# A Probable Case of Kava Induced Cholestatic Liver Injury with Causality Assessment by the updated RUCAM

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**Abstract:** Kava's safety profile continues to be debated as previous case reports have not performed adequate causality assessments or have only demonstrated possible causality. Furthermore, the pathogenicity of kava induced liver injury remains poorly understood. We describe here a case of cholestatic liver injury in a 48-year-old male with a two-month history of kava ingestion who presented with jaundice. After adjusting medications and stopping kava, the patient's liver enzymes trended down. Using the Roussel Uclaf Causality Assessment Method (RUCAM), which is the most up-to-date diagnostic causality algorithm for herb and drug induced liver injury, kava was determined to be the probable cause of the patient's liver injury along with possible causality from comedication. As comedication is a common feature among kava-induced liver injury, the pathogenicity may involve metabolic interactions between kavalactones and other exogenous substrates. Based on these findings, providers should continue warning patients of potentially fatal liver injury associated with kava use, especially with comedication, until quality control standards can ensure its safety.

**Keywords:** Herb induced liver injury, kava, RUCAM, causality assessment, dietary supplements.

## INTRODUCTION

In 2002, the FDA began advising consumers of the potential risk of severe liver injury associated with the use of kava-containing supplements after more than 25 reports emerged internationally of liver-related injury. The degree of liver injury associated with kava use also prompted regulatory agencies in Germany, Switzerland, France, Canada and the United Kingdom to issue warnings about the risks of kava ingestion, and in some instances, to ban the sale of kava-containing products [1,2]. In the United States, the FDA still urges consumers and health care providers to report any case of liver injury related to the use of kava-containing supplements as it seeks to further establish the relationship between kava and liver injury.

Kava is a psychoactive beverage made from the dried roots of the pepper plant *Piper methysticum.* The plant is indigenous to the South Pacific Islands where it has been used ceremonially and recreationally for centuries as a ritual beverage for its intoxicating calming effect [3]. Today, kava-containing supplements are widely available commercially and promoted to reduce stress, anxiety symptoms, inflammation, and to improve restful sleep. These claims, however, have not been evaluated by the FDA.

Results from the 2002 NHIS survey estimated that 2.4 million people, nearly one percent of Americans, had used kava in the prior 12 months for health reasons [4]. Due to its widespread use as a dietary supplement and its insufficient toxicity data, the National Cancer Institute nominated kava for toxicology assessment [5]. Research has largely focused on kava's anti-anxiety effects and its use as an alternative to anxiolytics. A 2010 meta-analysis found kava extract to be an effective treatment for symptoms of anxiety when compared to placebo, though the effect size was small and lacked robustness [6].

Kava's safety continues to be debated. While many case reports have documented kava use that exceeds the recommended dosage, other cases suggest there is still a risk of toxicity with normal daily doses and within the recommended usage duration [7-11]. With the passage of legislative and regulatory bans, critics have argued that the cases used as evidence by regulatory bodies relied on ad hoc evaluations that rarely demonstrated a clear causal relationship, or even the use of a causality assessment [12,13]. We present here a probable case of kava hepatoxicity using the Roussel Uclaf Causality Assessment Method, the most up-to-date causality assessment [14].

## CASE REPORT

A 48-year-old male with a past medical history of atrial fibrillation, hypertension, hyperlipidemia, alcohol abuse, anxiety, and depression presented to the emergency department complaining of four days of progressive jaundice. He reported that twelve days prior, he ran out of his prescribed Alprazolam and began consuming five beers per evening to fall asleep. He stated that over the past five years, he was

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compliant with his medications, which included Metoprolol, Pravastatin, Rivaroxaban, Clonidine, Alprazolam, Escitalopram, and Omega-3 Fatty Acids. He also reported taking kava root (Gaia Herbs, Inc., Cultivar: Vanuatu, other ingredients: alcohol USP and water, recommended use: 37.5 mg, 50 mg or 75 mg three times per day for maximum of one month) for the past two months for anxiety, as well as melatonin, and over-the-counter diphenhydramine for sleep. The patient reported accompanying dark urine, decreased appetite, and anxiety, but denied fever, chills, headache, nausea, vomiting, abdominal pain, and dysuria. He denied smoking history, sick contacts, and recent travel history.

On physical exam, the patient was hemodynamically stable on room air with bilateral scleral icterus and jaundiced skin. Preliminary laboratory tests were notable for aspartate aminotransferase (AST) of 60 U/L (reference: 8 to 33 U/L), alanine aminotransferase (ALT) of 50 U/L (reference: 4 to 36 U/L), alkaline phosphatase (ALP) of 335 U/L (reference: 20 to 130 U/L), as well as a total bilirubin of 23.1 mg/dL (reference: 0.1 to 1.2 mg/dL) with a direct bilirubin of 19.1 mg/dL. Urine drug screening was negative for routine illicit drugs and acetaminophen, and alcohol was not detectable in the serum. Subsequent studies performed to uncover the etiology of the patient's jaundice included antinuclear antibodies (ANA), anti-mitochondrial antibody, and smooth muscle immunoglobulin G. Likewise, infectious causes of increased transaminases were investigated, including Hepatitis A, B, and C testing, as well as testing for Human Immunodeficiency Virus (HIV), Cytomegalovirus (CMV) and Epstein Barr Virus (EBV). All these laboratory tests were negative except for prior EBV infection. Ferritin levels were within normal values, ruling out hemochromatosis.

