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Kava Kava

Updated: April 10, 2018.

OVERVIEW

Introduction

Kava kava is an herbal derived from roots of the plant Piper methysticum, which has been used for centuries as a recreational and ceremonial drink in Oceania and more recently in concentrated forms in herbal medications to treat anxiety and insomnia. Products labeled as kava have been linked to the development of clinically apparent acute liver injury which can be severe and even fatal.

Background

Kava kava is an herbal derived from roots of the plant Piper methysticum ("intoxicating Pepper" plant), a member of the pepper family found in the Western and South Pacific. More commonly referred to simply as "kava" (bitter), it has been used for centuries as a recreational and ceremonial drink in Oceania (Polynesia, Micronesia and Macronesia). It is prepared from the roots of the plant which are ground into a fine pulp to which water is added. The active ingredients are kavapyrones (kavalactones), which have effects similar to alcohol, such as relaxation, talkativeness, and euphoria, while reportedly maintaining mental clarity. For these reasons, kava has been proposed to be anxiolytic and used in patients with anxiety disorders and as treatment for insomnia, premenstrual syndrome and stress. Kava appears to have an abuse potential, but it is rare with conventional doses. Recently, concerns have arisen regarding the safety of kava products, in particular due to reports of liver injury. For this reason, the use of kava has been banned or restricted in many countries of the world such as Germany, Switzerland, France, Canada, and Great Britain. However, several groups have disputed the evidence for hepatotoxicity, suggesting that responsibility for liver injury lies with adulterants or concomitant drugs or herbals. Furthermore, the literature on liver injury from kava has included several incomplete or overlapping reports, and causality was rarely well shown. Nevertheless, there are a small number of cases of severe hepatic injury arising during therapy that are convincing. Kava in many formulations remains available from nutrition stores and the Internet.

The kava pyrones are believed to have anxiolytic, analgesic, muscle relaxing, and anticonvulsant effects, mediated by effects on the limbic system, the part of the brain linked to emotions. The mechanism of action of the pharmacological effects of kava has yet to be elucidated. Research has demonstrated that several factors, including concentration, type of preparation, kava pyrone content, and kava variety used may affect pharmacologic activity. Therapeutic uses of kava include the treatment of anxiety, insomnia, and stress. Its abuse potential is low, but not absent. Suggested dosage for treatment of nonpsychotic anxiety is 105 to 210 mg daily for three to four weeks. The most common side effects of kava are headache, dizziness, drowsiness, depression, diarrhea, and occasionally dermatologic manifestations.

Hepatotoxicity

The frequency of adverse reactions to kava, particularly liver injury, is not known. Based upon reported cases, the estimated frequency of clinically apparent liver injury due to kava is less than 1:1,000,000 daily doses. However, spontaneous reporting is believed to capture less than 1% of severe adverse events from the use of dietary supplements. Between 50 and 100 cases of clinically apparent liver injury have been published or discussed in the literature. Advocates of the herbal have strongly rejected these numbers, disputing both their accuracy and the causality assessment process. Still, there seem to be convincing evidence in some cases of severe hepatitis ending in fulminant hepatic failure, requiring liver transplantation, and even leading to death. Patients typically present with fatigue, nausea, elevations in serum aminotransferase levels, and jaundice 2 to 24 weeks after starting use of the product. The pattern of enzyme elevations is hepatocellular with marked elevations in serum aminotransferase and minimal increases in alkaline phosphatase levels. In some cases, features of immunoallergic hepatitis (rash, fever, eosinophilia, and recurrence on reexposure) are present. Liver biopsy findings include focal hepatocellular necrosis, lobular inflammation and intrahepatic cholestasis. In more severe cases there is massive or submassive necrosis.

Likelihood score: A (well known cause of clinically apparent liver injury).

Mechanism of Injury

The cause of hepatotoxicity from kava is unclear. In vitro studies suggest that the kavalactones are not intrinsically cytotoxic, although other components of kava preparations may be. Kava can also cause herb-drug interaction. Although in vitro studies suggest that kavalactones inhibit several cytochrome P450 isoenzymes, human studies suggest that it is a inhibitor of CYP 2E1 alone, and that its effects are modest. Clinical cases of hepatotoxicity due to kava suggest an idiosyncratic or immunoallergic pathogenesis. The possibility of mislabeling or adulteration with hepatotoxic herbals is always an issue.

Outcome and Management

The severity of liver injury ranges from transient and moderate enzyme elevations to symptomatic acute hepatitis to acute liver failure. In most instances, the liver injury subsides within 1 to 3 months of discontinuing the herbal product, but if fulminant hepatitis develops, a liver transplant may be required. Rechallenge leads to prompt recurrence and should be avoided.

Other Names: Intoxicating pepper, kavain, kawa pepper

Drug Class: Herbal and Dietary Supplements

CASE REPORTS

Case 1. Acute liver failure treated with liver transplantation after kava use.

[Modified from: Brauer RB, Stangl M, Stewart JR, Pfab R, Becker K. Acute liver failure after administration of herbal tranquilizer kava-kava (Piper methysticum). J Clin Psychiatry 2003; 64: 216-8. PubMed Citation]

A 22 year old woman presented with a 3 week history of nausea and fatigue, followed by jaundice 4 months after starting kava kava (240 mg daily). Her other medications included oral contraceptives (norgestimate, 180-250 µg and ethinyl estradiol, 35 µg) for a year and a half, and rizatriptan (10 mg) and acetaminophen (500 mg) approximately twice a month as needed for migraine headaches. She was initially found to be jaundiced with a serum bilirubin of 10.4 mg/dL. She was told to stop kava. A week later she was hospitalized for worsening jaundice and mental slowing. At that point, serum bilirubin was 40 mg/dL, ALT 2442 U/L, alkaline phosphatase

246 U/L, and the prothrombin time index <20% (Table). Tests for hepatitis A, B and C were negative. Autoantibodies were not detected and immunoglobulin levels were normal. Ultrasonography showed no gall stones and no evidence of biliary obstruction. Despite supportive care, she developed progressive hepatic encephalopathy and was placed on the liver transplant waiting list. Three days later a donor organ became available, and liver transplantation was performed. The explanted liver was small (780 g) and histology showed massive necrosis with few residual hepatocytes. Her posttransplant course was complicated by recurrent cytomegalovirus infections and prolonged jaundice, but she gradually improved and was discharged 12 weeks after transplantation. Six months after transplant she developed disseminated aspergillosis which led to her death from multiorgan failure.

Key Points

Medication:	Kava kava (240 mg of kavalactone daily)
Pattern:	Hepatocellular (R=71)
Severity:	5+ (liver transplantation, death)
Latency:	16 weeks
Recovery:	None
Other medications:	Norgestimate, ethinyl estradiol, rizatriptan, acetaminophen

Laboratory Values

Time After Starting	Time After Stopping	ALT (U/L)	Alk P (U/L)	Bilirubin (mg/dL)	Other
		Started kava (240 mg kavapyrone daily)			
16 weeks	0	519		10.4	Nausea and jaundice,
17 weeks	1 week	2442	246	40.0	Grade I encephalopathy
	1.5 weeks	453	287	28.5	Comatose grade II - IV
		Liver transplant performed			
7 months	14 weeks	115		12.9	Discharge
Normal Values		**<17**	**<130**	**<1.2**	

Comment

This patient developed a severe acute hepatitis-like syndrome 4 months after starting kava kava for depression. Other causes of acute liver injury were appropriately excluded. Progressive hepatic failure followed and led to emergency liver transplantation. Because at least a dozen instances of acute liver failure have been reported in patients taking kava, the agent has been banned in many countries as an over-the-counter product for therapy of anxiety or mood disorders. The argument that prescription anxiolytic agents have a similar rate of severe hepatic reactions is not correct. Prescription medications with the number of published instances of severe hepatic injury attributed to kava would be similarly withdrawn from use.

Case 2. Death from acute liver failure after kava kava use.

