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REVIEW ARTICLE

Kratom (*Mitragyna Speciosa*) Liver Injury: A Comprehensive Review

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Abstract
Kratom (*Mitragyna speciosa*) leaves contain the mu opioid Kupferschmidt,partial agonists mitragynine and 7-hydroxymitragynine. The US Drug Enforcement Agency considers it a 'drug of concern', and the US FDA is reviewing kratom, but there is a paucity of information regarding health effects. Liver injury is often cited as a potential health consequence, however the same few case reports are repeatedly referenced, without a broader context. Furthermore, reports have largely lacked standardized causality assessment methods. The objective is to evaluate causality in kratom liver injury, through a comprehensive scoping review of human cases, and by reviewing epidemiologic, animal, and mechanistic reports that relate to kratom liver injury. Hepatotoxicity causality was systematically examined using the Roussel Uclaf Causality Assessment Method (RUCAM) for case reports. Biopsy findings, potential pathophysiologic mechanisms, and management options are discussed. This review identified 26 case reports and abstracts, in addition to 7 cases reported from the Drug-Induced Liver Injury Network, 25 in FDA databases, and 27 in internet user forums. Latency periods to symptom onset had a median of 20.6 days and mean of 21 days (range 2–49). Common presenting signs and symptoms were abdominal discomfort, jaundice, pruritis, and dark urine. Histologic findings were predominantly cholestatic, although, biochemically, the condition was heterogenous or mixed; the median R ratio was 3.4 and the mean was 4.6 (range 0.24–10.4). Kratom likely causes liver injury based on the totality of low-quality human evidence, and, in the context of epidemiologic, animal, and mechanistic studies. It remains unclear which subgroups of users are at heightened risk.

1 Introduction

Mitragyna speciosa is a tropical tree native to Southeast Asia. Known colloquially as 'kratom' in Thailand and 'ketum' in Malaysia, the tree has large leaves that contain the partial mu opioid receptor agonists mitragynine and 7-hydroxymitragynine, among other alkaloids. While these compounds bind opioid receptors and have classical mu opioid effects, they are functionally biased, with unique downstream effects compared with classical opioids [1, 2]. The plant is anecdotally popular as a home remedy for opioid withdrawal and opioid use disorder, and few studies have formally investigated this popularity [3]. It is available as powder, extract, tea, tablets, or capsules with ground leaves. In the US and Thailand, regional poison centers have experienced increasing call volumes for kratom exposure [4, 5].

Kratom is illegal in numerous countries, and while sales in the US have been banned in several cities and states, it is not federally scheduled as a controlled substance. In 2016, the US Drug Enforcement Administration (DEA) declared its intention to list kratom as schedule I using emergency scheduling powers, but due to pressure from kratom advocacy groups, the public, and members of congress, scheduling was postponed [6]. The DEA considers kratom a 'drug of concern', and the US FDA is actively reviewing kratom, repeatedly expressing concern for abuse potential and harms associated with use [7, 8].

There is a paucity of information regarding kratom's health effects. Liver injury is cited as a potential health consequence, yet the same few case reports are repeatedly referenced, without a broader context. Furthermore, prior reports have largely lacked standardized methods of causality assessment for drug/herb-induced liver injury. The

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Key Points

Kratom likely causes liver injury based on the totality of low-quality human evidence in the form of case reports, US FDA databases, and online user forums, and in the context of epidemiologic, animal, and mechanistic studies.

Most users do not experience clinically apparent liver injury, and it is unknown which user subgroups are at heightened risk.

Laboratory parameters show heterogenous or mixed liver injury, while liver biopsies show predominantly cholestatic injury.

review evaluates the strength of causality in kratom-induced liver injury by performing the first comprehensive review of human cases, and reviewing the epidemiologic, animal, and mechanistic reports that relate to kratom-induced liver injury.

