

Hepatic Toxicity Possibly Associated With Kava-Containing Products – United States, Germany, and Switzerland, 1999-2002

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Since 1999, health-care professionals in Germany, Switzerland, and the United States have reported the occurrence of severe hepatic toxicity possibly associated with the consumption of products containing kava (i.e., kava kava or *Piper methysticum*). A total of 11 patients who used kava products had liver failure and underwent subsequent liver transplantation.¹⁻⁷ On March 25, 2002, in response to five such case reports (four in Europe and one in the United States), the Food and Drug Administration (FDA) issued a consumer advisory⁸ and subsequently completed an investigation already underway of a similar U.S. case. This report presents the investigation of the two U.S. cases of liver failure associated with kava-containing dietary supplement products and summarizes the European cases. FDA continues to advise consumers and health-care providers about the potential risk associated with the use of kava-containing products.

Case Reports

Case 1

In May 2001, a previously healthy woman aged 45 years reported the onset of nausea and weakness approximately 8 weeks after beginning use of a kava-containing dietary supplement that listed on the package label, "Kava kava extract (root), standardized to 30% kavalactones (75 mg), hops (strobiles), German chamomile (flower head), passion flower (flower and fruit), gelatin, and natural vegetable fiber." The patient reported taking one tablet twice daily, which was less than the package label recommendation of one tablet three times daily. The patient reported no concomitant medication or dietary supplement use and rare alcohol ingestion (one to two drinks a year). The patient was initially prescribed rabeprazole for acid reflux symptoms, and this drug was taken for 4 days. In addition, the patient discontinued use of the kava-containing supplement. Several days later, the patient was hospitalized with jaundice and hepatitis. Liver biopsy demonstrated subfulminant hepatic necrosis. Autoimmune and infectious hepatitis tests were negative. Liver transplantation was performed in July 2001, and the patient resumed daily activities following recovery from the procedure.

Case 2

In December 2000, a previously healthy girl aged 14 years reported the onset of nausea, vomiting, decreased appetite, weight loss, and fatigue. One week later, the patient had scleral icterus and was hospitalized with acute hepatitis. During late August to mid-December 2000, the patient reportedly used two kava-containing products. One product was taken intermittently in accordance with package directions (two capsules once daily). The patient estimated that she used the product on approximately 44 days during this period. The patient reported taking the second product in accordance with package directions (two capsules once daily) for 7 consecutive days at the beginning of the 4-month period. Because the product labels were unavailable, other product ingredients were unknown. The patient reported no use of alcohol or medications other than occasional ibuprofen. At the time of hospitalization, the patient's liver-function tests were markedly abnormal (alanine aminotransferase: 4,076 U/L, aspartate aminotransferase: 3,355 U/L, gamma-glutamyltransferase: 148 U/L, total bilirubin: 16.2 mg/dL, ammonia: 17 mg/dL, and prothrombin time: 29.4 seconds).⁵ Tests for human immunodeficiency virus (HIV), cytomegalovirus, Epstein-Barr virus, Wilson's disease, α -antitrypsin deficiency, antinuclear antibodies, and hepatitis A, B, C, and E were negative. Initial

liver biopsy revealed active fulminant hepatitis with extensive centrilobular necrosis, approximately 25% hepatocellular viability, and mixed inflammatory infiltrates consisting of lymphocytes, histiocytes, scattered eosinophils, and occasional neutrophils. No viral cytopathic changes were identified, and immunohistochemical stains for hepatitis B surface and core antigens were negative. The patient underwent successful orthotopic liver transplantation. Pathological examination of the native liver revealed active fulminant hepatitis with total hepatocyte necrosis and extensive parenchymal infiltration by lymphocytes, histiocytes, and occasional eosinophils.⁵ The patient resumed daily activities following recovery from the procedure.