[Modified from: Gow PJ, Connelly NJ, Hill RL, Crowley P, Angus PW. Fatal fulminant hepatic failure induced by a natural therapy containing kava. Med J Aust 2003; 178: 442-3. PubMed Citation]

In July 2002, a 56 year old Australian woman who had been taking a kava product for three months developed nausea and jaundice. The product was provided by a naturopath for anxiety to be taken three times daily: Kava 1800 Plus was labeled as containing 60 mg of kavalactones, 50 mg of Passiflora incarnata (maypop, passion

flower) and 100 mg of Scutellaria lateriflora (blue skullcap). She had no previous major medical problems except for benign monoclonal gammopathy. She had initially been seen with a two week history of fatigue, nausea and increasing jaundice. She had no risk factors for viral hepatitis, no history of liver disease and drank minimal amounts of alcohol. She had also been taking some vitamin and mineral supplements, but no other prescription medications. Examination upon hospital admission revealed deep jaundice, but no fever, rash or signs of chronic liver disease. Laboratory tests showed a total bilirubin of 12.2 mg/dL, ALT 4539 U/L, alkaline phosphatase 190 U/L, albumin 3.4 g/dL and INR 2.3 (Table). Tests for acute hepatitis A, B, and C were negative as were serology of acute Epstein Barr virus and cytomegalovirus infection. Serum copper and ceruloplasmin levels were normal. Antinuclear antibodies were present in a titer of 1:160, without smooth muscle antibodies and with stable serum immunoglobulin levels. Plasma acetaminophen levels were negative. An abdominal ultrasound revealed a small liver with normal flow in the hepatic arteries, hepatic veins and portal veins and no evidence of extrahepatic obstruction. A trans-jugular liver biopsy showed severe acute hepatitis with marked parenchymal necrosis and collapse. Over the next week, she developed deepening jaundice, coagulopathy and hepatic encephalopathy and was listed for transplantation which was performed on hospital day 17. The surgery was complicated by massive bleeding that did not correct following implantation of the donor liver, and the patient died of circulatory failure. Histological examination of the explanted liver confirmed the presence of massive hepatic necrosis.

Key Points

Medication:	Kava
Pattern:	Hepatocellular (R=55)
Severity:	5+ (liver transplantation, death)
Latency:	3 months (jaundice)
Recovery:	None
Other medications:	Passiflora incarnata, Scutellaria lateriflora, vitamins and minerals

Laboratory Values

Time After Starting	Time After Stopping	ALT (U/L)	Alk P (U/L)	Bilirubin (mg/dL)	Other
0	Pre	Started Kava 1800 Plus (180 mg kavalactones daily)			
12 weeks	0	4539	190	12.2	INR=2.3
14 weeks	17 days	438	357	35.5	INR=6.6
14 weeks	17 days	Liver transplantation: death from surgical complications			
Normal Values		**<55**	**<130**	**<1.2**	

Comment

This patient developed a severe acute hepatitis-like syndrome, followed by acute liver failure three months after starting a kava containing combination herbal medication. Other causes of acute liver injury were excluded. This case occurred after a warning was made by the Australian Regulatory agency and stresses the difficulty of managing risks that are very rare, but nevertheless potentially profound. While the herbal medication that she was taking included multiple components, the association of hepatic injury with kava has been far stronger than with the other listed herbals. The possibility of mislabeling or contamination of the herbal preparation was raised with the case, but these concerns affect all herbals that are not formally regulated.

Case 3. Acute hepatitis attributed to kava.

[Modified from: Bujanda L, Palacios A, Silvarino R, Sanchez A, Munoz C. [Kava-induced acute icteric hepatitis], Gastroenterol Hepatol 2002; 25: 434-5. PubMed Citation]

A 55 year old man using kava extract (250 mg capsule, 3 times daily) for 2 weeks began to experience weakness, fatigue and right upper quadrant discomfort. He continued taking the extract for 3 months when he developed jaundice. He denied taking any other medications and denied alcohol use or risk factors for viral hepatitis. Liver tests were known to have been normal in the past. On physical examination, he was jaundiced but had no signs of chronic liver disease, rash or fever. Laboratory tests showed a total serum bilirubin of 6.5 mg/dL, ALT 2300 U/L, AST 1506 U/L, alkaline phosphatase 514 U/L and GGT 874 U/L (Table). The prothrombin index was 60%. Tests for hepatitis A, B and C were negative as were routine autoantibodies. Abdominal ultrasound and magnetic resonance cholangiography showed no evidence of extrahepatic obstruction. A liver biopsy showed centrilobular hemorrhagic necrosis without steatosis, fibrosis, or cholestasis and with minimal mixed inflammatory infiltrates. Two weeks after stopping the kava product, liver tests began to improve and were near normal when he was seen four months later.

Key Points

Medication:	Kava
Pattern:	Hepatocellular (R=12.8)
Severity:	3+ (jaundice, hospitalization)
Latency:	2 weeks (fatigue, weakness), 3 months (jaundice)
Recovery:	4 months
Other medications:	None

Laboratory Values

Time After Starting	Time After Stopping	ALT (U/L)	Alk P (U/L)	Bilirubin (mg/dL)	Other
	Started kava (250 mg three times daily)				
3 months	0	2300	514	6.5	Kava stopped
4 months	1 month	1018	613	8.6	
5 months	2 months	200	454	3.8	
6 months	3 months	35	178	1.4	
Normal Values		**40**	**130**	**<1.2**	

Comment

The hepatocellular pattern of serum enzyme elevations with jaundice arising within 3 months of starting kava without other explanations is strong evidence supporting a diagnosis of kava induced hepatic injury.

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Kava Kava – Generic

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DRUG CLASS

Herbal and Dietary Supplements

SUMMARY INFORMATION

Fact Sheet at National Center for Complementary and Integrative Health, NIH

Fact Sheet at Office of Dietary Supplements, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Kava Kava	9000-38-8	Herbal mixture	Not applicable

ANNOTATED BIBLIOGRAPHY

References updated: 10 April 2018

Zimmerman HJ. Unconventional drugs. Miscellaneous drugs and diagnostic chemicals. In, Zimmerman, HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott,1999: pp. 731-4.

(Expert review of hepatotoxicity published in 1999; several herbal medications linked to liver injury are discussed, but not kava).

Seeff L, Stickel F, Navarro VJ. Hepatotoxicity of herbals and dietary supplements. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2013, pp. 631-58.

(Review of hepatotoxicity of herbals including kava mentions that more than 100 cases of liver injury have been attributed to kava products, used for their relaxing and anxiolytic properties).

Mathews JD, Riley MD, Fejo L, Munoz E, Munos E, Milns NR, Gardner ID, et al. Effects of the heavy usage of kava on physical health: Summary of a pilot survey in an aboriginal community. Med J Aust 1988; 148: 548-55. PubMed PMID: 3374423.

(Survey of health of kava users among Aboriginal community in Australia found GGT levels 4 to 6 fold higher in heavy kava users compared to non-users; ALT levels not tested).

Singh YN. Kava: an overview. J Ethnopharmacol 1992; 37: 13-45. PubMed PMID: 1453702.

(Historical review of kava and its uses in Oceania; initially used for ceremonial purposes, kava has come to occupy a central place in everyday life and has become a drug of abuse in some populations; because of its relaxing and socializing effects, kava has been introduced into Western countries as an anxiolytic herbal usually as an alcohol extract in pill form).

Strahl S, Ehret V, Dahm HH, Maier KP. [Necrotizing hepatitis after taking herbal remedies] Dtsch Med Wochenschr 1998; 123: 1410-4. German. PubMed PMID: 9856112.

(39 year old woman developed acute hepatitis after taking kavapyrone for 5 months [bilirubin 1.7 rising to 12.3 mg/dL, ALT 796 U/L, Alk P 389 U/L], resolving within 2 months of stopping and recurring soon upon restarting).

Almeida JC, Grimsely EW. Coma from the health food store: Interaction between kava and alprazolam. Ann Int Med 1996; 125: 940-1. PubMed PMID: 8967683.

(54 year old man developed disorientation and coma 3 days after starting kava, while also taking alprazolam and cimetidine, drug-interactions perhaps explaining the serious neurological adverse event; liver tests not reported).