2 Methods

A scoping review was performed to broadly examine the current heterogenous evidence for kratom causing hepatotoxicity. A literature search for human cases was performed from inception through 20 November 2019, using the PubMed, Scopus, Embase, and Google Scholar electronic databases. The searched keywords were (kratom OR ketum OR Mitragyna OR mitragynine) AND (liver OR hepatic OR hepatotoxic OR hepatotoxicity OR hepatitis OR DILI OR HILI OR cholestatic OR cholestasis OR transaminitis OR transaminases OR LFT OR jaundice OR hepatomegaly). An additional search was performed in the National Health Institute (NIH) LiverTox database.

A literature search for relevant animal studies was also performed using the above timeframes and databases, based on (kratom OR ketum OR Mitragyna OR mitragynine) AND (animal OR model OR rat OR rats OR rodent OR rodents OR mouse OR mice) AND (toxicity OR toxic OR liver OR hepatic OR hepatotoxic OR hepatotoxicity OR hepatitis OR DILI OR HILI OR cholestatic OR cholestasis OR transaminitis OR transaminases OR LFT OR jaundice OR hepatomegaly).

For human and animal studies, only English-language articles were identified. A manual search of relevant article references was performed to further expand the search. Articles were included if they described a unique human exposure or animal study with suspected liver injury.

Causality of hepatotoxicity was systematically examined by calculating Roussel Uclaf Causality Assessment Method (RUCAM) scores for all case reports, and by utilizing a global approach to interpret RUCAM scores in the context of these alternate avenues of evidence.

3 Causality Assessment of Drug-Induced Liver Injury

Drug-induced liver injury (DILI) and herb-induced liver injury (HILI) are terms for a heterogenous group of disorders. The primary mechanisms for DILI are mitochondrial dysfunction, oxidative stress, and altered bile acid homeostasis [9]. Cholestatic DILI likely involves either direct injury of canalicular membranes or cholangiocytes by cytotoxic substances excreted in bile, or inhibition of transporter proteins. Heterogeneity between substances and people complicates attribution of causation.

A number of systems have been developed to evaluate causality, including the Naranjo Adverse Drug Reactions Probability Scale and World Health Organization-Uppsala Monitoring Center (WHO-UMC) criteria, which were not designed specifically for liver injury [10]; the Maria and Victorino scale, which does not account for liver injury pattern [11]; the Digestive Disease Week-Japan scale, which includes specific lymphocyte tests [12]; and a structured expert opinion process used by the Drug-Induced Liver Injury Network (DILIN) [13].

The RUCAM score has also been referred to as the Council for International Organizations of Medical Sciences (CIOMS) score [14]. When compared with the complex structured expert opinion process, the RUCAM tends to underestimate causality [15]. The RUCAM performed well when validated against re-exposure liver injury as the gold standard [16]. RUCAM is ideally used prospectively to ensure completeness of data collection, but has frequently been applied retrospectively, including in the validation study of the original RUCAM [16–18]. The drawback of retrospective use is the risk of incomplete information, resulting in a lower probability estimate.

The RUCAM criteria were modified in 2016 to define the degree of alcohol intake as a risk factor and to shift hepatitis E virus testing from group II to group I of nondrug causes for exclusion [17]. The RUCAM has several drawbacks, as noted by García-Cortés et al. and Shapiro and Lewis, which were only partially addressed by the updates [19, 20]. These obstacles include handling of incomplete data, atypical presentations, changing patterns of liver injury during the illness course, exclusion of histologic information, and subjectivity of some data elements. The RUCAM also has problematic test–retest and interrater reliability [21]. Overall, the

RUCAM remains the most commonly used method of causality assessment for DILI and HILI [17].

While the term DILI is often used to refer to herbal etiologies, HILI is a more specific term. Evaluating causality form herbal drugs has additional complexities that do not exist with pharmaceutical good manufacturing practices [22]. Herbal products can vary significantly, with unknown source harvesters and manufacturers, inconsistent plant parts used, variable solvents and impurities, varying chemical composition and active ingredient strength, and potentially the inclusion of multiple plant species. This multifactorial confounding does not negate the importance of causality assessment, but conclusions must be considered in this context. The RUCAM score has not been specifically validated for HILI but is commonly used to assess causality for herbal etiologies and is considered of value.