Summary of European Case Reports

Eight hepatic transplant cases following hepatic failure associated with the use of kava-containing products have been reported in Europe (six in Germany and two in Switzerland). Two male patients aged 32 and 50 years and six females aged 22-61 years required liver transplants after using kava-containing products. The duration of kava use ranged from 8 weeks to 12 months. The products were used at doses ranging from 60 mg to 240 mg per day. Seven patients used kava prepared either by ethanol or acetone extraction methods; one patient used an unspecified type of kava-containing product. The patients had varying symptoms, including influenza-like symptoms and jaundice. Each patient's condition worsened and progressed to fulminant hepatic failure. Four of these cases have been reported in medical literature.¹⁻⁴ Additional information about these cases is available from the German regulatory authority, the Federal Institute for Drugs and Medical Devices, Bonn, Germany, at <http://www.bfarm.de>. A ninth European transplant case was reported directly to FDA's MedWatch System by a U.S. pharmaceutical manufacturer.

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CDC Editorial Note:

Kava is a botanical product derived from the rhizome and roots of *Piper methysticum*, a shrub indigenous to the South Pacific. In the United States, kava-containing products are sold as dietary supplements and marketed for the treatment of anxiety, occasional insomnia, premenstrual syndrome, and stress. These supplements often are in the form of raw plant material or concentrated extracts, which are obtained by using either acetone or ethanol extraction or cryoprecipitation. Preparations marketed for human consumption contain a mixture of components collectively known as kava pyrones (i.e., kavalactones). Kava-containing products might differ based on the absolute amount of kava pyrones present and on the relative distribution of kava pyrones. Several countries, including Germany, Switzerland, Canada, Australia, and France, have restricted the sale of kava-containing products based on the occurrence of hepatic adverse events and the documented hepatic toxicity following rechallenge with a kava-containing product.⁹ FDA research suggests that <1% of the severe adverse events that occur with the use of dietary supplements are reported to FDA.¹⁰

FDA has advised consumers and health-care providers about the potential risk for hepatic toxicity associated with the use of kava-containing products.⁷ Additional caution by persons who have pre-existing liver disease or are at risk for liver disease might be warranted. Health-care providers should consider questioning patients with evidence of hepatic injury about the use of dietary supplements and herbal products. Adverse events associated with the use of any dietary supplement should be reported to FDA's MedWatch Program, telephone 800-332-1088, or <http://www.fda.gov/medwatch>.

REFERENCES

1. Brauer RB, Pfab R, Becker K, Berger H, Stangl M. Fulminantes Leberversagen nach Einnahme des

pflanzlichen heilmittels kava-kava. Z Gastroenterol. 2001;39:491.

2. Escher M, Desmeules J, Giostra E, et al. Hepatitis associated with kava, a herbal remedy for anxiety. BMJ. 2001;322:139. [MEDLINE](#)

3. Kraft M, Spahn TW, Menzel J, et al. Fulminant liver failure after administration of the herbal antidepressant kava-kava. Dtsch Med Wochenschr. 2001;126:970-2. [MEDLINE](#)

4. Sass M, Schnabel S, Kröger J, Liebe S, Schareck WD. Acute liver failure from kava-kava—a rare indication for liver transplantation. Z Gastroenterol. 2001;39:491.

5. 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. [MEDLINE](#)

6. Humbertston C, Akhtar J, Krenzelok E. Acute hepatitis induced by kava kava, an herbal product derived from Piper methysticum. J Clin Toxicol. 2001;39:549.

7. Russmann S, Lauterburg BH, Helbling A. Kava hepatotoxicity. Ann Intern Med. 2001;135:68-9. [MEDLINE](#)

8. Food and Drug Administration. Letter to health-care professionals: FDA issues consumer advisory that kava products may be associated with severe liver injury. Rockville, Maryland: U.S. Department of Health and Human Services, Food and Drug Administration, 2002. Available at: <http://www.cfsan.fda.gov/~dms/addskava.html>.

9. Strahl S, Ehret V, Dahm HH, Maier KP. Necrotizing hepatitis after taking herbal remedies. Dtsch Med Wochenschr. 1998;123:1410-4. [MEDLINE](#)

10. Walker AM. The relation between voluntary notification and material risk in dietary supplement safety. Food and Drug Administration docket 00N-1200, 2000. Available at <http://www.fda.gov/ohrms/dockets/00n1200>.