Escher M, Desmeules J, Giostra E, Mentha G. Hepatitis associated with Kava, a herbal remedy for anxiety. BMJ 2001; 322: 139. Erratum in: BMJ 2001; 322: 1097. PubMed PMID: 11159570.

(50 year old man developed jaundice 2 months after starting kava capsules [3-4/day] [bilirubin 16.9 mg/dL, ALT 70 times ULN, Alk P 430 U/L, prothrombin index 25%], with progressive hepatic failure requiring emergency liver transplantation).

Russmann S, Lauterburg BH, Helbling A. Kava hepatotoxicity. Letter. Ann Intern Med 2001; 135: 68-9. PubMed PMID: 11434754.

(33 year old woman developed jaundice 3 weeks after a second use of Laitan [kavalactone] [bilirubin 23 mg/dL, ALT 2430 U/L, Alk P 299 U/L], positive lymphocyte transformation test to kavalactone, resolving in 8 weeks).

Kraft M, Spahn TW, Menzel J, Senninger N, Dietl KH, Herbst H, Domschke W, et al. [Fulminant liver failure after administration of the herbal antidepressant kava-kava]. Dtsch Med Wochenschr 2001; 126: 970-2. German. *(60 year old woman developed jaundice while taking kava kava for an unknown duration [bilirubin 30 mg/dL, ALT 1350 U/L, Alk P 580 U/L, prothrombin index <10%], with progressive hepatic failure requiring liver transplantation 11 days later* - PubMed PMID: 11544547.

18th case of kava related acute liver failure).

Bujanda L, Palacios A, Silvarino R, Sanchez A, Munoz C. [Kava-induced acute icteric hepatitis], Gastroenterol Hepatol 2002; 25: 434-5. Spanish. PubMed PMID: 12069710.

(55 year old man developed jaundice 3 months after starting kava extract [bilirubin 8.6 mg/dL, ALT 2300 U/L, Alk P 514 U/L, prothrombin index 65%], with recovery 4 months after stopping: Case 3).

Wooltorton E. Herbal kava: reports of liver toxicity. CMAJ 2002; 166: 777. PubMed PMID: 11944767.

(Canadian health care alert after 25 cases of severe liver injury were reported from Europe, listing multiple names for kava).

De Smet PA. Safety concerns about kava not unique. Lancet 2002: 1336. PubMed PMID: 12414243.

(Letter indicating that celandine, like kava, has been linked to several cases of severe liver injury and a warning label added in Germany).

Ernst E. Safety concerns about kava. Lancet 2002; 359: 1865. PubMed PMID: 12044412.

(The European Agency for Evaluation of Medicinal Products has identified 30 cases of liver injury, including 6 cases of liver failure attributable to kava; UK retailers have removed kava from shelves).

Centers for Disease Control and Prevention. Hepatic toxicity possibly associated with kava-containing products-United States, Germany, and Switzerland, 1999-2002. JAMA 2003: 36-7. PubMed PMID: 12500906.

(Report of 2 cases of liver failure attributable to kava in the US; 15 and 45 year old females developing jaundice 2 and 3.5 months after starting kava, both of whom required emergency liver transplant).

BfArM (Federal Institute for Drugs and Medicinal Products in Germany) 2002. http://www.scribd.com/doc/49052596/BfArM-Public-Statement-on-Withdrawal-Kava-Kava-Assessment-Report-14-06-2002

(German warning about kava).

Center for Food Safety and Applied Nutrition (CFSAN): Kava-containing dietary supplements may be associated with severe liver injury. US Department of Health and Human Services, Food and Drug Administration, Rockville, Maryland, March 25, 2002. (http://www.cfsan.fda.gov/~dms/ds-warn.html). 2002.

(Letter reporting over 25 cases of liver adverse events from kava in other countries. Advisory warning of removal of kava from the marketplace in Germany, Switzerland, France, Canada, and the UK noted. Consumers asked to report any new instances of liver injury).

Center for Food Safety and Applied Nutrition (CFSAN): Consumer advisory: kava-containing dietary supplements may be associated with severe liver injury(document issued March 25, 2002), Rockville, Maryland: US Department of Health and Human Services, Food and Drug Administration, 2002. (http://www.fda.gov/Food/ResourcesForYou/Consumers/ucm085482.htm).

(Advisory about the potential risk of hepatotoxicity from kava).

Denham A, McIntyre M, Whitehouse J. Kava—the unfolding story: report on a work-in-progress. J Altern Complement Med 2002; 8: 237-63. PubMed PMID: 12165183.

(Article written on behalf of the Traditional Medicines Evaluation Committee protesting the decision in Germany to warn the public about kava hepatotoxicity based on 30 reported cases of liver injury from kava, claiming that evidence of causality was poor, some cases were duplications and that the concentrated extracts differ from the aqueous extracts in traditional use).

Bilia AR, Gallon S, Vincieri FF. Kava-kava and anxiety: growing knowledge about the efficacy and safety. Life Sci 2002; 70: 2581-97. PubMed PMID: 12269386.

(Review of the activity of kava in decreasing anxiety, relieving stress at doses that are well tolerated and not associated with addiction; the recent report of liver toxicity was unexpected and remains unexplained and possibly due to contaminants).

Parkman CA. Another FDA warning: Kava supplements. Case Manager 2002; 13: 26-8. PubMed PMID: 12131903.

(FDA consumer warning and short review of the efficacy and side effects of kava, encouraging reporting of adverse events to MedWatch).

Campo JV, McNabb J, Perel JM, Mazariegos GV, Hasegawa SL, Reyes J. Kava induced fulminant hepatic failure. J Am Acad Child Adolesc Psychiatry 2002; 41: 631-2. PubMed PMID: 12049436.

(Case reported above by FDA of 14 year old girl who developed fulminant hepatic failure requiring liver transplantation after taking a kava containing herbal for 3 months [bilirubin 16.2 mg/dL, ALT 4076, GGT 148 U/L], first report of fatal kava hepatotoxicity in a child).

Stevinson C, Huntley A, Ernst E. A systematic review of the safety of kava extract in the treatment of anxiety. Drug Safety 2002; 25: 251-61. PubMed PMID: 11994028.

(Systematic review of safety of kava: 9 published cases of liver damage, arising 3 weeks to 4 months after starting, often with immunoallergic features; another 24 unpublished reports made to German regulatory agency with 1 death and 3 liver transplants; conclusion that kava is well tolerated when taken short term in recommended doses; however, further research is needed).

Schmidt M. Are kavalactones the hepatotoxic principle of kava extracts? The pitfalls of the glutathione theory. J Altern Complement Med 2003; 9: 183-7. PubMed PMID: 12804070.

(Detailed summary of animal toxicology studies with kava showing no evidence of hepatotoxicity of kavalactones in vitro or in vivo).

Brauer RB, Stangl M, Stewart JR, Pfab R, Becker K. Acute liver failure after administration of herbal tranquilizer kava-kava (Piper methysticum). J Clin Psychiatry 2003; 64: 216-8. PubMed PMID: 12633134.

(22 year old woman developed nausea 4 months after starting kava [240 mg of kavapyrone daily], with bilirubin 10.5 rising to 40 mg/dL, ALT 2442 U/L, Alk P 246 U/L and subsequent progressive hepatic failure and liver transplantation: Case 1).

Schulze J, Raasch W, Ciegers CP. Toxicity of kava pyrones, drug safety and precautions – a case study. Phytomedicine 2003; 10 Suppl 4: 68-73. PubMed PMID: 12807347.

(Editorial questioning the appropriateness of the ban placed on kava, based upon the cases of hepatic injury reported to German and Swiss regulatory authorities, arguing that the evidence that kava was the cause of the liver injury was poor and the efficacy of kava outweighs its hepatotoxic risks).

Gow PJ, Connelly NJ, Hill RL, Crowley P, Angus PW. Fatal fulminant hepatic failure induced by a natural therapy containing kava. Med J Aust 2003; 178: 442-3. PubMed PMID: 12720510.

(56 year old woman developed jaundice 3 months after starting kava [bilirubin 12.2 mg/dL, ALT 4539 U/L, Alk P 190 U/L, INR 2.3], with progressive liver failure requiring liver transplantation, dying post-operatively: Case 2).