4 Epidemiologic Studies

Epidemiologic and cross-sectional studies have reported limited details regarding liver injury, making conclusions difficult to impossible. In 1975, a report on kratom users in Thailand noted that long-term users develop "an appearance similar to a hepatic face", and describes a 55-year-old male with "an appearance similar to a hepatic face", however no jaundice was reported and no laboratory studies were performed [23].

In Malaysia, a structured interview on kratom use in 562 subjects found six subjects who responded 'yes' to "Have you had a medical problem as a result of your Ketum use (e.g. memory loss, hepatitis, convulsions, bleeding, etc.)" [24]. No further details were reported, and it is unknown if these were cases of kratom-induced liver injury.

In a Malaysian cross-sectional study comparing 58 male regular kratom users with 19 nonusing male controls, there was no difference in transaminases [25]. The authors defined regular kratom use as self-reported consumption at least twice daily for at least 2 years, and subjects were excluded if they had ethanol or illicit drug use, nonalcoholic fatty liver disease, viral hepatitis, cirrhosis, coronary artery disease, or diabetes. Snowball sampling allowed authors to identify eligible subjects but may limit generalizability.

Between 2011 and 2017, among 1807 calls to US poison centers for kratom, 59 were for aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 100 (5%), 30 were for increased bilirubin (2.6%), and 18 were for other liver test abnormalities (1.5%) [4]. No further details are available and causality cannot be estimated. A retrospective, single poison center study from 2002 to 2016 examined calls from healthcare facilities for kratom exposure. Of 12 included patients, one was found to have elevated transaminases and bilirubin after presenting with nausea, abdominal pain, and jaundice [26]. The patient had underlying nonalcoholic steatohepatitis, and 1 month prior he discontinued lupus medications and started using kratom three times daily. Unclear evaluation by gastroenterology did not uncover alternate etiologies to explain his acute presentation. Laboratory values are unknown and transaminases improved after a 21-h course of N-acetylcysteine (NAC).

5 Human Case Reports

Articles state that only a few kratom liver injury cases have been described; however, searching revealed a total of 26 formally described cases: 11 case reports [27–37], 13 conference abstracts representing 12 unique cases [38–50], 1 case not formally published [51], and 2 cases in the NIH LiverTox database (Table 1) [52, 53]. In instances of data omission, we contacted authors to determine whether missing data were available.

The median age was 31.5 years, mean 35.4 years (range 19–70), and 65% of patients were male. Kratom formulations were powder (37%), unknown (37%), tea (15%), capsules (7%), and crushed leaves (3.7%). Among 18 cases with clearly reported latency periods from the start of kratom use to symptom onset, the median was 20.6 days and the mean was 21 days (range 2–49). Common presenting signs and symptoms were abdominal discomfort, jaundice, pruritis, and dark urine. Many cases also had chills and light-colored stools. Dosing amounts and frequency varied significantly and were poorly reported on, preventing dose–response estimation. The latency findings in the above cases are consistent with the separate seven-patient series produced by the DILIN, in which median latency to onset was 22 days (range 15–49).

A RUCAM score could not be calculated for three cases due to an unknown interval between initiating kratom and the onset of liver injury (latency) [29, 36, 41]. One of these cases may have involved re-exposure, which would otherwise likely have had a high RUCAM score [41]. RUCAM separately could not be calculated for one case owing to a lack of documented alkaline phosphatase (ALP), which is required to calculate an R ratio for RUCAM [44, 47].

Most case reports met the laboratory criteria for DILI based on consensus case definitions [54]. Three cases did not meet the DILI criteria; two further cases had insufficient documentation and were excluded [41, 44], and one was included due to an otherwise suggestive case [27, 44]. The included case that did not meet the DILI criteria had mild elevation in transaminases and ALP, and a direct hyperbilirubinemia of 28.6 mg/dL. Isolated hyperbilirubinemia is not considered a DILI; however, we chose to include this case because DILI consensus criteria are based on level 2b evidence, and given the otherwise suggestive elements of

