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Kava: A Risk-Benefit Assessment

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In November 2001 the German Health Authority (BfArM; see Appendix 1 for abbreviations used) announced that it was intending to ban the use of kava (*Piper methysticum*) because of reported cases linking kava consumption with hepatotoxicity. Despite submissions from manufacturers, therapeutic use of kava was banned altogether in Germany in 2002 and several other countries such as Japan, France, and Canada followed suit. Late in 2002 it was announced that the Medicines Control Agency (MCA) in the United Kingdom would also be banning kava; in February 2003 Swissmedic (formerly IKS) in Switzerland followed. At the time of writing, the Australian government is currently considering whether availability of therapeutic goods containing kava should be restricted.

Since the action of the German authorities, government health administrations throughout the world have examined their databases for evidence of hepatotoxicity from kava use. Not surprisingly, more cases have come to light, but many of them are tenuous or inadequately reported. This chapter will review all known reported cases as of February 2003, with a view to arriving at an assessment as to whether the actions by the various health authorities have been justified. Much depends on the risk to benefit perspective. How much risk is acceptable for a herbal product? How good does the evidence need to be to arrive at a favourable risk-benefit assessment? The question must also be asked whether the interests of the consumer have been served by the complete banning of a herb that offered a viable alternative to conventional anxiolytic drugs, which are well known to have many risks associated with their use.

SUMMARY AND CRITIQUE OF CASE REPORTS

A number of case reports of hepatotoxic effects possibly attributed to kava have been documented by various health authorities around the world. These are provided in tabular form in Appendix 2.

The table in Appendix 2 contains the case numbers used by relevant regulatory bodies (BfArM, MCA, European Agency for the Evaluation of Medicinal Products [EMEA], Food and Drug Administration (United States) [FDA], IKS, and Therapeutic Goods Administration (Australia) [TGA]) and other

relevant information including literature and press sources. The case number assigned in the first column will be used throughout this document to enable easy reference to the case reports. Variation in the MCA numbers occurs in other documents, but that variation is not reported here.

Information provided in Appendix 2 was obtained from the following sources:

- The Committee on Safety of Medicines (CSM, part of MCA) analysis of case reports received worldwide to 10 July 2002 (68 case reports; listed as #1 to #68).[1]
- A literature review by Schmidt from the University of Muenster dated May 2003, which analysed 82 case reports dating from 1990 to 2003 (including #1 to #68) and details from the Adverse Reaction Monitoring System of the U.S. FDA (which provided an additional 12 case reports [#69 to #80]). Most of the FDA kava reports were provided by the American Herbal Products Association in a spreadsheet entitled "FDA kava reports, 1994-2002: Initial organization of 51 cases". Of the 51 cases provided in this FDA spreadsheet (last entry dated 25 February 2002), 31 did not describe hepatic adverse events. Recent case reports, one each from BfArM and the FDA, subsequent to the data listed here were obtained from the Schmidt review (#81, #82). The information listed in Appendix 2 for #81 did not appear in the official BfArM line listing (24 May 2002) and was obtained from the literature.[2] (There is no BfArM line listing available for #82, so it has not been included in Appendix 2.) Information for case #71 obtained from two sources (literature and the FDA) has been included for comparison.
- Australian TGA with details obtained from the adverse drug reactions system (1 case report, listed as #83).

The case details obtained from the MCA analysis are presented as provided. However, they do not list all the known information, and additional details are provided in the individual case discussions below. Additional details of those U.S. cases listed by the MCA (#51 to #63) can also be found in the FDA spreadsheet provided for the Waller analysis.[3]

Of these 83 case reports three have been identified as possible or definite duplicates (#26 and #28, #29 and #30, and #31 and #33).

Appendix 2 does not contain the three cases of hepatitis possibly associated with kava use in New Zealand, reported in the CSM *Risk–benefit analysis of Kava-kava*, 12 February 2002,[4] as sufficient details were not available.

A detailed analysis of the 83 cases follows. In addition to the information initially provided via spreadsheets from government regulatory bodies, additional case details have been obtained from the Schmidt, MCA, and Waller reviews and the FDA spreadsheet of 51 cases. The Schmidt review obtained additional information from the following sources:

- additional details provided by the BfArM with the ban of kava products dated 14 June 2002;
- additional details provided by an expert report from the BfArM for a law suit against the German authorities filed by some German producers;
- additional details from the producers of the implicated kava medications;
- detailed background data from the Swiss IKS forwarded to the producers of kava products in the process of the drug safety protocol of 2000;
- additional information obtained from the FDA; and
- case reports from the literature.

Botanical names have been noted here to assist the reader in recognising the herbs listed in the products allegedly consumed in the case reports. It should not imply that the botanical identity of these ingredients was verified either by the product label or by analysis.

Case #1

Case also identified as: MCA #1, MCA Case Report, EMEA #1

The 40-year-old man drank six bottles of wine per week, which may have caused or contributed to the abnormal liver function tests. This, combined with the symptoms of sore throat and nose bleeds, may indicate preexist-

ing pathology unrelated to kava use. Although the outcome is recorded as recovery after stopping kava, no details are supplied regarding the cessation of alcohol intake.[5] If alcohol intake had continued, one possible explanation is that kava may have acted synergistically.

Assessment: Unlikely; case involved a large intake of alcohol.

Case #2

Case also identified as: MCA #2, MCA Case Report, EMEA #2

The female patient of unknown age was taking Prozac (fluoxetine) in addition to kava. At the time the data were compiled, the case was ongoing with a biopsy pending. The outcome is listed as "reaction continues," with no explanation of whether the kava intake had ceased. Fluoxetine is known to cause hepatotoxicity.[6]

Assessment: Unlikely; probably connected to concomitant medication.

Case #3

Case also identified as: MCA #3, MCA Case Report #3

The 48-year-old man with raised liver enzymes is listed as recovering after withdrawal of kava. The case report indicates he was also taking bendrofluazide (a thiazide diuretic). Liver damage is listed as a side-effect of this drug,[7] and it should be used with caution in hepatic insufficiency, which may be unpredictably aggravated.[8] The patient stopped taking kava after 8 years of occasional use for air sickness, during which he had stable but increased liver enzymes. The liver appeared to take time to recover.

Assessment: Possible, but connection to kava is not proven as the effect of concomitant medication and a preexisting problem cannot be ruled out.

Case #4

Case also identified as: MCA #4, BfArM #93/0351, EMEA #3

Reported by Schwabe GmbH & Co

Further details supplied by Schwabe, the company that reported this case, indicate that the 68-year-old woman displayed elevated liver enzymes prior to ingesting the kava product (210 mg/day of kava lactones) and the enzyme values did not worsen during the kava treatment.[9]

Assessment: Unlikely, no connection to kava and should not have been listed as an adverse reaction.

Case #5

Case also identified as: MCA #5, EMEA #4

Lit: Strahl et al, 1998

This is a reasonably well-documented case[10] in which a 39-year-old woman had her elevated liver enzyme (glutamic-pyruvic transaminase [GPT]) level return to normal after cessation of the kava and other medications (below). The enzyme level rose after she resumed intake of the kava product (the other medications were not resumed). Although not defined in the literature, the kava product (providing 60 mg/day of kava lactones) is understood to have been an ethanol extract. Liver biopsy revealed acute necrotising hepatitis. Viral, autoimmune, and metabolic causes of the hepatitis were excluded. The patient was also taking paroxetine (antidepressant, 20 mg/day), a contraceptive (0.15 mg desogestrel + 0.02 mg ethinyl oestradiol per day, for 6 years) and occasionally St. John's wort (*Hypericum perforatum*, no product details). Paroxetine has caused abnormal liver function tests and severe liver toxicity.[8,11] Liver function may also be impaired by contraceptive use.[8,11,12]

Further testing[13] of this patient indicated that she was a poor metaboliser of debrisoquine (indicating a cytochrome P450 CYP2D6 deficiency). (Cytochrome P450 2D6, which is responsible for the metabolism of several antidepressants and neuroleptics, is constitutionally deficient in up to 10% of the population.[14])

By differential diagnosis an autoimmune aetiology was ruled out and a lymphocyte transformation test was not conducted after the positive rechallenge to kava. However, the shortened latency period points to an immunological sensitisation on initial intake.[11]

Assessment: Probable, due to genetic deficiency in detoxifying enzyme (CYP2D6) causing an idiosyncratic-immunologic hepatitis and perhaps exacerbated by concomitant medications.

Case #6

Case also identified as: MCA #6, EMEA #5

Lit: Kraft et al, 2001

A 60-year-old woman was admitted to hospital and was transferred to an intensive care unit with progressive liver failure, concomitant renal failure, and progressive encephalopathy. Biochemical tests revealed acute liver failure (hepatocellular necrosis with intrahepatic cholestasis) and serological tests ruled out viral hepatitis, metabolic, or autoimmune causes of liver failure. The patient received a liver transplant.[15]

The patient had suffered from pulmonary embolism 11 years earlier, with cardiopulmonary resuscitation, and had undergone an ovariectomy and cholecystectomy 21 years previously. For 8 years she had suffered depression.[16]

Concomitant medications included piretanide (a diuretic) which, according to the authors of the report,[15] could not be ruled out as contributing to the liver failure. Piretanide may cause cholangitis with intrahepatic cholestasis and increased transaminases.[17] The dosage of kava taken exceeded the recommended daily dosage regularly (4 tablets). Information from a relative revealed that the patient took extra kava doses ad libitum in addition to the already excessive regimen. Some statements indicated the use of up to 10 tablets per day.[16] The daily recommended dosage of this preparation when first released was 1 to 2 tablets per day but was recently reduced to 1 tablet per day (120 mg/day of kava lactones).

Assessment: Possible, but if so, due to excessive dosage of kava and probably connected to concomitant medication.

Case #7

Case also identified as: MCA #7, IKS #1999-2596, EMEA #6

As well as taking a kava product (an acetone extract providing 140 mg/day of kava lactones), the 46-year-old woman was also taking propranolol (80 mg) and an antihypertensive tablet containing valsartan (angiotensin II receptor antagonist) and hydrochlorothiazide (a thiazide diuretic) for 4.5 and 5.5 months, respectively. Elevated liver enzyme values and hepatitis are known possible side-effects of propranolol, valsartan can also cause elevation of liver enzyme levels, and thiazides can produce occasional cases of cholecystitis or icterus.[18]

Assessment: Possible, but may not be due to kava alone.

Case #8

Case also identified as: MCA #8, IKS #2000-0014, EMEA #7

The case of a 33-year-old woman who developed cholestatic hepatitis with icterus (jaundice) has also been described in the literature.[13,19] In addition to kava, she had taken a homoeopathic combination product for a period of 15 days about 1 month after beginning the kava.[20] The liver parameters were still deteriorating even 10 days after discontinuing medication. Values normalised within 8 weeks of discontinuation of kava. The finding of slightly higher IgM against Epstein–Barr virus (EBV) in this patient was not significant, since histology and serology results did not support evidence of EBV hepatitis. A lymphocyte transformation test performed after recovery indicated strong and concentration-dependent T-cell reactivity to the kava product, but not to the homoeopathic product.[13,21]

The patient consumed a massive amount of alcohol about 1 week before symptoms resulted in her hospitalisation. Pain medication was taken the day after the alcohol intake and consisted of a tablet containing propyphenazone, dihydroergotamine mesylate, and caffeine, and another tablet containing paracetamol, propyphenazone, and caffeine. Obstruction of the bile ducts and autoimmune disease was excluded, and liver biopsy suggested drug-induced hepatitis, not due to alcohol intake.[20]

Phenotyping of cytochrome P450 CYP2D6 activity with debrisoquine showed that the patient was a poor metaboliser.[13]

Assessment: Probable due to genetic deficiency in detoxifying enzyme (CYP2D6) causing an idiosyncratic immune-mediated hepatitis.

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Case #9

Case also identified as: MCA #9, IKS #2000-2330, EMEA #8

The 59-year-old patient was diagnosed with painless jaundice with elevation of liver enzymes. Two weeks after discontinuing intake of a kava product, the liver values improved. The patient had also been taking celecoxib (a nonsteroidal antiinflammatory drug [NSAID], cyclooxygenase-2 [COX-2] inhibitor), which is known to cause raised liver function values, liver impairment, and hepatitis.[8,22] It is not known whether the celecoxib was also discontinued.

Assessment: Possible, but may be connected to concomitant medication.

Case #10

Case also identified as: MCA #10, IKS #2000-3502, EMEA #9

This Swiss case involving a 50-year-old man was also reported in the literature.[19,23] He presented with jaundice and very high liver enzyme values. Liver failure with rapid decline and encephalopathy developed. Obstruction of the bile ducts and a viral aetiology were excluded. He received a liver transplant. Histology of his liver showed extensive necrosis and infiltration of lymphocytes and eosinophils. Paracetamol was taken while in hospital after the onset of symptoms. Despite the case information listed in Appendix 2, the literature reports that he did not consume alcohol. He was also taking evening primrose oil (*Oenonthera biennis*).

The patient had been consuming the kava product above the maximum recommended therapeutic dosage (400 mg of extract [containing 280 mg/day of kava lactones] versus the recommended dose of 300 mg of extract).

Assessment: Probable, but dosage of kava was exceeded.

Case #11

Case also identified as: MCA #11, BfArM #90003882, EMEA #10

The 69-year-old woman developed cholestatic hepatitis, and was taking a preparation containing synthetic kavain (a kava lactone) and the following drugs: acetylsalicylic acid (unknown dosage), dehydrosanol (a diuretic combination containing bemetizide and triamterene) and pentoxifylline. Each of the orthodox medications is documented as causing an increase in liver enzymes and/or liver function impairment and jaundice.[24]

Assessment: Unlikely, probably connected to concomitant medication.

Case #12

Case also identified as: MCA #12, BfArM #92901203, EMEA #11

The case details of a 35-year-old man who suffered cholestatic hepatitis after ingesting a product containing synthetic kavain are inadequate for analysis. Duration of usage, concomitant medication and preexisting medical conditions are unknown.[25]

Assessment: Unassessable due to insufficient information.

Case #13

Case also identified as: MCA #13, IKS #93/0274, BfArM #93015209, EMEA #12

The symptoms of the 39-year-old woman, which included jaundice, started 12 weeks after intake of a kava product (210 mg/day of kava lactones). Alcohol was excluded as a cause but viral hepatitis was not excluded. Concomitant medications included L-thyroxine (taken for 3 months), diazepam (for 6 months), and a contraceptive containing ethinyloestradiol and levonorgestrel (for 16 years). Cholestatic jaundice has been reported in users of this contraceptive, as has cholelithiasis and hepatitis.[8] The BfArM excluded the causality of the contraceptive agent on the basis that abnormal liver function did not develop during its long-term use, which does not, however, prove that such an adverse event did not occur. Very rare cases of jaundice and increase in transaminases can occur from diazepam intake.[8] BfArM denied the ingestion of diazepam as it was not recorded in the physician's report from the hospital. The intake

of diazepam, albeit irregular, was confirmed by the patient's general practitioner. BfArM further indicated that since ingestion was irregular it could not have been the cause, despite the fact that it was ingested prior to the onset of symptoms. The hospital physician indicated that viral hepatitis could not be excluded.[26]

Assessment: Possible, but connection to concomitant medication or an alternative aetiology is also possible.

Case #14

Case also identified as: MCA #14, BfArM #94006568, IKS #94/0259, EMEA #13

In this case of a 68-year-old woman, jaundice and cholestatic hepatitis were reported as side effects. In addition to kava, her other medications included a St. John's wort preparation (*Hypericum perforatum*, taken for 1 year) and an antacid (Maaloxan, aluminium–magnesium hydroxide, taken when needed). Liver biopsy indicated severe toxic–cholestatic liver damage and was consistent with an immunologically triggered hypersensitivity reaction, which led to an idiosyncratic damage of liver tissue. Drug-induced toxicity was not confirmed and an autoimmune process was not excluded. Normally the latency period for drug-induced idiosyncratic toxic hepatitis is 50 to 90 days. The two herbal products were taken for much longer than this before the adverse reaction occurred.[27]

Assessment: Possible, but an immunologically triggered hypersensitivity reaction not associated with kava cannot be ruled out.

Case #15

Case also identified as: MCA #15, BfArM #94901308, IKS#94/0117), EMEA #14

Adverse events for a 50-year-old woman were recorded as liver damage, hepatitis, jaundice, and elevated liver enzymes. In addition to kava (210 mg/day of kava lactones, taken for 2–3 months), her other medication included a diuretic containing furosemide and triamterene (unknown duration), atenolol (beta-blocker, 5 to 6 years) and terfenadine (antihistamine, 12 years). A biopsy suggested drug-induced hepatitis, and alcohol was eliminated as a cause. Histological results indicated previous infection with hepatitis A, although liver function was not abnormal prior to the advent of the adverse effect. Although specific autoimmune antibodies could not be detected, there were signs of autoimmune hepatitis. Histological investigation also indicated that the liver reaction had begun prior to the first intake of the kava product. Prior to the adverse event, the patient had suffered viral infections, including hepatitis A, EBV, cytomegalovirus (CMV), and herpes simplex virus (HSV), all of which can have liver involvement. Three weeks after discontinuation of the kava product, a renewed increase of the transaminase levels occurred, which is not typical of drug-induced liver problems.[28]

Despite the fact that furosemide is documented as causing adverse effects on the liver,[8] BfArM denied the existence of such adverse effects. Although individual cases of severe liver damage occur for atenolol ingestion, a rechallenge with this drug during the patient's hospital stay had no effect on her liver function. The terfenadine was considered to be not implicated by BfArM as it had been taken for over 12 years, but this does not eliminate the possibility of an idiosyncratic immunological reaction. Hepatic side effects are documented for this drug,[28] which was being ingested at a higher dosage (300 mg/day) than is normally recommended (60 to 120 mg/day).

Assessment: Unlikely to be connected to kava, more likely to be caused by concomitant medication or autoimmune hepatitis.

Case #16

Case also identified as: MCA #16, BfArM #97002825; probable duplicate case with BfArM #97003551 (not listed here), EMEA #15

In this poorly documented case (or cases) a woman over 70 years of age presented with jaundice, liver damage, and cholestatic hepatitis. The ingested herbal product contained ginseng (*Panax ginseng*), kava (ethanol extract), devil's claw (*Harpagophytum procumbens*),

hawthorn leaf and flower (*Crataegus monogyna*), pancreatin, bromelain, and papain. Other medications were a vitamin supplement named Eunova and prednisone; the latter was taken (although not originally listed) reportedly for a long time. The composition of the vitamin supplement was unclear: alpha-tocopherol 400 mg or 4000 IU vitamin A plus vitamins B_1, B_2, B_6, B_{12}, C, D_3, and E; nicotinamide, calcium pantothenate, biotin, rutoside, iron, copper, magnesium, potassium and manganese sulphate, zinc oxide, sodium molybdate, and dibasic calcium phosphate. This could indicate the vitamin supplement was a multivitamin and mineral mixture or a vitamin E preparation. The dosages of the herbal product and the vitamin supplement are unknown. The recommended dosage for the vitamin supplement Eunova is 2 tablets per day which would provide 8000 IE of vitamin A, an amount that can potentially cause hepatotoxic reactions.[27]

Assessment: Unassessable due to insufficient information.

Case #17

Case also identified as: MCA #17, BfArM #98004297, EMEA #16

The outcome of an 81-year-old woman who presented with jaundice, liver failure, and acute cholestatic hepatitis was death. The patient had been taking a kava product (120 mg/day of kava lactones) for over 10 months, a product containing hawthorn (*Crataegus monogyna*) extract and homoeopathics (8 months), hydrochlorothiazide (antihypertensive, 3 months) and a nitrendipine-containing product (antihypertensive, discontinued 5 months previously). Autopsy revealed acute hepatic dystrophy with histological signs of toxic hepatitis, with damage by alcohol not excluded. Histological data also showed cirrhotic transformation of the liver, which probably started at least 1.5 years prior to her death (long before the first administration of kava). One of BfArM's listings of this case contained a reference to alcohol abuse, but this appears to have been ignored in the official BfArM assessment. Rare cases of jaundice and liver impairment are known to occur from hydrochlorothiazide and drugs of similar structure to nitrendipine. Alcoholic liver disease was worsened by intake of the latter.[29]

In addition, 3 months prior to the adverse reaction the patient was reportedly enrolled into the placebo group of the SCOPE study (Study on Cognition and Prognosis in the Elderly), which was designed to assess the effect of angiotensin II type 1 receptor blockers on major cardiovascular events in elderly patients with mild hypertension. BfArM suggested that inclusion into the study group would not have taken place if any irregularities of liver function had been noted.[29] However, this does not explain the histological data suggesting an earlier onset of reaction.

Assessment: Unlikely; connection to alcohol abuse likely.

Case #18

Case also identified as: MCA #18, BfArM #99500453, EMEA #17

The case involved a 59-year-old woman with hepatic cellular damage. She was taking hyoscine butylbromide (butylscopolammonium bromide) as needed and had been doing so for 15 years. According to the case report, sporadic notifications of hepatic side effects have occurred from intake of this drug.

There is some debate as to whether this patient took the kava product (ethanol extract providing 240 mg/day of kava lactones) listed in Appendix 2.[30] No data regarding preexisting medical conditions, laboratory or diagnostic tests, or alcohol consumption are available.

Assessment: Unassessable due to insufficient information.

Case #19

Case also identified as: MCA #19, BfArM #99062501, EMEA #18

This case of a 37-year-old woman originated from Brazil. Hepatitis was reported. Apart from the kava product (140 mg/day of kava lactones), concomitant medication included diclofenac (single treatment prior to the

advent of the adverse reaction) and the contraceptive Microdiol (desogestrel + ethinyloestradiol, for 6 years). A rechallenge was negative for all three medications (kava, diclofenac, contraceptive), which excludes the possibility of an immunological aetiology.[31]

Diclofenac, a NSAID, has known hepatic side effects: elevation of serum aminotransferase enzymes (up to 2%), hepatitis with or without jaundice (<1%), fulminant hepatitis (isolated cases).[8] Hepatitis caused by a NSAID does not necessarily lead to a renewed hepatitis on rechallenge.[31,32]

Assessment: Unlikely, connection to concomitant medication likely.

Case #20

Case also identified as: MCA #20, BfArM #99003911, EMEA #19

A 62-year-old woman was hospitalised for jaundice, and a report of liver cell impairment was made. She had been taking a kava preparation for an unknown duration. Concomitant medication existed, but was not specified. She reputedly recovered after discontinuation of all medication. There was supposedly a rechallenge to the kava product, with recurrence of symptoms, but details were not provided by the treating physicians. Further diagnostic information and information concerning alcohol consumption were unavailable.[33]

Assessment: Unassessable due to insufficient information.

Case #21

Case also identified as: MCA #21, BfArM #99006005, EMEA #20

A 33-year-old woman was hospitalised with symptoms of acute hepatitis. Concomitant medication included cisapride taken for 4 months. A kava product (180 mg/day of kava lactones) had also been ingested for 4 months. Alcohol was ruled out as a cause, but antibodies were detected and she was treated for autoimmune hepatitis. The product manufacturer indicated that an alleged positive rechallenge occurred, resulting in toxic hepatitis, but further details could not be obtained from the treating physicians. Cisapride has caused reversible liver function impairment.[6,34]

Assessment: Possible, but further information required and concomitant medication cannot be ruled out as the cause.

