

Kava Induced Hepatotoxicity In Sacramento County

Ashwin Sidhu^{1*}, Supreet Atwal², Lauren Bliss³

¹California Northstate University College of Medicine, 9700 W. Taron Dr., Elk Grove, CA, USA

²University of Pikeville Kentucky College of Osteopathic Medicine, 147 Sycamore St., Pikeville, KY, USA

³University of California Santa Cruz, 1156 High St., Santa Cruz, CA, USA

***Corresponding Author:** Ashwin Sidhu, California Northstate University College of Medicine, 9700 W. Taron Dr., Elk Grove, CA, USA. ORCID ID: 0000-0001-7531-0095.

Received date: 14 July 2023; **Accepted date:** 21 July 2023; **Published date:** 27 July 2023

Citation Sidhu A, Atwal S, Bliss L (2023) Kava Induced Hepatotoxicity In Sacramento County. J Med Case Rep Case Series 4(12):

<https://doi.org/10.38207/JMCRCS/2023/JUL04120376>

Copyright: © 2023 Ashwin Sidhu. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Abstract

Kava, a traditional herbal remedy, has gained popularity worldwide for its purported anxiolytic and sedative properties. However, growing data indicates a possible connection between kava use and hepatotoxicity. Several countries have imposed limitations or outright prohibitions on the sale and use of kava because of regulatory worries about its safety. This case report seeks to provide an overview of the current understanding of acute liver failure brought on by kava poisoning, including its clinical manifestation, underlying mechanisms, diagnostic markers, management, and public health implications. This case report demonstrates the need for additional investigation to elucidate the mechanisms underlying kava-induced hepatotoxicity and create uniform recommendations for its safe usage. Despite the rarity, it is imperative to have kava-induced toxicity on the differential diagnosis for a patient with acute liver failure.

Kava-induced acute liver failure is a rare but serious adverse event associated with this herbal remedy. The clinical presentation of kava poisoning-induced acute liver failure varies, ranging from mild symptoms such as jaundice and fatigue to more severe manifestations, including coagulopathy. The underlying mechanisms of kava-induced hepatotoxicity remain unclear, but proposed theories include the modification of CYP450 enzymes and the formation of active metabolites. Elevated liver enzymes and bilirubin levels are critical diagnostic markers for kava poisoning-induced acute liver failure. Management of kava poisoning-induced acute liver failure primarily involves discontinuing kava use and supportive care. In severe cases, liver transplantation may be necessary to improve patient outcomes.

Keywords: Kava, Hepatotoxicity, Herbal remedy, Liver transplantation, Case report

Introduction

Kava (kava-kava, ava, and awa) is the dried pulverized root of various *Piper methysticum* species. Kava is known to have psychoactive properties, like those in alcohol, and can be ingested through pills, herbal medicine, or in beverage form [1]. The active ingredients in the plant are kavapyrones (kavalactones), which provide similar effects as alcohol, such as muscle relaxation, euphoria, and improved overall well-being [2]. Historically, it has been used as a recreational and ceremonial beverage throughout Oceania (Polynesia, Micronesia, and Micronesia), but more recently, kava has been used in treating anxiety, insomnia, and stress worldwide [3]. These herbal kava supplements can be purchased over the counter for as little as \$12 for 30 capsules online and in supermarkets.

Kava products have recently been linked to acute liver injury resulting in hepatitis, cirrhosis, liver failure, and even death [4]. There have been 16 reported cases of liver injury from 1984-2021, with 13 of these cases requiring hospitalization and 6 of these cases requiring a

liver transplant. The number of publications addressing herbal hepatotoxicity has significantly risen between 2001-2021 [5]. Other side effects have been reported, such as dizziness, drowsiness, tremors, loss of appetite, loss of hair, and yellow skin discoloration [4]. There is a potential for abuse of kava products, but it is rare when conventional dosages are taken [2].

Kava is not a controlled substance in the United States but has various regulations in other countries, such as Australia, the United Kingdom, and the European Union [6]. Since 2007, Australian law has required a special permit from the Department of Health to sell and import kava [7]. In 2017, Belgium determined that kava was too toxic to be included in food supplements, and in 2002 all kava-containing products were withdrawn from the market in Hungary [8]. In the Czech Republic and Spain, all kava products have been removed from the market since 2002 [8]. The United Kingdom prohibited kava in all unlicensed medicines in 2003, and in 2002, France suspended preparations containing kava unless they were homeopathic remedies

with dilutions of 1/500 or greater [8]. Kava herbal supplement global policies are summarized in **Table 1**. Liver injury severity has ranged

from elevated enzymes to hepatitis to liver transplantation because of acute liver failure.

Table 1: Kava Herbal Supplement Global Policies

Banned	Regulated	Unregulated
Belgium	France	United States of America
Czech Republic	Australia	---
Spain	United Kingdom	---
Hungary	---	---

Case Presentation

Case 1:

Kava toxicity leading to acute liver failure requiring liver transplantation.

A 59-year-old female with a medical history of migraines, chronic neck, and back pain, and total hysterectomy in 2006 presented to the emergency department in early March of 2023 with her husband for a chief complaint of right-sided abdominal pain. Her abdominal pain started 6 to 7 days prior and was described as an aching 8/10 pain radiating to the back. She had associated nausea, nonbloody, nonbilious emesis, anorexia, and generalized weakness. Also, she had been having subjective fever and sweats for the past few days. However, on review of systems, she denied myalgias, constipation, rash, focal weakness, cough, shortness of breath, chest pain, palpitation, diarrhea, dysuria, or urinary frequency. She has been taking about 4 g of Tylenol daily for 10-15 years for migraine headaches and chronic neck and back pain. Other medications include Nortriptyline 50 mg, which she takes 2 tablets by mouth daily at bedtime, and Armour Thyroid 30 mg, which she takes 2-3 oral pills in the morning. In addition, she recently started taking 2 tablets of the herbal supplement Kava every night for at least the past 10 months. The patient has no history of tobacco use and consumes alcohol rarely (about 1-2 drinks per year). She has no record of hepatitis and denies a family history of liver disease or liver cancer.

The patient’s vitals on presentation were stable, except for mild tachycardia. She was afebrile, her blood pressure was 132/77 mmHg, her pulse was 103 beats/min, and her respiratory rate was 16 breaths/minute with an oxygen saturation of 98% on room air. The patient was awake, alert, and oriented to person, place, and time on the physical exam. The patient’s eyes showed scleral icterus and an abdominal exam revealed a soft, non-distended abdomen that was mildly tender to palpation in the right upper quadrant without rebound or guarding. The remainder of the physical exam was benign.

Immediately in the ED, the patient was started on ceftriaxone 1 g IV, metronidazole 500 mg PO, 2 L of lactated Ringer’s, morphine 4 mg

IV, and Zofran 4 mg IV. Workup in the ED was significant for abnormal liver enzymes. Alanine transaminase (ALT) was 3697, aspartate transaminase (AST) was 5100, alkaline phosphatase (ALP) was 263, and total bilirubin was 5.0 (**Table 2**). Ultrasound of the right upper quadrant was routine, and CT of the abdomen and pelvis revealed hepatic steatosis but no acute findings. Acetaminophen level was 30. Upon more labs, the patient’s WBC count was 18.5, and lactate was 8.7. The patient’s basic metabolic panel was standard except for a mildly low bicarbonate level of 19 (**Table 2**). Blood cultures, and hepatitis A, B, and C panels were in progress, while the COVID-19 screen was negative. Chest x-ray and urinalysis were unremarkable.

Gastroenterology was consulted, who recommended starting acetylcysteine IV, trending liver enzymes, obtaining an international normalized ratio (INR), and follow-up on hepatitis serology.

The next day, the patient’s condition worsened. Her blood pressure was low in the 80s symbolically, and she was started on Levophed. INR returned at 9, and lactate was up to 11 from acute liver failure. The ammonia level was 483. She was lethargic with asterixis. ALT, AST, and ALP had increased. However, total bilirubin was down-trending. The patient was also noted to have elevated creatinine of 1.64 (**Table 2**). The patient had an acidotic venous blood gas with a pH of 7.19 (pCO₂ 34, pO₂ 66, HCO₃⁻ 12). As a result, a sodium bicarbonate drip was started. Hepatitis serology and blood cultures came back negative.

The Liver Transplant Advisory Board was called, and a transfer to the University of California, San Francisco (UCSF) was approved. The case was discussed with the UCSF liver transplant team, who recommended continuous renal replacement therapy (CRRT) for worsening kidney function. The patient was transferred to UCSF and underwent liver transplantation.

Table 2: Case 1 Patient's Laboratory Results

	Day 1 (Admission Date)	Day 2	Reference Range
Aspartate Transaminase (AST)	5100 (High)	13851 (High)	8-20 U/L
Alanine Transaminase (ALT)	3697 (High)	8684 (High)	8-20 U/L
Alkaline Phosphatase (ALP)	263 (High)	295 (High)	20-70 U/L
Total Bilirubin	5.0 (High)	4.7 (High)	0.1-1.0 mg/dL
Ammonia	---	483 (High)	11-32 µmol/L
Sodium	135	137	135-145 mEq/L
Potassium	4.4	4.2	3.5-5.0 mEq/L
Bicarbonate	19 (Low)	18 (Low)	22-28 mEq/L
Chloride	96	97	95-105 mEq/L
Blood urea nitrogen (BUN)	13	16	7-18 mg/dL
Creatinine	0.83	1.64 (High)	0.6-1.2 mg/dL
Calcium	9.0	8.4	8.4–10.2 mg/dL
Phosphorus	5.2 (High)	6.5 (High)	3.0–4.5 mg/dL
Magnesium	2.0	1.9	1.5–2.0 mg/dL
Lactate	8.7 (High)	11.0 (High)	1-2 mmol/L
Lipase	37	----	10-140 U/L
White blood cell (WBC)	18.5	----	4500–11,000/mm ³
Hemoglobin	15.6	----	12.0–16.0 g/dL
Prothrombin time (PT)	----	72.3 (High)	11–15 seconds
International normalized ratio (INR)	----	>9.0 (High)	0.9-1.1

Case 2:

Kava toxicity in a patient with chronic hepatitis B.

The patient is a 43-year-old male with a history of chronic hepatitis B who presented with a chief complaint of elevated liver enzymes in April of 2023. Per the patient, about 3 weeks ago, he started using Kava powder. He estimated he was using about half a pound every day. For the past few days before the presentation, he noticed his eyes were yellowing. He denied using any other supplements or herbal medication. He denied any family history of liver disease or liver cancer. Also, the patient stated that he had not used Tylenol excessively or drunk alcohol. On admission, the patient's transaminases were significantly elevated at an ALT of 2642 and AST of 2198. Alkaline phosphatase was mildly elevated, but total bilirubin was 10.6 (**Table 3**). Ultrasound of the abdomen showed no acute abnormality. The patient's chronic hepatitis B is eAg antigen

negative, and he had a hepatitis B DNA level < 10, thus inconsistent with hepatitis B flare. The patient had a MELD score of 20.

The patient was admitted to the hospital to manage acute severe hepatitis, likely due to drug-induced liver injury from Kava use. He was treated with supportive care and N-acetylcysteine (NAC) infusion. Also, the patient was started on Entecavir empirically at 1 mg, given the concern for occult cirrhosis with a history of low platelets (**Table 3**). A UCSF liver transplantation hepatologist was consulted and recommended continuous NAC infusion until total bilirubin stabilizes and continuing Entecavir.

Throughout his admission, his liver enzymes trended downward and continued to improve, and INR remained near normal. He eventually tolerated oral intake without nausea or vomiting, and his mental status remained normal. He was cleared for discharge by gastroenterology

about a week after admission. Follow-up liver function tests were ordered, and close outpatient gastroenterology follow-up was planned. The patient was counseled to avoid all supplements, over-

the-counter medicines, and alcohol intake. Entecavir was continued on discharge.

Table 3: Case 2 Patient's Laboratory Results

	Day 1 (Admission Date)	Day 2	Reference Range
Aspartate Transaminase (AST)	2198 (High)	2162 (High)	8-20 U/L
Alanine Transaminase (ALT)	2642 (High)	2360 (High)	8-20 U/L
Alkaline Phosphatase (ALP)	106 (High)	95 (High)	20-70 U/L
Total Bilirubin	10.6 (High)	10.3 (High)	0.1-1.0 mg/dL
Lipase	69	----	10-140 U/L
Sodium	135	139	135-145 mEq/L
Potassium	3.7	3.9	3.5-5.0 mEq/L
Bicarbonate	30	29	22-28 mEq/L
Chloride	99	104	95-105 mEq/L
Blood urea nitrogen (BUN)	16	10	7-18 mg/dL
Creatinine	0.80	0.62	0.6-1.2 mg/dL
Magnesium	----	2.1	1.5–2.0 mg/dL
White blood cell (WBC)	6.6	4.8	4500–11,000/mm
Hemoglobin	15.4	14.5	12.0–16.0 g/dL
Platelet	101 (Low)	83 (Low)	150,000–400,000/mm ³
Prothrombin time (PT)	17.8 (High)	----	11–15 seconds
Partial thromboplastin time (PTT)	32.1	----	25–40 seconds
International normalized ratio (INR)	1.5 (High)	----	0.9-1.1

Discussion

The mechanisms by which Kava incites hepatotoxicity remain to be determined. However, there are two potential courses of action. The first method involves kava-drug interactions through modification of CYP450 enzymes, which can affect drug metabolism. A study by Stral et al. showed that a woman who consumed Kava for 3 weeks had hepatotoxicity and inhibition of cytochrome P450 [9]. Another study showed that Kava caused a 3-to-4-fold increase in CYP3A4 expression compared to control CYP3A4 mRNA [10]. Most therapeutic drugs in the market are targeted by CYP3A4 enzymes [11]. Therefore, kava consumption can affect drug metabolism through modification of enzyme expression.

The second mechanism by which Kava can induce hepatotoxicity involves the possible formation of active metabolites [12]. A study done by Johnson et al. was completed by incubating a kava extract with hepatic microsomes, NADPH, and GSH in vitro. An electrospray and ion scanning were used to elucidate the structures. Using a screening assay, they identified two Kava electrophilic quinoid metabolites. The formation of the metabolites by hepatic microsomes suggests that these metabolites can contribute to hepatotoxicity by altering metabolic pathways by drug interaction or enzyme expression through possible covalent bonds to DNA.

It cannot be confirmed that Kava is the cause of hepatotoxicity or other liver-related injuries. In fact, through recent studies,

hepatotoxicity has not been reproducible in experimental preclinical models on whole kava extracts [13]. However, kava consumption is still under the Food and Drug Administration (FDA) regulatory advisory notifying consumers of possible liver-related injuries, including hepatitis, cirrhosis, and liver failure in over 25 reports of adverse events in other countries, a few requiring liver transplantations. In some cases, it is used for treatment of generalized anxiety disorder. Experts advise that an effective dose ranges from 70 to 250 mg and that exceeding 250 mg may lead to adverse reactions [14].

Presentation of liver injury due to kava consumption varies depending on the individual; however, patients generally present with fatigue, nausea, scleral icterus, and jaundice like the patients in the case presentation. Symptoms typically begin 2-24 weeks after consistently

Conclusion

These cases underscore the significance of considering Kava as a potential causative factor in situations involving sudden, severe liver injury that is not explained by other possible causes. The presented cases demonstrate an association between kava consumption and the onset of hepatotoxicity, as evidenced by significant elevations in liver enzymes and clinical symptoms consistent with acute liver injury. As a result, healthcare professionals must be more aware of the possible hepatotoxic consequences of Kava, particularly in patients who have pre-existing liver disorders or are taking concurrent medications.

It is essential to promptly identify and diagnose kava-induced liver toxicity to provide proper therapy and prevent further liver damage.

References

- Soares RB, Dinis-Oliveira RJ, Oliveira NG (2022) An Updated Review on the Psychoactive, Toxic and Anticancer Properties of Kava. *Journal of Clinical Medicine*. 11(14): 4039.
- Kava Kava (2012) *LiverTox: Clinical and Research Information on Drug-Induced Liver Injury*. National Institute of Diabetes and Digestive and Kidney Diseases.
- Pepping J (1999) Kava: Piper methysticum. *American Journal of Health-System Pharmacy*. 56(10): 957–958.
- Kava Kava Information Mount Sinai—New York (2023) Mount Sinai Health System.
- Drug Enforcement Administration (2019) Kava- Other Names: Ava, Intoxicating Pepper, Kawa Kawa, Kew, Sakau, Tonga, Yangona. Diversion Control Division Drug & Chemical Evaluation Section
- Assis MH, Alves BC, Luft VC, Dall'alba V (2022) Liver injury induced by herbal and dietary supplements: A pooled analysis of case reports. *Arquivos de Gastroenterologia*. 59(4): 522–530.
- Imported Food Risk Statement Kava (Piper methysticum) (2021) Australia New Zealand Food Standards Code. (1): 2-4.
- Assessment Report on Piper methysticum G. Forst., rhizoma (2017) European Medicines Agency: Science, Medicines, Health. 10-13.
- Strahl S, Ehret V, Dahm HH, Maier KP (1998) Necrotizing hepatitis after taking herbal remedies. *Dtsch Med Wochenschr*. 123(47): 1410–4.
- Raucy JL (2003) Regulation of CYP3A4 expression in human hepatocytes by pharmaceuticals and natural products. *Drug Metab Dispos*. 31(5): 533-9.
- Belpaire FM, Bogaert MG (1996) Cytochrome P450: genetic polymorphism and drug interactions. *Acta Clinica Belgica*. 51(4): 254–260.
- Whitton PA, Lau A, Salisbury A, Whitehouse J, Evans CS (2003) Kava lactones and the kava-kava controversy. *Phytochemistry*. 64(3): 673–9.
- Teschke R, Sarris J, Lebot V (2012) Contaminant Hepatotoxins as culprits for kava hepatotoxicity - fact or fiction? *Phytotherapy Research*. 27(3): 472-4.
- Sarris J, Stough C, Teschke R, Wahid ZT, Bousman CA, et al. (2013) Kava for the treatment of generalized anxiety disorder

using the product [15]. Some cases include immunologic hepatitis, which may involve fever and rash on presentation. Liver-related injury can be confirmed through lab work, typically showing elevations in serum aminotransferase and minor increases in alkaline phosphatase levels. A case series from New Caledonia also showed high serum γ GT activities in most cases and marginally elevated AST activities in a few heavy users of traditional kava extracts [16]. In severe cases, liver biopsy can show subfulminant hepatic necrosis, which may require a liver transplant. For moderate cases, treatment can include N-acetylcysteine infusion and supportive care, although there is no current standard of treatment for kava-related liver injury. The long-term effects of Kava consumption have not yet been determined. Although the FDA has issued warnings about liver-related damage, Kava is still available in the United States.

In these situations, immediate cessation of kava use and careful monitoring of liver function tests are essential. As patients may only sometimes give such information voluntarily, healthcare professionals should also ask about using herbal treatments and supplements during initial patient assessments. By disseminating knowledge and promoting evidence-based practices, we can improve patient outcomes and prevent future cases of kava-induced liver toxicity.

Acknowledgment: We would like to thank Dr. Gary Chu for his mentorship during the writing of this report.

- RCT: analysis of adverse reactions, liver function, addiction, and sexual effects. *Phytotherapy Research*. 27(11): 1723-8.
15. Wooltorton E (2002) Herbal kava: reports of liver toxicity. *CMAJ* 166(6): 777.
16. Russmann S, Barguil Y, Cabalion P, Kritsanida M, Duhet D, et al. (2003) Hepatic injury due to traditional aqueous extracts of kava root in New Caledonia. *Eur J Gastroenterol Hepatol*. 15(9): 1033-6.