Table 1 Summary of published cases

Article	Description	Diagnostics
Kupferschmidt 2011 [38]	A 30-year-old female used kratom powder 5 g with ethanol (unknown amount), 2 days apart. One day after the second use, the patient had fever and myalgias, which resolved in 1 day. Five days after the second use, the patient had pruritis and jaundice. Pruritis was treated with an antihistamine and a corticosteroid. At 35 days, transaminases and bilirubin normalized	Peak bilirubin total 9.4, ALP 174, ALT 482, AST 271. Unremarkable ultrasound, MR cholangiography, serum electrophoresis, ceruloplasmin, iron, ferritin, autoimmune antibodies, viral hepatitis, EBV, CMV
Kapp et al. 2011 [27]	A 25-year-old male used kratom powder twice daily for 2 weeks, and servings increased from approximately 3 g to approximately 12 g. 2 days after cessation, the patient had chills, and by day 8 had abdominal pain and dark urine. Bilirubin remained markedly elevated for 3 weeks after presentation, then gradually fell	Initial bilirubin total 30.9 (direct 28.6), ALP 173, ALT 94, AST 66. Negative viral hepatitis, ANA. Ultrasound and CT showed steatosis. Detectable urine/serum mitragynine. Biopsy found cholestatic injury
Rivera et al. 2011 [44]	A 26-year-old male used kratom, and had fever, abdominal pain, and jaundice. LFTs normalized over 1 month after stopping kratom	Bilirubin total 7.8, ALT 97, AST 57. Negative ANA, AMA, SMA, hepatitis serologies, CMV, herpes simplex virus, EBV. Negative studies for hemochromatosis and Wilson's disease. Ultrasound was normal
Kesar et al. 2013 [39]	A 34-year-old female used kratom half-spoon (unknown formula) on 2 adjacent days. Within 1 week, the patient had pruritis, dark urine, and light stools. The patient was treated with N-acetylcysteine for possible APAP toxicity, then started on ursodiol and hydroxyzine. At 40 days, tests normalized	Initial bilirubin total 10.6, ALP 298, ALT 93, AST 61. Negative viral hepatitis, EBV, CMV. Excluded autoimmune hepatitis, Wilson's disease, AAT deficiency, hemochromatosis, and primary biliary cholangitis. Ultrasound and hepatobiliary scan found no common bile duct obstruction
Dorman et al. 2015 [28]	A 58-year-old male used kratom powder daily for 1 month, stopped when he had jaundice and dark urine. The patient also had grade I hepatic encephalopathy. 1-year prior, the patient had jaundice after using kratom powder 1 tablespoon daily for 3 months, with bilirubin 9.7 that resolved with discontinuation	Initial bilirubin total 25.6 (direct 17.1), ALP 790, ALT 106, AST 49, ammonia 161 µmol/L Negative viral hepatitis, ANA, SMA. Ultrasound showed irregular liver texture without obstruction
Arens et al. 2015 [48]	A 26-year-old male with no past medical history, ingested, in 24 h, ethanol 15–20 drinks and kratom 15 g. Two days later, the patient had chills and right upper quadrant pain, and 2 weeks later presented again with dark urine. In the hospital, the patient had fever to 38.6 °C and tachycardia and was treated symptomatically. Transaminases peaked at ALT 703 and AST 483. The patient then improved and was discharged on hospital day 3. The time course of transaminase improvement was unknown	Initial bilirubin total 2.3, ALP 171, ALT 448, AST 483, undetectable APAP. Ultrasound found diffuse gallbladder wall thickening and pericholecystic fluid, without cholelithiasis or sludge. Negative acute viral hepatitis, normal ceruloplasmin, and 24-h urine copper. Initial serum mitragynine 13 ng/mL and urine mitragynine 356 ng/mL
Sullivan 2016 [51]	A 19-year-old female used kratom tea made by friends; however, the next morning, the patient had emesis, epigastric pain, fever, and myalgias. By day 6, the patient had pruritis, pale stools, and 'neon yellow' urine. On day 7, the patient had jaundice and went to hospital. Her friends had no ill effect. She had used kratom once approximately 3 weeks earlier without issue. Throughout the illness, the patient took 6 × 325 mg APAP tablets. She had been taking oral contraceptives for > 1 year, and was an occasional binge drinker, but not recently. Symptoms rapidly improved, and 2 weeks later the laboratory tests normalized, and were still normal at follow-up > 1 year later	Initial bilirubin total 5.8, ALP 181, ALT 215, fasting serum bile acids 225 µmol/L (normal < 10). Acute viral hepatitis tests negative, ultrasound normal, ANA 1:80, which may be present in healthy patients. Negative SMA, AMA, and liver kidney microsomal antibodies. Normal ceruloplasmin and AAT