Case #22

Case also identified as: MCA #22, BfArM #00003608, EMEA #21

A 21-year-old woman made a full recovery after treatment for jaundice, hepatitis and elevated liver enzymes, and other nonhepatic symptoms. The kava product that she had been taking for 7 months contained synthetic kavain in addition to standardised kava ethanol extract (total kavain per tablet equalled 50 mg). It was taken in much higher doses than normally recommended (up to 10 tablets per day, i.e. 500 mg/day of kava lactones, which is more than four times the maximum dose recommended by the Commission E). The recommended dosage was a maximum of 6 tablets per day.[35] Recorded concomitant medications included metoclopramide, paracetamol (prior to the adverse event, dosage unknown), pantoprazole (prior to adverse event, dosage unknown), a homoeopathic product containing celandine and a basil extract. There was also suspected use of the illegal drug Ecstasy within the same time frame. Complications of Ecstasy use (active component: methylenedioxymethamphetamine [MDMA]) include liver failure.[36] Her relatives caused postponement of a drug screening test at the time. Paracetamol, although a known hepatotoxin, had not been consumed long term. Metoclopramide is documented as causing raised liver enzymes, and pantoprazole and Ecstasy as causing liver failure. It is possible that the three medications may have acted synergistically. Histological investigations 4 months after the date of adverse reaction state an unchanged clinical picture of an autoimmune hepatitis.[37]

Assessment: Unlikely, concomitant medication, possible Ecstasy abuse, and/or autoimmune aetiology more likely.

Case #23

Case also identified as: MCA #23, BfArM #00005994, EMEA #22

Lit: Sass et al, 2001

The case of a 50-year-old woman diagnosed with fulminant liver failure was also reported in the medical literature.[38] Signs and symptoms included jaundice, elevated liver enzymes, general poor health, hepatic encephalopathy, and coma. She had been taking a kava preparation (60 mg/day of kava lactones for 6 to 7 months) and several orthodox medications: Amaryl (glimepiride, a sulphonylurea, for 7 months), metformin (a biguanide, unknown period), an oral contraceptive containing oestradiol valerate + levonorgestrel (unknown period) and St. John's wort (*Hypericum perforatum*, 6 months).[39]

Liver biopsy indicated progressive necrosis of hepatic cells and she received a liver transplant. Contraceptive combinations are known to cause cholestasis, hepatitis, and cholestatic jaundice. Hepatic adverse effects are documented for both metformin and glimepiride. A known adverse reaction of metformin is lactic acidosis, the beginnings of which may have been present in this patient, which can lead to coma.[39]

Assessment: Possible, but concomitant medication cannot be ruled out as the cause.

Case #24

Case also identified as: MCA #24, BfArM #00008627, EMEA #23

Lit: Brauer et al, 2001

Controversy surrounded the case of a 22-year-old woman, with some dubious reporting in the German media. Details of the case were reported in the scientific literature.[40] She had been taking a kava product for 4 months (240 mg kava lactones per day). Concomitant medications included rizatriptan (as needed), pain relief (possibly NSAID, as needed) and contraceptives (norgestimate + ethinyloestradiol; ethinyloestradiol + dienogest).[41]

The patient presented to the hospital because of persisting fatigue and nausea. She had very elevated serum bilirubin and increased liver enzymes. Medications were stopped but she developed fulminant liver failure. Liver biopsy was negative for viral hepatitis and alcohol was eliminated as a cause. Necrosis of hepatic tissue and damage to the parenchyma was observed. She received a liver transplant, but a CMV infection and intrahepatic arterial stenosis occurred postsurgically. She then developed an *Aspergillus* infection (not viral hepatitis as stated by BfArM) due to immunosuppression, which finally led to her death.[41]

Contraceptive combinations are associated with cholestasis and jaundice. The other medications are unlikely to have contributed significantly. An investigation with the treating physician revealed that the patient had a hepatic incident over 3 years preceding this event. A drug-related aetiology was suspected, but the cause was not identified. The patient was an employee in a pharmacy and would have had relatively easy access to potential hepatotoxic medications. This lends weight to the drug-related aetiology.[41] Confirmation of the patient's employment was documented in the newspaper article.[42]

Assessment: Possible, but connection to kava is not proven as a preexisting hepatic problem cannot be ruled out.

Case #25

Case also identified as: MCA #25, BfArM #01003089, EMEA #24

This case involved a 34-year-old woman who had been taking L-thyroxine (duration unknown, probably long term) and a kava product (120 mg/day of kava lactones for 3 months). Hepatitis and elevated liver enzymes were recorded as side effects. Use of alcohol and differential diagnostic information were not provided. Hepatotoxicity associated with L-thyroxine has occurred rarely.[43]

Assessment: Possible, but not enough data available.

Case #26

Case also identified as: MCA #26, BfArM #01004110 (EMEA #25); duplicate case BfArM #99006200, EMEA #27

A female patient (aged 34 or 35) recovered fully from jaundice, elevated liver enzymes,

and hepatitis upon discontinuation of medication which included paracetamol (as needed), a St. John's wort product (*Hypericum perforatum*) and a kava product (120 mg/day of kava lactones, duration unknown). Information received from the manufacturer of the kava product indicated that the patient suffered from multiple sclerosis. The patient's physician did not provide any information regarding treatment for the multiple sclerosis.[44]

Assessment: Unassessable due to insufficient information regarding concomitant medication for the treatment of multiple sclerosis.

Case #27

Case also identified as: MCA #27, BfArM #99005139, EMEA #26

In a 47-year-old woman, a transient increase in liver enzyme levels was recorded with concomitant use of fish oil (high dosage) and a kava product. Despite the information listed in Appendix 2 by BfArM, the liver values returned to normal without discontinuation of kava. Elevated liver enzymes can be a rare occurrence following a high dosage of fish oil.[45]

Assessment: Unlikely, no connection to kava.

Case #28

Case also identified as: MCA #28, BfArM #99006200, EMEA #27; duplicate case BfArM #01004110, EMEA #25

This was recognised by the MCA as a duplicate of case #26 (above).

Assessment: Unassessable due to insufficient information regarding concomitant medication for the treatment of multiple sclerosis.

Case #29

Case also identified as: MCA #29, BfArM #01001228, EMEA #28; duplicate case #01001924, EMEA #29 (see Case #30 below) and also BfArM #01001928 (not listed here)

A man aged 38 or 39 was reported to experience liver cell damage and hepatitis. Duplicate entries by BfArM appear to have occurred for this case, in which penicillin (intake for 1 day) and "no other drugs" were listed in the concomitant medication field. The kava product (70 mg/day of kava lactones) was taken for 1 to 2 weeks. It is unclear why the patient took the antibiotic for 1 day. Either the adverse effect occurred after the ingestion of the antibiotic or, despite the usual recommendation, the entire course of antibiotics was not taken. No other details regarding differential diagnosis or alcohol intake are available. Although the incidence of hepatic adverse effects caused by penicillin are rare, hypersensitivity may occur on one intake, with hepatic side effects occurring with second intake.[46]

Assessment: Unlikely, difficult to assess with inadequate information, and a link to concomitant medication is possible.

Case #30

Case also identified as: MCA #30, BfArM #01001924, EMEA #29; duplicate case (see case #29 above)

This was recognised by BfArM and the MCA as a duplicate of case #29 (above).

Assessment: Unlikely, difficult to assess with inadequate information, and a link to medication is possible.

Case #31

Case also identified as: MCA #31, BfArM #01003950, EMEA #30; duplicate case BfArM #01003951, EMEA #32

This case refers to the same patient as in Case #33. Following a hepatitis incident in 2001, the female patient filed a self-report of a former supposed drug-induced hepatitis in 1993, which the patient said was due to the intake of Kavain Harras or Kava-ratiopharm (both ethanolic extracts). However, both products were commercially unavailable in 1993 and, according to the physician's records, no causative agent could be identified to explain the 1993 incident. In addition, there was no record with the BfArM in 1993 concerning a hepatitis connected to kava intake.[47,48]

In 2001, the then 56-year-old patient suffered from a slight increase in liver enzymes following oral administration of either Kavain

Harras N or Kava-ratiopharm. The product involved was not confirmed by the hospital's physicians, who filed the event as a transaminitis of unclear origin, possibly drug-related. Based on the supposed yet unconfirmed incident in 1993, BfArM lists a positive rechallenge to kava.

Concomitant to the kava intake in 2001, the following medications were taken: omeprazole (Antra MUPS, as needed), candesartan cilexetil (antihypertensive, intake for 2 months but discontinued 5 months before the onset of the hepatitis), losartan-potassium + hydrochlorothiazide (Lozaar plus, antihypertensive, taken since the discontinuation of candesartan cilexetil), oestradiol valerate (Estragest TTS, transdermally, long-term treatment), L-thyroxine (long-term treatment of Hashimoto thyroiditis), acetylcysteine (unknown duration) and several common cold remedies unlikely to have any impact on the liver. Each of these medications (excluding the cold remedies) has documented hepatic side effects: L-thyroxine (hepatotoxicity, rarely), transdermal oestradiol (asymptomatic impaired hepatic function, cholestatic jaundice; rarely), candesartan cilexetil and losartan (raised liver enzymes), hydrochlorothiazide (jaundice, cholecystitis; rare), omeprazole (hepatitis, liver failure, and hepatic-related encephalopathy). The combination of these drugs would have increased the chance of an hepatic side effect.[48]

The MCA analysis of this case indicates that the patient restarted kava while also taking her other medications,[1] although this information was not provided by BfArM.

Assessment: Unassessable on the basis of confusion in the listings and insufficient information; cause by concomitant medications quite possible.

Case #32

Case also identified as: MCA #32, BfArM #01006229, EMEA #31

A 32-year-old man received a liver transplant after a range of liver symptoms including elevated liver enzymes and liver necrosis necessitated such action. The patient had been taking a kava preparation for about 3 months (240 mg/day of kava lactones) and a valerian preparation occasionally. Viral and autoimmune hepatitis were excluded. Although no other concomitant medications, including drugs, are listed, it is not clear that this was the case.[49]

Assessment: Possible but further information required, including verification of no other concomitant medications.

Case #33

Case also identified as: MCA #33, BfArM #01003951, EMEA #32; duplicate case BfArM #01003950, EMEA #30

This case is a duplicate of case #31 (above).

Assessment: Unassessable on the basis of confusion in the listings and insufficient information; cause by concomitant medications quite possible.

Case #34

Case also identified as: MCA #34, BfArM #01006939, EMEA #33

A 36-year-old man with liver damage had no previous history of liver disorders. A viral or autoimmune hepatitis could be excluded. Further details of this case are scant except that a kava preparation (70 mg/day kava lactones) was taken over 6 weeks. The existence of this case report became known only after the ban on kava products was instigated (and not when it occurred in August 2000). The timing of the reporting of the case casts doubt on its validity.[50]

Assessment: Unassessable due to insufficient information and poor protocol of reporting.

Case #35

Case also identified as: MCA #35, BfArM #01008989, EMEA #34

A 39-year-old man reported a tendency to bleeding and hepatitis. He was taking a kava preparation (120 mg/day of kava lactones for over 7 months) and interferon beta-1a (intramuscularly, for over 5 years until less than 1 month prior to the adverse reaction). Interferon beta-1a is associated with abnormal liver function, hepatitis, and changes in blood

cell composition, and doctors are advised to monitor the liver function of patients taking this medication. The hepatic adverse reaction occurred within a reasonable time period of the last injection.[51]

Assessment: Unlikely, probably connected to concomitant medication.

Case #36

Case also identified as: MCA #36, BfArM #01009681, EMEA #35

A 45-year-old man taking a kava ethanol extract (120 mg/day of kava lactones for 3 months) experienced elevated liver enzymes. No more information is available.[52]

Assessment: Unassessable due to insufficient information.

Case #37

Case also identified as: MCA #37, BfArM #01010222, EMEA #36

A 55-year-old man receiving hypoglycaemic medication (glibenclamide, presumably taken long-term) experienced elevated liver enzymes. He had also been taking a kava and valerian product for about 1 month (30 mg of kava lactones per day). No other information is available.[53] Increased hepatic enzymes, abnormal hepatic function, cholestasis, and cholestatic hepatitis are reported side effects of sulphonylureas.[8]

Assessment: Unlikely, difficult to assess with inadequate information, and causation by concomitant medication is possible.

Case #38

Case also identified as: MCA #38, BfArM #01010536, EMEA #37

A 45-year-old slightly obese woman complained of fatigue, abdominal pains, discoloured faeces, and dark urine when admitted to hospital. She had been taking an ethanol extract of kava (45 mg of kava lactones per day for 4 months), extract of globe artichoke (*Cynara scolymus*, occasionally) and St. John's wort (*Hypericum perforatum*) prior to administration of kava. She had elevated liver enzymes and serum bilirubin and low serum protein. C-reactive protein, creatinine, and urea were within the normal range. Alcohol abuse was excluded, blood tests for infections were negative. Ultrasound examination ruled out focal lesions, hepatomegaly, portal vessel thrombosis, and blocked bile ducts. There were signs of an ascites. A biopsy was not performed. She discontinued the kava and no other treatment was administered. The patient subsequently participated in an Internet discussion involving her case to which she added that she stated she had toxic effects on the kidneys and hair loss, which were not mentioned in the hospital report.[54]

Causes of ascites include cirrhosis of the liver and protein–calorie malnutrition. The use of globe artichoke by the patient suggests she may have been self-medicating a preexisting condition such as hyperlipidaemia or poor bile flow. It is unlikely that the globe artichoke would cause the above side effects or mask a major liver problem.

Assessment: Possible, but further information required and a preexisting condition cannot be ruled out.

Case #39

Case also identified as: MCA #39, EMEA #38

A 54-year-old woman experienced gall bladder pain. She had been consuming a kava preparation over an unknown period of time. Concomitant medications taken for an unknown period of time included triamterene (diuretic), L-thyroxine, and benalapril (enalapril, angiotensin-converting enzyme [ACE] inhibitor). No further information is available regarding preexisting medical conditions or examinations of the patient. Gall bladder pain does not indicate an adverse effect on the liver, especially hepatotoxicity.[55]

Assessment: Unlikely, further information required and should not have been listed as an adverse reaction of suspected hepatotoxicity.

Case #40

Case also identified as: MCA #40, BfArM #02000370, EMEA #39

A 46-year-old woman was hospitalised with the early stages of cirrhosis of the liver. She had

been taking an ethanol extract of kava for 3.5 months (providing 240 mg/day of kava lactones), contraceptives (ethinyloestradiol valerate + levonorgestrel) and cyclandelate (vasodilator). Viral and autoimmune hepatitis were eliminated. After discontinuation of all medications the patient's condition slowly improved. Hepatic adverse effects are known for contraceptive use. According to the manufacturer, the patient was occupationally exposed to mercury. The time frame of kava intake (3.5 months) is of quite a short duration for it to be responsible for liver cirrhosis. Further biochemical and histological information is required.[56]

Assessment: Unassessable due to insufficient information, occupational exposure to hepatotoxin is more likely.

Case #41

Case also identified as: MCA #41, BfArM #02001135/#02002378, EMEA #40

A 61-year-old woman died as a result of necrotic liver failure. Apart from the medications she was taking there are no other details of preexisting medical conditions or further details of the liver pathology. She was taking the following medications: a kava product (ethanol extract providing 120 mg/day of kava lactones over 3 months); multivitamin and mineral product, Ginkgo product (12.5 mg/day ginkgo flavonoids, 3 mg/day terpene lactones, for 13 months), dehydrosanol (a diuretic combination containing bemetizide and triamterene, taken for 7 days), hymecromone (spasmolytic, choleretic, taken for 10 years) and omeprazole (3 years).[57]

The diuretic combination is known to have caused rare cases of jaundice. Hepatitis and hepatic failure are documented adverse effects of omeprazole, the incidence of hepatic side effects is calculated as 2.1 cases per 100,000.[8] Omeprazole had been ingested for 3 years, long enough for an adverse event to occur. BfArM discarded omeprazole as a possible cause on the basis that an adverse event had not occurred previously during the treatment period.[57]

Assessment: Possible, but connection to concomitant medication is more likely.

Case #42

Case also identified as: MCA #42, BfArM #02001414, EMEA #41

The 46-year-old woman experienced elevated liver enzymes and jaundice. She had taken a kava product (ethanol extract providing 360 mg/day for 1 month) (this exceeds the recommended dosage). No concomitant medications were listed. Viral hepatitis and infection with EBV could be excluded, but a CMV infection could not be excluded. According to the kava manufacturer, the patient was not assessed by a gastroenterologist and the case was poorly documented.[58]

Assessment: Unassessable due to insufficient information.

Case #43

Case also identified as: MCA #43, BfArM #02001776, EMEA #42

A 27-year-old man had been taking several anti-HIV medications for an unknown time period (nevirapine, stavudine, and lamivudine) and a kava preparation (ethanol extract providing 120 mg/day of kava lactones), also for an unknown period. Reported adverse effects included discoloured faeces and urine but no overt liver symptoms. No other information, including results of laboratory analyses, is available for this case report.[59]

Even if hepatic adverse effects had been reported, these could be explained by the intake of anti-HIV medications, as each of these drugs has documented hepatic adverse events associated with their use (e.g. hepatotoxicity [nevirapine], elevated serum transaminases, hepatitis, liver failure [stavudine], and elevated liver enzymes [lamivudine]).[8] The other symptoms reported by this patient, anxiety and sweating, are also side effects associated with use of stavudine.[59]

Assessment: Unlikely, concomitant medication more likely, and uncertain if the patient suffered hepatotoxicity.

Case #44

Case also identified as: MCA #44

Information received from MCA spreadsheet

This case report of a woman of unknown age from Germany was obtained from the MCA. She consumed a kava product for a period of 1 year. The adverse reaction is listed as increased liver enzymes. No other details are recorded.

It is understood that she was anorexic and taking fluoxetine, a drug known to produce liver toxicity.[60] The timing of the kava and fluoxetine intake are unknown.

Assessment: Unassessable due to insufficient information.

Case #45

Case also identified as: MCA #45, BfArM #02002732, EMEA #44

A 24-year-old woman is reported to have experienced elevated liver enzymes and jaundice. She had taken an ethanol extract of kava (120 mg/day of kava lactones) for a period of 3 months. No other medications were listed. No other details are recorded.[61]

Assessment: Unassessable due to insufficient information.

Case #46

Case also identified as: MCA #46, BfArM #02002090/#02002836, EMEA #45

Elevated liver enzymes were found as a result of a routine check-up in response to gastrointestinal complaints by a 26-year-old obese woman. Medications other than a kava product (see below) included sulfasalazine (for 5 months), diclofenac + colestyramine (5 months), hyoscine butylbromide, contraceptive (medroxyprogesterone acetate, by injection, long-term treatment) and omeprazole (40 mg/day; probably long term) (Table 12-1).[62]

Some of the conventional drugs the patient was taking have adverse effects associated with the liver, particularly omeprazole (elevated liver enzymes, hepatitis, liver failure, and hepatic-related encephalopathy), diclofenac (elevated liver enzymes, hepatitis [including isolated cases of fulminant hepatitis]) and sulfasalazine (hepatitis).[8,32,62,63] The dose of omeprazole as maintenance treatment in the long term (>8 weeks) is normally 20 mg/day; this patient was taking 40 mg/day.

The kava product was taken for 1 week only. The reaction is more likely to be due to omeprazole and/or diclofenac, which had been ingested over a longer period of time. Although liver parameters were normal in February 2002, diclofenac had only been resumed for 2 weeks and an adverse reaction to this drug cannot be ruled out.

Assessment: Unlikely, connection to concomitant medication is more likely.

Case #47

Case also identified as: MCA #47, BfArM #02003010, EMEA #46

BfArM received a report on 30 December 2002 of a 47-year-old woman with a range of symptoms including bilirubinaemia, elevated liver enzymes, jaundice, and liver failure. Eventually a liver transplant was scheduled. She was taking a range of products, many of which were not listed in the BfArM case report, and included: a liquid mineral supplement, amino acid complex, silymarin (constituent group of St. Mary's thistle [*Silybum marianum*]), kava, and an antirheumatic homoeopathic remedy. Despite taking this range of products for the treatment of the liver and rheumatic complaints, BfArM indicated that the patient was in perfect health prior to the reported adverse event.[64]

Results of laboratory tests were negative for hepatitis A, B, and C and there were no autoimmune antibodies present. Liver biopsy indicated fibrosis and liver cell necrosis, which may have been drug induced. Magnetic resonance imaging suggested a long-existing sclerotic transformation of liver tissue, which had started prior to the ingestion of kava.[64]

The reporting of the kava dosage varied as shown in Table 12-2.[64]

Assessment: Unlikely, more likely due to preexisting liver damage.

Table 12-1 **Case #46 Medication History**

June 2001	• Diagnosed with ankylosing spondylitis
	• Started sulfasalazine + diclofenac
Oct 2001	• No deviation in liver parameters
	• Part of ongoing monitoring re: sulfasalazine therapy
End Nov 2001	• Stress with pending exam
	• Ingestion of 4-6 capsules of kava product over a 1 week period (50 mg kava lactones per capsule; ethanol extract)
2 Dec 2001	• Went to hospital and complained of unspecified abdominal pain
	• Elevated serum GPT (80 U/L); normal value: <23 U/L
4 Dec 2001	• Liver parameters reanalysed and found to be elevated:
	– Serum GPT (572 U/L)
	– Serum GOT (220; normal value: <19 U/L)
	– Serum GGT (174; normal range: 6–28 U/L)
6 Dec 2001	• Admitted to hospital with suspected toxic hepatitis
	• All medications discontinued
	• Liver parameter results:
	– Serum GPT (306 U/L)
	– Serum GOT (within normal range)
	– Serum GGT (72 U/L)
	• Laboratory tests showed negative for viral hepatitis, including EBV and CMV; autoimmune antibodies not detected
21 Dec 2001	• Discharged from hospital with normal liver parameters
25 Jan 2002	• Antirheumatic medication not taken due to upcoming exam on 25/1/02
After the exam dated 25 Jan 2002	• Sulfasalazine and diclofenac restarted
	• New gastrointestinal complaints occurred
11 Feb 2002	• Liver function parameters analysed and found to be in normal range
	• Omeprazole restarted
13 Feb 2002	• Case reported to BfArM

Case #48

Case also identified as: MCA #48, BfArM #02003278, EMEA #47

The case of a 50-year-old man with increased liver enzymes was reported to BfArM. No information is available regarding preexisting medical conditions, concomitant medication, or the reported liver disorder. He is recorded as taking an acetone extract of kava (140 mg/day of kava lactones) for 3 months.[65]

Assessment: Unassessable due to insufficient information.

Table **12-2 Reports Showing Varied Kava Dosages**

21 Jan 2002 (phone call from GP to the manufacturer)	1 capsule per day (50 mg/day of kava lactones) for 3 months
28 Jan 2002 (phone call from GP to the manufacturer)	17 capsules per day (850 mg/day of kava lactones) for an unknown period of time
Report to BfArM by GP	2 capsules (100 mg of kava lactones) taken twice per week for approximately 4 months just prior to the adverse event report
Report to the hospital by GP	16 tablets per day, time period not specified
Report when patient admitted to the transplant centre	Up to 10 capsules per day, time period not specified

Case #49

Case also identified as: MCA #49, BfArM #02003559, EMEA #48

A similar lack of detail is available for the case of another 50-year-old man with jaundice. He had been taking an ethanol extract of kava (120 mg/day of kava lactones) for over 6 months.[66]

Assessment: Unassessable due to insufficient information.

Case #50

Case also identified as: MCA #50, BfArM #02004364, EMEA #49

A 32-year-old woman is reported to have experienced elevated liver enzymes and hepatitis. In addition to an ethanol extract of kava (240 mg/day of kava lactones for over 1 month) she had been taking a contraceptive (desogestrel + ethinyloestradiol) for an unknown period of time. Liver function may be impaired by this type of contraception. However, there is insufficient information to determine causality.[67]

Assessment: Unassessable due to insufficient information.

Case #51

Case also identified as: MCA #51, FDA #14538, EMEA #50

A 60-year-old woman experienced fatigue, urinary tract infection, and an increase in liver enzymes. She had been taking the following medications for unknown duration and in unknown dosage: a kava product, a licorice product, chaparral leaf (*Larrea tridentata*), capecitabine and fluorouracil combined (antineoplastic and immune suppressant), docusate (laxative), piperazine oestrone sulphate, and an analgesic containing paracetamol and oxycodone. The patient had a locally advanced rectal cancer and was being treated with irradiation and chemotherapy. (The Waller analysis referred to metatastic rectal cancer.) Former surgical intervention included a thoracotomy 22 years previously and a lumbar disk surgery.[3,68]

In addition to fatigue, capecitabine can cause cholestatic hepatitis, hepatitis, and hepatic fibrosis.[8] All of the conventional medications are metabolized by the liver and can be associated with liver damage. The adverse reaction report indicated only that the patient's liver function tests revealed an increase in serum bilirubin and enzymes during the course of her treatment for cancer, but the liver appeared normal by ultrasound. The patient recovered after cessation of all medications. Although the reported resumption of two of the three chemotherapy drugs resulted in no further increase in liver enzyme values, there is no indication if the dose was adjusted or if other medications were also continued.[3]

The herb chaparral is known to cause hepatotoxicity in humans. A review of 18 case reports of adverse events associated with the ingestion of chaparral reported to the FDA between 1992 and 1994 found there was evidence of hepatotoxicity in 13 cases. Jaundice with a marked increase in serum liver enzymes

occurred 3 to 52 weeks after the ingestion of chaparral.[69]

Assessment: Unlikely, more likely due to concomitant medication.

Case #52

Case also identified as: MCA #52, FDA #14723, EMEA #51

A 44-year-old woman suddenly suffered from chest and back pain during a medical checkup following an aortic dissection and a descending thoracic aneurysm resection. The routine laboratory examination showed an increase of lipase and LFTs and neutropenia. The treating physicians diagnosed the liver incident as a consequence of the recent surgical interventions which led to a focal ischaemia in the liver (also known as shock liver). Blood work also indicated signs of a possible viral hepatitis. The neutropenia was discussed as possibly drug-related; however, it was stated that such effects might occur with ingestion of virtually any drug. A connection to kava was not established.

However, when the report was filed by the pharmacist, the event was described as a symptom-free neutropenia, possibly connected to the intake of kava and B vitamins, whereas warfarin, celecoxib, oxycodon, citalopram, and an oestrogen patch were indicated as comedication. Increases of liver enzyme activity are labelled for the antidepressant citalopram, the anticoagulant warfarin, and the antiinflammatory drug celecoxib.[3,70]

Assessment: Unrelated, diagnosed as a surgery-related ischaemic hepatitis (shock liver).

Case #53

Case also identified as: MCA #53, FDA #14810, EMEA #52

A 33-year-old woman is listed with several adverse effects including jaundiced skin, nausea, diarrhoea, and easy bruising. She was prepared for possible liver transplant. She had received chemotherapy for lymphoma 1 month prior to admission. Her medications included: unnamed chemotherapy, ranitidine hydrochloride, echinacea/golden seal, an energy product containing ginseng, B100 (vitamin B?) and guarana; TUMS (calcium supplement?), a contraceptive (norethindrone acetate + ethinyloestradiol), women's vitamins and juices. The first case report also mentioned the intake of nizatidine. After detailed analysis of the labels of the products taken by the patient, the original report was corrected: there was no intake of nizatidine, kava was not a component of the herbal medicines taken by the patient, which in fact were a combination of golden seal (*Hydrastis canadensis*) and echinacea (*Echinacea* spp.), and a combination of ginseng, guarana (*Paullinia cupana*), and B vitamins. Hepatic adverse effects are known for ranitidine and are likely for the unknown chemotherapy.[71]

Assessment: Unrelated as no kava was ingested.

Case #54

Case also identified as: MCA #54, FDA #15035/ #15274, EMEA #53

A 45-year-old woman reported jaundice, pruritus, and cholestatic hepatitis, and successfully received a liver transplant. She had been taking a herbal extract containing kava, hops (*Humulus lupulus*), German chamomile (*Matricaria chamomilla*), and passionflower (*Passiflora incarnata*) for between 2 and 4 months with no intake on weekends. The daily dose of kava lactones corresponded to 150 mg. Concomitant medication included rabeprazole (proton pump inhibitor, structurally similar to omeprazole) taken for four consecutive days, only days before the onset of the incident. Preexisting medical conditions included reflux and she indicated she had no allergies to food or drugs.

The patient consumed a very small amount of alcohol on rare occasions. Results were negative for viral hepatitis (A, B, C). Adverse effects on the liver are known for omeprazole and a case of liver failure has been documented for a patient taking rabeprazole and an antifungal medication (terbinafine).[63,72] The FDA was reported to be particularly concerned about this case, which was also investigated by the U.S. Centers for Disease Control and

Prevention (CDC).[73] The CDC investigation suggested that the rabeprazole was prescribed after the patient presented with nausea and weakness (and possible liver damage from her herbal preparation) and was only continued for 4 days.

The identity of the herbal components of the suspected medication was not analytically confirmed, even though a potential adulteration was discussed by the toxicologists. The FDA obtained a sample of the product for chemical analysis but the results are not known.[3] In the course of the follow-up, only kava was discussed as a possible cause, based on the current discussion of potential hepatic effects. The effects of the other herbal components and of rabeprazol were not considered.

Additional follow-up information was obtained for this case but it raises further questions, because of discrepancies between the physician's original report and information obtained in the follow-up. The discrepancies mainly concern the duration of a preexisting condition and the dosage and duration of kava intake (half the recommended dose for 8 weeks versus 2 tablets for about 4 months [as indicated above]).

Assessment: Possible, but concomitant medication cannot be ruled out as a cause.

Case #55

Case also identified as: MCA #55, FDA #15250, EMEA #54

A female obese patient (225 lb/102 kg) of unknown age herself reported to the FDA that high liver enzymes and a fatty liver occurred as adverse effects, detected by routine laboratory work and subsequent examination. The patient had taken a kava product with 30 mg kava lactones per day over a period of 2 years. Concomitant medication included a multivitamin preparation. Preexisting issues included environmental allergies, allergy-related asthma, excess weight, and moderate alcohol consumption.

A connection of the fatty liver and, as a consequence, elevated LFTs with kava is highly questionable. Obesity in middle-aged women is recognised as an infrequent, but major, cause of subsequent nondrug-induced liver failure. In addition, neither the discussed liver cases within this review nor the observations from traditional medicine indicate that kava intake might lead to fatty liver, which, however, would have to be expected in obesity.[74]

Assessment: Unassessable due to insufficient information.

Case #56

Case also identified as: MCA #56, FDA #15281, EMEA #55

The case report of a 27-year-old woman includes a range of symptoms: jaundice, nausea, vomiting, ascites, abdominal pain, and elevated liver enzymes with possibly stage 3 hepatic encephalopathy. Her medications included two kava products (taken for 6 months), psyllium (*Plantago ovata*), vitamins B_6 and E, St. John's wort (*Hypericum perforatum*) extract and a phyto-oestrogen containing Mexican yam (species undefined), black cohosh (*Cimicifuga racemosa*) and dong quai (*Angelica sinensis*, taken for 4 months). The case details from the FDA indicate that "other aetiologies [were] excluded"; however, no further details are provided. An abdominal hysterectomy is listed as a preexisting medical condition. The MCA assessment indicates that alcohol had not been consumed in over 5 years.[75] Apparently, no analysis of the components of the "Sleepy tea" herbal mixture and the kava monopreparation were made.

Assessment: Possible, but connection to kava is not proven due to insufficient information and unknown composition of the concomitantly ingested product, and a preexisting problem cannot be ruled out.

Case #57

Case also identified as: MCA #57, FDA #15317, EMEA #56

Hepatitis was listed as an adverse effect in the case report of a 38-year-old man who ingested kava (product details unknown, duration unknown) in a binge once or twice per month. Eight capsules of 250 mg (presumably of kava

extract) were taken. He also used St. John's wort extract. He drank alcohol regularly (three to four glasses of wine per week). No other medications or preexisting medical conditions were described. Within the case documentation of the FDA, liver infection was documented as the cause of the hepatitis, even though, according to the line-listing of the MCA, but not to the case documentation of the FDA, negative results were obtained for hepatitis A, B, and C.[1,76] The information provided is unclear: Did a liver infection occur at the time of reporting or did it exist as an earlier event?

Assessment: Unassessable due to insufficient information.

Case #58

Case also identified as: MCA #58, FDA #15319, EMEA #57

A 63-year-old man experienced nausea, haematemesis, hepatitis C, and hepatocellular liver injury. He had been taking a product which contained kava, magnesium orotate, and additional herbs for a period of 6 weeks. Hypertension was listed as a pre-existing medical condition and he had been taking enalapril maleate (ACE inhibitor) and hydrochlorothiazide (a thiazide diuretic) which was started 5 months prior to the kava intake.[77]

Thiazides can produce occasional cases of cholecystitis or icterus and ACE inhibitors can cause hepatotoxicity. The likely cause, however, was hepatitis C.[77]

Assessment: Unlikely, more likely due to preexisting medical conditions.

Case #59

Case also identified as: MCA #59, FDA #15466, EMEA #58

A 39-year-old woman experienced fatigue, influenza-like symptoms, jaundice, and hepatitis. She had been taking a kava product (which contained 70 mg of kava lactones per unit) and drinking a tea containing kava with 36 mg kava lactones per day, which totals 106 mg kava lactones per day for 6 months. Her liver function parameters returned to normal within 4 weeks. Preexisting medical conditions included asthma and allergies to dust and animal dander. Concomitant medications included a contraceptive (undefined), tetracycline (2 times, including once right before the adverse effects), salbutamol (as needed), diphenhydramine, and undefined over-the-counter (OTC) drugs. Tetracycline is known to cause hepatic adverse effects and as the adverse reaction occurred right after the second intake, it may have been responsible. As information regarding the hepatitis, history of alcohol intake, and concomitant medications is lacking, an association to kava intake cannot be made.[78]

Assessment: Unlikely, more likely due to concomitant medication.

Case #60

Case also identified as: MCA #60, FDA #14951, EMEA #59

A 51-year-old woman was reported with elevated liver enzymes. She had been taking an undefined kava product for a period of 4 months. Other medications included: vitamin D, fish oil, multivitamin and mineral supplement, omega-3 and ginkgo extract. The patient had also complained of foot cramping. The symptoms reportedly ceased upon discontinuation of the kava product. No further information was provided regarding the dosage of the other medications or regarding her liver.[79]

Assessment: Unassessable due to insufficient information.

Case #61

Case also identified as: MCA #61, FDA #14995, EMEA #60

A 37-year-old woman experienced jaundice and fatty infiltration of the liver. She had taken a kava product (150 mg/day of kava lactones) at more than 2.5 times the recommended dosage for a period of 3–4 weeks. Other medications included: two homoeopathic remedies, various multivitamin, mineral and herbal products, bovine colostrum (to counter

underweight and malabsorption syndrome), and a four-product "suite" with fish oil, additional minerals, vitamins, enzymes, and diverse herbal extracts (mountain mahogany leaves [*Cerocarpus montanus*], ragweed [*Ambrosia artemisifolia*], golden seal [*Hydrastis canadensis*], quince seed [*Cydonia oblonga*], boldo leaves [*Peumus boldus*], spearmint leaves, rose hips [*Rosa canina*], sete sangrias [*Cuphea* spp.], red beet [*Beta vulgaris*], and cha de bugre [*Cordia salicifolia*]) for 6 weeks until 1 week prior to the adverse event. She was underweight. Given this range of products it is likely that there are more preexisting conditions than were recorded. Alcohol intake was denied.[80]

None of the herbal extracts ingested in this case is known to cause adverse liver effects. However, several of the ingested plants are uncommon as medicinal plants, therefore the lack of data concerning hepatic effects does not automatically imply that they are harmless. Vitamin A was ingested in a dosage of approximately 7500 IU/day, which surpasses the U.S. Recommended Dietary Allowance (RDA) by 150% and is in a dosage range with potential adverse liver effects.

Assessment: Unassessable due to insufficient information.

Case #62

Case also identified as: MCA #62, FDA #15252, EMEA #61

A female of unknown age reported the following adverse effects to the FDA: fatigue, nausea, vomiting, and extremely elevated liver function parameters. She took a kava product (150 to 225 mg/day of kava lactones) for a period of 3 months. Other medications included a green tea formula containing green tea (*Camellia sinensis*), bitter orange peel (*Citrus aurantium*), Siberian ginseng (*Eleutherococcus senticosus*), fenugreek (*Trigonella foenum-graecum*), guarana (*Paullinia cupana*), kola (*Cola nitida*), ginger (*Zingiber officinale*), licorice (*Glycyrrhiza glabra*), additional caffeine, vanadium amino acid chelate, and chromium dinicotinate glycinate; coenzyme Q10 and a product called Snorease (containing bitter orange, coenzyme Q10 and bromelain). There was no previous medical history of liver problems, alcohol intake was denied. According to the labelling, fatigue and nausea are also observed with the intake of coenzyme Q10 products, and nausea and vomiting with the intake of bromelain.

There is no information regarding the self-reported "extremely elevated LFTs", virus serology, or other preexisting medical conditions or intake of orthodox drugs.[1,81]

Assessment: Unassessable due to insufficient information.

Case #63

Case also identified as: MCA #63, FDA #15267, EMEA #62

This adverse reaction report involved a 51-year-old woman who experienced elevated liver enzymes, which reportedly returned to normal after ceasing intake of kava, ginkgo (*Ginkgo biloba*) extract, ginseng extract, St. John's wort (*Hypericum perforatum*) extract, vitamins A, D, and E, a calcium/magnesium complex and MSM (methylsulphonylmethane, a supplement generally used to treat arthritis). The duration of use of kava was listed as 2 months. There is no additional information regarding alcohol intake, dosage of these products (especially vitamin A which may effect the liver in high doses), virus serology, and preexisting medical conditions (did she have, for example, an arthritic condition which was, or had been, treated with conventional drugs?).[3,82]

Assessment: Unassessable due to insufficient information.

Case #64

Case also identified as: MCA #64, EMEA #63

Nausea and elevated serum gamma-glutamyl transpeptidase (GGT) was experienced by a 60-year-old woman who had been taking a kava product for at least 1 year at an unknown dosage. The patient recovered after stopping kava. No concomitant medications were stated.[83] Without further information regarding

preexisting and previous medical conditions, as well as concomitant medications, it is not possible to associate kava with the cause of the adverse reaction.

Assessment: Unassessable due to insufficient information. Moreover, elevated GGT has been recorded after kava intake, but is not necessarily indicative of hepatotoxicity.

Case #65

Case also identified as: MCA #65, EMEA #64

A 39-year-old woman experienced increased transaminases. She had taken a kava product for a period of 2 months. Concomitant medication was not specified but "may cause hepatotoxicity".[84]

Assessment: Unlikely, more likely due to concomitant medication and/or preexisting medical condition.

Case #66

Case also identified as: MCA #66, EMEA #65

A female of unknown age experienced abnormal hepatic function. She had taken a kava product in the long term. Concomitant medication and outcome are unknown.

Assessment: Unassessable due to insufficient information.

Case #67

Case also identified as: MCA #67, EMEA #66

Abnormal liver function test results and jaundice were recorded as adverse effects in a 53-year-old woman. She had taken a kava product, St. John's wort (*Hypericum perforatum*), and multivitamins for an unknown period of time. The patient recovered after ceasing intake of "kava and other herbal preparations". The patient had a history of inflammation of the liver and at the time she had been drinking 6 beers per day. She stated that she has not been drinking since then. There is no further information regarding viral or autoimmune aetiologies.[85]

Assessment: Unassessable due to insufficient information.

Case #68

Case also identified as: MCA #68, EMEA #67

A 38-year-old man reported increased transaminases and hepatitis. There is no information regarding preexisting medical conditions, concomitant medication, or other medical information regarding his liver function and histology. According to the MCA, no other drugs were taken. He had been taking a kava product in the very low dose of 24 drops/day for a period of 2 weeks.[86]

Assessment: Unassessable due to insufficient information, but unlikely, due to the low dose taken and short duration of intake.

Case #69

Case also identified as: BfArM #02005178

Liver cell damage and liver damage was experienced by a woman of unknown age. She had taken a kava product (70 mg/day of kava lactones) for over 2 months. No other information is available.[87]

Assessment: Unassessable due to insufficient information.

Case #70

Case also identified as: BfArM #02002541

A 52-year-old woman experienced elevated transaminases. She had been taking a kava product (60 mg/day of kava lactones) for 3.5 months. No other information is provided.[88]

Assessment: Unassessable due to insufficient information.

Case #71

Case also identified as: FDA #14627

Lit: Humbertston et al, 2001

A 14-year-old girl was admitted to hospital with fulminant hepatic failure and received a liver transplant. Biopsy indicated necrosis consistent with drug-induced hepatitis. The LFTs were markedly elevated. Alternative causes of liver failure were negative. She had taken a herbal tea with vitamin C, vitamin B_6, vitamin B_{12}, a blend of Siberian ginseng root (*Eleutherococcus*

senticosus), chamomile (*Matricaria chamomilla*), and kava root (equivalent to 60 mg of kava extract, standardised to 30% kava lactones), plus a mixture of peppermint leaves (*Mentha piperita*), cinnamon (*Cinnamomum zeylanicum*), lemon grass (*Cymbopogon* spp.), ginger root (*Zingiber officinalis*), licorice root (*Glycyrrhiza glabra*), natural lemon flavour and other natural flavours, roasted chicory root (*Cichorium intybus*) and catnip leaves (*Nepeta cataria*). Ingestion was stated as 2 tea bags per day (the FDA actually speaks of tablets, which is impossible as both stated brands are exclusively marketed in the form of tea bags), corresponding to 36 mg of kava lactones per day for seven consecutive days in August 2000. Between September and December 2000, she took another brand of herbal tea containing a blend of chamomile flowers (*Matricaria chamomilla*), Tilia estrella flowers (*Ternstroemia pringlei*), valerian root (*Valeriana officinalis*) and kava root, plus spearmint leaves, lemon grass (*Cymbopogon* spp.), hawthorn berries (*Crataegus monogyna*), and orange blossoms (*Citrus* spp.). This product was ingested in a dosage of two tea bags per day for a period of 44 days in total. The nature of the kava preparation in the tea (extract or powder, standardisation?) is not known.[89] As a concomitant medication, the occasional use of ibuprofen was stated (which has been linked to hepatotoxic reactions[8]). The intake of alcohol was denied. Virus serology and testing for autoantibodies were negative.

The FDA was reported to be particularly concerned about this case, which probably explains why the CDC also investigated this case further.[73] The CDC reported that the patient was in fact taking capsule versions of these products (which is definitively wrong), but that the other product ingredients (other than kava) were unknown to them.

According to the published case report, the causality of kava is supported by the circumstances. However, the products ingested had further components, which were not taken into consideration as potential causative agents. In addition, ibuprofen can also induce adverse hepatic effects as a class reaction to NSAIDs.[90]

Assessment: Possible, but the potential causative role of ibuprofen and the other herbal product components require further investigation.

Case #72

Lit: Stuckhard P, 2002

The case of a 43-year-old woman requiring a liver transplant was reported to a German newspaper.[91] It was apparently not reported to BfArM. She had supposedly taken a kava product at the recommended dosage for 6 weeks. Concomitant medication included St. John's wort (*Hypericum perforatum*), an iodine compound for the thyroid, and a beta-blocker.[92] See Table 12-3 for full chronological details of this patient's case.

The patient reported in a newspaper report that she was not sure whether the liver function test was indeed conducted in January 2001. The surgery she underwent earlier may have contributed, due to the use of anaesthesia which can cause liver problems. There is insufficient information to link this case to kava ingestion. Kava was not even taken before the first symptoms were presented. The original treating physician and physicians at three different hospitals were unable to find the cause.[92]

Assessment: Unlikely, more likely due to preexisting medical conditions.

Case #73

Lit: Hinzpeter W, 2002

The case of a 60-year-old woman was reported to the German media.[42] It was apparently not reported to BfArM. Liver failure with subsequent liver transplant were the reported adverse effects. She had reportedly taken a kava product at the recommended dosage for 3 months. There is no other information available.[93]

Assessment: Unassessable due to insufficient information.

Case #74

Case also identified as: FDA #10257

A 70-year-old woman with a long history of coronary heart disease was hospitalised for stroke and a prolapsed mitral value. During the course of her stay it was noted that some of her liver function parameters (GOT and GGT) were elevated by a factor of 2 to 3. She had been taking a multicompound preparation containing

Table 12-3 **Details of Case #72**

End of 2000	• Patient underwent surgery for unknown reasons
	• Patient stated she never really recovered from the surgery in that she suffered fatigue and depression
Jan 2001	• Her physician conducted a urine and blood test (which reportedly included liver parameters)
	• Thyroid gland examined
	• Physician gave her sample packets of kava and St. John's wort
12 Jan 2001	• Patient presented complaining of fatigue
	• Reportedly her physician confirmed that the liver values were normal
	• Her physician prescribed the iodine preparation at a dosage of 1 tablet/week as a preventive measure, although the results of the thyroid tests were not yet available
20 Feb 2001	• Patient's health worsened, even after the first dose of the thyroid tablet she reported nausea, increased heart rate and erythema on her breast
	• Physician told her to discontinue the iodine preparation and prescribed a beta-blocker
22 Feb 2001	• Patient's health state worsened, she passed discoloured urine, her eyes were yellow
	• According to the patient this time the liver values "were really examined" and showed abnormality
	• Physician assumed a viral hepatitis
Several days later	• Patient visited a different physician and after a liver function test was admitted to hospital
	• Cause unknown but viral hepatitis was excluded
13 Mar 2001	• Patient scheduled for liver transplant

kava for an undisclosed time period: Herbalife K8 with "kava kava 40 mg" and "Biokawa 20 mg" containing 14.3% kavain, 15 mg DL-phenylalanine, 30 mg L-tryptophan, unknown amounts of extracts from alfalfa (*Medicago sativa*), ginger (*Zingiber officinale*), hops (*Humulus lupulus*), valerian (*Valeriana officinalis*), vervain (*Verbena officinalis*), and Yerba santa (*Eriodictyon californicum*). Concomitant medication included: propranolol (long term), aspirin (long term), fish oil and several vitamins (she described herself as a "vitamin freak"). When the patient was admitted, warfarin and lisinopril were prescribed to counter blood thickening (this was after the onset of the increased transaminases).

The case was filed as an adverse drug effect because the patient was thought to have suffered a blood thickening effect caused by ingestion of a vitamin K product. The ingested product later turned out not to contain vitamin K, but the above-mentioned mixture of herbs. The elevated transaminases were detected by routine laboratory analyses.

Elevated liver values and hepatitis are known and recorded for propranolol. Aspirin is known to produce increase of transaminases and is documented as causing impaired liver function in individual cases. Elevated transaminases are considered a class reaction of NSAIDs and are usually transient without treatment.

The herbs presumedly ingested are unlikely to cause adverse liver reactions, whereas the ingestion of high doses of fish oil is known to produce transient elevations of the liver enzymes as a nonpathological reaction pattern. During her hospitalisation her serum GOT fluctuated and increased despite the discontinuation of the herbal product.[94]

There is no information regarding possible exclusion of virus, autoimmune, or alcohol-induced hepatitis. It is unclear when the elevated liver enzymes occurred.

Assessment: Unassessable due to insufficient information.

Case #75

Case also identified as: FDA #11444

A 24-year-old man was hospitalised with hepatic encephalopathy and fulminant hepatic failure, and subsequently died. The patient, who was a body builder, denied the intake of steroidal hormones. He was taking a product "suite" with more than 121 components (which included vitamins, minerals, diverse herbals, enzymes, "vitaminoids" and basic nutrients, amongst which kava was part of a herbal blend [quality, form, and amount unknown]) until 3 weeks prior to the hospital admission. However, the symptoms were already present 3 weeks before the discontinuation of the products. According to the hospital's physician, the first symptoms of illness started after 2 months of exposure to the medication, with a 6-week history of feeling malaised and tired. Hepatitis A and B could be excluded. Hepatitis C testing was negative, but not entirely excluded. Blood chemistry showed elevated liver function parameters.[95]

The product HG1, for which ma huang (Herba Ephedrae) was indicated on the label, was analysed for ephedrine content. The tablets contained 3.3 mg of ephedrine per tablet. The OTC medications and formulas were reviewed by medical toxicologists; however, they were unable to find any specific aetiology for the liver failure. According to the evaluation, none of the ingredients of the formulas and OTC medications were suspected of causing fulminant liver failure, with the exception of an unconfirmed case of hepatotoxicity by ma huang (Herba Ephedrae). This, however, is only correct for the ingredients of the products within their single dosage as indicated on the labels. It should have been taken into account that the same ingredients were found in several of the products. The recommended U.S. RDAs were, in several cases, exceeded by the factor of several 100%, thus changing the overall picture, especially for trace minerals such as chromium. The evaluation of heavy metal toxicity by the hospital's toxicologists was aimed at typical liver toxins (arsenic, bismuth, mercury). As could be expected, this analysis yielded a negative result. However, it was not directed on the ingredients of the formulas, especially the grossly overdosed ones. The determination of chromium might have given another result.

Among the minerals taken, manganese overdosage (taken in a dosage of 21 mg/day, surpassing the U.S. recommendation by the factor of 10) might have contributed to the liver failure according to the literature. Vanadium, taken in a dosage of 34 mg/day clearly surpassed the dosage range considered as safe. In addition, chromium intake in a dosage scheme of 1.3 mg/day extremely surpassed the recommended safe upper limit of 250 µg. Hepatitis and abnormal liver function parameters are known as a reaction to the intake of corresponding amounts of chromium.

Among the vitamins, the intake of niacin in a dosage scheme corresponding 1000% of the U.S. RDA (200 mg/day) might also have contributed to the incident, as highly dosed niacin may cause hepatitis. The same is true for vitamin A, which was taken in a dosage scheme of 20,000 IU per day, surpassing the RDA by 400%.

The herbal drugs ingested included white willow (*Salix alba*), lettuce (*Lactuca sativa*), hawthorn (*Crataegus* spp.), peppermint (*Mentha piperita*), guarana, cayenne (*Capsicum frutescens, C. annuum*), raspberry (*Rubus idaeus*), rosemary (*Rosmarinus officinalis*), chamomile (*Matricaria chamomilla*), Chinese yam (*Dioscorea batatas*), ginseng (*Panax ginseng*), passionflower (*Passiflora incarnata*), aloe (*Aloe vera*), rose hips (*Rosa canina*), horsetail (*Equisetum arvense*), ginkgo (*Ginkgo biloba*), garlic (*Allium sativum*), borage oil (*Borago officinalis*), wheat grass (*Triticum* spp.), barley grass (*Hordeum* spp.), bilberry (*Vaccinium myrtillus*), green tea (*Camellia sinensis*), golden seal (*Hydrastis canadensis*), Echinacea (*Echinacea* spp.), parsley (*Petroselinum crispum*), valerian (*Valeriana officinalis*) and spirulina, which are not known to cause liver problems. Samsara (*Bidens ferulifolia*) and saussurea (*Saussurea* spp.) do not seem to be well investigated.

One case of jaundice induced by *p*-aminobenzoic acid was published in 1967,[95]

and a 1986 review of 390 patients indicated that acute hepatic reaction to potassium *p*-aminobenzoate is at least uncommon if not rare.[96]

This incident was filed as a liver failure with unknown aetiology, possibly caused by hepatis C virus infection. However, a closer examination also shows other possible causes, among these iron in combination with a possible hepatitis C, chromium, vanadium, vitamin A, niacin, ephedra and *p*-aminobenzoic acid qualify at least as suspicious factors. A causality of kava was never proposed and, under the given circumstances, would be rather questionable.

Assessment: Unlikely, probably caused by chromium/vanadium or niacin toxicity.

Case #76

Case also identified as: FDA #13198

This adverse reaction report involved a 52-year-old woman who was hospitalised for treatment of congestive heart failure, acute renal failure, anasarca (generalised oedema) with weight gain, hyperkalaemia, and metabolic alkalosis. A biopsy confirmed liver cirrhosis. She had taken a kava preparation occasionally. Concomitant medication included regular intake of MSM (methylsulphonylmethane), a "green" product with spirulina, dry wheat grass juice (*Triticum* spp.), sprouted barley juice (*Hordeum* spp.), flaxseed/linseed oil (*Linum usitatissimum*), chlorella, bee pollen, ginseng (*Panax ginseng*), garlic (*Allium sativum*), Echinacea (*Echinacea* spp.), St. Mary's thistle (*Silybum marianum*), golden seal (*Hydrastis canadensis*), ginger root (*Zingiber officinalis*), ginkgo (*Ginkgo biloba*), cayenne (*Capsicum frutescens*), vitamins (unknown kind and amounts), minerals (unknown kind and amounts), bioflavonoids, enzymes, a multiglandular product, alfalfa and an amino acid/vitamins/mineral complex.

Occasional intake of a nettle (*Urtica dioica*) extract, an OTC product with grapefruit extract, glucomannan, vitamin B_6, lecithin, kelp, cider vinegar, uva ursi (*Arctostaphylos uva-ursi*) extract and L-phenylalanine, a St. Mary's thistle (*Silybum marianum*) seed extract, herbal sleeping tablets with valerian (*Valeriana* spp.) extract, passionflower (*Passiflora incarnata*), celery seed (*Apium graveolens*), catnip (*Nepeta cataria*), hops (*Humulus lupulus*) and dried orange peel (*Citrus aurantium*), a coenzyme Q10 product with bioperine, "water pills" with buchu (*Agathosma betulina*), uva-ursi (*Arctostaphylos uva-ursi*), parsley (*Petroselinum crispum*), juniper berries (*Juniperus communis*) and potassium 120 mg, a lactobacillus/bifidobacterium combination product, an immune stimulating product with additional vitamins, minerals, gland extracts, enzymes and herbs, four different "antiallergic" homoeopathic multicomponent products, guaifenesin, and sodium cromoglycate. The patient had a history of hyperthyroidism and exposure to hepatitis C. Her alcohol intake was 1 to 2 drinks per day with binge drinking on weekends.[97]

Hepatitis A and B antibodies were negative. The products ingested point to a number of otherwise unknown preexisting medical conditions, among others allergies, liver problems, and a recent cold.

On closer inspection, none of the ingredients of the range of formulas would seem sufficiently suspicious as a causative agent in liver disease. Kava was never suspected by the FDA; in addition, the frequency of intake of the kava product was only indicated as "occasionally". With regard to the general health status, the hepatitis C infection, and the binge drinking of alcohol there is a high probability that kava had no part in the evolution of this liver failure.

Assessment: Unlikely, more likely due to alcohol intake with possible involvement of preexisting medical conditions.

Case #77

Case also identified as: FDA #15465; possible duplicate case FDA #15476 (listed together)

A 48-year-old man experienced what was described as liver pain. He had taken an undefined kava product for a period of 1 to 2 days at a dosage of 1 to 2 units (capsules/tablets not defined). A preexisting liver dysfunction was noted, which was later specified as hepatitis C.[98] The patient already had elevated liver function parameters prior to taking kava due to the hepatitis C, and after the kava ingestion

the LFTs were not checked. From the nature and paucity of the information presented on this case it is a wonder it was ever recorded as an adverse reaction associated with kava.

Assessment: Unlikely, more likely due to preexisting medical condition (hepatitis C).

Case #78

Case also identified as: FDA #15556

A 72-year-old man himself reported to the FDA that he believed kava had aggravated a preexisting liver problem. He had taken a kava product for 2 weeks. Previous medical history included liver damage by hepatitis C. Concomitant medication included valerian.[99] This also should not have been recorded as an adverse reaction to kava when liver damage was already known.

Assessment: Unlikely, more likely due to preexisting medical conditions.

Case #79

Case also identified as: FDA #15249

A 53-year-old man himself reported to the FDA that he had experienced pain in the liver area. He indicated episodical kava ingestion for several years. He filed the report as he had heard of the investigation of the FDA regarding liver effects of kava. He had taken a kava product for 2 days, once on the day the adverse reaction occurred and again on an unknown occasion. In both cases he stated a "distinct painful sensation in the liver area". Following this incident, the patient took kava products of other manufacturers without any problem. Preexisting medical conditions included allergies and no concomitant medication was stated.[100]

Assessment: Should not have been included as there is no evidence of liver damage.

Case #80

Case also identified as: FDA #15320

Acute liver failure was experienced in a 41-year-old woman on 9 May 1999, which led to a liver transplant 11 days later. She had been taking an ethanol extract of kava for an unknown period of time at unknown dosage. Concomitant medications included: loratadine (antihistamine, taken for 3 months prior to the adverse event), St. John's wort powder (*Hypericum perforatum*, taken from 21 January 1999 until the day of the event), contraceptive containing ethinyloestradiol and an infusion of hypericin dissolved in 0.9% sodium chloride for phototherapy. In March 1999, the patient started loratadine for the treatment of an allergic reaction to the intravenous application of hypericin, taking a total of 160 mg loratadine over a 6-day period. After this allergic episode, the patient orally ingested St. John's wort until the day of the hepatic diagnosis.

There are case reports of hepatic adverse reactions to loratadine.[101] However, the intake occurred only for 6 days, 3 months prior to the incident. Contraceptives containing ethinyloestradiol are associated with hepatic adverse events, including hepatitis.[12] There is a lack of information regarding the liver failure and alcohol intake.

The effect of the administration of intravenous hypericin and oral St. John's wort extract on this patient's liver is not known. Phototoxic (skin) reactions to hypericin (a constituent of St. John's wort) have been noted in humans, usually from injection of hypericin or oral administration of high quantities of hypericin. Mild reversible liver enzyme elevations were recorded in some patients receiving St. John's wort extract. (Refer to the St. John's wort safety monograph.)

Assessment: Possible, but may not be due to kava alone, intravenous administration of hypericin may have contributed.

Case #81

Case also identified as: BfArM #02007130

A 38-year-old woman showed symptoms of an acute liver failure, but recovered. She had taken an ethanolic kava extract with 120 mg kava lactones per day over a period of at least 4 weeks for the treatment of anxiety. There was no co-medication stated. Nothing is known on preexisting medical conditions, virus serology, alcohol intake, or other relevant risk factors of liver disease.

Assessment: Unassessable due to insufficient information.

Case #82

Case also identified as: FDA #15564

An overweight patient (231 lb, 96 kg) of unknown age experienced hepatitis and liver cirrhosis, and ultimately died from fulminant liver failure. The patient did not smoke, and the relatives denied alcohol intake. His medication consisted of about 25 dietary supplements including herbals and minerals, among others magnesium (regularly taken every 2 hours), valerian (*Valeriana officinalis*), and saw palmetto (*Sabal serrulata*). In addition, an occasional intake of kava (exact preparation unknown) with 50 to 100 tablets over 1 year was stated. As preexisting medical conditions, polycythema rubra vera, arthralgia, and anxiety were mentioned. According to the relatives, the patient did not use steroid-type drugs.

Liver biopsy showed micronodular cirrhosis. No further information is available, especially on concomitant medication and further examinations such as virus serology or autoimmune antibody screening. The patient himself suggested the causality of kava, as during the hospitalisation he found references to the kava discussion on the Internet.

Assessment: Unassessable due to insufficient information.

Case #83

Case also identified as: ADRS #177303

A 56-year-old woman experienced symptoms of fatigue, jaundice, and hepatic necrosis. She died as a result of complications of liver failure during a liver transplant operation. She had been taking five separate complementary medicines for a period of 4 months: vitamin E; a vitamin B/mineral complex with chromium, B-group vitamins, calcium, magnesium, zinc and manganese; vitamin C, selenium; a combination of amino acids, vitamins and minerals; and a product labelled to contain kava with 60 mg kava lactones per tablet, passionflower (*Passiflora incarnata*), and supposedly skullcap (*Scutellaria lateriflora*).[60] Daily dosage unknown, duration of intake for all mentioned drugs was approximately 3 to 4 months. Prior to taking these she had been taking several other complementary medicines (details of which were not disclosed by the Australian TGA) for about 3 months. She had not been taking any prescribed medicines, and drank only a minimal amount of alcohol. On admission, she had markedly abnormal liver function tests, with highly elevated transaminases, and elevations of bilirubin, alkaline phosphatase, and GGT. Liver biopsy showed a severe acute hepatitis with confluent necrosis, consistent with a viral or drug aetiology.[102]

According to the information in the ADRS line listing, the patient had a past infection or had been immunised with hepatitis A antigen. The case was subsequently reported in the *Medical Journal of Australia*. Assays for acute hepatitis A, B, and C viruses, Epstein–Barr virus, and cytomegalovirus were all negative. She had been previously well, except for a history of benign monoclonal gammopathy which had been diagnosed 12 months previously.[103] Monoclonal gammopathy is not connected to the occurrence of fulminant liver failure; however, heteroclonal gammopathy is. The correct diagnosis in this case has to be taken for granted.

Testing by the TGA of the suspected kava product confirmed the presence of kava and passionflower, but *Scutellaria lateriflora* was not detected. The identity of the third ingredient remains to be established. The presence of some other herbs reported to be hepatotoxic has been excluded.[102] Two independent analyses[104,105] of three batch samples of this product indicated that *Scutellaria lateriflora* was not present; however, the nature of the adulterants could not be established to date. Skullcap was possibly exchanged for the hepatotoxic *Teucrium* species (e.g. *T. chamaedrys*, one of the species commonly known as germander). This is an accidental adulteration frequently observed for this plant. Given the unknown composition of the kava-containing product, it is not possible to conclusively associate kava with the causality.

Chromium was also ingested amongst the complementary medicines she had been taking. Chromium may have contributed to hepatotoxicity.[106,107]

Assessment: Possible, but link to kava not established due to an unknown constituent of the kava-containing product. Previous medical conditions need closer examination given the mention of gammopathy, hepatitis A, and the apparent lack of information regarding other pathogens.

CRITICAL OVERVIEW OF THE EVIDENCE SUPPORTING AN HEPATOTOXIC REACTION FROM KAVA

Ideally, the investigation of an adverse drug reaction should result in some attribution of causality. Many schemes for classification of causality have been proposed in different countries. Table 12-4 outlines a recent scheme that is gaining popularity.[108]

Using this assessment, the CSM determined the classification of the 68 cases included in their analysis (#1 to #68), as described in Table 12-5.[1,4]

The above criteria for assessment were not universally applied. A comparative assessment of causality by three different government regulatory bodies of 16 (German and Swiss) cases, as described in Table 12-6, illustrates the differing assessments made. Note that many cases described as probable by the BfArM were rated as only possible or even given lower ratings (such as not assessable) by other authorities.[109]

In the Schmidt review shown in Table 12-7 the causal assessments were assigned for 80 cases (duplicates excluded).

In other words, only three cases could be attributed to kava with a high probability.

Table 12-4 **A Scheme Defining Causality Assessment of Suspected Adverse Drug Reactions**

Criteria	Assessment
Certain	• A clinical event, including a laboratory test abnormality, that occurs in a plausible time relation to drug administration, and which cannot be explained by concurrent disease or other drugs or chemicals
	• The response to withdrawal of the drug (dechallenge) should be clinically plausible
	• The event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge procedure if necessary
Probable/likely	• A clinical event, including a laboratory test abnormality, with a reasonable time relation to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge)
	• Rechallenge information is not required to fulfil this definition
Possible	• A clinical event, including a laboratory test abnormality, with a reasonable time relation to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals
	• Information on drug withdrawal may be lacking or unclear
Unlikely	• A clinical event, including a laboratory test abnormality, with a temporal relation to administration of the drug, which makes a causal relation improbable, and in which other drugs, chemicals, or underlying disease provide plausible explanations
Conditional/unclassified	• A clinical event, including a laboratory test abnormality, reported as an adverse reaction, about which more data are essential for a proper assessment or the additional data are being examined
Unassessable/unclassifiable	• A report suggesting an adverse reaction that cannot be judged, because information is insufficient or contradictory and cannot be supplemented or verified

Table 12-5 **Assessment of 68 Cases by the MCA**

Classification	Number of reports	Case #
Probable	14	5, 8, 10, 20, 30*, 31*, 32, 54, 55, 56, 57, 60, 62, 68
Possible	30	1, 2, 3, 6, 7, 9, 12, 13, 14, 15, 16, 18, 19, 21, 22, 23, 24, 25, 26*, 28, 29*, 41, 52, 53, 59, 61, 63, 64, 65, 67
Unassessable	19	11, 33*, 34, 35, 36, 37, 38, 39, 40, 42, 43, 44, 45, 46, 47, 48, 49, 50, 66
Unlikely	5	4, 17, 27, 51, 58

*Duplicate cases: 26/28, 29/30, 31/33.

In a report prepared by Dr. Waller for the American Herbal Products Association, the Professor of Pharmacology and Toxicology assessed the 30 German and Swiss case reports ("Data provided by BfArM" and a translation of the preliminary and the still incomplete Schmidt review) (Table 12-8).[3] Dr. Waller accepted the duplications indicated by Schmidt, and so reviewed 28 cases. Duplicate cases are indicated in brackets.

Waller suggested that there are only a few of these cases in which kava might be directly associated with liver damage, although more complete information is required for a scientific conclusion. These cases may have been hypersensitivity or idiosyncratic responses.

Table 12-9 is an assessment of 30 German and Swiss cases (with overlap of two) by the Traditional Medicines Evaluation Committee (TMEC), a subcommittee of the European

Table 12-6 **Evaluations of Identical Case Data by Different Authorities (Criteria Unknown)**

Case #	BfArM	MCA	EMEA
6	Probable	Possible	Possible
13	Probable	Possible	Possible
14	Possible	Possible	Possible
15	Probable	Not assessable	Possible
17	Probable	Unlikely	Unlikely
21	Probable	Not assessable	Possible
24	Probable	Possible	Possible
26/28	Probable	Possible	Possible
31/33	Certain	Probable	Probable/not assessable
32	Probable	Not assessable	Probable
34	Probable		Not assessable
38	Probable		Not assessable
40	Probable		Not assessable
42	Probable		Not assessable
46	Probable		Not assessable
47	Possible		Not assessable

Table 12-7 **Analysis of Cases by Schmidt**

Classification	Number of reports	Case #
Unrelated to kava	20	1, 4, 15, 17, 27, 39, 47, 52, 53, 55, 57, 58, 59, 72, 75, 76, 77, 78, 79, 80
Probably connected to concomitant medication	20	2, 6, 7, 9, 11, 13, 19, 21, 22, 23, 29, 31, 35, 37, 41, 43, 46, 51, 54, 74
Connection to kava doubtful	6	14, 16, 24, 56, 64, 67
Connection to kava not assessable due to insufficient documentation	31	3, 12, 18, 20, 25, 26, 32, 34, 36, 38, 40, 42, 44, 45, 48, 49, 50, 60, 61, 62, 63, 65, 66, 68, 69, 70, 71, 73, 81, 82, 83
Possible connection to kava with Commission E monograph-conforming dosage	1	5
Possible connection to kava with overdosing	2	8, 10

Herbal Practitioners' Association (EHPA). The classification contains some overlap, with cases appearing in more than one group.

Waller also reviewed 26 FDA cases provided to him at the time by the AHPA and considered only five to identify a liver-related symptom or problem in persons who were reported to be consuming kava. (The spreadsheet detailing the FDA information on these 26 cases is appended in his report. It is not known how these 26 cases were selected for analysis.) These five are reviewed below (#51, #52, #54, #63, and #76). In reviewing the non–liver-related adverse reaction cases he notes that there are two cases of chronic and high-dose consumption of kava that were not associated with any significant liver damage, which provides evidence that kava is not a direct hepatotoxin, even in extremely high concentrations. He concludes with the opinion that there is no scientifically supported association of liver disease with the use of kava which can be found using the FDA adverse reaction case reports. Overall, considering the evidence in the European and U.S. cases, and based on currently available information, kava, when taken in appropriate doses for reasonable periods of time, has no scientifically established potential for causing liver damage.[3]

Table 12-8 **Analysis of German and Swiss Case Reports by Dr. Waller**

Classification	Number of reports	Case #
Cases not attributable to kava	4	4, 17, 19, 27
Cases involving concomitant medication usage with known hepatic toxicity	10	7, 9, 11, 13, 15, 21, 22, 23, 29 (30), 33 (31)
Insufficient information to conclusively identify or fully eliminate kava as a potential causal agent, which include:	14	
• those with vastly inadequate information	6	12, 18, 20, 25, 26 (28), 32
• those with additional or confounding factors	5	8, 14, 16, 24, 28 (27)
• those with less inadequate information	3	5, 6, 10

Table 12-9 **Assessment by TMEC January to April 2002**[110]

Classification	Number of reports	Case #
Cases of most concern, assessed as probable	5	5, 8, 10, 20, 31/33
Cases associated with taking synthetic kavain (a kava lactone)	4	11, 12, 22, 31/33
Patients taking oral contraceptive pills or hormone replacement therapy together with drugs that can be associated with liver damage	6	5, 13, 19, 23, 24, 31/33
Patients who were taking drugs that can be associated with liver damage	10	6, 7, 9, 11, 15, 17, 21, 22, 26/28, 29/30
Cases in which drugs not associated with liver damage, herbal medicines, or dietary supplements or kavain alone were taken	8	12, 14, 16, 18, 20, 25, 26/28, 27
Cases associated with an overdose of alcohol	2	8, 17
Cases not associated with other drug usage	2	10, 32

Overall, the quality of the data provided in these case reports was poor in most circumstances, there was little proof by rechallenge, and assessment of causality to kava was made, in most instances, without due consideration of concomitant medication. Investigation of preexisting medical conditions was also poor.

The assessments provided in "Summary and Critique of Case Reports" rate 3 cases as probable, 18 cases as possible (as defined in Table 12-4), 26 cases as unlikely, 33 cases as unassessable, 2 as unrelated to kava, and 1 which should not have been included.

Our extensive assessment of the data provided in "Summary and Critique of Case Reports" rates only three probable cases associated with kava use. For two of these three cases the kava was extracted with acetone (information is not available for the third case). Given the extensive time frame for gathering of data (e.g., #11 BfArM date October 1990) and the widespread use of kava (70 million daily doses in Germany per year at the time of its restriction), the incidence of a hepatic adverse reaction to kava is likely to be very rare. These data support the frequencies suggested in "Predicted Frequency of Response" (p.186).

THE PRODUCT INVOLVED IN THE AUSTRALIAN CASE REPORT

The product involved in the single Australian case report of hepatotoxicity linked to kava ingestion was labelled as containing kava, skullcap (*Scutellaria lateriflora*), and passionflower (*Passiflora incarnata*). Following reports from the TGA that the product did not contain skullcap, two current batches of the product were tested by an Australian company for the presence of kava, skullcap, passionflower, and two species of germander. Samples were run under three different high-performance liquid chromatography (HPLC) methods.[111] Germander (*Teucrium* spp., specifically *T. chamaedrys* and *T. canadensis*) was included in the analysis because species of *Teucrium* have been implicated in cases of hepatotoxicity and have been documented as substitutes for skullcap. In fact, the description given for dried skullcap in the *British Herbal Pharmacopoeia* 1983 is actually a description of a species of germander, and adulterations of *Scutellaria* with *Teucrium* species are reported rather frequently in the literature.

The assay of the two batches of the product could not confirm the presence of *Scutellaria*

lateriflora, a second *Scutellaria* species (specifically *Scutellaria baicalensis*), or *Passiflora incarnata*. The presence of two selected species of germander could also not be confirmed, but this does not rule out germander substitution, since another species could be involved.

It is possible that the product contained another species of *Scutellaria*. However, this is not very likely since both batches of the product contained extremely low levels of flavonoids and *Scutellaria* species are known phytochemically to accumulate a considerable amount of flavonoids. In fact, levels of flavonoids found in the batches were more consistent with the levels corresponding to germander species.

Analysis of a third batch of the product performed by a German research group, using thin-layer chromatography (TLC) and HPLC methods, yielded similar results: the presence of kava and the absence of both *Scutellaria lateriflora* and *Passiflora incarnata*.[105] Subsequent analysis of the *Passiflora* raw material used in the product showed that it was indeed this herb, but was a poor-quality extract. This explains why its presence in the product was difficult to confirm.[111]

The issue of germander substitution for skullcap and resultant hepatotoxicity could be highly relevant to the current Australian market. A recent publication in the *Medical Journal of Australia*[112] reported six cases of hepatotoxicity attributed to use of herbal products. Of the six products involved, three supposedly contained skullcap (at least according to their labels). Given this news, linking hepatotoxicity to other Australian products labelled as containing skullcap, it is reasonable to suggest that an association with kava for the single Australian case must be seriously questioned.

In addition, chromium may have contributed to the hepatotoxicity.[106,107]

IS KAVA INHERENTLY HEPATOTOXIC?

Kava and its isolated constituents have not to date demonstrated toxic effects on liver parameters in standard experimental models (in vitro and in vivo). Some of the most relevant studies have not been published.[113,114]

A letter describing one of the Swiss cases mentioned above provides strong evidence that the hepatotoxicity was immune-mediated.[13] Also a deficiency of the drug-metabolising enzyme CYP2D6 (which occurs in 9% of the population) could be a predisposing factor.[13]

An Australian study of kava use in Aboriginal communities appears to support the contention that kava is inherently hepatotoxic.[115] However, concurrent use of alcohol is often widespread in such communities and any observed liver damage could be readily accounted for by this. Studies in Australia have shown that kava drinkers have markedly elevated levels of the liver enzyme GGT, and this has been construed as further proof of the inherent hepatotoxicity of kava.[116] However, while a survey of heavy kava drinkers in New Caledonia (8 g of kava lactones per week) did find evidence of raised GGT in about one-third, there were no signs of liver damage. The authors concluded that the probable explanation for the elevated GGT is enzymatic induction (as occurs with phenobarbital users), not hepatotoxicity. They concluded that cases of hepatotoxicity linked to kava are due to a rare immunoallergic mechanism.[117]

In a letter to the *Medical Journal of Australia* on 5 May 2003, two field researchers advised that the previously reported liver enzyme levels of Aboriginal kava users do not suggest acute inflammation and are not consistent with herb-induced hepatotoxicity. Clinical surveillance in the Northern Territory over 20 years has not documented any cases of fulminant hepatic failure attributable to kava use. This is despite the ingestion of doses estimated to be 10 to 50 times the recommended therapeutic doses for herbal products.[118]

PREDICTED FREQUENCY OF RESPONSE

Kava

The annual use of kava products, based on sales figures, has been estimated by one group at over 70 million daily doses in Germany and over 100 million daily doses in Europe.[119] According to the conservative sales figures of the German Institute of Medicinal Statistics, approximately 250 million daily doses of kava (ethanol extract) were sold during the past 10

years in German-speaking countries.[120] The sales of the acetone extract would have to be added to that number.

It has been suggested that 12 cases of probable liver toxicity have been reported to date in Germany and Switzerland (probably late 2001), for a calculated incidence of 0.23 cases per 1 million daily doses. This number does not allow for differentiation between products extracted with ethanol and acetone.[121]

According to the manufacturing company, a total of 80 million daily doses of the leading ethanol-based kava product Antares were taken from its introduction in 1992 up to the end of 1999. Only one single suspicious case was reported in that time (case #5, see above).[122]

On the basis of our assessment of the German and Swiss case reports (#4 to #50, #69, #70, #72, #73, and #81) only three cases of hepatotoxicity are probably associated with kava intake (#5, #8, and #10, and in the latter cases the dose exceeded the recommended dose). These data were gathered from 1990 to mid-2002. Using the following information the incidence can be estimated:

- a total of 80 million daily doses of the leading ethanol-based kava product (Antares) in Germany for 8 years (1992 to end of 1999);
- a total of 10 million capsules (corresponding to 5 million daily doses) of the ethanol-based kava product Kavasedon worldwide in the same time frame;
- 70 million daily doses in Germany per subsequent year (each year for 2000 to 2002);
- $85 + (70 \times 3) = 295$ million daily doses of kava;
- 3 cases of probable hepatotoxicity;
- incidence = 0.01 per million daily doses.

However, assuming a worst case scenario that every German and Swiss case (around 50) was probably associated with kava ingestion, and that data were only credibly gathered over 3 years, this gives an upper level of frequency of 0.24 cases per million daily doses. This frequency is still well below those documented for benzodiazepine drugs (see below), for which kava is considered by many as a credible and safer alternative.

Benzodiazepines/antianxiety/tranquillisers/psychotropics

The frequencies shown in Table 12-10 were calculated from cases of (suspected) hepatotoxicity reported to BfArM and corresponding drug sales in Germany for the period from September 1999 to August 2000. On the same basis, kava was estimated at causing 0.89 cases of hepatotoxicity per million daily doses.[121] In comparison to other treatments with potential for hepatotoxicity, this incidence has to be accepted as an extremely low figure.[121] So, while the frequency for kava given below is higher than those numbers arrived at elsewhere and above, it is still at the lower end of the hepatotoxicity incidences calculated for benzodiazepines.

In a randomised, placebo-controlled, multicentre trial, potentially serious reactions to alprazolam occurred in 10 of 263 subjects who received the drug (mean daily dose 5.7 mg). These included three cases of acute intoxication and two cases of hepatitis (i.e. frequency

Table **12-10** **Relative Incidence of Suspected Hepatotoxic Reactions for Common Benzodiazepine Drugs and Kava**

	Incidence (n/Million Daily Doses)
Bromazepam	0.90
Oxazepam	1.23
Diazepam	2.12
Kava (ethanol and acetone extracts)	0.89

of hepatic adverse events equalled a very high 0.8%). This drug is commonly prescribed.[123]

Hepatotoxicity of psychotropic drugs occurs in a variable but small proportion of users and therefore can be considered unpredictable or idiosyncratic. When these uncommon adverse events occur in association with rash, eosinophilia, and/or a rapid positive rechallenge, sufficient circumstantial evidence exists to ascribe the medication to an immune-mediated hypersensitivity reaction. Acute overt reactions to drugs tend to have clinicopathological features of hepatitis, cholestasis, or both.[124]

Other Drugs

Antipsychotics

There is a high incidence of liver test abnormalities (>20%) with phenothiazine use, and a lower incidence of overt liver disease (0.1% to 1%). Features of hypersensitivity are seen in about half of the cases, including positive rechallenge.[125–128]

A survey of prescriptions in the UK from 1985 to 1991 revealed an overall incidence of chlorpromazine jaundice of 0.16%, increasing to 0.3% over age 70, more than 10 times higher than in those below age 50.[128]

A mild, transient increase in serum GPT occurred in 37% of recipients of clozapine.[129]

Antidepressants

Monoamine-oxidase inhibitors are all potential hepatotoxins. Overt hepatitis occurred in 1% of patients treated with iproniazid, with case fatalities approaching 20%.[130] The drug was withdrawn.

Hepatotoxic reactions, such as abnormal hepatic function, hepatitis (including cholestasis), hepatic failure, or necrosis and aggravation of hepatic damage, to the serotonin reuptake inhibitor fluoxetine have been reported, but are very rare (<0.01% of patients). Hepatitis and jaundice have been reported in less than 0.1% of patients using paroxetine. Hepatic failure, hepatitis, and jaundice have been reported in 0.01% to 0.1% of recipients of sertraline.[8] These incidences of hepatotoxicity are substantially higher than for kava.

Nefazodone (serotonin receptor blocker) has been associated with three cases of fulminant hepatic failure within 14 to 28 weeks of starting the drug. Liver transplantation was necessary in two cases, one of these patients died.[131]

Elevated transaminase and alkaline phosphatase levels are common (1% to 10%) in patients using the tricyclic antidepressants imipramine and clomipramine. Hepatitis with or without jaundice, acute hepatitis, and hepatic necrosis have been reported in less than 0.01% of patients using imipramine or clomipramine.[8]

The incidence of liver injury for the commonly used antidepressant amitriptyline is disturbingly high at 0.5% to 1%.[124]

NSAIDs

NSAID-induced liver injury results in 2.2 hospitalisations per 100,000 population per year.[132] While the incidence of NSAID-related jaundice may be as low as 0.1%, 0.01%, or even lower among recipients, plasma levels of transaminases may be abnormal in 5% to 15% of patients.[133]

The adjusted odds ratio for hepatotoxicity with sundilac has been estimated at almost twice that of indomethacin (5.0 vs. 2.6, respectively) despite their being in the same chemical class.[134] At least 25 individual cases of sundilac-associated jaundice have been reported in the literature.[133] About 20% of cases had hepatocellular injury, with about 5% of cases of jaundice ending in death.[135]

Significant hepatotoxicity occurs in approximately 1 to 5 per 100,000 diclofenac-exposed patients.[136] Abnormal aminotransferase plasma levels develop in about 15% of patients taking this drug. It has been implicated in at least 50 published reports of hepatocellular damage.[133] Massive necrosis with fulminant hepatic failure and death have been noted in about 10% of icteric cases.[137]

Estimates of clinically manifested hepatic toxicity associated with diclofenac, naproxen, or piroxicam range from 0.05 to 0.001%.[138] The incidence of liver damage (overt "hepatitis") induced by phenylbutazone was cited as 0.25% in one study.[139]

Piroxicam is one of the most widely used NSAIDs worldwide. Piroxicam caused a 1% to 2% incidence of elevated aminotransferase levels in early studies.[140] Instances of hepatic injury have been described, several of which involved fatal hepatic necrosis. Others showed severe cholestatic or mixed jaundice.[133]

Ibufenac was withdrawn when adverse liver reactions were observed in approximately 5% of individuals.[141,142] Ibufenac led to elevated aminotransferase levels in over 30% and jaundice in approximately 5% of individuals.[133]

Other Drugs

For most drugs, the risk of hepatotoxicity is 1 to 10 cases per 100,000 individuals exposed.[136] Kava would be below the lower end of this frequency, even if all reported cases were assumed to be linked.

In the United States, drugs and toxins account for as many as one-third of the cases of fulminant hepatic failure. The prognosis for drug-induced hepatitis is somewhat worse than that for viral hepatitis, with fatality rates approaching 10%.[136]

The Acute Liver Failure Study Group started in 1998 and collects data from 14 sites around the United States. The registry had enrolled 150 patients by the year 2000. Preliminary analysis suggests that 50% are related to drug hepatotoxicity (paracetamol toxicity in 32% and idiosyncratic reactions in 18%).[143]

Beard et al identified 12 hospitalisations for liver disorders judged possibly or probably attributable to use of outpatient medications other than anticancer drugs among 280,000 members of a managed care organisation during a 5-year period from 1977 through 1981.[144] This corresponds to an incidence of approximately one per 10^5 person-years (py) of exposure within the organisation. Walker and Cavanaugh found three cases of new-onset cases of liver disease of uncertain cause during the year 1989 among 71,000 adult members of a managed care organisation, yielding incidences of $4/10^5$ py and $24/10^5$ py, respectively.[145]

The incidence of liver function abnormalities in the general population of Massachusetts, in a study using computerised data files from a health maintenance organisation, found that drug-associated abnormalities were the most common. The incidence was 40.6 persons per 100,000 persons per year, with a 95% confidence interval of 29.3 to 51.8, based on a total of 50 cases. The study evaluated only outpatient use of prescription drugs, including NSAIDs, lipid-lowering agents, isoniazid, methotrexate, oral erythromycin, sulpha drugs, and chemotherapeutic drugs.[146]

Serum alanine aminotransferase exceeds the upper limit of normal in about 50% of recipients of tacrine. In 25%, the value is more than three times the upper limit, and in 2%, it is increased 20-fold.[147]

Troglitazone, a thiazolidinedione diabetic agent, produced severe and unpredictable hepatotoxicity and 61 related deaths.[148] The incidence of troglitazone-induced acute liver failure is estimated to be 1 in 8000 to 1 in 20,000 patients treated.[149] It took more than 3 years and 100 deaths or transplanted patients before the drug was withdrawn from the U.S. market.[150,151] It produced alanine aminotransferase elevations greater than three times upper limit of normal in 1 in 50 patients in clinical trials.[143] Abnormal liver function tests have not been recorded in any patients receiving kava in clinical trials (see "Efficacy of Kava" [p. 193]).

Toxic hepatitis developed in 1 of 127 peptic ulcer patients treated with cimetidine. Hepatocyte microsomal oxidase function noticeably declined in 1 in 8 patients subjected to the continuous 5-week treatment and in 1 in 5 patients given the treatment for a longer time.[152]

Hepatitis and cholestatic jaundice (occasionally severe) have been reported with a frequency of about 1 in 15,000 exposures of flucloxacillin.[8]

Dicloxacillin (a penicillin) has been associated with cholestatic hepatotoxicity and jaundice. The patterns of liver function test results and biopsy histology are similar to those with flucloxacillin. Information collected by the Swedish Adverse Drug Reaction Advisory Committee (SADRAC) over the period 1981 to 1994 provides 20 reports of liver damage possibly or probably caused by dicloxacillin. Over this period a total of 10.7 million defined daily doses (DDD) of dicloxacillin were prescribed in Sweden, giving a frequency of 1.8 reactions per million DDD. Over the period there were 127 reports of liver damage possibly or probably caused by flucloxacillin, at a frequency of 4.3 reactions per million DDD. Although there are obvious limitations of retrospective data reliant upon spontaneous doctor reporting, the SADRAC figures suggest that adverse hepatic events occur, or at least

are reported, less frequently with dicloxacillin than flucloxacillin.[8]

CONFOUNDING FACTORS

One possibility that deserves consideration is the apparent higher prevalence of reaction for the acetone extract of kava. This could be due to the market leadership of this extract in Switzerland, but could also reflect on the particular phytochemical balance of an acetone-based extract. On the other hand, some of the reported cases involved ethanolic kava extracts. But the use of ethanolic extracts has not been confirmed in any of the cases rated as probable by us (and use of ethanolic extracts was definitively reported in only a few of the cases rated as possible).

If mode of preparation of kava is not an issue, and this remains to be established, the kava plant part used might be. In Europe, kava preparations are often manufactured from the root peelings or kava stumps (let alone the aerial peelings), which represent a cheap source of kava lactones. (In the South Pacific the kava root is often peeled and the locals drink this pale yellow root and export the darker peelings.) Kava preparations made from the whole peeled root, as used traditionally, could be less likely to cause hepatotoxicity (given the lack of reports of liver damage from Fiji and Vanuatu). In light of recent in vitro research (see below) this difference may be very important.

It is this factor, rather than the fact that traditional preparations of kava are water-based, which could explain the apparent lack of hepatotoxicity from kava use in the Pacific Islands (see "Indigenous Use of Kava and Safety" [p.192]). Indigenous use of kava in these regions can result in a chronic overdosage syndrome known as kava dermopathy, so it can hardly be suggested that the use of water-based preparations results in a lower exposure to kava phytochemicals. One reason for this is that the kava is often consumed as the finely ground root powder suspended in water, so in fact the whole root is being consumed. (However, one cannot rule out that there may be something protective missing from ethanolic or acetone extracts of kava which is present in water-based preparations.)

A new piperidine alkaloid (3α,4α-epoxy-5β-pipermethystine) has been isolated from the stem peelings (from the basal stem 0 to 20 cm above the ground) of one cultivar originating from Papua New Guinea (called Isa, and known in Hawaii as PNG). This constituent was present at a concentration of 0.93%, and was absent from the 10 other cultivars tested. Traditionally Isa has been used only occasionally for drinking purposes, since it causes prolonged nausea. However, as a pharmaceutical source it has recently gained popularity. In Hawaii, it is the only cultivar currently known to be less affected by the devastating viral disease known as kava dieback.[153] The safety implications of this discovery remain to be understood.

It is speculated that two potentially hepatotoxic 7,8-epoxidised kava lactones (based on in vitro tests) can be isolated from the hexane fraction of an acetone extract of kava root. The concentration of these epoxides in the Vanuatu kava root were very low (total of both amounting to 4 mg/kg). (The production of epoxides is a phase I metabolic reaction, which may have hepatotoxic consequences.) Incubation of six kava lactones with P450 enzymes and oxygen failed to produce kava lactone epoxides, but chemical oxidation of desmethoxyyangonin and 5,6-dihydromethysticin produced the kava lactone epoxides. Kavain and methysticin (which contain a double bond at C7–C8) combined with P450 enzymes produce desmethoxyyangonin and 5,6-dihydromethysticin respectively. Dihydrokavain and dihydromethysticin (lacking a double bond at C7–C8) could not be converted into desmethoxyyangonin and 5,6-dihydromethysticin. The authors hypothesised that the concomitant use of alcohol and/or prescription drugs in some patients may have primed the liver for hepatotoxicity by inducing the formation of P450 isoforms that were capable of transforming unsaturated kava lactones into 7,8-kavalactone epoxides.[154]

As a specific example of the issue of plant part, some kava extracts are a bright yellow colour indicating the presence of flavokavains. These are often lacking from European extracts (presumably prepared from peelings and stumps), as evidenced by their grey or brownish coloration, and are even intentional-

ly removed for unknown reasons in the preparation of the acetone-based extract. The flavokavains, and perhaps other antioxidant compounds, from whole peeled kava root could provide a level of protection against hepatotoxic activity, as per the discussion below.

Chaparral is a herb suspected of causing hepatotoxicity. Linseed (also known as flaxseed [*Linum usitatissimum*]) and chaparral (*Larrea tridentata*) contain chemical components from the lignan group. A paper by scientists at the United States Food and Drug Administration described the development of methods to measure the specific lignans in these two herbs, and speculated on possible toxicity problems associated with their use.[155]

Linseeds contain the glucoside of the lignan secoisolariciresinol. Upon ingestion, this glucoside is hydrolysed enzymatically to the aglycone and transformed by intestinal microflora into the phyto-oestrogens enterodiol and enterolactone (Figure 12-1). While the authors concede that no adverse effects have been reported from the consumption of linseed products, they hypothesise that these phyto-oestrogens may have the potential to cause hepatotoxicity through mechanisms similar to those of hormonal oestrogens.

In contrast, chaparral contains nordihydroguaiaretic acid (NDGA) and other related lignans, and the use of this herb has been connected to hepatotoxicity. The authors provide an interesting theory to explain possible occasional hepatotoxicity from chaparral ingestion. They suggest that, under certain conditions, antioxidant compounds such as NDGA can become oxidant and generate free radicals. Moreover, if hepatic detoxification mechanisms are compromised, these compounds can also have toxic effects. (Every antioxidant compound exists in a reduced and an oxidised form, and if the oxidised form predominates, that compound will then act as a pro-oxidant.) Chemical studies of chaparral extracts indicate the presence of a number of reactive free-radical species and also the potentially toxic pro-oxidant compound guaiaretic acid diquinone (see Figure 12-1).

It is conceivable that under certain circumstances highly reactive pro-oxidant compounds may be produced from the kava lactones (Figure 12-2), which could result in haptenisation and immune-mediated hepatotoxicity.

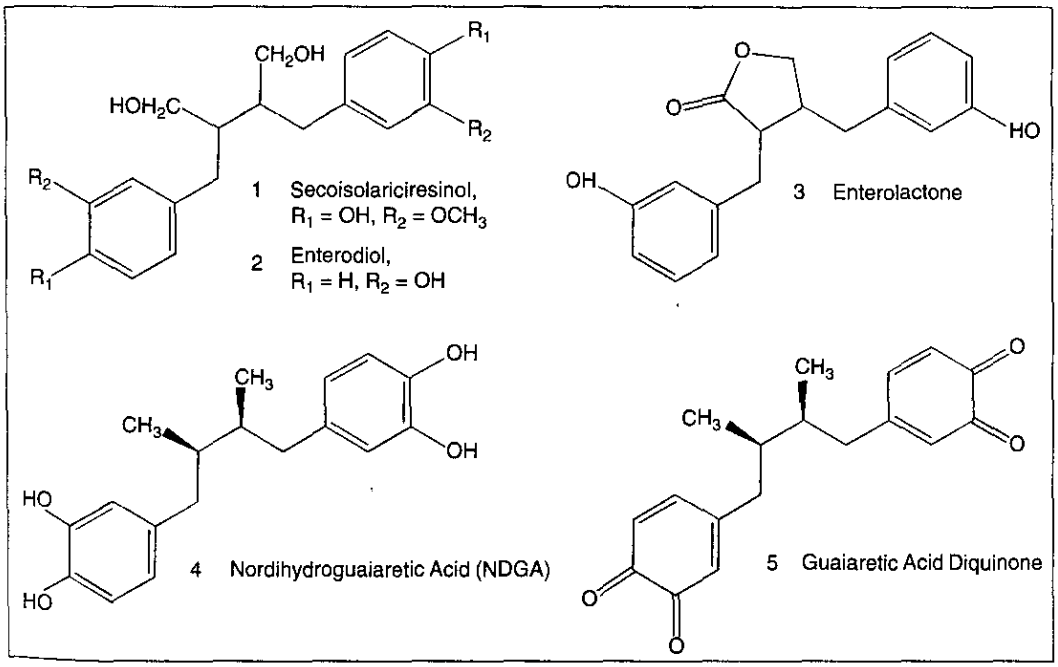

Figure 12-1. Constituents of chaparral (*Larrea tridentata*).

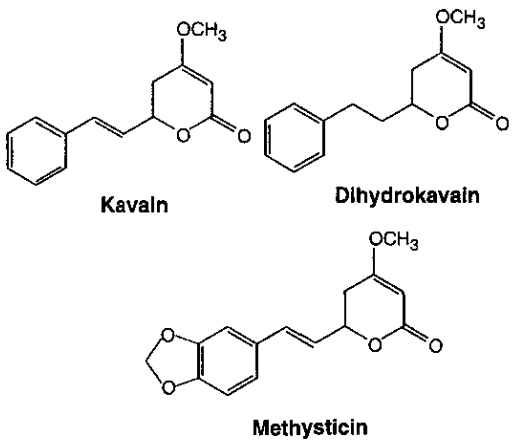

Figure 12-2. Constituents of kava (*Piper methysticum*).

Use of the whole root may help to prevent against this, because antioxidant phytochemicals are also coextracted. However, immunological reactions to kava do not seem to occur frequently. The number of suspect cases does not surpass the average allergic reaction occurring with virtually any otherwise unsuspect medication or food component.

INDIGENOUS USE OF KAVA AND SAFETY

Kava has a long history of safe use in the Pacific Islands and cases of hepatotoxicity have not been noted. An extensive review of the ethnobotany, history, and chemistry of kava, focusing on the Pacific Islands, published in 1993, makes no mention of adverse effects on the liver from even excessive use of kava.[156] Kava is, or was, consumed in a wide range of Pacific Ocean societies, from coastal areas on the large Melanesian island of New Guinea in the west to isolated Polynesian Hawaii, 7000 km distant to the north-east.

Kava became an integral part of island religious, economic, political, and social life, and even today it is a regular activity for many islanders. Traditionally, islanders ingested the kava lactones by drinking cold water infusions of chewed, ground, pounded, or otherwise macerated kava stumps and roots. In addition to its ceremonial and social function, kava was also used medicinally.

The principal author of the above review recently indicated that he drinks traditionally prepared kava every day and his regular annual medical check-up confirms that his liver is in good condition.[157] According to Singh and Singh,[158] in the South Pacific only men drink kava, often habitually and in much larger amounts than used in the West, yet their incidence of liver toxicity is low and similar to that of island women who do not take kava.

Is long-term consumption of kava generally safe? While more studies are needed, a recent epidemiological study found a substantially *lower* incidence of cancer among kava users, which contrasts strongly with the use of alcohol and tobacco.[159]

An Australian GP recalls that he spent 2 years living in Vanuatu, observing the regular, and occasionally heavy, kava consumption. Clinical evaluation revealed occasional cases of kava-related dermopathy and presumptive kava-related cerebral damage. At no time during his 2-year stay did he encounter any case of unexplained hepatitis, despite his vigilance, since 20% of the population were hepatitis B carriers.[160] A GP working in Auckland with the Pacific Island community reported a similar lack of hepatotoxicity in frequent kava users.[161]

Various reasons have been proposed for this lack of observed hepatotoxicity in the Pacific Islands, including the mode of preparation of kava and the part used (see "Confounding Factors" [p. 190]). However, another reason could be the relatively low use of alcohol and modern drugs by these communities. It could be that many or most of the cases attributed to kava in the West were, in fact, due to concomitant alcohol or drug consumption. There might even be the situation where the kava acted synergistically with these agents.

Aboriginal people living mostly in Arnhem Land began using kava in the early 1980s. They purchased imported powdered kava as an alcohol substitute.[156] As described above, the Australian study of kava use in Aboriginal communities does not support the inherent hepatotoxicity of kava.[115]

The Northern Territory government enacted legislation (Kava Management Act and Regulations) 11 May 1998. The legislation was

introduced as part of a comprehensive package to minimise the harmful effects of kava use and to penalise illegal kava traders. The legislation was enacted in response to concerns about potential harmful effects of kava outlined in the report from the Menzies School of Health Research (referred to above).[116] A kava licensing system was proposed to assist communities to control the amount of kava consumed, reduce health damage through overuse, and diminish black market kava sales.[162] Presumably, the Northern Territory government would not have instigated legal use of kava if they had substantial concerns about its potential for hepatotoxicity.

This is supported by scientists investigating kava use within Aboriginal communities.[118] The abnormal but reversible GGT and alkaline phosphatase levels seen there in heavy kava drinkers does not appear to reflect a hepatotoxic process. Recommendations include monitoring of potential adverse effects of kava use in Aboriginal communities and Pacific countries, in addition to initiatives encouraging moderation in consumption. These field researchers working in the Northern Territory have suggested that the lack of hepatotoxicity observed there could be due to the fact that Western herbal products often involve different methods of extraction to those used traditionally (and in the Aboriginal communities).

EFFICACY OF KAVA

Recent Clinical Trials and Reviews

Standardised kava extract was significantly superior to placebo in the treatment of anxiety disorders of nonpsychotic origin in a randomised, double-blind trial lasting 5 weeks and involving 40 patients who had previously been treated with benzodiazepines. During the first treatment week, the dosage of kava extract was increased from 50 to 300 mg/day in the test group. Pretreatment with benzodiazepines was tapered off over 2 weeks. These dosage adjustments were followed by 3 weeks of treatment with kava extract or placebo. The authors concluded that further symptom reduction was shown after the change-over from benzodiazepine treatment. Kava extract was well tolerated.[163]

In an open, observational, multicentre study involving 52 outpatients suffering from anxiety of nonpsychotic origin, 81% of patients rated the treatment as "very good" or "good" on a global improvement scale. Symptoms of anxiety, restlessness, and tension showed a pronounced decrease from baseline on a physician-rated scale. Patients received 200 to 600 mg of standardised kava extract per day (corresponding to 100 to 300 mg/day of kava lactones) for a mean treatment duration of 51 days. Adverse events were rare and mild.[164]

Fifty-four healthy volunteers underwent a standardised mental stress task and were then randomised to treatment with either kava extract (120 mg/day) or valerian extract (120 mg/day) or to a nonplacebo control group. After 1 week they repeated the task. The kava and valerian groups reported feeling under less pressure and their systolic blood pressure (BP) was significantly reduced compared to results a week earlier. Heart rate (HR) was reduced in the valerian group but not the kava group, and diastolic BP did not change in either group. There were no significant differences in BP, HR, or subjective reports of pressure in the control group.[165]

A meta-analysis[166] assessing seven randomised, double-blind, placebo-controlled trials found that kava extract significantly reduced anxiety (compared to placebo). The dosage of standardised kava extract prescribed varied and contained 60 to 240 mg/day of kava lactones. The duration of treatment ranged from 1 to 24 weeks. One trial[167] investigated the reduction in anxiety for preoperative patients who received kava extract the night before and 1 hour prior to surgery. This meta-analysis has also been published by the Cochrane Collaboration in 2002.[168] The authors of one of the trials[169] included in the meta-analysis concluded that the efficacy and tolerability of standardised kava extract recommend it as an alternative to tricyclic antidepressants and benzodiazepines for the treatment of anxiety.

Kava has also been shown to have therapeutic benefit in cases of situational anxiety. In a

randomised, double-blind, placebo-controlled trial, standardised kava extract taken for 1 week significantly reduced anxiety compared to placebo in patients awaiting the results of medical diagnostic tests for suspected breast carcinoma. Fatigue, introverted behaviour, excitability, and depression were decreased and alertness was increased in patients receiving kava extract. The administered daily dose of kava contained 150 mg of kava lactones and corresponded to approximately 2.5 g of dried root.[170]

Preliminary findings suggest a beneficial effect of kava on baroreflex control of heart rate (BRC). Significantly more patients with generalised anxiety disorder exhibited improved BRC following treatment with kava compared to a placebo. There was no effect on respiratory sinus arrhythmia, a measure of the heart rate changes occurring with respiration. Patients in the study were a subgroup of a larger randomised, double-blind trial and received standardised kava extract or placebo for 4 weeks.[171]

In a pilot study, patients suffering from stress-induced insomnia were treated in each phase for 6 weeks with kava, then valerian, then a combination of kava and valerian, with washout periods between each treatment phase of 2 weeks. Total stress severity was significantly relieved by the kava and valerian single treatments (stress was measured in three areas: social, personal, and life events). Insomnia was significantly relieved by the combination of kava and valerian.[172]

Kava plus hormone replacement therapy significantly reduced menopausal anxiety compared to hormone replacement therapy alone in a controlled trial.[173]

Earlier Studies

The following information is an excerpt from *Principles and Practice of Phytotherapy: Modern Herbal Medicine* which reviewed the clinical trial information available on kava to 1998.[174]

Anxiety

Earlier trials used purified kavain at a dose of 400 mg/day. In a placebo-controlled, double-blind study of 84 patients with anxiety symptoms, kavain improved vigilance, memory, and reaction time.[175] In comparison with an antianxiety drug (oxazepam) in a placebo-controlled, double-blind trial of 38 patients with anxiety associated with neurotic disturbances, kavain demonstrated equivalent activity.[176] The substances proved to be equivalent in the nature and the potency of their anxiolytic action. Both treatments caused progressive improvement in two different anxiety scores over a 4-week period.

In a randomised, placebo-controlled double-blind study of 58 patients with anxiety not caused by psychotic disorders, a standardised kava extract significantly improved measures of anxiety and depression.[177,178] Patients received standardised kava extract (300 mg/day, containing 210 mg kava lactones) or placebo over a 4-week period. For patients receiving the kava extract, there was a significant reduction of anxiety, as measured by the Hamilton anxiety rating scale (HAM-A) (total score, $P < 0.02$). The difference in anxiety between kava and placebo began in the first week and increased during the course of treatment. No adverse effects were reported for the kava extract.

A standardised extract of kava was compared to the benzodiazepine drugs bromazepam and oxazepam in a randomised, controlled, double-blind study. One hundred and seventy-six outpatients were divided into three approximately equal groups. One group received kava extract equivalent to 210 mg of kava lactones per day, the second group received 15 mg of oxazepam per day and the third group received 9 mg of bromazepam. The total HAM-A score was reduced from 27.3 to 15.6 after 6 weeks of kava treatment, compared to 27.3 down to 13.4 for bromazepam and 27.7 down to 16.6 for oxazepam. Statistical analysis showed that kava treatment was equivalent to the benzodiazepine drugs. Side effects were higher in the conventional drug groups.[179]

Although there have been positive outcomes for the use of kava demonstrated in the above controlled trials, none of the trials lasted for more than 6 weeks, the inclusion criteria were insufficiently defined, and patient numbers were relatively small. These issues

were addressed in a subsequent study. In a randomised, placebo-controlled, double-blind, multicentre study, 100 patients presenting with nervous anxiety, tension, and restlessness of nonpsychotic origin (DSM-III-R) were followed over a period of 6 months. Patients were randomised to receive either 300 mg/day of a concentrated kava extract containing 210 mg of kava lactones (equivalent to about 4 g of dried root) or placebo. Assessment was based on changes in the cumulative HAM-A score in addition to other assessments. Comparison of the pre- and post-therapy HAM-A scores revealed a significant ($P = 0.0015$) superiority of the kava treatment as against placebo. The difference between the two treatment grqups was even apparent at 8 weeks ($P = 0.055$). Kava treatment led to a marked reduction in the symptoms of anxiety, together with its physical and psychic manifestations. In addition, the accompanying depressive component was positively influenced by kava. During the study, six adverse events in five patients were reported in the kava group. Four of these were rated by the investigator as not being related to the treatment, two (in both cases stomach upset) were rated as "possibly related". Fifteen adverse events from nine patients were reported in the placebo group. Seven patients dropped out under placebo and three under kava (two of these three were due to improvement of symptoms). There was no significant change in biochemical parameters during the study period and the overall tolerability of kava was rated as excellent. The authors concluded that their results support kava as a treatment alternative to tricyclic antidepressants and benzodiazepines in anxiety, with proven long-term efficacy and none of the tolerance problems associated with these drugs.[169,180]

Other Conditions

Past and recent clinical trials indicate kava extract and kava pyrones (especially dihydromethysticin) are not suitable for the treatment of epilepsy. Although effective in grand mal seizures, the trials were abandoned due to incidence of side effects (mainly skin problems) when used long term and in high doses. No efficacy was observed with petit mal.[181,182]

In a randomised, placebo-controlled, double-blind trial of 40 patients with neurovegetative symptoms associated with menopause, standardised kava extract (210 mg kava lactones per day for 8 weeks) produced a significant reduction in anxiety ($P < 0.01$), depression, severity of symptoms, and menopausal symptoms. The subjective well-being of patients improved with kava and the treatment was well tolerated.[183]

RISK–BENEFIT ANALYSIS AND THE OPINIONS OF EXPERT COMMITTEES

The Complementary Medicines Evaluation Committee (CMEC) of the Australian TGA considered the safety of kava-containing medicines on 8 and 12 August 2002. The Committee recommended to the TGA that it impose a strong warning statement on the label of all kava-containing medicines. It recommended that the warning statement indicate to consumers that kava-containing medicines:

- have been implicated in serious liver damage;
- be taken only under the supervision of a health care practitioner; and
- be used only for short periods of time, not exceeding 6 weeks.

Clearly CMEC is of the view that a risk-benefit assessment of kava indicates that it still should be available, but under more controlled conditions of use. This could involve the registration (as opposed to listing) of appropriate kava products and their sale through professional channels only.

In contrast, according to the Australian Adverse Drug Reactions Committee (ADRAC), which represents a more orthodox perspective, the risks associated with kava exceed the benefits and it should be completely withdrawn from the market in Australia.

At the meeting of the ADRAC held on 9 August 2002, the Committee considered the details of the adverse drug reaction report surrounding the death of the Australian woman after taking a number of complementary medicines, including one containing kava:

> Members considered that with exclusion of other identifiable possible causes, kava was a plausible explanation for the patient's liver failure. . . . Members considered the potential benefits of kava for the indications in which it is used (anxiety, stress, restlessness). There are other agents of proven benefit for these indications. . . . The Committee considered that with this Australian case and the overseas reports of hepatotoxicity, the risks associated with kava exceed the benefits.
>
> The Committee recommended that all manufactured products containing kava extracts be withdrawn from the market in Australia.

In a surprising move, the German Commission E, the expert committee on herbal medicines established by the German government, has published a strongly dissenting view from the BfArM.[184] It is signed by all the Commission E members (professors, scientists, and medical doctors). According to the Commission E they were taken aback by the precipitous action of the BfArM on kava and feel bypassed and that their scientific competence, and indeed role, has been questioned by this move. The members of the Commission E, all eminent experts in the field of herbal medicines, view the risk-benefit assessment for kava positively, provided certain precautions (appropriate for the German situation) are observed. One can only wonder at the motives of a government authority that appoints a committee with expertise in herbal matters and then bypasses its views and recommendations.

CONCLUSIONS AND RECOMMENDATIONS

It appears likely that certain types of kava products have the potential to cause a rare immune-mediated liver damage with an extremely low frequency of occurrence. The type of reaction that occurs appears to be typical of drug-induced liver damage, a phenomenon that can occur after the intake of many of the prescription and OTC drugs commonly available throughout the world. However, the frequency of hepatotoxicity for kava is, on current information, substantially lower than for these conventional drugs.

On the basis of the current information it can not be confirmed that all preparations of kava involving all types of raw materials will cause this hepatotoxic reaction. Probable cases, based on our assessment, have only been confirmed for the acetone extracts commonly used in Germany and Switzerland, with the exception of one case report (#5) from the intake of an ethanol-based extract, a case where the patient was shown to have an unusual metabolic enzyme pattern and at the same time developed an immunological reaction to kava intake (allergy). The absence of reported cases of hepatotoxicity in the Pacific Islands adds weight to this assertion.

The issue with kava raises a fundamental question for the regulation of herbal products. It is important that any outcomes for kava are credible to all stakeholders in this situation: regulators, industry, practitioners, and patients/customers. The question is: At what level of risk should a herbal product be completely restricted from use? It is quite likely that other popular herbs will be found to cause a low frequency of hepatotoxicity. Will they then be banned from use? Supplementary to this is the question: Can a mechanism be found to maintain the availability of kava which mitigates against the (low level) risk associated with its use?

If kava is made unavailable, then it is quite likely that, with modern communications, patients/consumers will source it for themselves through the Internet or via legal loopholes. This problem has already developed in Germany, where kava was totally banned.[185] So in the modern situation "banning" may in fact involve deregulation, not regulation of kava use.

As a way forward, it is recommended that kava products should carry warnings similar to those already recommended by the Australian CMEC in August 2002.

Also, kava is one of a growing number of herbal products which are probably best made available only on professional advice. That way its safe use can be monitored closely. It is suggested that companies selling kava through

mass market and health food stores should reconsider this mode of distribution.

Finally, the issue of product liability insurance needs to be mentioned. Liability insurance is becoming more difficult to obtain in the dietary supplements area and many companies have already withdrawn kava from the U.S. market because of high insurance premiums or exclusion clauses listing kava (along with asbestos and thalidomide). The irony of this debate is that the insurance companies may have the final word on the risk-benefit assessment.

REFERENCES

In the references listed below Review 1 refers to the constantly updated document: Schmidt M: Is kava really hepatotoxic? An analysis of the known data on adverse effects of kava preparations on the liver, version 30/4/2003. Downloaded from www.uni-muenster.de/Chemie/PB/Kava/analyse.htm

1. Medicines Control Agency Assessment Report: *Kava-kava* (Piper methysticum) *and hepatotoxicity,* July 2002.
2. Loew D, Gaus W: Kava-kava: Tragedy of a wrong decision [in German], *Z Phytother* 23:267-281, 2002.
3. Waller DP: *Report on kava and liver damage,* February 15, 2002.
4. Medicines Control Agency: *Risk-benefit analysis of Kava-kava*, February 12, 2002.
5. Review 1, Section 3.19
6. Review 1, Section 4.19
7. Olsson R: Liver damage due to antihypertensive drugs, *Acta Med Scand Suppl* 628:53-56, 1979.
8. E-MIMS. Version 4.00.0457. Havas MediMedia International, 2000.[electronic version]
9. Review 1, Section 3.3
10. Strahl S, Ehret V, Dahm HH, et al: Necrotizing hepatitis after taking herbal remedies [in German], *Dtsch Med Wschr* 123:1410-1414, 1998.
11. Review 1, Section 7.1
12. Review 1, Section 9.2
13. Russmann S, Lauterburg BH, Helbling A: Kava hepatotoxicity, *Ann Intern Med* 135:68-69, 2001.
14. Pollock BG, Mulsant BH, Sweet RA, et al: Prospective cytochrome P450 phenotyping for neuroleptic treatment in dementia, *Psychopharmacol Bull* 31:327-331, 1995.
15. Kraft M, Spahn TW, Menzel J, et al: Fulminant liver failure after administration of the herbal antidepressant Kava-Kava [in German], *Dtsch Med Wschr* 126:970-972, 2001.
16. Review 1, Section 4.20
17. Bellaiche G, Lamouri N, Slama JL, et al: Cytolytic hepatic lesion associated with the ingestion of piretanide [in French], *Gastroenterol Clin Biol* 19:444-445, 1995.
18. Review 1, Section 4.8
19. Stoller R: Liver damage with kava extracts [in German], *Schweiz Arztezeit* 81:1335-1336, 2000.
20. Review 1, Section 8.1
21. Russmann S, Escher M, Stoller R, et al: Hepatotoxicity of Kava Kava (*Piper methysticum*) containing herbal drugs. Recent cases in Switzerland and investigations regarding the mechanism, *J Exp Klin Pharmakol Toxicol* 363:S40, 2001.
22. Review 1, Section 4.9
23. Escher M, Desmeules J, Giostra E, et al: Hepatitis associated with Kava, a herbal remedy for anxiety, *BMJ* 322:139, 2001.
24. Review 1, Section 4.1
25. Review 1, Section 6.1
26. Review 1, Section 4.2
27. Review 1, Section 5.1
28. Review 1, Section 3.4
29. Review 1, Section 3.1
30. Review 1, Section 6.3
31. Review 1, Section 4.10
32. Review 1, Section 9.4
33. Review 1, Section 6.2
34. Review 1, Section 4.3
35. Personal communication from the manufacturer of Kavain Harras Plus, October 22, 2002.
36. Pennings EJ, Konijn KZ, de Wolff FA: Clinical and toxicologic aspects of the use of Ecstasy [in Dutch], *Ned Tijdschr Geneeskd* 142:1942-1946, 1998.
37. Review 1, Section 4.4
38. Saß M, Schnabel S, Kröger J, Liebe S, et al: Acute liver failure from kava-kava – a rare indication for liver transplant [in German], *Z Gastroenterol* 39:491, 2000.
39. Review 1, Section 4.5
40. Brauer R-B, Pfab R, Becker K, et al: Fulminant liver failure after ingestion of the herbal medicine kava-kava [in German], *Z Gastroenterol* 39:491, 2000.
41. Review 1, Section 5.3
42. Hinzpeter W: Attack on the liver [in German], *Stern* May 29:23, 2002.
43. Review 1, Section 6.4
44. Review 1, Section 6.5
45. Review 1, Section 3.2
46. Review 1, Section 4.6
47. Review 1, Section 2.3
48. Review 1, Section 4.7
49. Review 1, Section 6.6
50. Review 1, Section 6.12
51. Review 1, Section 4.11
52. Review 1, Section 6.7
53. Review 1, Section 4.12
54. Review 1, Section 6.8
55. Review 1, Section 3.20
56. Review 1, Section 6.9
57. Review 1, Section 4.13
58. Review 1, Section 6.17
59. Review 1, Section 4.14
60. Review 1, Section 6.31
61. Review 1, Section 6.11
62. Review 1, Section 4.15

63. Review 1, Section 9.3
64. Review 1, Section 3.5
65. Review 1, Section 6.13
66. Review 1, Section 6.14
67. Review 1, Section 6.15
68. Review 1, Section 4.17
69. Sheikh NM, Philen RM, Love LA: Chaparral-associated hepatotoxicity, *Arch Intern Med* 157:913-919, 1997.
70. Review 1, Section 3.16
71. Review 1, Section 3.8
72. Review 1, Section 4.16
73. Centers for Disease Control and Prevention: Hepatic toxicity possibly associated with kava-containing products – United States, Germany and Switzerland, 1999-2002, *MMWR* 51:1065-1067, 2002. Available online: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5147a1.htm. Accessed 9 December 2002.
74. Review 1, Section 3.10
75. Review 1, Section 5.4
76. Review 1, Section 3.11
77. Review 1, Section 3.12
78. Review 1, Section 3.18
79. Review 1, Section 6.19
80. Review 1, Section 6.20
81. Review 1, Section 6.21
82. Review 1, Section 6.22
83. Review 1, Section 5.6
84. Review 1, Section 6.27
85. Review 1, Section 5.5
86. Review 1, Section 6.26
87. Review 1, Section 6.16
88. Review 1, Section 6.10
89. Humbertson CL, Akhtar J, Krenzelok EP: Acute hepatitis induced by kava kava, a herbal product derived from *Piper methysticum*, *J Toxicol* 39:549, 2001.
90. Review 1, Section 6.25
91. Stuckhard P: Poisoned liver after kava-kava [in German], *Neue Westfälische*, July 5, 2002.
92. Review 1, Section 3.6
93. Review 1, Section 6.18
94. Review 1, Section 4.18
95. Review 1, Section 3.15
96. Zarafonetis CJ, Dabich L, DeVol EB, et al: Potassium para-aminobenzoate and liver function test findings, *J Am Acad Dermatol* 15:144-149, 1986.
97. Review 1, Section 3.7
98. Review 1, Section 3.13
99. Review 1, Section 3.14
100. Review 1, Section 3.9
101. Review 1, Section 3.17
102. Therapeutic Goods Administration: *Information for sponsors: safety of kava-containing medicines. Guidance for sponsors of kava-containing medicines -August 2002*, August 28, 2002. Available online: http://www.health.gov.au:80/tga/docs/html/kavaspon.htm (accessed October 29, 2002).
103. Gow PJ, Connelly NJ, Hill RL, et al: Fatal fulminant hepatic failure induced by a natural therapy containing kava, *Med J Aust* 178:442-443, 2003.
104. Lehmann R, Penman K: Information on file, MediHerb Research Laboratory, University of Queensland, St. Lucia, Queensland 4072, Australia, 2002.
105. Schmidt M, Thomsen M: Poor quality in Australian kava product made responsible for hepatotoxicity: two out of three components not detectable on analysis, In-house report redinomedica AG, Munich, Germany, manuscript for publication in preparation.
106. Cerulli J, Grabe DW, Gauthier I, et al: Chromium picolinate toxicity, *Ann Pharmacother* 32:428-431, 1998.
107. Lanca S, Alves A, Vieira AI, et al: Chromium-induced toxic hepatitis, *Eur J Intern Med* 13:518-520, 2002.
108. Edwards IR, Aronson JK: Adverse drug reactions: definitions, diagnosis, and management, *Lancet* 356: 1255-1259, 2000.
109. Review 1, Introduction section "Some background data—different evaluation"
110. Traditional Medicines Evaluation Committee: Response to concerns about *Piper methysticum* Forst. f., Kava, submission date January 11, 2002.
111. Lehmann R, Penman K: Private communication, MediHerb Pty Ltd, PO Box 713, Warwick Qld 4370, Australia.
112. Whiting PW, Clouston A, Kerlin P: Black cohosh and other herbal remedies associated with acute hepatitis, *Med J Aust* 177:432-435, 2002.
113. Sorrentino L: Toxicology Report/Kavapyron Complex (Kavasedon), Department of Experimental Pharmacology, University of Neapel, In-house report *Harras Pharma*, 1990.
114. Gebhardt R: Studies of the hepatotoxicity of Kava semi liquid extract in cultivated liver cells [in German], Internal report, *Harras Pharma Curarina*, 2001.
115. Mathews JD, Reiley MD, Fejo L, et al: Effects of the heavy usage of kava on physical health: summary of a pilot survey in an Aboriginal community, *Med J Aust* 148:548-555. 1988.
116. d'Abbs P, Burns C: Draft report on inquiry into the issue of kava regulation [prepared for the Sessional Committee on the Use and Abuse of Alcohol by the Community], Menzies School of Health Research, Darwin, September 1997.
117. Barguil Y: Kava and gamma-glutamyltransferase increase: hepatic enzymatic induction or liver function alteration. Electronic letter published http:/bmj.com March 21, 2001 in response to Escher M, Desmeules J, Giostra E, et al: Drug points: Hepatitis associated with kava, a herbal remedy for anxiety, *BMJ* 322:139, 2001.
118. Currie BJ, Clough AR: Kava hepatotoxicity with Western herbal products: does it occur with traditional kava use? *Med J Aust* 178:421-422, 2003.
119. Gruenwald J, Freder J: Kava – the present European situation, *Nutraceuticals World* Jan/Feb:22-24, 2002:
120. Schmidt M, Nahrstedt A: Is kava liver toxic? An analysis of the known facts regarding the liver risk of kava products [in German], *Dtsch Apoth Ztg* 142:1006-1011, 2002.
121. Schulze J, Meng G, Siegers CP: Safety assessment of kavalactone-containing herbal drugs in comparison to other psychotropics. Poster presentation, Annual Meeting of Swiss Society of Pharmacology, September 2001.

122. No authors listed. Adverse effects from kava-kava [in German], *Z Phytother* 21:188, 2000.
123. Noyes R, DuPont RL, Pecknold JC, et al: Alprazolam in panic disorder and agaraphobia: results from a multicenter trial. II. Patient acceptance, side effects and safety, *Arch Gen Psychiatry* 45:423-428, 1988.
124. Selim K, Kaplowitz N: Hepatotoxicity of psychotropic drugs, *Hepatology* 29:1347-1351, 1999.
125. Hollister L: Allergy to chlorpromazine manifested by jaundice, *Am J Med* 23:870-878, 1957. Cited in Selim K, Kaplowitz N: Hepatotoxicity of psychotropic drugs, *Hepatology* 29:1347-1351, 1999.
126. Zimmerman HJ: Update of hepatotoxicity due to classes of drugs in common clinical use: non-steroidal drugs, anti-inflammatory drugs, antibiotics, antihypertensives, and cardiac and psychotropic agents, *Semin Liver Dis* 10:322-338, 1990. Cited in Selim K, Kaplowitz N: Hepatotoxicity of psychotropic drugs, *Hepatology* 29:1347-1351, 1999.
127. Ishak KG, Irey NS: Hepatic injury associated with the phenothiazines, *Arch Pathol* 93:283-304, 1972. Cited in Selim K, Kaplowitz N: Hepatotoxicity of psychotropic drugs, *Hepatology* 29:1347-1351, 1999.
128. Derby L, Gutthann SP, Jick H, et al: Liver disorders in patients receiving chlorpromazine and isoniazid, *Pharmacotherapy* 13:354-358, 1993. Cited in Selim K, Kaplowitz N: Hepatotoxicity of psychotropic drugs, *Hepatology* 29(5):1347-1351, 1999.
129. Hummer M, Kurz M, Kurzthaler I, et al: Hepatotoxicity of clozapine, *J Clin Psychopharmacol* 17:314-317, 1997.
130. Rosenblum LE, Korn RJ, Zimmerman H: Hepatocellular jaundice as a complication of iproniazid therapy, *Arch Intern Med* 105:115-125, 1960. Cited in Selim K, Kaplowitz N: Hepatotoxicity of psychotropic drugs, *Hepatology* 29:1347-1351, 1999.
131. Aranda-Michel J, Koehler A, Bejarano B, et al: Nefazodone-induced liver failure: report of three cases, *Ann Intern Med* 130:285-288, 1999.
132. Carson JL, Strom BL, Duff A, et al: Safety of nonsteroidal anti-inflammatory drugs with respect to acute liver disease, *Arch Intern Med* 153:1331-1336, 1993.
133. Boelsterli UA, Zimmerman HJ, Kretz-Rommel A: Idiosyncratic liver toxicity of nonsteroidal antiinflammatory drugs: molecular mechanisms and pathology, *CRC Crit Rev Toxicol* 25:207-235, 1995.
134. Zimmerman HJ: Acetominophen poisoning and NSAID toxicity, Presented at the American Association for the Study of Liver Diseases Postgraduate Course, Chicago Illinois, November 7, 1997: Cited in Tolman KG: Hepatotoxicity of non-narcotic analgesics, *Am J Med* 105:13S-19S, 1998.
135. Andrejak M, Davion T, Gineston JL, et al: Cross hepatotoxicity between non-steroidal anti-inflammatory drugs, *BMJ* 295:180-181, 1987. Cited in Boelsterli UA, Zimmerman HJ, Kretz-Rommel A: Idiosyncratic liver toxicity of nonsteroidal antiinflammatory drugs: molecular mechanisms and pathology, *CRC Crit Rev Toxicol* 25:207-235, 1995.
136. Tolman KG: Hepatotoxicity of non-narcotic analgesics, *Am J Med* 105(1B):13S-19S, 1998.
137. Banks T, Zimmerman HJ, Harter J, et al: Diclofenac-associated hepatic injury analysis of 181 cases, *Hepatology* (in press). Cited in Boelsterli UA, Zimmerman HJ, Kretz-Rommel A: Idiosyncratic liver toxicity of nonsteroidal antiinflammatory drugs: molecular mechanisms and pathology, *CRC Crit Rev Toxicol* 25:207-235, 1995.
138. Jick H, Derby LE, Rodriguez LAG, et al: Liver disease associated with diclofenac, naproxen, and piroxicam, *Pharmacotherapy* 12:207, 1992. Cited in Boelsterli UA, Zimmerman HJ, Kretz-Rommel A: Idiosyncratic liver toxicity of nonsteroidal antiinflammatory drugs: molecular mechanisms and pathology, *CRC Crit Rev Toxicol* 25:207-235, 1995.
139. Kuzell WC, Schaffarzick RW, Naugler WE: Phenylbutazone, further clinical evaluation, *Arch Intern Med* 92:603, 1953. Cited in Boelsterli UA, Zimmerman HJ, Kretz-Rommel A: Idiosyncratic liver toxicity of nonsteroidal antiinflammatory drugs: molecular mechanisms and pathology, *CRC Crit Rev Toxicol* 25:207-235, 1995.
140. Brogden RN, Heel RC, Speight TM, et al: Piroxicam. A reappraisal of its pharmacology and therapeutic efficacy, *Drugs* 28:292, 1984. Cited in Boelsterli UA, Zimmerman HJ, Kretz-Rommel A: Idiosyncratic liver toxicity of nonsteroidal antiinflammatory drugs: molecular mechanisms and pathology, *CRC Crit Rev Toxicol* 25:207-235, 1995.
141. Thompson M, Stephenson P, Percy JS: Ibufenac in the treatment of arthritis, *Ann Rheumat Dis* 23:397, 1964. Cited in Boelsterli UA, Zimmerman HJ, Kretz-Rommel A: Idiosyncratic liver toxicity of nonsteroidal antiinflammatory drugs: molecular mechanisms and pathology, *CRC Crit Rev Toxicol* 25:207-235, 1995.
142. Hart FD, Boardman PL: Ibufenac (4-isobutylphenyl acetic acid), *Ann Rheumat Dis* 24: 61, 1965. Cited in Boelsterli UA, Zimmerman HJ, Kretz-Rommel A: Idiosyncratic liver toxicity of nonsteroidal antiinflammatory drugs: molecular mechanisms and pathology, *CRC Crit Rev Toxicol* 25:207-235, 1995.
143. PhRMA/FDA/AASLD drug-induced hepatotoxicity white paper postmarketing considerations, November 2000.
144. Beard K, Belic L, Aselton P, et al: Outpatient drug-induced parenchymal liver disease requiring hospitalization, *J Clin Pharmacol* 26:633-637, 1986.
145. Walker AM, Cavanaugh RJ: The occurrence of new hepatic disorders in a defined population, *Post Marketing Surveillance* 1:107-117, 1992. Cited in PhRMA/FDA/AASLD drug-induced hepatotoxicity white paper postmarketing considerations, November 2000.
146. Duh MS, Walker AM, Kronlund KH: Descriptive epidemiology of acute liver enzyme abnormalities in the general population of central Massachusetts, *Pharmacoepidemiol Drug Saf* 8:275-283, 1999. Cited in PhRMA/FDA/AASLD drug-induced hepatotoxicity white paper postmarketing considerations, November 2000.

147. Watkins PB, Zimmerman HJ, Knapp MJ, et al: Hepatotoxic effects of tacrine administration in patients with Alzheimer's disease, *JAMA* 271:992-998, 1994.
148. Bailey CJ: The rise and fall of troglitazone, *Diabet Med* 17:414, 2000. Cited in O'Moore-Sullivan TM, Prins JB: Thiazolidinediones and type 2 diabetes: new drugs for an old disease, *Med J Aust* 176:381-386, 2002.
149. Lumpkin MM cited in O'Moore-Sullivan TM, Prins JB: Thiazolidinediones and type 2 diabetes: new drugs for an old disease, *Med J Aust* 176:381-386, 2002.
150. Gitlin N, Julie NL, Spurr CL, et al: Two cases of severe clinical and histologic hepatotoxicity associated with troglitazone, *Ann Intern Med* 129:36-38, 1998. Cited in Lee WM: Assessment causality in drug-induced liver injury, *J Hepatol* 33:1003-1005, 2000.
151. Neuschwander-Tetri BA, Isley WL, Oki JC, et al: Troglitazone-induced hepatic failure leading to liver transplantation. A case report, *Ann Intern Med* 129(1):38-41, 1998. Cited in Lee WM: Assessment causality in drug-induced liver injury, *J Hepatol* 33:1003-1005, 2000.
152. Geller LI, Bessonova GA, Griaznova MW: The effect of cimetidine and gastrozepin on liver function and the pharmacotherapy of "hepatogenous" gastroduodenal ulcers and erosions [in Russian], *Ter Arkh* 63:78-81, 1991.
153. Dragull K, Yoshida WY, Tang CS: Piperidine alkaloids from *Piper methysticum*, *Phytochem* 63:193-198, 2003.
154. Ono M, Chen S: Kava liver toxicity: possible causes and possible cures, 'Awa in 2002 a research update, University of Hawaii, Komohana Building, Hilo, 17 August 2002.
155. Obermeyer WR, Musser SM, Betz JM, et al: Chemical studies of phyto-oestrogens and related compounds in dietary supplements: flax and chaparral, *Proc Soc Exp Biol Med* 208:6-12, 1995.
156. Lebot V, Merlin M, Lindstrom L: *Kava—the Pacific elixir: the definitive guide to its ethnobotany, history and chemistry*, Yale University Press, 1992, New Haven.
157. Personal communication from Vincent Lebot, October 15, 2002.
158. Singh YN, Singh NN: Therapeutic potential of kava in the treatment of anxiety disorders, *CNS Drugs* 16:731-743, 2002.
159. Steiner GG: The correlation between cancer incidence and kava consumption, *Hawaii Med J* 59:420-422, 2000.
160. Personal communication from Graham Pinn, June 15, 2002.
161. Personal communication from Dr. Fiona McLean, October 15, 2002.
162. Northern Territory Treasury: Racing, Gaming and Licensing: Kava. Available online: http://www.nt.gov.au/ntt/licensing/kava/kava.htm (accessed October 29, 2002).
163. Malsch U, Kieser M: Efficacy of kava-kava in the treatment of non-psychotic anxiety, following pretreatment with benzodiazepines, *Psychopharmacology (Berl)* 157:277-283, 2001.
164. Scherer J: Kava-kava extract in anxiety disorders: An outpatient observational study, *Adv Ther* 15:261-269, 1998.
165. Cropley M, Cave Z, Ellis J, et al: Effect of kava and valerian on human physiological and psychological responses to mental stress assessed under laboratory conditions, *Phytother Res* 16:23-27, 2002.
166. Pittler MH, Ernst E: Efficacy of kava extract for treating anxiety: systematic review and meta-analysis, *J Clin Psychopharmacol* 20:84-89, 2000.
167. Mittmann U, Schmidt M, Vrastyakova J: Acute anxiolytic efficacy of kava semiliquid special extract and benzodiapenines as premedication in surgical interventions [in German], *J Pharmakol Ther* 9:99-108, 2000.
168. Pittler MH, Ernst E: Kava extract for treating anxiety, *Cochrane Database Syst Rev* 2:CD003383, 2002.
169. Volz HP, Kieser M: Kava-kava extract WS 1490 versus placebo in anxiety disorders – A randomized placebo-controlled 25-week outpatient trial, *Pharmacopsychiatry* 30:1-5, 1997.
170. Neuhaus W, Ghaemi Y, Schmidt T, et al: Treatment of perioperative anxiety in suspected breast carcinoma with a phytogenic tranquilizer [in German], *Zentralbl Gynakol* 122:561-565, 2000.
171. Watkins LL, Connor KM, Davidson JRT: Effect of kava extract on vagal cardiac control in generalized anxiety disorder: preliminary findings, *J Psychopharmacol* 15:283-286, 2001.
172. Wheatley D: Stress-induced insomnia treated with kava and valerian: singly and in combination, *Human Psychopharmacol* 16:353-356, 2001.
173. De Leo V, la Marca A, Morgante G, et al: Evaluation of combining kava extract with hormone replacement therapy in the treatment of postmenopausal anxiety, *Maturitas* 39:185-188, 2001.
174. Mills S, Bone K: *Principles and practice of phytotherapy: Modern herbal medicine*, Churchill Livingstone, Edinburgh, 2000, pp 460-462.
175. Scholing WE, Clausen HD: On the effect of d,l-kavain: experience with neuronika [in German], *Med Klin* 72:1301-1306, 1977.
176. Lindenberg D, Pitule-Schoedel H: D,L-kavain in comparison with oxazepam in anxiety disorders. A double-blind study of clinical effectiveness [in German], *Fortschr Med* 108:49-50, 53-54, 1990.
177. Kinzler E, Kromer J, Lehmann E: Effect of a special kava extract in patients with anxiety-, tension-, and excitation states of non-psychotic genesis. Double blind study with placebos over 4 weeks [in German], *Arzneim-Forsch* 41:584-588, 1991.
178. Lehmann E, Kinzler E, Friedemann J: Efficacy of a special Kava extract (*Piper methysticum*) in patients with states of anxiety, tension and excitedness of non-mental origin -A double-blind placebo-controlled study of four weeks treatment, *Phytomedicine* 3:113-119, 1996.
179. Woelk H, Kapoula O, Lehrl S, et al: A comparison of kava special extract WS 1490 and benzodiazepines in patients with anxiety [in German], *Z Allg Med* 69:271-277, 1993.
180. Volz HP: A randomized double-blind study on the anxiolytic effects of kava special extract WS 1490 in longterm

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181. Kret
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182. Haer
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therapeutic use [in German], 6th Phytotherapy Conference, Berlin, October 5-7, 1995.

181. Kretzschmar R: Pharmacological examinations of the central nervous effects and the mechanism of action of kava (*Piper methysticum*) and its crystalline active substances [in German]. In Loew D, Rietbrock N (eds): *Herbal medicines in research and clinical application*, Steinkopff (Verlag), Darmstadt, 1995, pp 29-38.
182. Haensel R: Kava-kava (*Piper methysticum* G. Forster) in modern drug research: Portrait of a medicinal plant [in German], *Z Phytother* 17:180-195, 1996.
183. Warnecke G: Psychosomatic dysfunctions in the female climacteric. Clinical effectiveness and tolerance of Kava Extract WS 1490 [in German], *Fortschr Med* 109:119-122, 1991.
184. German Commission E: Kava-Kava: Declaration of the commission E [in German], *Z Phytother* 4:158, 2002.
185. Stafford N: Germans warned against kava products on Internet, Reuters Press Release, October 24, 2002.
186. Personal communication from M. Schmidt, August 2003.

Appendix 1 Abbreviations Used in Chapter 12

ACE	Angiotensin-converting enzyme
AdM	Agence du Médicament = French Medicines Agency
ADRAC	Adverse Drug Reactions Advisory Committee (TGA, Australia)
AFSSAPS	L'Agence française de sécurité sanitaire des produits de santé = French Health Products Safety Agency
AHPA	American Herbal Products Association
ARMS	Adverse Reaction Monitoring System of the FDA
BAH	Bundesverband der Arzneimittel-Hersteller e.V. = German Drug Manufacturer's Association
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte = German Federal Institute for Drugs and Medical Devices
BPI	Bundesverband der Pharmazeutischen Industrie e.V. = German Pharmaceutical Industry Assocn
CDC	Centers for Disease Control and Prevention (U.S.)
CIOMS	Council for International Organizations of Medical Sciences (WHO/UNESCO)
CMEC	Complementary Medicines Evaluation Committee (TGA, Australia)
CMV	Cytomegalovirus
COX-2	Cyclooxygenase-2
CSM	Committee on Safety of Medicines (U.K., part of MCA)
EBV	Epstein-Barr virus
EHPA	European Herbal Practitioners Association
EMEA	European Agency for the Evaluation of Medicinal Products
FDA	Food and Drug Administration (U.S.)
FSA	Food Safety Agency (U.K.)
GGT	Gamma-glutamyl transpeptidase
GOT	Glutamic-oxaloacetic transaminase (Also known as asparate aminotransferase [AST])
GP	General practitioner (medical doctor practising general medicine)
GPT	Glutamic-pyruvic transaminase (also known as alanine aminotransferase [ALT])
HAM-A	Hamilton anxiety rating scale
HPLC	High performance liquid chromatography
HSV	Herpes simplex virus
IKS	Interkantonale Kontrollstelle der Schweiz = Intercantonal Office for the Control of Medicines (Switzerland). Renamed Swissmedic in 2002
IMB	Irish Medicines Board
LFTs	Liver function tests
MCA	Medicines Control Agency (of U.K.)
MSM	Methylsulphonylmethane
NSAID	Nonsteroidal antiinflammatory drug
OICM	Office intercantonal de contrôle des médicaments

Appendix 1 Abbreviations Used in Chapter 12—Cont'd

PhVWP	Pharmacovigilance Working Party (of the EMEA, Europe)
RDA	Recommended dietary allowance
SADRAC	Swedish Adverse Drug Reaction Advisory Council
SSRI	Selective serotonin reuptake inhibitor
Swissmedic	Swiss Agency for Therapeutic Products (formerly IKS)
TGA	Therapeutic Goods Administration (Australia)
TLC	Thin layer chromatography
TMEC	Traditional Medicines Evaluation Committee (of the EHPA)

Appendix 2 Data Relating to Case Reports of Suspected Hepatotoxicity Associated with Kava from Germany, Switzerland, the United States, Canada, France, and Australia

NOTE: The information presented here is the officially distributed data as supplied, which is not necessarily complete or correct. Errors in this table are corrected in the discussion of these cases in the body of this article

#	Where reported	MCA #	Other case #	Age	Sex	Suspect product	Concomitant medication	Onset of reaction	Nature of reaction	Outcome	Further relevant information
1	UK	1	MCA Case Report; EMEA #1	40	m	Kava	None stated	3 months	Sore throat, nose bleeds, abnormal LFTs	Recovered after stopping Kava	Drinks approx. 6 bottles of wine a week
2	UK	2	MCA Case Report; EMEA #2	—	f	Kava (3 × 150 mg/day)	Prozac	2 months	Jaundice, increased LFTs	Reaction continues	Hospitalised for 7 weeks, biopsy pending
3	UK	3	MCA Case Report	48	m	Kava	Bendrofluazide	Approx. 8 years	Raised LFTs	Recovering after withdrawal of Kava	Patient stopped taking Kava due to the voluntary withdrawal, saw information on the website and after 8 years of stable, increased LFTs, the liver enzymes are returning to normal
4	Literature	4	Reported by Schwabe GmbH & Co; BfArM #93/0351; EMEA #3	68	f	3 × 70 mg/day (Laitan 100; acetone extract)			Increased liver enzymes		Hepatic problems prior to Kava treatment
5	Literature	5	Lit: Strahl et al., 1998; EMEA #4	39	f	60 mg/day?	Paroxetin, St. John's Wort PRN, hormonal ovulation inhibitors	6 months and 14 days after rechallenge	Severe hepatitis with confluent necrosis	Recovered on withdrawal of all drugs	Positive rechallenge with kava product. Hepatic side effects are described for hormonal ovulation inhibitors (been on them for 6 years)
6	Literature	6	Lit: Kraft et al., 2001; EMEA #5	60	f	Up to 480 mg/day (Antares 120 mg;	Etilefrin-HCl, Piretanid	Approx. 1 year	Fulminant liver failure	Received liver transplant	Sporadic notifications of hepatic side

6	Literature	6	Lit: Kraft et al., 2001; EMEA #5	60	f	Up to 480 mg/day (Antares 120 mg; ethanol-extract)	Etilefrin-HCl, Piretanid	Approx. 1 year	Fulminant liver failure	Received liver transplant	Sporadic notifications of hepatic side effects under Piretanid. Patient taking 4× recommended dose
7	Switz.	7	IKS #1999-2596; EMEA #6	46	f	2 × 70 mg kava lactone	Propanolol, HCT, valsartan	4.5 months	Severe liver damage with icterus	Recovered after Kava stopped	Hepatic side effects also described for concomitant medication
8	Switz.	8	IKS #2000-0014; EMEA #7	33	f	3 × 70 mg/day (Laitan 100; acetone extract)	1 × approx. 60 g alcohol	2-3 months	Cholestatic hepatitis with icterus	Recovery after 6 weeks	Lab tests confirmed drug-induced hepatic damage and ruled out alcohol-induced damage despite single episode of high alcohol intake
9	Switz.	9	IKS #2000-2330; EMEA #8	60	f	70 mg/day (Laitan; acetone extract) 3 Wochen	Celecoxib	3 weeks	Increased bilirubin and transaminases, indolent icterus	Recovery after 2 weeks	Hepatic side effects also known for concomitant medication
10	Switz.	10	IKS #2000-3502; EMEA #9	50	m	3-4 × 70 mg (Laitan; acetone extract)	Alcohol moderately, 1-2 × paracetamol, evening primrose oil	Approx. 2 months	Acute necrotizing hepatitis, irreversible liver damage	Received liver transplant	Notifications of hepatic side effects under Paracetamol exist
11	Germany	11	BfArM #90003882; EMEA #10	69	f	2 × 200 mg (Neuronika; contains synthetic Kavain)	ASS, Dehydrosanol, Rentylin		Cholestatic hepatitis	Recovered	Hepatic side effects are described for all concomitant medication

(Continued)

Appendix 2 **Data Relating to Case Reports of Suspected Hepatotoxicity Associated with Kava from Germany, Switzerland, the United States, Canada, France, and Australia—cont'd**

#	Where reported	MCA #	Other case #	Age	Sex	Suspect product	Concomitant medication	Onset of reaction	Nature of reaction	Outcome	Further relevant information
12	Germany	12	BfArM #92901203; EMEA #11	35	m	2 × 200 mg (Neuronika; contains synthetic kavain)		Prolonged period	Cholestatic hepatitis	Recovery after discontinuation of kava product	
13	Germany	13	IKS #93/0274; BfArM #93015209; EMEA #12	39	f	3 × 70 mg/day (Laitan 100; acetone extract)	Diazepam, Gravistat, L-Thyroxine	Approx. 2 months	Upper abdominal pressure, nausea, vomiting, jaundice	Recovery after discontinuation of all medication	Hepatotoxicity also known for the concomitant medication
14	Germany	14	BfArM #94006568; IKS #94/0259; EMEA #13	68	f	3 × 70 mg/day (Laitan 100; acetone extract)	Neuroplant forte, Maaloxan if required	Approx. 2 years	Cholestatic hepatitis, jaundice. Diagnosed as immunological hypersensitivity reaction resulting in idiosyncratic hepatic damage	Recovered	Recovery after 97 days; sporadic notifications of increased liver parameters under Maaloxan
15	Germany	15	BfArM #94901308; IKS#94/0117; EMEA #14	50	f	3 × 70 mg/day (Laitan 100; acetone extract)	Teldane, Atenolol, Hydrotrix	Approx. 2 months	Increased liver enzymes, liver cell impairment, acute hepatitis with icterus		Hepatic side effects also described for concomitant medication
16	Germany	16	BfArM #97002825; probable duplicate with #97003551 (not listed here); EMEA #15	72 (75)	f	Phyto-Geriatrikum (with 25 mg dry extract with ethanol)	Eunova	Approx. 6 months (2 years for duplicate)	Jaundice, cholestatic hepatitis, hepatitis, liver cell impairment		No hepatic side effects known for concomitant medication
17	Germany	17	BfArM #98004297; EMEA #16	81	f	2 × 60 mg (Kavatino;	Hct Isis 12,5, Cralonin,	Approx. 9 months	Toxic hepatitis with liver failure,	Died	Seldomly icterus under HCT, hepatic

			EMEA #15				with ethanol)			
17	Germany	17	BfArM #98004297; EMEA #16	81	f	2 × 60 mg (Kavatino; ethanol extract)	Hct Isis 12,5, Cralonin, Bayotensin (until 1/98)	Approx. 9 months	Toxic hepatitis with liver failure, acute yellow liver dystrophy	Died	Seldomly icterus under HCT, hepatic impairment by alcohol not excluded. Pathology showed that liver symptoms must have started at least 1.5 years prior to death. PMH -alcohol abuse
18	Germany	18	BfArM #99500453; EMEA #17	59	f	2 × 120 mg/day (Limbao 120)	Buscopan	Approx. 4 months	Liver cell impairment		Sporadic notifications of hepatic side effects under Buscopan, but not in SPC
19	Germany	19	BfArM #99062501; EMEA #18	37	f	2 × 70 mg/day (Laitan; acetone extract)	Microdiol since 5 years, 2 × Diclofenac im	2 months	Hepatitis	Recovered	Recovery after 3 months; hepatic side effects also known for concomitant medication. Negative rechallenge
20	Germany	20	BfArM #99003911; EMEA #19	62	f	(Kavatino; ethanol extract) 60 mg kava lactone	None denoted		Liver cell impairment	Recovered on withdrawal of all drugs	Positive rechallenge with kava product
21	Germany	21	BfArM #99006005; EMEA #20	33	f	(Kavatino; ethanol extract) 60 mg kava lactone	Cisapride	Approx. 4 months	Bilirubinaemia, hepatitis, increased liver enzymes, cirrhosis of the liver		Hepatic side effects also described for concomitant medication

(*Continued*)

Appendix 2 **Data Relating to Case Reports of Suspected Hepatotoxicity Associated with Kava from Germany, Switzerland, the United States, Canada, France, and Australia—cont'd**

#	Where reported	MCA #	Other case #	Age	Sex	Suspect product	Concomitant medication	Onset of reaction	Nature of reaction	Outcome	Further relevant information
22	Germany	22	BfArM #00003608; EMEA #21	21	f	8-10 × 50 mg (Kavain Harras plus)	Paspertin, Pantoprazol, Paracetamol, Basilikum-Tropfen	Approx. 6 months	Increased liver enzymes, jaundice, hepatitis		Patient was taking an excessive dose "overdose". Side effects also known for concomitant medication
23	Germany	23	BfArM #00005994; Lit: Sass et al. 2001; EMEA #22	50	f	60 mg/day (Kava-ratiopharm; ethanol extract)	Amaryl, Glucophage S, Gravistat followed by Klimonorm	Approx. 7 months	Fulminant liver failure	Received liver transplant	Hepatic side effects also known for concomitant medication
24	Germany	24	BfArM #00008627; Lit: Brauer et al. 2001; EMEA #23	22	f	2 × 120 mg (Antares; ethanol extract)	Maxalat if required, Pramino (beforehand Valette)	Approx. 3 months	Necrosis, complete destruction of the parenchyma, fulminant liver failure	Received liver transplant. Died	Hepatic side effects also known for Pramino
25	Germany	25	BfArM #01003089; EMEA #24	34	f	120 mg/day (Kava-ratiopharm; dry extract with ethanol)	Jodthyrox	Approx. 3 months	Hepatitis, increased liver enzymes	Recovery after discontinuation of the Kava medication	Sporadic notifications of hepatic side effects under Jodthrox
26	Germany	26	BfArM #01004110, EMEA #25; duplicate case #99006200, EMEA #27 (#28)	34	f	120 mg/day (Antares; ethanol extract)	St. John's wort	Approx. 3 month	Increased liver enzymes, jaundice, hepatitis	Recovered on withdrawal of Kava product	
27	Germany	27	BfArM #99005139; EMEA #26	47	f	(Antares 120; ethanol extract)	Fish oil capsules	Approx. 1 month	Increased liver enzymes	Recovered on withdrawal of all drugs	Kava product continued throughout
28	Germany	28	BfArM #99006200, EMEA #27; duplicate case #01004110,	35	f	120 mg/day (Antares; ethanol extract)	Paracetamol	Approx. 1 month	Increased liver enzymes, jaundice, hepatitis	Recovered on withdrawal of Kava product	Notifications of hepatic side effects under paracetamol

27	Germany	27	BfArM #99003139; EMEA #26	[illegible]	[illegible]	ethanol extract)		1 month	enzymes	withdrawal of all drugs	continued throughout
28	Germany	28	BfArM #99006200, EMEA #27; duplicate case #01004110, EMEA #25 (see #26)	35	f	120 mg/day (Antares; ethanol extract)	Paracetamol	Approx. 1 month	Increased liver enzymes, jaundice, hepatitis	Recovered on withdrawal of Kava product	Notifications of hepatic side effects under paracetamol
29	Germany	29	BfArM #01001228, EMEA #28; duplicate case #01001924, EMEA #29 (see #30) and #01001928 (not listed here)	38	m	(Laitan 100; acetone extract)	Penicillin-V	Approx. 1 week	Liver cell impairment		
30	Germany	30	BfArM #01001924, EMEA #29; duplicate case (see above #29)	39	m	(Laitan 100; acetone extract)		Approx. 2 weeks	Liver cell impairment		No other drugs
31	Germany	31	BfArM #01003950, EMEA #30; duplicate case #01003951, EMEA #32 (see #33)	56	f	(Kavain by Fa. Harras and kava-ratiopharm)	L-Thyroxine, Lorzaar plus, Estragest patch, Antra MUPS		Hepatitis (1993 and 2001)		Positive rechallenge. Hepatic side effects also known for concomitant medication
32	Germany	32	BfArM #01006229; EMEA #31	32	m	240 mg/day (Antares 120 mg; ethanol extract)	Valerian (occasionally)	Approx. 3 months	Necrotizing hepatitis with insufficiency of the liver, metabolic-toxic-allergic drug damage	Received liver transplant	

(Continued)

Appendix 2 **Data Relating to Case Reports of Suspected Hepatotoxicity Associated with Kava from Germany, Switzerland, the United States, Canada, France, and Australia—cont'd**

#	Where reported	MCA #	Other case #	Age	Sex	Suspect product	Concomitant medication	Onset of reaction	Nature of reaction	Outcome	Further relevant information
33	Germany	33	BfArM #01003951, EMEA #32; duplicate case #01003950, EMEA #30 (see #31)	–	f	Kavain Harras	–	–	Hepatitis		
34	Germany	34	BfArM #01006939; EMEA #33	36	m	Laitan 100 (70 mg/day)	–	1 month	Hepatitis		
35	Germany	35	BfArM #01008989; EMEA #34	39	m	Kava (120 mg/day)	Avonex	7 months	Hepatitis and coagulation problems		
36	Germany	36	BfArM #01009681; EMEA #35	45	m	Kava (120 mg/day)	–	3 months	Increased liver enzymes		
37	Germany	37	BfArM #01010222; EMEA #36	55	m	Kava 3/day	Euglucon	1 month	Increased liver enzymes		
38	Germany	38	BfArM #01010536; EMEA #37	–	f	Maoni 1/day		–	Hepatitis, increased liver enzymes		
39	Germany	39	EMEA #38	54	f	Kava (120 mg/day)	Triamteren, thyroxine, benalapril	–	Gall bladder pain		
40	Germany	40	BfArM #02000370; EMEA #39	46	f	Antares 120 (240 mg/day)	Natil, Kilmonorm	4 months	Cirrhosis, unwell		
41	Germany	41	BfArM #02001135/ #02002378; EMEA #40	61	f	Kava (120 mg/day)	Omeprazol, Centrum, dehydrosanol	3 months	Hepatitis, jaundice, abdominal pressure, eczema, liver necrosis		Died
42	Germany	42	BfArM #02001414; EMEA #41	46	f	Antares 120 (360 mg/day)	–	1 month	Increased liver enzymes, jaundice		

necrosis

42	Germany	42	BfArM #02001414; EMEA #41	46	f	Antares 120 (360 mg/day)		1 month	Increased liver enzymes, jaundice
43	Germany	43	BfArM #02001776; EMEA #42	27	m	Kava 2/day	Epivir, Viramune, Zerit	--	Discoloured faeces, abnormal urine, increased sweating, fear
44	Germany	44	Information received from MCA spreadsheet	–	f	Kava (120 mg/day)	–	1 year	Increased liver enzymes
45	Germany	45	BfArM #02002732; EMEA #44	24	f	Maoni forte (120 mg/day)	–	3 months	Increased liver enzymes, jaundice, abdominal pressure, generally unwell
46	Germany	46	BfArM #02002090/ #02002836; EMEA #45	26	f	Kavasedon (50 mg for 6 days)	Azulfidine, Nervogastrol, Buscopan, MCP, Voltaren Resinat	–	Hepatitis*; increased liver enzymes
47	Germany	47	BfArM #02003010; EMEA #46	47	f	Kava 2/day	–	3 months	Increased liver enzymes, increased prothombin time, anorexia
48	Germany	48	BfArM #02003278; EMEA #47	50	m	Laitan 100 (2 × 70 mg/day)	–	3 months	Increased liver enzymes
49	Germany	49	BfArM #02003559; EMEA #48	50	m	Kava (120 mg/day)	–	5 months	Jaundice

*Incorrectly included in the line-listing as per advice from the notifier.[186]

(Continued)

Appendix 2 **Data Relating to Case Reports of Suspected Hepatotoxicity Associated with Kava from Germany, Switzerland, the United States, Canada, France, and Australia—cont'd**

#	Where reported	MCA #	Other case #	Age	Sex	Suspect product	Concomitant medication	Onset of reaction	Nature of reaction	Outcome	Further relevant information
50	Germany	50	BfArM #02004364; EMEA #49	32	f	Kava (240 mg/day)	Marvelon	1 month	Hepatitis, increased liver enzymes		
51	US	51	FDA #14538; EMEA #50	60	f	Kava, chaparral	Xeloda, Eniluracil, Perocet, 5-FU	Not known	Fatigue, increased LFTs	Recovered after stopping all medication	Preexisting medical conditions: advanced rectal cancer -possible metastases in liver. Restarted chemotherapy without any further increases in LFTs
52	US	52	FDA #14723; EMEA #51	44	f	Kava	OxyContin, Coumarin, Celexa, Celebrex, oestrogen patch	Not known	Neutropenia, increased LFTs	Neutropenia recovered after stopping medication. Outcome of hepatic problems not known	PMH -Marfan syndrome
53	US	53	FDA #14810; EMEA #52	33	f	Kava, Zantac	Echinacea/ goldenseal, energy pack (ginseng, B100, guarana), Tums, LoEstrin, women's one a day.	Not known	Nausea, diarrhoea, jaundiced skin	Worked up for possible transplant	PMH -lymphoma with chemotherapy 1 month prior to admission
54	US	54	FDA #15035/ #15274; EMEA #53	45	f	Kava (1 tablet twice a day, but none at weekends, for about 4 months. Each tablet	Aciphex	4 months	Jaundice, puritus, cholestatic hepatitis	Received liver transplant	Hepatitis A-C = negative, low alcohol consumption on rare occasions

			#53			but none at weekends,					occasions
						for about 4 months. Each tablet contains 75 mg kava lactones)					
55	US	55	FDA #15250; EMEA #54		f	NutriZAC (50 mg Kava per tablet; 2 tablets/day for 2 years)	Multivitamins	2 years	Increased LFTs, fatty liver	Not known	Moderate alcohol consumption
56	US	56	FDA #15281; EMEA #55	27	f	Kava (Vitamin World; and 600 mg of kava in a tea 4/day for 6 months)	Psyllium, Vit B_6, Vit E, St. John's wort, phyto-oestrogen (Mexican yam, black cohosh, dong quai)	6 months	Nausea, vomiting, jaundice, increased LFTs, Stage 3 hepatic encephalopathy	Not known	Other aetiologies for liver disease excluded. No alcohol in 5 years. Preexisting medical condition: abdominal hysterectomy
57	US	57	FDA #15317; EMEA #56	38	m	Kava (product unknown), binge use described: 8 caps @ 250 mg 1-2 × per month	None stated	Not known	Liver infection, hepatitis	Recovered after stopping Kava	Repeated tests for viral causes of hepatitis all negative. 3-4 glasses of wine per week
58	US	58	FDA #15319; EMEA #57	63	m	Enalapril, Kava (50 mg/day for 1 month)	Vasotec (10 years)	1 month	Hepatocellular injury, nausea, haematemesis	Improving on stopping Kava and enalapril	PMH = hepatitis C

(Continued)

Appendix 2 **Data Relating to Case Reports of Suspected Hepatotoxicity Associated with Kava from Germany, Switzerland, the United States, Canada, France, and Australia—cont'd**

#	Where reported	MCA #	Other case #	Age	Sex	Suspect product	Concomitant medication	Onset of reaction	Nature of reaction	Outcome	Further relevant information
59	US	59	FDA #15466; EMEA #58	39	f	Kava (128 mg kava in 55% kava lactone extraction), Celestial Kava tea (60 mg kava in 30% kava lactone extraction)	Oral contraception, Albuterol, Benedryl, tetracycline	6 months	Tired, flu-like symptoms, jaundice	Recovered after Kava stopped	4 weeks for LFTs to return to normal
60	US	60	FDA #14951; EMEA #59	51	f	Kava (2 twice daily)	Vit D, Ginkgo, omega 3, multivitamins and minerals	4 months	Increased AST and ALT (1.5 times normal) and foot cramp	Recovered after stopping kava	
61	US	61	FDA #14995; EMEA #60	37	f	Kava Gold (acetone extract = 150 mg Kava lactones 5/ day for 1 month)	None stated	3 weeks	Jaundice	Recovering after stopping Kava	Ultrasound showed fatty infiltration of liver. No PMH of alcohol abuse
62	US	62	FDA #15252; EMEA #61		f	Kava (200 mg, 1-3/day for about 3 months)	Green tea formula (2 weeks during the 3 month use of kava), CoQ10, Snorease	3 months	Fatigue, nausea, vomiting and increased LFTs	Improving on stopping Kava	Preexisting medical conditions: allergic to sulpha drugs
63	US	63	FDA #15267;	51	f	Kava, Ginkgo,	St. John's wort,	2 months	Increased LFTs	Recovered after	+ve rechallenge

63	US	63	FDA #15267; EMEA #62	51	f	Kava, Ginkgo, MSM	St. John's wort, ginseng, Vit A, D + E, flaxseed oil	2 months	Increased LFTs	Recovered after stopping Ginkgo, MSM and Kava	+ve rechallenge (but no details provided). Hepatitis A-C negative
64	France	64	EMEA #63	60	f	Kava	None stated	1 year	Nausea, GGT increased	Recovered after stopping Kava	
65	France	65	EMEA #64	39	f	Kava	Not specified, but may cause hepatotoxicity	2 months	Increased transaminases	Recovered after stopping Kava	
66	Canada	66	EMEA #65	–	f	Kava-kava	None stated	Long term	Hepatic function abnormal	Not known	
67	Canada	67	EMEA #66	53	f	Kava	St. John's wort, multivitamins		Jaundice, abnormal LFTs	Recovering after stopping Kava and other herbal preparations	History of inflammation of the liver while she was drinking 6 beers a day. She has not been drinking since then
68	Canada	68	EMEA #67	38	m	Kava-kava (may contain 30% kava root and 5% kava lactones). 12 gtts po twice daily.		2 weeks	Increased transaminases, hepatitis	Recovered after stopping kava	Does not drink alcohol
69	Germany		BfArM #02005178	–	f	Laitan (70 mg kava lactones, acetone extract), 70 mg per day over 2 months		2 months	Liver cell damage, liver failure		

(Continued)

Appendix 2 **Data Relating to Case Reports of Suspected Hepatotoxicity Associated with Kava from Germany, Switzerland, the United States, Canada, France, and Australia—cont'd**

#	Where reported	MCA #	Other case #	Age	Sex	Suspect product	Concomitant medication	Onset of reaction	Nature of reaction	Outcome	Further relevant information
70	Germany		BfArM #02002541	52	f	Kava ratiopharm (60 mg kava lactones, ethanol extract), 60 mg per day over 3.5 months		3.5 months	Elevated transaminases		
71	US		FDA #14627	14	f	Celestial Seasonings Tension Tamer Extra and CSSleepytime Tea Extra (both tablets; both w/ kava); TT-2 tabs 1-5 ×/ week for 3-4 months; ST-2 tabs only 7 times at beginning of same period; taken from August to Dec 2000	None	3-4 months	Scleral icterus; hepatitis	Liver transplant	
	Literature		Lit: Humbertston	14	f	Kava-containing		6 months; had	Admitted to	Required liver	Liver biopsy showed

			to Dec 2000							
	Literature	Lit: Humbertston et al. 2001	14	f	Kava-containing product		6 months; had stopped taking for 1 month and resumed	Admitted to hospital with fulminant hepatic failure. Abnormal liver function tests	Required liver transplant	Liver biopsy showed hepatocellular necrosis consistent with chemical hepatitis. Alternative causes of liver failure were found to be negative
72	Literature (Press)	Lit: Stuckhard P. 2002.	43	f	Kava, recommended dosage	St. John's wort; iodine compound (for thyroid), betablocker		Liver failure with subsequent liver transplant	Elevated liver enzymes; liver transplantation	Viral hepatitis excluded. The patient had undergone surgery prior to taking kava
73	Literature (Press)	Lit: Hinzpeter W. 2002.	60	f	Kava, recommended dosage, for 3 months		3 months			
74	US	FDA #10257	70	f	K8 (Herbalife); ing. inc. "kava kava 40 mg" and "Biokawa 20 mg containing 14.3% kavain"; 3/day	Inderide and Aspirin (both for 15 years?); Coumadin and Zestril prescribed following event (?); fish oil; "several" vitamins (self-described "vitamin freak"); vitamin K (? Report is confusing -states Vit K but identifies K8 product as source, though states that label does not list this ingredient?)		Stroke; prolapsed mitral valve leading to prolonged (7 days?) hospitalisation; LFT elevated: GGT = 125-212, SGOT = 66-99, others normal range		Preexisting medical conditions: stroke 15 years earlier; self-described "chronic valve prolapse"; PCN allergy

(Continued)

Appendix 2 **Data Relating to Case Reports of Suspected Hepatotoxicity Associated with Kava from Germany, Switzerland, the United States, Canada, France, and Australia—cont'd**

#	Where reported	MCA #	Other case #	Age	Sex	Suspect product	Concomitant medication	Onset of reaction	Nature of reaction	Outcome	Further relevant information
75	US		FDA #11444	24	m	7 product "suite" -Cybergenics (L&S Research), "Hard Gainers" 1-6 and Mega Weight Gain pwd; kava is listed as ing in HG6 (1st of 6 herbs, total = 200 mg); also: Vanadyl sulphate, multi-vit; vit C and chromium picc; discontinued 3-4 weeks prior to hospitalisation	None prior to treatment	3-4 weeks	Hospitalized w/ hepatic encephalopathy; fulminant hepatic failure; death		Preexisting medical conditions: none known
76	US		FDA #13198	52	f	Kava Kava (*Piper methysticum*) 300 mg (Puritan's Pride); dose N/A; used occasionally	4 DS taken regularly: MSM; "green" product; multi-glandular; alfalfa; 14 other DS taken occasionally or listed; 3 OTC listed		Hospitalized for treatment of congestive heart failure (right and left sides); acute renal failure; anasarca with 45 kg weight gain; hyperkalaemia and metabolic alkalosis; biopsy confirmed liver cirrhosis		Preexisting medical conditions: history of hyperthyroidism and exposure to hepatitis C; 1-2 alcoholic drinks per day with binge drinking weekends

					occasionally	or listed; 3 OTC listed		45 kg weight gain; hyperkalaemia and metabolic alkalosis; biopsy confirmed liver cirrhosis	drinking weekends
77	US	FDA #15465; possible duplicate case FDA #15476 (listed together)	48	m	Kava; dose: 1 to 2 (?) per day; used for 5 days from 10 Dec to 15 Dec 2001	None stated	6 days	Liver pain	Preexisting medical conditions: liver dysfunction
78	US	FDA #15556	72	m	Kava capsules (Hi-Health); 2 capsules, used for 2 weeks	Valerian	2 weeks	Felt ill; believed kava aggravated existing liver problems; self-report	Preexisting medical conditions: hepatitis C; liver damage
79	US	FDA #15249	53	m	NaturPharma Kava (Spring Valley); 2 caps each of 2 days; used the day the adverse reaction occurred and ?	None stated	1 day	Felt pain in liver area; self-report	Preexisting medical conditions: some allergies
80	US	FDA #15320	41	f	Kava (Limbao / BASF Generics); dose unknown; use dates not known	Lisino (loratadine), 10 mg, 18 February to 24 February 1999; St. John's wort (brand not stated) "powder" from 21 January 1999 to 9 May 1999; ethinyl oestradiol; "infusion of NaCl 0.9%"		Acute liver failure	Preexisting medical conditions: ?

(Continued)

Appendix 2 **Data Relating to Case Reports of Suspected Hepatotoxicity Associated with Kava from Germany, Switzerland, the United States, Canada, France, and Australia—cont'd**

#	Where reported	MCA #	Other case #	Age	Sex	Suspect product	Concomitant medication	Onset of reaction	Nature of reaction	Outcome	Further relevant information
81	Germany		BfArM 02007130	38	f	Ethanolic kava extract, 1 × 120 mg daily	None	At least 4 weeks	Acute liver failure	Recovered	Intake of kava for treatment of anxiety
83	Australia		ADRS #177303	56	f	Kava 1800 Plus; 2 tablets daily (oral admin.)	From 25 March 2002 to 11 July 2002: alpha tocopherol, 670 mg daily; amino acids mos, 200 mg daily; ascorbic acid, 150 mg daily; magnesium amino acid chelate, 6.4 g daily	Date of onset: 29 July 2002; admitted to hospital 11 July 2002, operation 29 July 2002, date of death 29 July 2002	Jaundice, hepatic necrosis, fatigue	Death. Causality possible	Hepatitis A total detected - postinfection at immunisation for hepatitis A. Liver biopsy: severe acute hepatitis with confluent necrosis, appearance does not separate between a viral or drug reaction. Bilirubin: 209 (11/7/02), 396 (18/7/02), 534 (19/7/02), 551 (24/7/02); normal range = 18 mmol/L (?).SAP/ALP: 190 (11/7/02), 708 (18/7/02), 342 (19/7/02), 270 (24/7/02), normal range = 35 to 125 U/L. ALT/SGPT: 4539 (11/7/02), 1680 (18/7/02), 1651 (19/7/02),

			1651 (19/7/02),
			640 (24/7/02), normal range = 55 U/L. GGT/SGGT/GGTF: 323 (11/7/02), 169 (18/7/02), 196 (19/7/02), 331 (24/7/02), normal range = 60 U/L. Prothrombin time: 25 (11/7/02), 44 (24/7/02). International normalised ratio: 2.3 (11/7/02), 4.2 (24/7/02). Minimal alcohol intake

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