Currie BJ, Clough AR. Kava hepatotoxicity with western herbal products: Does it occur with traditional kava use? Med J Aust 2003; 178:421-2. PubMed PMID: 12720503.

(Editorial based on report by Gow [2003] mentioning the lack of liver injury among Aboriginal people who use kava, and linking adverse effects to the process [using alcohol and acetone] of extracting and concentrating kavalactone).

Whitton PA, Lau A, Salisbury A, Whitehouse J, Evans CS. Kava lactones and the kava-kava controversy. Phytochemistry 2003; 64: 673-9. PubMed PMID: 13679089.

(Analysis of extraction techniques in preparing kava; alcohol and acetone retrieve >95%, whereas water extracts ~3% of kavalactones; water extraction also retains glutathione which may help detoxify bioreactive components).

Clough AR, Jacups SP, Wang Z, Burns CB, Bailie RS, Cairney SJ, Collie A, et al. Health effects of kava use in an eastern Arnhem Land Aboriginal community. Int Med J 2003; 33: 336-40. PubMed PMID: 12895162.

(Cross sectional study of kava users in Northern Territory of Australia among Aboriginal Community showed a higher frequency of dermopathy, increased alkaline phosphatase and GGT levels [but not ALT] between users and non-users).

Clough AR, Bailie RS, Currie B. Liver function test abnormalities in users of aqueous kava extracts. J Toxicol Clin Toxicol 2003; 41: 821-9. PubMed PMID: 14677792.

(Cross sectional survey of 98 Australian aboriginal people for kava use, finding higher levels of GGT [78 vs 34 U/L] and Alk P [165 vs 109 U/L] in recent users vs non-users, but no differences in ALT [25.5 vs 24 U/L], the abnormalities being reversible and not associated with clinical symptoms).

Russmann S, Barguil Y, Cabalion P, Kritsanida M, Duhet D, Lauterburg BH. Hepatic injury due to traditional aqueous extracts of kava root in New Caledonia. Eur J Gastroenterol Hepatol 2003; 15: 1033-6. PubMed PMID: 12923378.

(Two cases of acute liver injury from a South Pacific Island in 55 and 59 year old women of Oceanian origin who started drinking kava regularly for 4 and 5 weeks and then presented with jaundice [bilirubin 1.8 and 12.9 mg/dL, ALT 568 and 1666 U/L], resolving in 3 months in both; a survey among 27 heavy kava users found GGT elevations in 85% and ALT elevations in 11%).

Humberston CL, Akhtar J, Krenzelok EP. Acute hepatitis induced by kava kava. J Toxicol Clin Toxicol 2003; 41: 109-13. PubMed PMID: 12733846.

(14 year old female developed jaundice after taking a kava containing herbal ["Tension Tamers"] for 4 months for anxiety over her parents separation [bilirubin 15.5 mg/dL, ALT >4400 U/L, GGT 127 U/L, INR 3.4], with progressive liver failure requiring emergency transplant; apparently same case as in Campo [2002], but some differences in details).

Estes JD, Stoplman D, Olyaei A, Corless CL, Ham JM, Schwartz JM, Orloff SL. High prevalence of potentially hepatotoxic supplement use in patients with fulminant hepatic failure. Arch Surg 2003; 138: 852-8. PubMed PMID: 12912743.

(Among 20 cases of acute liver failure referred for liver transplantation in 2001-2002, 7 were associated with herbal use including 3 patients taking kava, 2 "Lipokinetix", 1 Ma Huang and 1 chaparral).

Mills SY, Steinhoff B. Kava-kava: a lesson for the phytomedicine community. Phytomedicine 2003; 10: 261-2. PubMed PMID: 12725583.

(Editorial questioning the decision to ban kava in Germany and the UK: "A remedy with established efficacy and long standing popularity has been withdrawn, with severe damage to the economies of several small Pacific nations, on the basis of uncertain reports").

Teschke R, Gaus W, Loew D. Kava extracts: safety and risks including rare hepatotoxicity. Phytomedicine 2003; 10: 440-6. PubMed PMID: 12834011.

(Review of 19 cases of kava hepatotoxicity reported to regulatory groups questioning the causality and the basis of its ban; on closer scrutiny, only 1 case could be considered "probable", 1 "possible", 5 "unlikely" and 12 "unassessable" because of missing information).

Teschke R. [Kava, kavapyrones and toxic liver injury]. Z Gastroenterol 2003; 41: 395-404. German. PubMed PMID: 12772052.

(Kava extracts are recommended in daily doses of 60-120 mg of kavapyrones for up to 3 months; reports of hepatotoxicity have largely been in patients who exceeded these recommendations).

Stickel F, Baumuller H-B, Seitz K, Vasilakis D, Seitz G, Seitz HK, Schuppan D. Hepatitis induced by Kava (Piper methysticum rhizome). J Hepatol 2003; 39: 62-7. PubMed PMID: 12821045.

(Evaluation of 7 published and 29 unpublished [German] cases of liver injury attributed to kava between 1990 and 2002, rated 3 as "certain", 21 as "probable" and 12 as at least "possible"; 9 had acute liver failure, 8 underwent transplant and 3 died; latency was 2 weeks to 2 years [median=4.5 months], with idiosyncratic or immunoallergic mechanisms most likely, occurring with both acetone and alcohol extracts and from multiple commercial sources).

Clouatre DL. Kava kava: examining new reports of toxicity. Toxicol Lett 2004; 150: 85-96. PubMed PMID: 15068826.

(Review of efficacy and safety of kava concludes that hepatotoxicity is an idiosyncratic reaction and that the "risk-to-benefit ratio of kava extracts remains good" in comparison to other drugs for anxiety).

Thomsen M, Vitetta L, Schmidt M, Sali A. Fatal fulminant hepatic failure induced by a natural therapy containing kava. Med J Austr 2004; 180: 198-9. PubMed PMID: 14960147.

(Letter in response to Gow [2003] suggesting that a toxic factor or contaminant may have caused the hepatic injury rather than kava, the aqueous extracts of which show no hepatotoxicity in animal models; reply by authors states that this is possible but unlikely).

Anke J, Ramzan I. Pharmacokinetic and pharmacodynamic drug interactions with kava (Piper methysticum Forst. f.). J Ethnopharmacol 2004; 93: 153-60. PubMed PMID: 15234747.

(Several kavalactones found in kava extracts are potent inhibitors of P450 enzymes [CYP 1A2, 2C9, 2C19, 2D6, 3A4, 4A9/11] in vitro, suggesting that kava may have major herb-drug inactions).

Anke J, Ramzan I. Kava Hepatotoxicity: are we any closer to the truth? Planta Med 2004; 70: 193-6. PubMed PMID: 15114493.

(Discussion of the hepatotoxicity of kava containing herbal medications and possible mechanisms of liver injury).

Nerurkar PV, Dragull K, Tang C-S. In vitro toxicity of kava alkaloid, pipermethystine, in HepG2 cells compared to kavalactone. Toxicol Sci 2004; 79: 106-11. PubMed PMID: 14737001.

(In vitro studies identified pipermethystine, but not kavalactones as cytotoxic in HepG2 [hepatoma] cell lines).

Russo MW, Galanko JA, Shrestha R, Fried MW, Watkins P. Liver transplantation for acute liver failure from drug-induced liver injury in the United States. Liver Transpl 2004; 10: 1018-23. PubMed PMID: 15390328.

(Among ~50,000 liver transplants reported to UNOS between 1990 and 2002, 270 [0.5%] were done for drug induced acute liver failure, including 7 [5%] for herbal medications, one specifically attributed to kava).

Gurley JB, Gardner SF, Hubbard MA, Williams DK, Gentry WB, Han IA, Shah A. In vivo effects of goldenseal, kava kava, black cohosh, and valerian on human cytochrome P450 1A2, 2D6, 2E1, and 3A4/5 phenotypes. Clin Pharmacol Ther 2005; 77: 415-26. PubMed PMID: 15900287.

(In human volunteer studies, kava showed moderate inhibition of CYP 2E1 activity [40%] but no effect on CYP 1A2, 2D6 or 3A4, despite evidence in vitro that kava inhibits these isoenzymes; discussion raises issue of whether the dose of kava was high enough to show an effect).

Ulbricht C, Basch E, Boon H, Ernst E, Hammerness P, Sollars D, Tsourounis C, et al. Safety review of kava (Piper methysticum) by the Natural Standard Research Collaboration. Expert Opin Drug Saf 2005; 4: 779-4. PubMed PMID: 16011454.

(Systematic review of the safety of kava with a history of regulatory actions by country).

Weiss J, Sauer A, Frank A, Unger M. Extracts and kavalactones of Piper methysticum G. Forst (kava-kava) inhibit P-glycoprotein in vitro. Drug Metab Dispos 2005; 33: 1580-3. PubMed PMID: 16051732.

(Analysis of effects of kava extracts and purified components on the efflux transporter P-glycoprotein in an over expressing cell line found moderate to potent inhibitory activity of the extract and the kavalactones).

Andrade RJ, Lucena MI, Fernández MC, Pelaez G, Pachkoria K, García-Ruiz E, García-Muñoz B, et al. Drug-induced liver injury: an analysis of 461 incidences submitted to the Spanish Registry over a 10-year period. Gastroenterology 2005; 129: 512-21. PubMed PMID: 16083708.

(Reports of drug induced liver injury to a Spanish network found 570 cases, herbal medications accounted for 9 cases).

Jhoo JW, Freeman JP, Heinze TM, Moody JD, Schnackenberg LK, Beger RD, Dragull K, et al. In vitro cytotoxicity of nonpolar constituents from different parts of kava plant(Piper methysticum). J Agric Food Chem 2006; 54: 3157-62. PubMed PMID: 16608246.

(Analysis of in vitro cytotoxicity of extracts of various parts of the kava plant, higher degrees of toxicity were found with organic solvent extracts and "flavokavain B" was identified as a cytotoxic component).

Clough AR, Currie BJ, Yunupingu MW, Conigrave KM. Action is required to reduce kava supply in Arnhem Land . . . again! Med J Aust 2006; 184: 91-2. PubMed PMID: 16411879.

(Letter documenting the rise in abuse of kava among Aboriginal people in Australia and call for further regulatory actions).

Musch E, Chrissafidou A, Malek M. Acute hepatitis due to kava kava and St John's Wort: an immune-mediated mechanism? Dtsch Med Wochenschr 2006; 131: 1214-7. PubMed PMID: 16721710.

(48 year old woman developed jaundice 10 weeks after starting a kavain containing product [Neuronika] [bilirubin 1.6 rising to 20 mg/dL, ALT 412-752 U/L, Alk P 176-311 U/L], resolving in 3 months on prednisolone and azathioprine; authors argue for an immune mediated injury).

Loew D. [Acute hepatitis due to kava-kava and St John's Wort: an immune-mediated mechanism]. Dtsch Med Wochenschr 2006; 131: 1780. German. PubMed PMID: 16915553.

(Letter in response to Musch [2006] questioning the interpretation of the injury as due to kava versus kavain, a synthetic product).

Teschke R. [Acute hepatitis due to kava-kava and St John's Wort: an immune-mediated mechanism?]. Dtsch Med Wochenschr 2006; 131: 1880-1. German. PubMed PMID: 16915552.

(Letter in response to Musch [2006] questioning the link of the liver injury with kava [vs kavain] and the theoretical role of kava-cytochrome P450 interactions in causing hepatotoxicity).

Siegers CP, Schmidt M. [Acute hepatitis due to kava-kava and St John's Wort: an immune-mediated mechanism?]. Dtsch Med Wochenschr 2006; 131: 1881-2. German. PubMed PMID: 16915554.

(Letter in response to Musch [2006] questioning the interpretation of the hepatotoxicity as immunoallergic and the use of prednisolone and azathioprine).

Droege H. [Acute hepatitis due to kava-kava and St John's Wort: an immune-mediated mechanism?]. Dtsch Med Wochenschr 2006; 131: 18823. German. PubMed PMID: 16915556.

(Letter in response to Musch [2006] pointing out that the product was kavain, a synthetic product, rather than kava-kava).

Ernst E. A re-evaluation of kava(Piper methysticum). Br J Clin Pharmacol 2007; 64: 415-7. PubMed PMID: 17555466.

(Commentary on hepatotoxicity of kava which was banned in Germany in 2002 and UK in 2003 with 100 cases of liver injury attributed to kava worldwide).

Teschke R, Schwarzenboeck A, Hennermann KH. Kava hepatotoxicity: a clinical survey and critical analysis of 26 suspected cases. Eur J Gastroenterol Hepatol 2008; 20: 1182-93. PubMed PMID: 18989142.

(Detailed analysis of 26 German and Swiss cases of suspected kava hepatotoxicity applying RUCAM found that only 3 cases could be considered probable and 6 cases possible, and that many of the patients had taken higher than recommended doses for longer than recommended periods, so that only 1 case could be considered probable and 2 possible who had taken kava in the recommended regimen; many cases had inadequate documentation).

Teschke R, Schwarzenboeck A, Akinci A. Kava hepatotoxicity: a European view. N Z Med J 2008; 121: 90-8. PubMed PMID: 18841189.

(Review of kava hepatotoxicity pointing out that most reported cases were poorly documented, involved use of higher than recommended doses for longer than recommended times and may have been due to poor extraction techniques, contamination or co-medications; concluded that kava induced liver injury may be real, but is rare).

Pittler MH, Ernst E. Kava extract for treating anxiety. Cochrane Database Syst Rev 2008; (1): CD003383. PubMed PMID: 12535473.

(In a systematic review and meta analysis, kava was found to effective in treatment of anxiety although the effect was small; kava was safe in the short term [1-24 weeks] and in monitoring studies including 7078 patients no evidence of hepatotoxicity was found).

Lude S, Torok M, Dieterle S, Jaggi R, Buter KB, Krahenbuhl S. Hepatocellular toxicity of kava leaf and root extracts. Phytomedicine 2008; 15: 120-31. PubMed PMID: 18055189.

(Three different kava extracts [methanolic and acetonic root and methanolic leaf extract] appeared toxic to mitochondria, leading to inhibition of the respiratory chain, increased reactive oxidant species production, and a decrease in the mitochondrial membrane potential culminating in apoptosis).

Fu PP, Xia Q, Guo L, Yu H, Chan P-C. Toxicity of kava kava. J Environmental Science and Health Part C 2008; 26: 89-112. PubMed PMID: 18322868.

(Review of issue of hepatotoxicity and of mechanisms leading to hepatotoxicity, including summary of animal studies, short term cytotoxicity tests, issues of herb-drug interactions, and formation of activated metabolites).

Chalasani N, Fontana RJ, Bonkovsky HL, Watkins PB, Davern T, Serrano J, Yang H, Rochon J; Drug Induced Liver Injury Network (DILIN). Causes, clinical features, and outcomes from a prospective study of drug-induced liver injury in the United States. Gastroenterology 2008; 135: 1924-34. PubMed PMID: 18955056.

(Among 300 cases of drug induced liver disease in the US collected between 2004 and 2008, 9% of cases were attributed to herbal medications, but kava was not specifically mentioned).

García-Cortés M, Borraz Y, Lucena MI, Peláez G, Salmerón J, Diago M, Martínez-Sierra MC, et al. [Liver injury induced by "natural remedies": an analysis of cases submitted to the Spanish Liver Toxicity Registry]. Rev Esp Enferm Dig 2008; 100: 688-95. Spanish. PubMed PMID: 19159172.

(Among 521 cases of drug induced liver injury submitted to Spanish registry, 13 [2%] were due to herbals, 1 due to kava kava; 34 year old woman developed ALT elevations [18 times ULN] 5 months after starting kava; resolving slowly over 14 months after stopping).

Chitturi S, Farrell GC. Hepatotoxic slimming aids and other herbal hepatotoxins. J Gastroenterol Hepatol 2008; 23: 366-73. PubMed PMID: 18318821.

(General review of herbal hepatotoxicity including kava).

Teschke R, Genthner A, Wolff A. Kava hepatotoxicity: comparison of aqueous, ethanolic, acetonic kava extracts and kava-herbs mixtures. J Ethnopharmacol 2009; 123: 378-84. PubMed PMID: 19501269.

(Review of literature on kava hepatotoxicity applying RUCAM scoring for causality to 5 published cases attributed to aqueous and 9 to ethanol-extracted kava, suggesting that liver injury occurs with both).

Teschke R, Wolff A. Kava hepatotoxicity: regulatory data selection and causality assessment. Digest Liver Dis 2009; 41: 891-901. PubMed PMID: 19477698.

(Analysis of 20 cases of suspected kava hepatotoxicity reported to German regulatory agency, using RUCAM to assess causality, found low level of evidence largely because of lack of information on clinical course [dechallenge] and exclusion of other causes, and use of other potentially hepatotoxic medications).

Christl SU, Seifert A, Seeler D. Toxic hepatitis after consumption of traditional kava preparation. J Travel Med 2009; 16: 55-6. PubMed PMID: 19192130.

(42 year old man developed jaundice 4 weeks after heavy kava drinking on a trip to Samoa [bilirubin 9.3 rising to 31 mg/dL, ALT 2841 U/L, Alk P 285 U/L], resolving in 5 weeks).

Navarro VJ. Herbal and dietary supplement hepatotoxicity. Semin Liver Dis 2009; 29: 373-82. PubMed PMID: 19826971.

(Review of the problems of causality assessment in herbal and dietary supplement [HDS] associated liver disease, including the variable clinical presentations, the complexity and lack of information on their components, absence of controlled trials demonstrating safety and efficacy, the possibility of contamination or incorrect labeling and frequent underreporting of herbal use by patients. Regulation of HDS is under DSHEA, which requires manufacturers to determine safety and prohibits claims of efficacy in treating specific diseases. The US Pharmacopeia sets standards for food and drugs and includes HDS; HDS induced liver injury is a growing problem and currently accounts for at least 10% of cases of acute liver injury due to medications).

Jacobsson I, Jönsson AK, Gerdén B, Hägg S. Spontaneously reported adverse reactions in association with complementary and alternative medicine substances in Sweden. Pharmacoepidemiol Drug Saf 2009; 18: 1039-47. PubMed PMID: 19650152.

(Review of 778 spontaneous reports of adverse reactions to herbals to Swedish Registry; no mention of kava).

Reuben A, Koch DG, Lee WM; Acute Liver Failure Study Group. Drug-induced acute liver failure: results of a U.S. multicenter, prospective study. Hepatology 2010; 52: 2065-76. PubMed PMID: 20949552.

(Among 1198 patients with acute liver failure enrolled in a US prospective study between 1998 and 2007, 133 [11%] were attributed to drug induced liver injury of which 12 [9%] were due to herbals, but none were attributed to kava).

Teschke R. Kava hepatotoxicity: pathogenetic aspects and prospective considerations. Liver Int 2010; 30: 1270-9. PubMed PMID: 20630022.

(Review of the hepatotoxicity of kava).

Teschke R. Kava hepatotoxicity—a clinical review. Ann Hepatol 2010; 9: 251-65. PubMed PMID: 20720265.

(Review of the clinical features of kava hepatotoxicity with summaries of reported and published cases and discussion of difficulty in assigning causality to many).

Teschke R, Schulze J. Risk of kava hepatotoxicity and the FDA consumer advisory. JAMA 2010; 304: 2174-5. PubMed PMID: 21081732.

(Review of the evidence for and against the hepatotoxicity of kava: "Kava products of poor quality, non-adherence to usage recommendations or a combination of both appear to be the major causative factors").

Teschke R, Schulze J. Risk of kava hepatotoxicity and the FDA consumer advisory. JAMA 2010; 304: 2174-5. PubMed PMID: 21081732.

(Editorial on status of efforts to insure safety of kava, focusing on water extraction of kava roots only and licensing of specific growers; kava remains available in the United States).

Teschke R, Sarris J, Lebot V. Kava hepatotoxicity solution: A six-point plan for new kava standardization. Phytomedicine 2011; 18: 96-103. PubMed PMID: 21112196.

(Summary of approaches to insure the safety of kava, including licensing cultivars, use of peeled and dry roots only, aqueous extraction, limitations on dose and quality of kavalactones, further research and quality control).

Teschke R, Wolff A. Regulatory causality evaluation methods applied in kava hepatotoxicity: are they appropriate? Regul Toxicol Pharmacol 2011; 59: 1-7. PubMed PMID: 20854865.

(Commentary arguing that banning of kava was based upon faulty analysis of reported cases of hepatotoxicity and need for better and more objective causality assessment tools).

Stacy S. Relaxation drinks and their use in adolescents. J Child Adolesc Psychopharmacol 2011; 21: 605-10. PubMed PMID: 22136095.

(Review of relaxation drinks which now include more than 300 bottled beverages available in the US, some of which include kava as an anxiolytic and sleeping aid with names such as Bula and Malava).

Stickel F, Kessebohm K, Weimann R, Seitz HK. Review of liver injury associated with dietary supplements. Liver Int 2011; 31: 595-605. PubMed PMID: 21457433.

(Review of current understanding of liver injury from herbals and dietary supplements focusing upon Herbalife and Hydroxycut products, green tea, usnic acid, Noni juice, Chinese herbs, vitamin A and anabolic steroids; kava not discussed).

Baker JD. Tradition and toxicity: evidential cultures in the kava safety debate. Soc Stud Sci 2011; 41: 361-84. PubMed PMID: 21879526.

(Sociological analysis of the controversy surrounding the safety of kava stressing the cultural, social, and professional ["context-specific"] bases for differing interterpretations of the same data).

Teschke R, Lebot V. Proposal for a kava quality standardization code. Food Chem Toxicol 2011; 49: 2503-16. PubMed PMID: 21756963.

(Detailed proposals for standardization of the cultivation, harvesting, processing and manufacture of kava so as to insure high quality and lack of adulteration of kava products).

Olsen LR, Grillo MP, Skonberg C. Constituents in kava extracts potentially involved in hepatotoxicity: a review. Chem Res Toxicol 2011; 24: 992-1002. PubMed PMID: 21506562.

(Review of the phytochemical composition of kava preparations and the potential hepatoxicity of the individual components).

Teschke R, Qiu SX, Xuan TD, Lebot V. Kava and Kava Hepatotoxicity: Requirements for Novel Experimental, Ethnobotanical and Clinical Studies Based on a Review of the Evidence. Phytother Res 2011 Mar 28. [Epub ahead of print] PubMed PMID: 21442674.

(Review of kava hepatotoxicity and the phytochemistry of kava, suggesting that aflatoxin contamination may be the cause of the rare instances of liver injury).

Teschke R, Qiu SX, Lebot V. Herbal hepatotoxicity by kava: update on pipermethystine, flavokavain B, and mould hepatotoxins as primarily assumed culprits. Dig Liver Dis 2011; 43: 676-81. PubMed PMID: 21377431.

(Review of evidence that pipermethystine or flavokavain B might be hepatotoxic and contamination with aflatoxins might be the cause of liver injury attributed to kava ingestion).

Teschke R, Sarris J, Glass X, Schulze J. Kava, the anxiolytic herb: back to basics to prevent liver injury? Br J Clin Pharmacol 2011; 71: 445-8. PubMed PMID: 21284704.

(Review of the history of the discovery of kava and its introduction into Western medicine followed by reports of hepatotoxicity and possible explanations, concluding that for safety and optimal quality of kava products it is necessary "to go back to basics, back to using water extracts of peeled noble kava rhizomes and roots").

Rychetnik L, Madronio CM. The health and social effects of drinking water-based infusions of kava: a review of the evidence. Drug Alcohol Rev 2011; 30: 74-83. PubMed PMID: 21219501.

(Systematic review of the literature on safety of drinking kava found good evidence for side effects of skin rash, nausea, decreased appetite and weight loss, but no confirmed association with liver toxicity or permanent liver damage).

Sarris J, LaPorte E, Schweitzer I. Kava: a comprehensive review of efficacy, safety, and psychopharmacology. Aust N Z J Psychiatry 2011; 45: 27-35. PubMed PMID: 21073405.

(Review of the psychopharmacology, safety and efficacy of kava as an anxiolytic).

Teschke R, Fuchs J, Bahre R, Genthner A, Wolff A. Kava hepatotoxicity: comparative study of two structured quantitative methods for causality assessment. J Clin Pharm Ther 2010; 35: 545-63. PubMed PMID: 20831679.

(Analysis of 26 cases of suspected kava hepatotoxicity reported to regulatory agencies from Switzerland and Germany using the M&V and RUCAM causality assessment tools found most cases to be scored as "excluded" [16 and 15] or "unlikely" [7 and 2] by the two methods).

Sarris J, Teschke R, Stough C, Scholey A, Schweitzer I. Re-introduction of kava (Piper methysticum) to the EU: is there a way forward? Planta Med 2011; 77: 107-10. PubMed PMID: 20814850.

(Description of plans to evaluate the safety and efficacy of kava [Kalm project] in controlled trials with careful assessment of adverse events and mechanism of action using a well characterized kava product).

Teschke R, Sarris J, Schweitzer I. Kava hepatotoxicity in traditional and modern use: the presumed Pacific kava paradox hypothesis revisited. Br J Clin Pharmacol 2012; 73: 170-4. PubMed PMID: 21801196.

(Review and argument against the kava paradox, hepatotoxicity having occurred with traditional acqueous as well as with acetone or alcohol extracted preparations).

Teschke R, Wolff A, Frenzel C, Schulze J, Eickhoff A. Herbal hepatotoxicity: a tabular compilation of reported cases. Liver Int 2012; 32: 1543-56. PubMed PMID: 22928722.

(A systematic compilation of all publications on the hepatotoxicity of specific herbals identified 185 publications on 60 different herbs, herbal drugs and supplements, including 29 on kava).

Rowe A, Ramzan I. Are mould hepatotoxins responsible for kava hepatotoxicity? Phytother Res 2012; 26: 1768-70. PubMed PMID: 22319018.

(Letter arguing that the levels of alflatoxins reported to be found in kava preparations were not toxicologically significant and the most likely cause of kava hepatotoxicity are its natural constituents).

Sarris J, Stough C, Teschke R, Wahid Z, Bousman C, Murray G, Savage K, et al. Kava for the treatment of generalized anxiety disorder RCT: analysis of adverse reactions, liver function, addiction, and sexual effects. Phytother Res 2013; 27: 1723-8. PubMed PMID: 23348842.

(Controlled trial of kava [60-120 mg kavalactones twice daily] vs placebo for 6 weeks in 58 patients with generalized anxiety disorder found no change in ALT levels or other liver tests in either group).

Bunchorntavakul C, Reddy KR. Review article: herbal and dietary supplement hepatotoxicity. Aliment Pharmacol Ther 2013; 37: 3-17. PubMed PMID: 23121117.

(Systematic review of literature on HDS associated liver injury discusses the controversy over the potential hepatotoxicity of kava).

Toohey TP, Lu BY, Wada C. Toxic effects of psychotropics related to possible p450 enzyme inhibition by kava: report of 2 cases. Prim Care Companion CNS Disord 2013; 15 (5). pii. PubMed PMID: 24511438.

(Two women, ages 60 and 80 years old, on long term psychotropic agents [haloperidol, lorazepam, ropinirole] developed acute psychosis after starting or increasing daily kava use, suggesting herb-drug interactions).

Teschke R, Schulze J, Schwarzenboeck A, Eickhoff A, Frenzel C. Herbal hepatotoxicity: suspected cases assessed for alternative causes. Eur J Gastroenterol Hepatol 2013; 25: 1093-8. PubMed PMID: 23510966.

(Review of literature of case series of suspected HDS related liver injury found evidence of other explanations in 19 of 23 publications, involving 278 of 573 patients [49%] and including 50-58% of kava attributed cases; these other diagnoses weakened the causality assessment in most instances).

Teschke R, Sarris J, Lebot V. Contaminant hepatotoxins as culprits for kava hepatotoxicity--fact or fiction? Phytother Res 2013; 27: 472-4. PubMed PMID: 22585547.

(Commentary and proposal of possible solutions to kava hepatotoxicity based upon standardization of cultivation, harvest, avoidance of contamination, use of aqueous extracts and limitation of dose and duration of therapy).

Teschke R, Eickhoff A, Wolff A, Frenzel C, Schulze J. Herbal hepatotoxicity and WHO global introspection method. Ann Hepatol 2013; 12: 11-21. PubMed PMID: 23293189.

(Commentary on the WHO global introspection method because of its specificity for liver injury and attention to alternative explanations, such as hepatitis and other viral infections).

Sarris J, Stough C, Bousman CA, Wahid ZT, Murray G, Teschke R, Savage KM, et al. Kava in the treatment of generalized anxiety disorder: a double-blind, randomized, placebo-controlled study. J Clin Psychopharmacol 2013; 33: 643-8. PubMed PMID: 23635869.

(Controlled trial of 6 weeks of kava vs placebo in 58 patients with general anxiety disorder, found that 24% of kava vs 17% of placebo recipients developed elevated liver tests, but none developed clinically apparent liver injury [same study as described in Sarris et al. Phytotherapy Research 2013]).

Rossi S, Navarro VJ. Herbs and liver injury: A clinical perspective. Clin Gastroenterol Hepatol 2014; 12: 1069-76. PubMed PMID: 23924877.

(Review of current status of liver injury due to HDS including discussion of challenges of establishing causality and difficulties in identifying the potentially hepatotoxic component; discusses controversy surrounding hepatotoxicity of kava).

Björnsson ES, Bergmann OM, Björnsson HK, Kvaran RB, Olafsson S. Incidence, presentation and outcomes in patients with drug-induced liver injury in the general population of Iceland. Gastroenterology 2013; 144: 1419-25. PubMed PMID: 23419359.

(In a population based study of drug induced liver injury from Iceland, 96 cases were identified over a 2 year period, including 15 [16%] due to herbal and dietary supplements, none of which listed kava as a component).

Licata A, Macaluso FS, Craxì A. Herbal hepatotoxicity: a hidden epidemic. Intern Emerg Med 2013; 8: 13-22. PubMed PMID: 22477279.

(Review and commentary on herbal hepatotoxicity discusses kava).

Navarro VJ, Seeff LB. Liver injury induced by herbal complementary and alternative medicine. Clin Liver Dis 2013; 17: 715-35. PubMed PMID: 24099027.

(Review of HDS induced liver injury including regulatory problems, difficulties in diagnosis and causality assessment; mentions that kava containing products have been linked to cases of hepatitis, some of which were fatal or led to emergent liver transplantation).

Dağ MS, Aydınlı M, Oztürk ZA, Türkbeyler IH, Koruk I, Savaş MC, Koruk M, et al. Drug- and herb-induced liver injury: a case series from a single center. Turk J Gastroenterol 2014; 25: 41-5. PubMed PMID: 24918129.

(Between 2008 and 2012, 82 patients with drug or herbal supplement induced liver injury were seen at a single referral center in Turkey, 10 [12%] of which were due to HDS products, including 7 due to Teucrium polium [mountain germander] and 3 to green tea, but none to kava).

Teschke R, Genthner A, Wolff A, Frenzel C, Schulze J, Eickhoff A. Herbal hepatotoxicity: Analysis of cases with initially reported positive re-exposure tests. Dig Liver Dis 2014; 46: 264-9. PubMed PMID: 24315480.

(Reanalysis of 34 published cases of liver injury due to herbal medications in which there was a reported positive rechallenge, finding only 21 [62%] fulfilled the criteria of a positive rechallenge using RUCAM, the others having inconsistent [18%] or incomplete data [21%]; among 2 cases attributed to kava, 1 had a positive rechallenge and was considered highly probable while the other had an uninterpretable rechallenge yet was still considered probable).

Navarro VJ, Barnhart H, Bonkovsky HL, Davern T, Fontana RJ, Grant L, Reddy KR, et al. Liver injury from herbals and dietary supplements in the U.S. Drug-Induced Liver Injury Network. Hepatology 2014; 60:1399-408. PubMed PMID: 25043597.

(Among 85 cases of HDS associated liver injury [not due to anabolic steroids] enrolled in a US prospective study between 2004 and 2013, kava was a component of products taken by two patients , but both were also exposed to other potentially hepatotoxic herbs).

Navarro VJ, Lucena MI. Hepatotoxicity induced by herbal and dietary supplements. Semin Liver Dis 2014; 34: 172-93. PubMed PMID: 24879982.

(Review of HDS induced liver injury including regulatory problems, difficulties in diagnosis and causality assessment, mentions that kava has been linked to cases of cholestatic and hepatocellular hepatitis some of which were fatal).

Korth C. Drug-induced hepatotoxicity of select herbal therapies. J Pharm Pract 2014; 27: 567-72. PubMed PMID: 25546878.

(Review of liver injury due to selected HDS discusses the literature implicating kava, green tea extract, germander, pyrrolizidine alkaloids and Herbalife products).

Seeff LB, Bonkovsky HL, Navarro VJ, Wang G. Herbal products and the liver: a review of adverse effects and mechanisms. Gastroenterology 2015; 148: 517-32. PubMed PMID: 25500423.

(Extensive review of possible beneficial as well as harmful effects of herbal products on the liver mentions that there have been more than 100 reports of clinically apparent liver injury from kava).

Chalasani N, Bonkovsky HL, Fontana R, Lee W, Stolz A, Talwalkar J, Reddy KR, et al.; United States Drug Induced Liver Injury Network. Features and outcomes of 899 patients with drug-induced liver injury: The DILIN Prospective Study. Gastroenterology 2015; 148: 1340-52. PubMed PMID: 25754159.

(Among 899 cases of drug induced liver injury enrolled in a prospective database between 2004 and 2012, HDS were implicated in 145 [16%], the single major herbal cause being green tea and only 2 cases had exposure to a kava containing product [Navarro et al Hepatology 2014]).

Stickel F, Shouval D. Hepatotoxicity of herbal and dietary supplements: an update. Arch Toxicol. 2015; 89: 851-65. PubMed PMID: 25680499.

(Extensive review of liver injury due to HDS mentions that kava has been implicated in more than 100 cases of clinically apparent liver injury including 9 instances of acute liver failure, 3 of which resulted in deaths).

Aghdassi AA, Kraft M, Domschke W, Lerch MM, Weiss FU. Genetic polymorphisms in the UDP-glucuronosyltransferase UGT1A7 gene in patients with acute liver failure after kava-kava consumption. Arch Toxicol 2015; 89: 2173-4. PubMed PMID: 26298863.

*(Letter in response to Stickel [2015] suggesting that variants of UGT1A7*3 might explain the rare instances of kava related severe liver injury, the allele frequency being 37% in patients with acute liver failure attributed to kava, vs 16% to 36% of controls).*

Stickel F. Response to Aghdassi et al., Letter to the editor "Genetic polymorphisms in the UDP-glucuronosyltransferase UGT1A7 gene in patients with acute liver failure after kava-kava consumption". Arch Toxicol 2015; 89: 2175-6. PubMed PMID: 26475488.

*(Reply to the letter of Aghdassi [2015] arguing that the number of patients studied was few and that UGT1A7*3 is not expressed in the liver).*

Kuchta K, Schmidt M, Nahrstedt A. German kava ban lifted by court: the alleged hepatotoxicity of kava (Piper methysticum) as a case of ill-defined herbal drug identity, lacking quality control, and misguided regulatory politics. Planta Med 2015; 81: 1647-53. PubMed PMID: 26695707.

(Commentary and review of the 2014 German court reversal of the 2002 regulatory ban of kava [BfArM 2002]).

Pantano F, Tittarelli R, Mannocchi G, Zaami S, Ricci S, Giorgetti R, Terranova D, et al. Hepatotoxicity induced by "the 3Ks": kava, kratom and khat. Int J Mol Sci 2016; 17: 580. PubMed PMID: 27092496.

(Review of the components and laboratory and clinical evidence for hepatotoxicity of three herbals: kava, kratom and khat).

García-Cortés M, Robles-Díaz M, Ortega-Alonso A, Medina-Caliz I, Andrade RJ. Hepatotoxicity by dietary supplements: A tabular listing and clinical characteristics. Int J Mol Sci 2016; 17. pii: E537. PubMed PMID: 27070596.

(Listing of published cases of liver injury from HDS products, but does not list those attributed to kava).

Avigan MI, Mozersky RP, Seeff LB. Scientific and regulatory perspectives in herbal and dietary supplement associated hepatotoxicity in the United States. Int J Mol Sci 2016; 17: 331. PubMed Citation (Overview of the US regulations regarding herbal and dietary supplements and role of FDA, Department of Agriculture, Federal Trade Commission and Office of Dietary Supplements of the NIH in assessment of safety of HDS products including actions taken against Hydroxycut, Lipokinetix and OxyELITE Pro when reports of liver injury appeared in postmarketing phase).

Marcus DM. Dietary supplements: What's in a name? What's in the bottle? Drug Test Anal 2016; 8 (3-4): 410-2. PubMed Citation (Commentary on regulation of HDS products concludes: "the marketing of botanical supplements is based on unfounded claims that they are safe and effective", and "there is no reason to take herbal medicines whose composition and benefits are unknown and whose risks are evident").

Brown AC. An overview of herb and dietary supplement efficacy, safety and government regulations in the United States with suggested improvements. Part 1 of 5 series. Food Chem Toxicol 2017; 107 (Pt A): 449-71. PubMed PMID: 27818322.

(Summary of the US regulations on safety and efficacy of herbal and dietary supplements).

Brown AC. Liver toxicity related to herbs and dietary supplements: Online table of case reports. Part 2 of 5 series. Food Chem Toxicol 2017; 107 (Pt A): 472-501. PubMed PMID: 27402097.

(Description of an online compendium of cases of liver toxicity attributed to HDS products, lists at least 10 reports of liver injury attributed to kava).

Wong LL, Lacar L, Roytman M, Orloff SL. Urgent liver transplantation for dietary supplements: an under-recognized problem. Transplant Proc 2017; 49: 322-5. PubMed PMID: 28219592.

(Among 2048 adult liver transplants recipients enrolled in the Scientific Registry of Transplant Recipients [SRTR] between 2003 and 2015, 625 were done for acute hepatic necrosis due to drug induced liver injury, half being due to acetaminophen and the 4th most frequent cause [n=21] being HDS products).

de Boer YS, Sherker AH. Herbal and dietary supplement-induced liver injury. Clin Liver Dis 2017; 21: 135-49. PubMed PMID: 27842768.

(Review of the frequency, clinical features, patterns of injury and outcomes of HDS hepatotoxicity with specific mention of anabolic steroids, black cohosh, germander, green tea, kava, pyrrolizidine alkaloids and proprietary multiingredient nutrition supplements [MINS]).

Vega M, Verma M, Beswick D, Bey S, Hossack J, Merriman N, Shah A, et al; Drug Induced Liver Injury Network (DILIN). The incidence of drug- and herbal and dietary supplement-induced liver injury: preliminary findings from gastroenterologist-based surveillance in the population of the State of Delaware. Drug Saf 2017; 40: 783-7. PubMed PMID: 28555362.

(A prospective, population based registry of cases of drug induced liver injury occurring in Delaware during 2014, identified 20 cases [2.7 per 100,000] overall, including 6 due to HDS products, all of which were proprietary multiingredient products, none specifically listing kava as a component).

Navarro VJ, Khan I, Björnsson E, Seeff LB, Serrano J, Hoofnagle JH. Liver injury from herbal and dietary supplements. Hepatology 2017; 65: 363-73. PubMed PMID: 27677775.

(Review of the problems of liver injury and HDS products, specifically discusses anabolic steroids, green tea extract and OxyELITE Pro, but does not mention kava).