Abdominal ultrasound and CT of the abdomen and pelvis with intravenous contrast revealed hepatomegaly with hepatic steatosis. Gastroenterology specialists were consulted and per their recommendations, a Magnetic Resonance Cholangiopancreatography (MRCP) was obtained which again identified hepatomegaly with fatty infiltration of the liver. No evidence of biliary ductal dilatation or choledocholithiasis was found. The patient then underwent a CT-guided biopsy of his liver and the pathology report confirmed findings suggestive of moderate steatohepatitis, portal acute and chronic inflammation with scattered eosinophils and bile ductular proliferation. Trichrome and reticulin stain showed focal fibrous expansion of portal tracts, peri-cellular fibrosis, and rare stainable iron.

While hospitalized, the patient's medications were adjusted to minimize exposure to potentially hepatotoxic medications. His Atorvastatin was discontinued, his Rivaroxaban was changed to Apixaban, and his Metoprolol was changed to Carvedilol. Importantly, kava was stopped, and the patient was advised to discontinue taking any other herbal product following discharge. Toward the end of one week of hospitalization, the patient's liver enzymes were trending down. The patient was reassured that his conjunctival and skin discoloration would improve gradually, and he was discharged home in stable condition.

## DISCUSSION

Based on the designation criteria set for herb and drug induced liver injury, the patient described here presented with cholestatic liver injury [14]. A causality assessment was performed based on his cholestatic injury pattern using the updated Roussel Uclaf Causality Assessment Method (RUCAM) (Table **1**) [14]. Kava was scored 'probable' (score = 6) as the cause of his liver injury. An assessment was also performed for Rivaroxaban, as it too has been reported as a cause of drug induced liver injury [15]. Rivaroxaban was 'possible' (score = 4) as the cause of his liver injury. However, considering the patient had been taking Rivaroxaban for the past five years without issue, the course of his symptom onset is more compatible with the introduction of kava, in addition to taking other medications and consuming alcohol, which likely acted as an inciting event. The patient's other medications were also 'possible' (score = 3) contributors to his liver injury though previous hepatoxic reactions associated with their use are unknown.

Our case differs from other cases of kava hepatotoxicity as we have performed the most up-to-date causality assessment and found that kava was the 'probable' cause of the liver injury. In a review of kava hepatoxicity, only one patient of 14 was found to have 'probable' causality for kava with 'possible' comedication like our patient. Most patients in the review (nine of 14) were graded as having only 'possible' causality for kava ± comedication which in part has contributed to the ongoing debate of its safety profile. Unlike our patient, patients in the review were found to have high serum activities of ALT, but not ALP suggesting a hepatocellular type of liver injury [16].

**Table 1: Updated RUCAM for the Cholestatic or Mixed Liver Injury of DILI and HILI**

| Items for Cholestatic or Mixed Liver Injury | Score | Kava | Rivaroxaban |
|---|---|---|---|
| 1. Time to onset from beginning of the drug/herb | | | |
| 5-90 days (rechallenge: 1-90 days) | +2 | +2 | |
| <5 or >90 days (rechallenge >90 days) | +1 | | +1 |
| Alternative: Time to onset from cessation of the drug/herb | | | |
| (except for slowly metabolized chemicals: ≤30 days) | +1 | | |
| 2. Course of ALP after cessation of the drug/herb | | | |
| Percentage difference between ALP peak and N | | | |
| Decrease ≥50% within 180 days | +2 | +2 | +2 |
| Decrease <50% within 180 days | +1 | | |
| No information, persistence, increase, or continued drug/herb use | 0 | | |
| 3. Risk factors | | | |
| Alcohol use (current drinks/d: >2 for women, >3 for men) | +1 | +1 | +1 |
| Alcohol use (current drinks/d: ≤2 for women, ≤3 for men) | 0 | | |
| Pregnancy | +1 | | |
| Age ≥55 years | +1 | | |
| Age <55 years | 0 | | |
| 4. Concomitant drug(s) | | | |
| None or no information | 0 | | |
| Concomitant drug/herb with incompatible time to onset | 0 | | |
| Concomitant drug/herb with compatible or suggestive time to onset | -1 | | |
| Concomitant drug/herb known as hepatotoxin and with compatible or suggestive time to onset | -2 | -2 | -2 |
| Concomitant drug with evidence for its role in this case (positive rechallenge or validated test) | -3 | | |
| 5. Search for alternative causes | | | |
| Group I (7 causes) | Tick if negative | Tick if not done | |
| HAV: Anti-HAV-IgM | ✔ | | |
| HBV: HBsAG, Anti-HBc-IgM, HBV-DNA | ✔ | | |
| HCV: Anti-HCV-IgM, HCV-RNA | ✔ | | |
| HEV: Anti-HEV-IgM, anti-HEV-IgG, HEV-RNA | | ✔ | |
| Hepatobiliary sonography/color Doppler sonography of liver vessels/endosonography/CT/MRC | ✔ | | |
| Alcoholism (AST/ALT ≥2) | ✔ | | |
| Acute recent hypotension history (particularly if underlying heart disease) | ✔ | | |
| Group II (5 causes) | | | |
| Complications of underlying disease(s) such as sepsis, metastatic malignancy, autoimmune hepatitis, chronic hepatitis B or C, primary biliary cholangitis or sclerosing cholangitis, genetic liver disease | ✔ | | |
| Infection suggested by PCR and titer change for | | | |
| CMV (anti-CMV-IgM, anti-CMV-IgG) | ✔ | | |
| EBV (anti-EBV-IgM, anti-EBV-IgG) | | | |
| HSV (anti-HSV-IgM, anti-HSV-IgG) | | ✔ | |
| VZV (anti-VZV-IgM, anti-VZV-IgG) | | ✔ | |

**(Table 1). Continued.**

| Items for Cholestatic or Mixed Liver Injury | Score | Kava | Rivaroxaban |
|---|---|---|---|
| Evaluation of group I and II | | | |
| All causes-groups I and II – reasonably ruled out | +2 | | |
| The 7 causes of group I ruled out | +1 | +1 | +1 |
| 6 or 5 causes of group 1 ruled out | 0 | | |
| Less than 5 causes of group 1 ruled out | -2 | | |
| Alternative cause highly probable | -3 | | |
| 6. Previous hepatotoxicity of the drug/herb | | | |
| Reaction labelled in the product characteristics | +2 | +2 | |
| Reaction published but unlabeled | +1 | | +1 |
| Reaction unknown | 0 | | |
| 7. Response to unintentional reexposure | | | |
| Doubling of ALP with the drug/herb alone, provided ALP below 2N before reexposure | +3 | | |
| Doubling of ALP with the drug(s)/herb(s) already given at the time of first reaction | +2 | | |
| Increase of ALP but less than N in the same conditions as for the first administration | +1 | | |
| Other situations | 0 | 0 | 0 |
| Total score for the case | | 6 | 4 |

Abbreviations: ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; CMV, Cytomegalovirus; CT, Computer tomography; DILI, Drug induced liver injury; EBV, Epstein Barr virus; HAV, Hepatitis A virus; HBc, Hepatitis B core; HBsAg, Hepatitis B antigen; HBV, Hepatitis B virus; HCV, Hepatitis C virus; HEV, Hepatitis E virus; HILI, Herb induced liver injury; HSV, Herpes simplex virus; MRC, Magnetic resonance cholangiography; N, upper limit of the normal range; RUCAM, Roussel Uclaf Causality Assessment Method; VZV, Varicella zoster virus. Total score and resulting causality grading: ≤0, excluded; 1–2, unlikely; 3–5, possible; 6–8, probable; and ≥9, highly probable.

The pathogenicity of kava induced hepatoxicity remains poorly understood. In the case presented here, it seems probable that kava, along with the concomitant use of other prescription medications that are known to interact and potentiate each other's effect on liver function, as well as recent alcohol ingestion played an important role in the development of liver injury. In fact, comedication is a common feature among patients with kava-induced liver injury suggesting kava hepatoxicity may involve metabolic interactions between kavalactones and other exogenous substrates [13]. However, specific metabolic pathways including glutathione depletion, cyclooxygenase inhibition, P-glycoprotein, and genetic enzyme deficiency of cytochrome P450 2D6 remain speculative [13,17].

The current case report was limited as we were unable to ascertain the precise dose of kava taken by the patient. Without this information, we cannot say whether the patient overdosed on kava. We are certain however that the patient exceeded the recommended usage duration as we were able to identify the specific kava he used and its cultivar. The issue of kava product identification is also apparent in other reports which further complicates discussions surrounding kavas safety profile [8,18].

Kava remains a popular anxiolytic herbal supplement for many Americans despite the labeled warning for hepatoxicity on products. Cases of kava hepatotoxicity have occurred in the context of several forms of kava extraction methods, as well as with various solubilizers suggesting that the method of harvesting raw kava material may play an important role in its toxicity [13]. Teschke & Schulze (2010) have argued that liver injury by kava may be preventable with quality control standards since historically, kava use has been safe among Pacific Islanders where the beverage is consumed daily without apparent adverse effects. Although there may be some utility for kava use in the future, patients should still be advised of the potentially fatal liver injury associated with its use, especially with comedication. Similarly, in-line with the goals of the FDA, as well as public health, clinicians should continue to report on cases of suspected kava-induced hepatotoxicity.

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## AUTHOR CONTRIBUTION

Provision of patients' data and medical decision making: IP, IH, MC; Collection and assembly of data:

MC: Literature review, manuscript preparation and data interpretation: HZ; Final approval of manuscript to be submitted: All authors.

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