Table 1 (continued)

Article	Description	Diagnostics
Drago et al. 2017 [37]	A 23-year-old male used kratom powder over 6 weeks (estimated 85 g in total). 1 week after the last use, the patient presented with 4 days of jaundice, pale stools, and dark urine. He used 'moderate' alcohol. Over 2 weeks, the liver tests normalized	Initial bilirubin total 7.4, direct bilirubin 5.8, ALP 225, ALT 210, AST 129, INR 0.9 Unspecified tests for viral and autoimmune hepatitis were negative. Biopsy "was entirely consistent with cholestatic liver injury"
Bernier et al. 2017 [40]	A 41-year-old female used kratom 1 teaspoon, twice daily for 1 week. Ten days after stopping, the patient had jaundice, pruritus, diarrhea, and subsequently went to hospital	Initial bilirubin total 15, ALP 245, ALT 144, AST 66. Viral (including E) and autoimmune hepatitis tests negative. Biopsy showed cholestatic overload with discrete destruction of interlobular bile ducts compatible with cholestatic hepatitis. On recheck 51 days later, bilirubin total 6, ALP 126 (Le Boisselier, R, personal communication, 26 June 2019)
Shah et al. 2017 [41]	A 30-year-old female used kratom tea and presented with a few weeks of abdominal pain, jaundice, dark urine, and pruritis. The patient was admitted with similar complaints and similar laboratory test abnormalities as previously. The abstract does not describe timing between use and onset, or whether ethanol or other medications are used, and it is unclear if this was a case of re-exposure	Initial bilirubin total 18, ALP 100, ALT 47, AST 48. Unknown extensive work-up for liver disease was negative, including viral etiologies. MRI and endoscopic ultrasound excluded mechanical biliary obstruction. Biopsy showed intrahepatic cholestasis
Riverso et al. 2018 [29]	A 38-year-old male used kratom and then presented with 5 days of chills and was subsequently discharged with likely viral illness. The patient used five doses of APAP and continued kratom. He initially improved, then returned with dark urine and pale stools. Unknown time interval between kratom use and onset	Initial bilirubin total 5.1 (direct 4.0), ALP 304, ALT 389, AST 220. Unremarkable serum APAP, and serum AAT and phenotype. No active viral hepatitis. Biopsy showed mild centrilobular hepatocellular and canalicular cholestasis
Griffiths et al. 2018 [30]	A 21-year-old male used kratom for 2 weeks, up to 12 capsules daily, and 10 g in the 2 days before admission. The patient had emesis, fatigue, abdominal pain, and dark urine. He drinks 2 beers 3×/week, and uses hallucinogenic mushrooms, last used 2 weeks prior. Discharged after 2 days, lost to follow-up	Initial bilirubin total 2.9, ALP 193, ALT 319, AST 294. Undetectable serum APAP, negative viral hepatitis panel. MRI showed moderate hepatosplenomegaly and small ascites. Ultrasound showed common bile duct dilation per the article, but it was only 6.4 mm, with no cholelithiasis or other abnormality (Olin JL, personal communication, 4 June 2019)
Tayabali et al. 2018 [36]	A 32-year-old male used 60 kratom tablets over 1 week, in addition to powder. Two weeks before presenting, the patient had jaundice, nausea, fatigue, arthralgias, night sweats, pale stools, and dark urine. He used kratom for > 2 weeks, and symptom onset occurred while still using kratom, but unclear latency from the start of kratom use to onset (Tayabali K, personal communication, 22 November 2019). The patient occasionally used APAP for chronic pain, drank alcohol occasionally; neither were quantified. He was treated with NAC 150 mg/kg/h, but had anaphylaxis so therefore stopped	Initial bilirubin total 6.3, ALP 391, ALT 365, AST 222. