	kava lactones	194	Hepatic necrosis	Yes	Y	R	Recovered	2
26	F	56	Kava Ratiopharm	Ethanol	-		-	Hepatitis	Yes	Y	R	Recovered	3
32	F	33	Kavatino	Ethanol	180	kava lactones	(120)	Hepatitis toxic	Yes	Y	R	Recovered	3
33	F	62	Kavatino	Ethanol	60	kava lactones	-	Hepatocellular liver injury	NR	Y	R	Recovered	3
80	F	51	Kava		-		(60)	Hepatic function abnormal	NR	Y	R	Recovered	3

No	Report Id	Source	Other sources	Sex	Age	Concomitant	Comment	Histology
19	5	Literature (5)	Phytopharm 2.2.1, Denham 10	F	39	Paroxetine, COC (Pramino)	Rechallenge of kava only. Poor metaboliser.	Acute necrotising hepatitis
26	2851799	WHO		F	56	Esberitox, omeprazole		
32	99006005	BfArM	WHO 2598102, Phytopharm 2.6.4 (EMEA 20), Denham 14	F	33	Cisapride		
33	99003911	BfArM	Denham 13, Phytopharm 2.4.2 (EMEA 19)	F	62	Not recorded		
80	15267	FDA	Phytopharm 2.4.25 (EMEA 62)	F	51	Not recorded		

Table 11A Case reports of hepatotoxicity with kava: patients with liver transplant (basic data)

No	Sex	Age	Product	Extract	Dose	DoseType	Dur	Hepatic event	OPS	Dech	Rech	Outcome	Rel
11	F	22	Antares	Ethanol	240	kava lactones	120	Hepatic necrosis	Yes	Y	N	Died 6 months after transplant	3
12	M	32	Antares	Ethanol	240	kava lactones	(75)	Hepatic necrosis	Yes	Y	N	Transplant	3
18	F	60	Antares	Ethanol	480-1200	kava lactones	(365)	Hepatic failure	Yes	Y	N	Transplant	3
23	F	50	Kava Ratiopharm	Ethanol	60	kava lactones	(195)	Hepatic failure	Yes	Y	N	Transplant, Died	3
31	F	47	Kavasporal forte	Ethanol	-		-	Hepatic failure	NS	X	X	Transplant	6
36	F	41	Limbao	Ethanol	-		-	Hepatic failure	Yes	X	X	Transplant	
47	M	50	Laitan	Acetone	210-280	kava lactones	30	Hepatitis toxic	Yes	Y	N	Transplant	3
56	F	45	Combination NOS		150	kava lactones	56	Hepatitis cholestatic	Yes	Y	X	Transplant	3
66	F	33	Kava		-		-	Jaundice	Yes	X	X	Transplant	6
73	F	43	Kava		-		14	Hepatic failure	Yes	X	X	Transplant	3
75	F	44	Kava		200		119	Hepatitis fulminant	Yes	Y	N	Transplant	3
84	F	60	Kava		-		(90)	Hepatic failure	NR	X	X	Transplant	6
86	F	14	Kava (2 products)		-		105	Hepatitis fulminant	No	Y	N	Transplant	3
87	F	56	Kava 1800 Plus		180	kava lactones	(90)	Hepatic failure	Yes	Y	N	Transplant, Died	3

Table 11B Case reports of hepatotoxicity with kava: patients with liver transplant (additional data)

No	Report Id	Source	Other sources	Sex	Age	Concomitant	Comment	Histology
11	8627	Literature (3)	WHO 2767171. Phytopharm 2.5.3 (EMEA 23), BfArM 8627	F	22	COC (Pramino)		Cholestatic hepatitis. Pronounced necrosis.
12	1006229	BfArM	WHO 2852999, Phytopharm 2.4.6 (EMEA 31), Denham 30	M	32	Valerian		Necrotising hepatitis
18	8	Literature (8)	Phytopharm 2.6.23 (EMEA 5), similar to case 85 (Weekly Magazine)	F	60	Piretanide	Overdose	Necrosis & intrahepatic cholestasis
23	6	Literature (6)	Denham 20, Stickel, Phytopharm 2.6.6 (EMEA 22), BfArM 5994	F	50	COC (Gravistat), glimepiride, metformin		Necrosis liver cells
31	2003010	BfArM	Phytopharm 2.7.4 (EMEA 46)	F	47	None suspect		Drug-induced cell necrosis and fibrosis
36	15320	FDA	Phytopharm 2.4.26	F	41	COC (Diane)		
47	9	Literature (9)	Denham 18, Phytopharm 2.3.2 (EMEA 9), WHO 2458938, IKS 2000-3502	M	50	'Moderate alcohol' (BfArM, Denham 18)	Paracetamol just before transplant.	Toxic-necrotic hepatitis
56	15035	FDA	FDA 15274, Phytopharm 2.6.18 (EMEA 53)	F	45	Rabeprazole		Subfulminant hepatic necrosis
66	14810	FDA	Phytopharm 2.7.7 (EMEA 52)	F	33	COC (LoEstrin), chemotherapy		
73	275	Press report	Phytopharm 2.7.5	F	43	Beta blocker, anaesthetic		
75	1939507	Brazil		F	44	Diclofenac, famotidine		Toxic hepatitis
84	2001	Weekly Magazine	Phytopharm 2.4.18; similar to case 18 (literature (8)/Phytopharm 2.6.23)	F	60	Not recorded		
86	3	Literature (1, 2)	Phytopharm 2.4.31	F	14	None		Hepatocellular necrosis / chemical hepatitis
87	7	Literature (7), TGA		F	56	Passiflora incarnata		Severe acute hepatitis, massive necrosis

Table 12 Case reports of hepatotoxicity with kava: patients who died

No	Sex	Age	Product	Extract	Dose	DoseType	Dur	Hepatic event	OPS	Dech	Rech	Outcome	Rel
11	F	22	Antares	Ethanol	240	kava lactones	120	Hepatic necrosis	Yes	Y	N	Transplant, Died (6 months)	3
23	F	50	Kava Ratiopharm	Ethanol	60	kava lactones	(195)	Hepatic failure	Yes	Y	N	Transplant, Died	3
27	F	61	Kava Ratiopharm	Ethanol	120	kava lactones	(90)	Hepatic failure	Yes	X	X	Died	3
34	F	81	Kavatino	Ethanol	120	kava lactones	(300)	Hepatic failure	Yes	Y	N	Died	3
57	M	24	Hard Gainers 6		200	product (6 herbs)	24	Hepatic failure	Yes	Y	N	Died	3
64	F	30	Kava		200		60	Hepatitis fulminant	Yes	Y	N	Died	3
87	F	56	Kava 1800 Plus		180	kava lactones	(90)	Hepatic failure	Yes	Y	N	Transplant, Died	3

No	Report Id	Source	Other sources	Sex	Age	Concomitant	Comment	Histology
11	8627	Literature (3)	WHO 2767171. Phytopharm 2.5.3 (EMEA 23), BfArM 8627	F	22	COC (Pramino)		Cholestatic hepatitis. Pronounced necrosis.
23	6	Literature (6)	Denham 20, Stickel, Phytopharm 2.6.6 (EMEA 22), BfArM 5994	F	50	COC (Gravistat), glimepiride, metformin		Necrosis liver cells
27	2001135	BfArM	BfArM 2002378, Phytopharm 2.6.14 (EMEA 40)	F	61	Bemetizid, omeprazole		Necrotising hepatitis
34	98004297	BfArM	Denham 9, Phytopharm 2.7.1 (EMEA 16)	F	81	Alcohol, nitrendipin, hydrochlorothiazide	Cirrhosis preceded kava	Toxic hepatopathy
57	11444	FDA		M	24	Chromium piccolinate, vanadyl sulphate		
64	2003422	Brazil		F	30	Passiflora		
87	7	Literature (7), TGA		F	56	Passiflora incarnata		Severe acute hepatitis, massive necrosis

Table 13 Potential drug interactions with kava: alphabetical listing by drug

Drug	ATC code
abciximab	B01AC
acenocoumarol	B01AA
acetaminophen	N02BE
acetophenazine	N05AB
adinazolam	
alfentanil	N01AH
alprazolam	N05BA
alteplase	B01AD
amantadine	N04BB
amiodarone	C01BD
amisulpride	N05AL
amlodipine/atorvastatin	
amobarbitol	N05CA
anagrelide	N05CA
ancrod	B01AD
anisindione	B01AA
anistreplase	B01AD
anithrombin iii	B01AB
aprobarbital	N05CA
ardeparin	B01AB
argatroban	B01AE
aspirin	N02BA
aspirin/dipyridamole	
atorvastatin	C10AA
azathioprine	L04AX
becaplermin	D03AX
benperidol	N05AD
bentazepam	N05BA
bivalirudin	B02BD
bromazepam	N05BA
bromocriptine	N04BC
brotizolam	N05CD
butobarbital	N05CA
butalbital	N02BE
calusterone	L02AX
carisoprodol	M03BA
carmustine	L01AD
cerivastatin	C10AA
certoparin	B01AB
chlordiazepoxide	N05BA
chlordiazepoxide/amitriptyline	
chlorpromazine	N05AA
chlorprothixene	N05AF
chlorzoxazone	M03BB
cilostazol	B01AC
clobazam	N05BA
clonazepam	N03AE
clopidogrel	B01AC
clorazepate	N05BA
clorgyline	
codeine	R05DA
dalteparin	B01AB
danaparoid	B01AB
danazol	G03XA
dantrolene	M03CA
defibrotide	B01AX
delorazepam	N05BA
dermatan	
desirudin	B01AE
dextromethorphan/morphine	
diazepam	N05BA
diclofenac	S01BC
diclofenac/misoprostol	
dicumarol	B01AA
dihydroergotamine/heparin	
dipyridamole	B01AC
dixyrazine	N05AB
enoxaparin	B01AB
epoprostenol	B01AC
eptifibatide	B01AC
estazolam	N05CD
eterobarb	
ethanol	V03AZ
ethopropazine	N04AA
ezetimibe/simvastatin	
fentanyl	N01AH
fluconazole	D01AC
flunitrazepam	N05CD
fluoxymesterone	G03BA
fluphenazine	N05AB
flurazepam	N05CD
flutamide	L02BB
fluvastatin	C10AA
fondaparinux	B01AX
halazepam	N05BA
haloperidol	N05AD
heparin	B01AB
hydrocodone	R05DA
hydromorphone	N02AA
ibuprofen	M01AE
iloprost	B01AC
isocarboxazid	N06AF
isoniazid	J04AC
itraconazole	J02AC
ketazolam	N05BA
ketoconazole	D01AC
lamifiban	B01AX
lazabemide	N04BD
lepirudin	B01AE
levodopa	N04BA
levodopa/benserazide	
levodopa/carbidopa	
levodopa/carbidopa/entacapone	N02AF
levorphanol	N05CD
loprazolam	N05BA
lorazepam	N05CD
lormetazepam	C10AA
lovastatin	N05BA
medazepam	N02AB
meperidine	N03AA
mephobarbitol	N05BC
meprobamate	L01BB
mercaptopurine	N05AC
mesoridazine	N05BA
metadazepam	M03BB

Table 13 Potential drug interactions with kava: alphabetical listing by drug (continued)

Drug	ATC code
metaxalone	
methdilazine	R06AD
methenolone	M03BA
methocarbamol	L04AX
methotrexate	A03FA
metoclopramide	N05CD
midazolam	N06AG
moclobemide	N05AE
molindone	N02AA
morphine	N05AC
nadroparin	B01AB
nandrolone	A14AB
niacin	C04AC
niacin/lovastatin	
nitrazepam	N05CD
oxandrolone	A14AA
oxazepam	N05BA
oxycodone	N02AA
oxymetholone	A14AA
oxymorphone	N02AA
parnaparin	B01AB
pentobarbital	N05CA
pentosan polysulfate sodium	C05BA
perazine	N05AB
pergolide	N04BC
periciazine	N05AC
perphenazine	N05AB
perphenazine/amitriptyline	
phenelzine	N06AF
phenindione	B01AA
phenobarbital	N03AA
phenprocoumon	B01AA
pimozide	N05AG
pinazepam	N05BA
pioglitazone	A10BG
pipotiazine	S01BC
piroxicam	L01DC
plicamycin	N04BC
pramipexole	C10AA
pravastatin	N05BA
prazepam	N03AA
primidone	N05AB
prochlorperazine	N05AA
promazine	R06AD
promethazine	N05CM
propiomazine	N02AC
propoxyphene	N05CD
quazepam	N01AH
remifentamil	B01AD
reteplase	B01AB
reviparin	N04BC
ropinirole	A10BG
rosiglitazone	
rosiglitazone/metformin	N05CA
secobarbital	N04BD
selegiline	B10AC
sibrafiban	C10AA
simvastatin	A14AA
stanozolol	B01AD
streptokinase	
sufentanil	N01AH
sulfinpyrazone	M04AB
sulodexide	B01AB
tacrine	N06DA
temazepam	N05CD
tenecteplase	B01AD
terbinafine	D01BA
testosterone	G03BA
tetrazepam	N05BA
thiopental	N01AF
thioridazine	N05AC
ticlopidine	B01AC
tinzaparin	B01AB
tirofiban	B01AC
tramadol/acetaminophen	
tranylcypromine	N06AF
treprostinil	B01AC
triazolam	N05CD
trifluoperazine	N05AB
triflupromazine	N05AA
troglitazone	A10BG
urokinase	B01AD
valproic acid	N03AG
warfarin	B01AA
xemilofiban	

(From DrugDex 2005)

Table 14 Potential kava-drug interactions by ATC code

Drug	ATC	Drug	ATC
metoclopramide	A03FA	anistreplase	B01AD
pioglitazone	A10BG	reteplase	B01AD
rosiglitazone	A10BG	streptokinase	B01AD
troglitazone	A10BG	tenecteplase	B01AD
oxandrolone	A14AA	urokinase	B01AD
oxymetholone	A14AA	argatroban	B01AE
stanozolol	A14AA	desirudin	B01AE
nandrolone	A14AB	lepirudin	B01AE
acenocoumarol	B01AA	defibrotide	B01AX
anisindione	B01AA	fondaparinux	B01AX
dicumarol	B01AA	lamifiban	B01AX
phenindione	B01AA	bivalirudin	B02BD
phenprocoumon	B01AA	amiodarone	C01BD
warfarin	B01AA	niacin	C04AC
antithrombin iii	B01AB	pentosan polysulfate sodium	C05BA
ardeparin	B01AB	atorvastatin	C10AA
certoparin	B01AB	cerivastatin	C10AA
dalteparin	B01AB	fluvastatin	C10AA
danaparoid	B01AB	lovastatin	C10AA
enoxaparin	B01AB	pravastatin	C10AA
heparin	B01AB	simvastatin	C10AA
nadroparin	B01AB	fluconazole	D01AC
parnaparin	B01AB	ketoconazole	D01AC
reviparin	B01AB	terbinafine	D01BA
sulodexide	B01AB	becaplermin	D03AX
tinzaparin	B01AB	fluoxymesterone	G03BA
abciximab	B01AC	testosterone	G03BA
cilostazol	B01AC	danazol	G03XA
clopidogrel	B01AC	itraconazole	J02AC
dipyridamole	B01AC	isoniazid	J04AC
epoprostenol	B01AC	carmustine	L01AD
eptifibatide	B01AC	mercaptopurine	L01BB
iloprost	B01AC	plicamycin	L01DC
sibrafiban	B01AC	calusterone	L02AX
ticlopidine	B01AC	flutamide	L02BB
tirofiban	B01AC	azathioprine	L04AX
alteplase	B01AD	methotrexate	L04AX
ancrod	B01AD	ibuprofen	M01AE
carisoprodol	M03BA	dixyrazine	N05AB
methocarbamol	M03BA	fluphenazine	N05AB
chlorzoxazone	M03BB	perazine	N05AB
metaxalone	M03BB	perphenazine	N05AB
dantrolene	M03CA	prochlorperazine	N05AB
sulfinpyrazone	M04AB	trifluoperazine	N05AB
thiopental	N01AF	mesoridazine	N05AC
alfentanil	N01AH	periciazine	N05AC
fentanyl	N01AH	pipotiazine	N05AC
remifentanil	N01AH	thioridazine	N05AC
sufentanil	N01AH	benperidol	N05AD
hydromorphone	N02AA	haloperidol	N05AD
morphine	N02AA	molindone	N05AE
oxycodone	N02AA	chlorprothixene	N05AF
oxymorphone	N02AA	pimozide	N05AG
meperidine	N02AB	amisulpride	N05AL
propoxyphene	N02AC	alprazolam	N05BA
levorphanol	N02AF	bentazepam	N05BA
aspirin	N02BA	bromazepam	N05BA
acetaminophen	N02BE	chlordiazepoxide	N05BA
butalbital	N02BE	clobazam	N05BA
mephobarbital	N03AA	clorazepate	N05BA
phenobarbital	N03AA	delorazepam	N05BA
primidone	N03AA	diazepam	N05BA
clonazepam	N03AE	halazepam	N05BA
valproic acid	N03AG	ketazolam	N05BA
ethopropazine	N04AA	lorazepam	N05BA
levodopa	N04BA	medazepam	N05BA
amantadine	N04BB	metaclazepam	N05BA
bromocriptine	N04BC	oxazepam	N05BA
pergolide	N04BC	pinazepam	N05BA
pramipexole	N04BC	prazepam	N05BA
ropinirole	N04BC	tetrazepam	N05BA
lazabemide	N04BD	meprobamate	N05BC
selegiline	N04BD	amobarbital	N05CA
chlorpromazine	N05AA	anagrelide	N05CA
promazine	N05AA	aprobarbital	N05CA
triflupromazine	N05AA	butobarbital	N05CA
acetophenazine	N05AB	pentobarbital	N05CA
secobarbital	N05CA	quazepam	N05CD
brotizolam	N05CD	temazepam	N05CD
estazolam	N05CD	triazolam	N05CD
flunitrazepam	N05CD	propiomazine	N05CM
flurazepam	N05CD	isocarboxazid	N06AF
loprazolam	N05CD	phenelzine	N06AF
lormetazepam	N05CD	tranylcypromine	N06AF
midazolam	N05CD	moclobemide	N06AG
nitrazepam	N05CD	tacrine	N06DA
codeine	R05DA		
hydrocodone	R05DA		
methdilazine	R06AD		
promethazine	R06AD		
diclofenac	S01BC		
piroxicam	S01BC		
ethanol	N05BA		
adinazolam			
amlodipine/atorvastatin			
aspirin/dipyridamole			
chlordiazepoxide/ amitriptyline			
clorgyline			
dermatan			
dextromethorphan/ morphine			
diclofenac/misoprostol			
dihydroergotamine/ heparin			
eterobarb			
ezetimibe/simvastatin			
levodopa/benserazide			
levodopa/carbidopa			
levodopa/carbidopa/ entacapone			
methenolone			
niacin/lovastatin			
perphenazine/ amitriptyline			
rosiglitazone/metformin			
tramadol/acetaminophen	B01AC		
treprostinil			
xemilofiban			

Table 15 Potential kava-drug interactions by ATC groups

ATC	Count	Drug Type
N05A Antipsychotics		
N05AA	3	phenothiazine (aliphatic) antipsychotics
N05AB	7	phenothiazine (piperazine) antipsychotics
N05AC	4	phenothiazine (piperidine) antipsychotics
N05AD	2	butyrophenone derivatives antipsychotics
N05AE	1	indole antipsychotics
N05AF	1	thioxanthine antipsychotics
N05AG	1	diphenylbutylpiperidine antipsychotics
N05AL	1	benzamide antipsychotics
N05B Anxiolytics		
N05BA	17	benzodiazepine anxiolytics
N05BC	1	carbamate anxiolytics
N05C Hypnotics and sedatives		
N05CA	6	barbiturates
N05CD	11	benzodiazepine hypnotics & sedatives
N05CM	1	other hypnotics and sedatives
B01A Antithrombotic agents		
B01AB	12	heparin group
B01AC	10	platelet aggregation inhibitors (excl heparin)
B01AD	7	enzymes
B01AA	6	vitamin K antagonists
B01AX	3	other antithrombotic agents
B01AE	3	direct thrombin inhibitors
C10A Cholesterol and triglyceride reducers		
C10AA	6	HMG CoA reductase inhibitors
N01A Anaesthetics, general		
N01AF	1	barbiturate anaesthetics
N01AH	4	opioid anaesthetics
N02A Opioids		
N02AA	4	natural opium alkaloids
N02AB	1	phenylpiperidine opioids
N02AC	1	diphenylpropylamine opioids
N02AF	1	orphinan opioids
N02B Other analgesics and antipyretics		
N02BE	2	anilide analgesics
N02BA	1	alicylic acid & derivatives
N03A Antiepileptics		
N03AA	3	barbiturate antiepileptics
N03AE	1	benzodiazepine antiepileptic
N03AG	1	fatty acid antiepileptic
N04A Anticholinergic agents		
N04AA	1	tertiary amine anticholinergic
N04B Dopaminergic agents		
N04BA	1	dopa & dopa derivatives
N04BB	1	adamantane dopaminergic agents
N04BC	4	dopamine agonists
N04BD	2	MAO B inhibitors
N06A Antidepressants		
N06AF	3	MAO inhibitors
N06AG	1	MAO A inhibitor
N06D Antidementia drugs		
N06DA	1	anticholinesterase anti-dementia
A10B Oral blood glucose lowering agents		
A10BG	3	thiozolidinediones (glitazones)
A14A Anabolic steroids		
A14AA	3	androstan anabolic steroids
A14AB	1	estren anabolic steroid
M03B Muscle relaxants, centrally acting agents		
M03BA	2	carbamic acid esters centrally acting muscle relaxants
M03BB	2	oxazol, thiazine & triazine centrally acting muscle realaxants
M03C Muscle relaxants, directly acting agents		
M03CA	1	dantrolene directly acting muscle relaxant

Table 16 Case reports of hepatotoxicity with kava: excluded cases

Source	Sex	Age	Medicine	Extract	Dose	Dur	Hepatic	Other	Dech	Rech	Outcome	Rel
EMEA	F	54	Kava		120	-	Gall bladder pain	Yes	X	X	Unknown	6
France	F	60	Kava		-	(365)	GGT increased	NR	Y	X	Recovered	6
BfArM	F	68	Laitan 100	Acetone	210	(60)	Hepatic enzymes increased	NR	X	X	Unchanged	4
BfArM	M	27	Kavacur	Ethanol	120	2	Faeces discoloured	Yes	X	X	Unknown	6
WHO	M	48	Kava		-	-	GGT increased	Yes	Y	N	Improving	3
FDA	M	53	Nature Pharma Kava		-	-	Pain right hypochondrium	NR	X	X	Unknown	6

Sex	Age	Source	Report Id	Other sources	Comment	Concom	Histology
F	54	Phytopharm (EMEA id)	38	Phytopharm 2.7.13 (EMEA 38)	Not hepatic	Enalapril, Triamterene	
F	60	France (EMEA id)	63	Phytopharm 2.5.6 (EMEA 63)	Non-specific	NR	
F	68	BfArM	93.0351	Denham 3	Abnormal LFTs before kava.	NR	
M	27	BfArM	2001776	Phytopharm 2.6.15 (EMEA 42)	Non-specific	HIV treatment	
M	48	WHO	8098467		On kava 8 years & GGT elevated over that time.	Bendroflumethiazide	
M	53	FDA	15249		Not specifically hepatic	NR	

Discussion

There are differences between the case review findings of this report for WHO and that of others. The valuable, detailed, comprehensive and most recent review is that of Schmidt (2003). This contains follow-up information not available to earlier reviewers such as Waller (2002) and Denham (2002). Some of the differences between this WHO review and that of Schmidt are discussed below, but similar comments are applicable to some of the findings of Waller and Denham.

The Schmidt review records 20 cases that are said to be 'unrelated to kava intake'. The conclusions about the relationship of the hepatic events to the kava products taken are generally at variance with this WHO report. The comparisons are summarized in Table 17. Apart from four cases excluded because they are clinically irrelevant, none of these 20 cases were regarded as 'unrelated' to the outcome in our review. They were either 'possible' or 'unassessable' because of insufficient information. If unassessable, they cannot be classified as 'unrelated' (or related).

Table 18 compares the cases coded as probable in this report with the assessments of Schmidt.

Table 17 Cases considered 'unrelated to kava intake' by Schmidt (2003)

Key: 'Schmidt ref' refers to the case reference used by Schmidt (2003), 'Case No.' refers to the case number of this (WHO) report and 'Rel' refers to the relationship assigned in this report (3=possible, 6=unassessable) (see table 1).

Schmidt ref	Case No.	Rel	Comment
3.1	34	3	The patient had pre-existing liver disease, but it is possible that kava made the condition worse and induced liver failure.
3.2	17	3	Considered by Schmidt as unrelated because there was recovery with stopping co-medication and continuing kava, but an interaction was possible with the co-medication which was stopped. Therefore coded as 'possible'.
3.3	-	-	Excluded from this review (table 16)
3.4	54	3	Had liver abnormalities before kava, but whatever the cause of the abnormality, if kava is hepatotoxic, then it may have made the abnormality worse. Kava-drug interaction is also 'possible'.
3.5	31	6	Unassessable because of insufficient data. This means the causality of the event cannot be assessed and so it should not be included in the 'unrelated' group.
3.6	73	3	There is a question over pre-existing liver disease. If present, it could have been aggravated by the kava product. Therefore 'possible'.
3.7	92	6	As for 3.5.
3.8	66	6	As for 3.5
3.9	-	-	Excluded from this review (table 16)
3.10	91	3	Took kava for 2 years. LFTs returned to normal on withdrawal. Schmidt attributes the problem to obesity, but there is no record of weight reduction associated with the LFT recovery. Therefore 'possible'.
3.11	68	6	As for 3.5.
3.12	89	3	History of hepatitis C, but this does not exclude kava as contributory or causal. LFTs improved to near normal (ALT 997 ⊠ 46 IU) 5 weeks after withdrawal of kava.
3.13	-	-	Excluded from this report.
3.14	59	6	Unassessable. Pre-existing hepatitis C does not exclude hepatic damage by kava as claimed by Schmidt.
3.15	57	3	Other medications may have affected the liver, but this does not exclude kava as a cause. Hepatitis C could not be completely excluded.
3.16	74	6	As in 3.5.
3.17	36	6	As in 3.5.
3.18	6	3	Considered by Schmidt to be 'hepatitis caused by tetracycline' (even though 'the data is insufficient'), but this does not exclude kava as an interacting agent. Apparently there was a negative rechallenge to kava alone, not indicated in earlier report details.
3.19	88	3	Probably alcoholic (Schmidt). Alcohol &/or fluoxetine could have caused liver problems, but this does not exclude kava either as an interacting agent or as contributory to the event.
3.20	-	-	Excluded from this report (table 16).

Table 18 Cases coded 'probable' in this report compared with the evaluation of Schmidt (2003)

Schmidt ref	Case No.	Rel	Comment
5.4	3	2	'Doubtful' causality by Schmidt because of other possible components of 'Sleepy tea', one of two kava containing products taken. However, this case fulfils the key criteria for 'probable': recovery on withdrawal and no other identifiable suspect cause.
-	4	2	Not included in Schmidt's review.
7.1	19	2	'Probable' relationship agreed.
6.4	21	2	Regarded by Schmidt as unassessable because, 'There is no information on the differential diagnostics, virus serology and ethanol consumption.' However, the basic pharmacovigilance data for a 'probable' relationship are present. Recovery on withdrawal of kava suggests the absence of virus and alcohol problems.
6.3	37	2	Same comment. Schmidt states that the outcome was unknown. If this is correct then the relationship should be 'possible', but the WHO database report states that the 'reaction abated' on withdrawal.
6.8	39	2	Schmidt suggests that the taking of an artichoke extract might mean that the patient was suffering from pre-existing 'hepatic insufficiency' and that the case was 'unassessable'. This is a vague assumption and the basic pharmacovigilance data for a 'probable' relationship are present. She was investigated in hospital for causes other than kava and none found.
8.1	43	2	'Probable' relationship agreed.
-	82	2	Not included in Schmidt's review.

The reviewers of the case reports of hepatotoxicity linked with kava have to date taken a purely clinical approach with the examination of each report individually and have largely neglected the epidemiological type of assessment used in pharmacovigilance and pharmacoepidemiology. While clinical assessment is essential, it must be supported by epidemiological assessment. In pharmacovigilance, the clinical data is usually incomplete and imperfect, as has been found with the kava case reports, but there are other means, as demonstrated in this review, of evaluating the strength of a signal or validating a causal association when looking at the aggregation of reports as a whole. In pharmacovigilance there are frequent intra- and inter-individual inconsistencies in the relationship (causality) assessment of individual case reports. These assessments, though important, are seldom anything more than provisional and their main value is in establishing a plausibility for a suspected causal association which may lead to further investigation.

Whatever the individual assessments of the case reports, probably the most important finding of this review is that amongst an aggregation of 93 worldwide case reports of hepatotoxicity associated with the use of kava, there are differences between the extracts which provides scientific evidence that this association is not a random phenomenon. This evidence suggests that the organic extracts of kava are associated with a higher rate of hepatic events than synthetic products. It might be thought that the possibility of a small number of unidentified duplications in the case reports arising from Stickel's case series (up to four) could affect these statistical comparisons of the extracts, but this is not so. None of the unmatched case reports from Stickel et al. (2003) provided the name of the product used or type of extract and so they were not included in the statistical comparisons.

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Section III Regulatory issues

Regulation / registration of kava products

Table 1 Country status of kava usage before the ban in Europe

Country	Food Supplements (yes/no)	Medicine (yes/no)	Approved use
Australia	yes	no	Traditional form and food supplements
Austria	no	yes	Treatment for anxiety
Belgium	no	yes	As drugs (treatment for anxiety)
Brazil	no	yes	As drugs (treatment for anxiety)
Canada	yes	yes	Food supplement and as treatment for anxiety
Denmark	yes	no	Food supplement
Finland	yes	no	Food supplement
France	yes	no	Food supplement
Germany	no	yes	As drugs to treat anxiety disorders
Greece	yes	no	Food supplement
Ireland	yes	yes	As food supplements and as treatment for anxiety
Italy	yes	no	As food supplements
Liechtenstein	yes	no	As food supplements
Netherlands	yes	no	As food supplements
New Zealand	yes	no	As food supplements and traditional form
Norway	yes	no	As food supplements
Portugal	no	yes	Licensed drug for anxiety treatment
Singapore	yes	no	As food supplements
Spain	yes	no	As food supplements
Sweden	yes	no	As food supplements
Switzerland	no	yes	Treatment for anxiety
UK	yes	yes	As food supplements and as treatment for anxiety
USA	yes	no	As food supplements + traditional form

In the Pacific Islands, people have used kava as a traditional drink before and after the ban. Only water extracts have been used in the Pacific Islands whereas the countries mentioned in the table above have principally used organic solvent extracts such as either ethanol or acetone extracts.

Regulatory actions on kava containing products

Table 2 outlines the regulatory actions taken by various countries around the world from the year 2000 after concerns about hepatotoxicity were first raised in Germany.

The total number of worldwide reports of suspected liver toxicity associated with kava-containing products was 68 in June 2002. Of the 68 reports, there were three deaths and six liver transplants.

While the United States of America has issued numerous warnings to both consumers and physicians, the herb is still available for sale throughout the country.

Table 2 Regulatory actions on kava containing products

Year	USA	Canada	Germany	Australia	France	UK
2000			Small number of cases of liver damage reported to the German regulatory authority (BfArM).1, 2			
2001	In a letter issued by the Food and Drug Administration (FDA) on December 18, the agency stated it is investigating whether kava-containing products are a health concern. The FDA noted 26 cases of liver toxicity in Germany and Switzerland, including one fatality and one liver transplant that were reportedly associated with kava products.3		In November, Germany's Federal Institute for Drugs and Medical Development (BfArM) reported 24 recent kava-related cases of liver damage, including one death. BfArM asked kava manufacturers to respond to the reports and stated that licenses to market the herb could be withdrawn.1		Two non-serious liver case reports were filed with regulatory authorities.1 However, no kava product was registered for sale in France because it is traded as a food supplement. On January 8, the French Agency for the Safety of Health Products halts kava sales for one year based on German and Swiss reports.4	The Committee on Safety of Medicines (CSM) first considers safety of kava. The Medicines Control Agency (MCA) and CSM call for a voluntary suspension of kava-containing products.1 MCA said it knows of 68 cases of liver problems worldwide suspected to be associated with kava kava, including liver failure resulting in six transplants and three deaths.12
2002	US Centers for Disease Control and Prevention issued a report on hepatotoxicity associated with kava-containing products. On March 25, the FDA warned that kava is linked to serious liver damage, including hepatitis, cirrhosis, and at least four urgent liver transplants in other countries. A letter was also issued urging healthcare professionals to review cases of liver toxicity to determine if they were associated with kava.	On January 16, Health Canada begins safety assessment of kava and advises consumers not to use kava-containing products. The investigation found that as of August 21, three cases of liver toxicity associated with kava were reported. A stop-sale order was issued for all kava-containing products.1	Forty cases of severe liver damage were reported to BfArM from 1999-2002. Of the forty cases, three were fatal and six patients required transplants.5	On August 15, kava-containing products were recalled by the Therapeutic Goods Administration (TGA). The recall was sparked after a reported death of a woman from complications of fulminant hepatic failure associated with the use of a kava-containing medicine.1,6	There is no evidence that kava was allowed back on the shelves, all reports say it is still banned.	Three reports of liver toxicity (none fatal) were reported to the MCA up to June. On July 18, the MCA considers proposal that prohibits the supply of kava in unlicensed medicinal products.7
2003	As of March, the FDA advised that 21 adverse event reports had been received in the U.S.A Five stated some type of liver disorder.3			In January, the TGA established a committee, called the Kava Evaluation Group (KEG) to review the safety of kava products.6		The Committee on Safety of Medicines and the Medicines Commission found evidence linking kava to cases of liver toxicity. The MCA noted 70 worldwide reports of adverse liver reactions, In January, the Medicines and Healthcare products Regulatory Agency (MHRA), bans kava-containing products.7
2004						
2005	Kava products remain available for purchase.		Germany is giving consideration to making kava a prescription drug.			MHRA is reviewing the ban on kava. (If the regulatory agency can find evidence that kava is safe, the herb may enter the United Kingdom market once again.) 8

Table 2 Regulatory actions on kava containing products (continued)

Year	Portugal	Switzerland	Singapore	Austria	Ireland	New Zealand
2000		In September 2000, the government warned marketers of safety concerns related to kava, based on four case reports.1				
2001		Health authorities, (Swissmedic) issued a safety protocol.1,4				
2002	Portugal followed France and suspended all kava-containing products for one year. 1,4 There were no local reports of hepatotoxicity.		In January, the country's Health Sciences Authority (HSA) warned consumers of the potential adverse effects of kava. On July 25, kava was banned. While no adverse effects associated with kava were reported in Singapore, HAS prohibited the importation and sale of kava products in the country based on German and Swiss case reports.1	Following the German ban of kava, Austria banned kava. The recall of all kava products followed a single case of liver failure associated with kava consumption.	On February 4, the Irish Medicines Board while acknowledging that there were no reports of liver ADRs associated with kava in Ireland, issued a voluntary recall of kava products in conjunction with the industry, based on the reports in Germany and Switzerland.11	On January 16, the New Zealand Ministry of Health announced that it was investigating overseas concerns about kava and liver damage. The ministry noted that available evidence is poor because of additional liver-affecting factors, such as alcohol consumption. On August 16, the NZ Food Safety Authority issued a warning to consumers about the safety of kava-containing products.4 No case reports of hepatotoxicity.1,4
2003		In February, the Swissmedic banned the sale of kava-containing products.1				
2004						
2005						

Year	New Caledonia	South Africa	Wales	South America	Asia
2000					
2001					
2002	On January 11, the Health and Social Department announced a ban on the sale of kava-containing products sold in pharmacies. Traditional kava preparations and kava products sold in supermarkets were exempt from the ban.1 Two cases of hepatic injury with recovery associated with traditionally prepared kava drink.13	In November 2002, the South African Medicines Control Council (MCC) issued a drug alert, stating that kava may cause irreversible liver damage. No cases of liver damage were reported to the MCC.1	The National Assembly for Wales bans all kava-containing products under The Kavakava in Food (Wales) Regulations 2002 in December 2002.		April-May—Japan: begins action on kava.
2003			The National Assembly for Wales reversed a two-year ban on the sale of kava-containing products. The decision went into effect in October.10	Brazil- Two cases of hepatotoxicity reported.	
2004					
2005			Fresh regulations to ban kava were proposed but an appeal is currently under consideration by the court. 14		

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Section IV Conclusions and recommendations

Background

Kava is a perennial shrub native to some islands of the South Pacific that has been cultivated for centuries. Water-based extracts of its rhizoma are used traditionally to prepare a psychoactive beverage and acetonic and ethanolic extracts of kava have been used in considerable quantity as a herbal anxiolytic in many countries. Until the ban of kava products in 2002, kava was available in Europe as an herbal medicine. Kava is still available for use in the United States of America and some other countries as a dietary supplement.

Warnings about the safety of the plant were initiated in the late 1990s when several cases of hepatotoxicity including liver failure and death were reported to regulatory agencies mainly in the European Union (EU) in 1998 after almost a decade of widespread use of kava extracts in Europe (Strahl et al. 1998; Russmann et al. 2001a). The first reported cases were presented to the Federal Institute for Drugs and Medical Devices (BfArM) in Germany, where out of 76 spontaneous adverse drug reaction (ADR)- reports on kava, 24 were associated with impaired liver function or symptoms that could be linked to impaired liver function. One out of four reports of liver dysfunction from Switzerland was of fulminant liver failure and required liver transplantation. Other hepatic events were hepatitis, jaundice, cirrhosis of the liver, and elevated liver enzyme and bilirubin concentrations. There was also a highly publicized death (Brauer et al. 2001).

Suddenly other agencies in different countries started documenting cases of hepatotoxicity possibly induced by kava preparations available in the market at the time. By late 2001 and early 2002 both the Medicines Control Agency (MCA) in the UK and the Food and Drug Administration (FDA) in the USA received 3 and 17 reports of liver toxicity in association with kava. Four published cases of hepatic injury associated with kava were reported in Canada in February 2002. A total of 82 documented adverse event reports involving liver toxicity existed as of December 2002. As a result kava products were banned by individual countries in the EU such as Germany, Switzerland, France and Spain, and the controversy began.

More recently two cases of fulminant hepatitis (one death) suspected to be related to kava consumption were reported to the Brazil regulatory agency late in 2003. Other cases of liver toxicity particularly hepatitis have been reported in Spain, Australia and Switzerland (Bujanda 2002; Gow 2003; Russman 2003).

I. Ralph Edwards, Director of the WHO Collaborating Centre for International Drug Monitoring (*the* Uppsala Monitoring Centre) has stated, *'There are valid arguments on both sides about the level of attribution that can be ascribed to kava products as causing liver damage. This is common in drug safety according to where one applies the benefit of any doubt. When there are more than a few suspected cases, and when the outcome is serious (liver transplantation and death), I believe there is a 'case to answer''.*

Possible mechanisms

Toxicological and clinical studies vary in their results addressing kava hepatotoxicity, but experimental studies and clinical trials suggest that water extracts are devoid of toxic effects on the liver. Several factors analysed in this report have been implicated in the apparent cause-effect relationship between ingestion of acetonic or ethanolic (organic) kava extracts and the liver toxicity observed in the case reports, but the exact mechanism of toxicity (if any) remains unknown. In a few reports there is a suggestion of an idiosyncratic immune mediated process and in two cases, a metabolic abnormality with CYP 2D6 enzyme deficiency. Further research is necessary to determine all the chemical constituents of kava in the different types of preparation and their exact metabolic pathways. In terms of drug-drug interactions, kava appears to inhibit or induce multiple CYP 450 enzymes.

Differing opinions

As described in Section IIA, some experts consider kava to be a medicinal plant with a very favourable risk profile and to have at the same time, excellent efficacy in the treatment of anxiety and as a muscle relaxant, mood enhancer and sedative. As a reaction to the ban of kava products in Germany, the scientists in the official German expert group for phytotherapy (Commission E) publicly stated that according to their point of view the ban of kava was an overreaction. They disagreed with the ban and reiterated their view in July 2002 that they were *'convinced of the presented scientific data on the efficacy of Kava and consider the benefit-risk ratio and the therapeutic benefit for the patient positive'*. According to some experts (Hagemann 2003; Corrigan 2005) this is an extremely important fact because it has been stated that the German ban was as a consequence of an assumed lack of kava efficacy.

Incidence

It has also been claimed that the majority of case reports were probably not related to kava and that the benefit-risk ratio for kava is positive when compared with other available treatments for anxiety disorders. According to Mathias Schmidt (2003) *'from the cases where a causal relationship seemed probable, an incidence rate of less than 0.02 cases per one million daily doses is calculated, corresponding to less than one case in 50 million days of application. This incidence calculation is far below the liver risk for diazepam with one case on 472,000 days of application'*. In addition, some experts have pointed to an imbalance in the benefit-risk analysis resulting in an underestimation of efficacy and an overestimation of risk.

However, estimates of the incidence of adverse events based on spontaneous reporting are usually much lower than the true incidence, because, with modern pharmaceuticals, only 5% or less of all adverse reactions are reported. Adding to the uncertainty of Schmidt's estimate is the fact that the reporting rate for herbal medicines is very much lower than

for modern pharmaceuticals. Therefore the true incidence of adverse events related to kava is not known, but it appears to be quite low. A true incidence figure can only be ascertained by a proper epidemiological study.

Clinical trials

In the reviewed clinical trials serious adverse events related to kava are listed as non-existent or negligible. There have not been any case control studies for relative risk determination. *'Based on empirical data from other benefit-risk evaluations, it can be stated that severe liver damage caused by Kava-Kava occurs only very rarely'* (Corrigan 2005)

Would even more thorough clinical trials before kava extracts were widely marketed have solved the issue of kava's safety with regard to the liver? Probably not. It is widely accepted that most hepatic drug reactions involve only a small proportion of individuals. This fact makes it difficult to detect even direct hepatotoxicity at the time of drug development (Gruenwald 2003), but it may be worth evaluating this problem in future clinical trials and in prospective observational cohort studies (cohort event monitoring).

Causality

When case reports of hepatic side effects are discussed, a range of potential causes has to be taken into consideration. Drug-induced hepatic diseases are only one of the possibilities in differential diagnosis, and would account for less than 5% of all hepatic illness. It is well established that alcohol abuse and viral infections are still the leading causes of hepatic diseases.

In general, drug-induced disease mimics non-iatrogenic disease and examination of the clinical characteristics recorded in case reports will often not assist in differential diagnosis. Many of the clinical and histological features in the kava case series would be consistent with viral hepatitis, but the evidence as outlined in the section on differential diagnosis, largely points to their exclusion.

As with many different types of ADR, reliance must be placed on the closeness of the association between drug and disease and the collective characteristics of the reports. Eight reports met the requirements of having a probable relationship. A probable relationship means that there was a new (or worsening) hepatic event within a plausible time period after the administration of kava, that there was no other plausible reason identified for the event and that the patient recovered soon after withdrawal of kava. In addition to the probable reports, there were five reports with a positive rechallenge. Although these contained confounding elements that prevented their classification as 'certain', a positive rechallenge with the suspect agent is a strong indication of cause and effect. Further evidence for a causal relationship comes from the reports classified as possible. These were classified according to strict criteria and the absence of information on dose, duration, dechallenge or outcome, or the presence of a potentially hepatotoxic drug, prevented their classification as probable even though the association of drug and event was otherwise strong. Some of the concomitant drugs had a very low likelihood of causing a hepatic reaction e.g. phenoxymethylpenicillin and some had been used continuously for several years without problems, but with the hepatic event occurring only after the administration of kava. It is of note that the reports stated that there was no other therapy in seven and in eight others the concomitant therapy mentioned is assessed as not causing hepatotoxicity.

Benefit-risk

A comprehensive assessment of the safety of kava preparations would have to weigh the claimed relative benefits of kava against its perceived (or, ideally measured) comparative risk. In future, new studies evaluating the mechanism of toxicity, or data on product characteristics, manufacturing and quality control, as well as post-marketing surveillance studies, will contribute to this assessment. Appropriate study outcomes and biological assays may have to be developed. The issue of the synergistic effect of multiple plant constituents, part of the plant used in the preparation of the extracts and type of extraction method should also be considered when evaluating both safety and efficacy of kava preparations (Spinella 2002). Hagemann (2003), states that a complete evaluation also has to take into consideration the possible effects of regulatory decisions such as cancelling a license or banning a product a priori without an evidence-based justification. Such decisions must not result in a shift to therapeutic alternatives that may be even less researched, or whose application entails greater or more severe risks, or that may be more costly.

Several initiatives have been established to address these and other important issues. The most recent is that of the MHRA agency in the UK that has called stakeholders to participate in a review process of available kava evidence. The final report 'Report of the Committee of Safety of Medicines Expert Working Group on the Safety of kava' is available from the website: www.mhra.gov.uk.

Post-marketing surveillance

Current cases of adverse events associated with kava raise many new (and controversial) issues. However, according to our literature review, alcohol and acetone extracts appear acceptable and safe for the treatment of anxiety and related disorders. But a lot of uncertainties remain. Good post-marketing surveillance studies are essential and should not rely exclusively on spontaneous reporting. Case-control studies and prospective observational cohort studies are essential, but because the putative hepatotoxicity appears rare, the cohort studies would need to be large. The accumulation of large cohorts of kava users, taking a variety of kava products, should provide many opportunities for scientific study, including real incidence, differences between extracts, ethnic or regional differences, identification of risk factors, case-control studies, identification of interactions and pharmacogenetic studies.

Toxicological research

Further comparative toxicity studies among kava users, both in indigenous populations and Western populations are required. Further evidence-based research should focus on the safety of all the different types of kava preparations (organic extracts, synthetic and water based) used in clinical practice. Controlled clinical and non-clinical studies are necessary to determine the possible mechanisms of liver toxicity of the various kava lactones and other chemicals identified.

Such studies may then lead to the development of less toxic kava products, to the identification of a subpopulation of individuals that should not use kava or to additional mandatory cautionary requirements, including label claims and warnings, if needed (Anke and Ramsan 2004). In the meantime physicians and patients should continue to be alert to possible hepatotoxic side effects in the course of kava treatment, to stop the treatment at first suspicion and to undertake a careful diagnostic work-up ruling out all other causes (Teschke 2003). Further research into kava products is necessary to gain information about the pharmacokinetics, particularly distribution, metabolism, and hepatic elimination mechanisms as well as the mechanism of liver toxicity itself.

Quality control

Of primary importance on the producer side, is the development of adequate quality control and regulated production. Standards for the cultivation and processing of kava before its pharmaceutical processing need to be established and enforced. It would appear that the 'correct' cultivar(s) and plant parts for medicinal use are known. The use of other cultivars or similar species, or aerial parts of the plant, could increase the risk of toxic effects. Raw kava produced for manufacture should be certified according to the standards set and pharmaceutical companies have a responsibility for using only those sources that meet these standards.

Clinical review of case reports

Preceding comments derive from the literature review. With a pharmacovigilance and pharmaco-epidemiological approach, there is evidence that there is a greater risk of hepatotoxicity with the organic extracts than with synthetic or water products. The case report analysis suggests a likelihood that kava products of any type can be harmful to the liver and that this can be serious. This problem appears to occur rarely, but there is no good information on incidence. While there is evidence that some of the cases are due to direct toxicity, there is evidence that other factors may, perhaps more often, be responsible. These include pre-existing liver disease e.g. hepatitis C, or alcohol related liver problems, kava-drug or kava-herb interactions, idiosyncratic responses either immune mediated or metabolic, and overdose. The use of kava with known hepatotoxic drugs should be avoided. In terms of potential interactions, kava should not be used with antipsychotics, other anxiolytics and anticoagulants. Where pharmacogenetic testing is available, it would be desirable to determine the presence or absence of enzyme abnormalities in the cytochrome P450 system. Some pharmacogenetic laboratories have developed straightforward and cheap methods of doing this without reliance on blood samples.

Interactions

Kava products have a high propensity to cause kava-drug, and probably kava-herb interactions. Over 200 possible or potential kava-drug interactions have been listed (Section IIB tables 13-15). Some of these will affect the liver. Co-medication with anxiolytics, antipsychotics and antithrombotics should be avoided and a decision on the use of other drugs with kava should only be undertaken after the potential for interaction has been checked. Use with other potentially hepatotoxic drugs should be avoided.

Pharmacoepidemiology

Using denominator data in the form of daily doses of various kava products sold, it has been possible to compare rates of hepatic events by extract type. The results suggest that there is a higher rate of hepatotoxicity with acetonic and ethanolic extracts than with synthetic products. This is a key finding, although the rates are based on sales figures only and numbers are small. The results also show that the differences are independent of age, gender, dose, duration of use, concomitant therapy and alcohol use and are unlikely to be confounded by other disease states. This suggests, at least in part, that the liver toxicity is not due to the kava lactone content, but other chemicals extracted that are not present in the synthetic product and not bioavailable in water suspensions of kava. It is impossible to make a comparison of rates with water-based products.

Risk factors

In the absence of epidemiological studies it is difficult to identify risk factors for hepatic reactions with certainty. However there is evidence for the following:

- Acetonic and ethanolic extracts
- Alcohol
- Co-medication with potentially hepatotoxic medicines
- Co-medication with potentially interacting medicines: kava has been shown to inhibit a variety of cytochrome P450 enzymes.
- Pre-existing liver disease
- Significant overdose (see section on liver transplants), but within the usual range, there is no evidence that higher dose carries increased risk
- Genetic polymorphisms of cytochrome P450 enzymes. 2D6 deficiency has been associated with cases, but there may be others that are significant.

Pharmacovigilance versus clinical trials

It might be considered that the findings of the review of case reports are inconsistent with the findings of the review of clinical trials and experimental studies. However, this apparent incompatibility is a common situation. Clinical trials usually involve insufficient numbers of patients and do not continue for a sufficient length of time to reliably detect rare reactions. In addition, they are generally designed to assess efficacy and while they collect safety information, the methodology is not primarily aimed at detecting potential toxic effects. Many common or serious reactions have been missed in good quality clinical trials and have been revealed only through effective pharmacovigilance, prospective observational cohort studies such as cohort (prescription) event monitoring, published case reports in the literature or case control studies following signal identification. The absence of reports of hepatotoxicity in clinical trials does not mean that these reactions do not occur.

Recommendations

Should kava products be used as medicines, then the following are recommended in terms of safety:

- Ethanolic and acetonic extracts should be avoided.
- Synthetic products should be available.
- Products should be developed from water-based suspensions of kava.
- A pharmacopoeial standard for kava products should be created.
- Further research should be undertaken on the identification and toxicology of the chemical constituents of acetonic and ethanolic extracts.
- Cohort event monitoring studies should be undertaken on all products, including those that are synthetic and water-based.

Overall summary

Conclusions

1. The case reports of liver injury associated with the use of kava products provide a significant concern of a causal relationship in the absence of other identifiable risks of liver disease.
2. The chemical component(s) of kava products responsible for hepatotoxicity have not been identified.
3. The strong potential for kava-drug interactions, genetic differences in the cytochrome P enzyme system, heavy alcohol use and previous liver disease are potential risk factors for hepatotoxicity with kava. In addition, the cultivar of *Piper methysticum* used and the plant part are relevant to safety.
4. Other mechanisms proposed for hepatotoxic effects are immune mediated idiosyncrasy, the presence of the alkaloid pipermethystine in organic solvent extracts and loss of the protective effect on the liver of glutathione with the organic solvent extracts.
5. The incidence of hepatotoxicity with kava is unknown. Published estimates are unrealistically low. Nevertheless, the incidence is likely to be uncommon or rare.
6. There is some evidence of a higher risk of hepatotoxicity with acetonic and ethanolic extracts. This suggests that hepatic events occurring with products prepared from these extracts are non-random.
7. Alcoholic and acetonic extracts of kava may include toxic substances e.g. alkaloids, not present in synthetic products, or not bioavailable in water extracts.
8. On present knowledge, synthetic products and water extracts should have a lower risk of hepatotoxicity.
9. A variety of cultivars of *Piper methysticum*, and some other similar species have been used by pharmaceutical companies for the preparation of medicinal kava. A variety of plant parts has also been used.
10. The chemical composition of raw material from different species, cultivars and plant parts is not equivalent and in some instances has not been investigated.
11. Clinical trials of kava have not revealed hepatotoxicity as a problem.
12. Most experimental studies have failed to demonstrate a toxic effect on liver cells by kava.

Summary of findings

1. Of the 93 case reports of hepatotoxicity that have been collected and analysed there were seven fatalities and 14 liver transplants.
2. Eight cases were classified as having a probable relationship between the use of kava and liver disorder. This means that there was no factor present other than kava that was likely to cause liver injury.
3. There were 53 cases classified as having a possible relationship. Some of these cases will have a causal relationship with kava and some will not.
4. Five patients had a positive rechallenge, presumably to kava alone.
5. All seven deaths were classified as having a possible relationship with the use of kava, as were 10 of the 14 liver transplants. By definition of the term 'probable' in pharmacovigilance practice, deaths and transplants cannot be coded as such. It is likely that some of these cases were related to kava use.
6. Five of the case reports were from the use of water 'extracts' (but only two were prepared in the traditional manner); two were coded as probable and three possible.

Summary of recommendations

1. Further research into kava products is necessary, in particular to identify and gain information about the toxicology of the non-kava lactone constituents. This needs to include any differences between root and rhizome.
2. Should any kava product be considered for approval by regulatory authorities, the following should be important considerations:
   - 2.1. Post-marketing surveillance and research
     - 2.1.1. A risk management plan should be drawn up early in the approval process. This plan would include suggestions for pharmacoepidemiological studies, in particular cohort event monitoring, preferably with international collaboration. These studies should be undertaken on all products, including synthetic and water-based. Reliance should not be placed on spontaneous reporting alone for post-marketing surveillance.
     - 2.1.2. Pharmacogenetic studies should be undertaken to determine differences in cytochrome P450 metabolic enzyme activity and any relationship to hepatotoxicity. This could be undertaken using case control studies, ideally nested case control studies of cohorts of users of kava from cohort event monitoring studies.
     - 2.1.3. Products from water-based suspensions and further synthetic preparations should be developed and tested in clinical trials and consideration given to using these in preference to acetonic and ethanolic extracts.
   - 2.2. Conditions of use
     - 2.2.1. It would seem advisable that all kava products prepared as pharmaceuticals be available on prescription only in order to better monitor their use and apply necessary controls.
     - 2.2.2. Kava should not be used in patients with liver disease or a history of such, nor in patients who take excessive alcohol.

2.2.3. Warnings should be made available about the extensive risk of interactions with other drugs or herbal preparations. In particular, kava should not be used with antipsychotics, other anxiolytics or antithrombotics because of the risk of interactions which could include effects on the liver.

2.3. Standards

2.3.1. A pharmacopoeial standard for kava should be created. This should address the issues of quality, plant parts, dosage and methods of preparation. The findings of this review indicate that:

2.3.2. Only the root or rhizome of *Piper methysticum* G Forst should be used for preparation of medicinal kava. No other species and no aerial parts should be used. Agreement should be reached on the appropriate cultivar(s).

2.3.3. Adequate quality control measures standardized across the producing countries with agreed standard operating procedures, should be instituted for growth, harvesting and processing of the raw kava root or rhizome.

Opinion on key question

1. Evidence from our review of case reports suggests that kava lactones in any type of product may rarely cause hepatic adverse reactions because of kava-drug interactions, excessive alcohol intake, metabolic or immune mediated idiosyncrasy, excessive dose or pre-existing liver disease.
2. In addition to this background incidence, products made from acetonic and ethanolic extracts appear to be hepatotoxic on rare occasions, seemingly from non-kava lactone constituents. The incidence is unknown, but is more significant than the background effect in '1'.

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WHO Advisory Committee on Safety of Medicinal Products

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Information sources

A listing of information sources is attached. The references have been sorted by type e.g. case reports; general reviews. The list is by no means complete, but we have attempted to include significant sources of information used as background in preparation of the report, as well as those referenced in the text. There are no doubt errors, but we have made strenuous efforts to avoid such and hope that these are minimal.

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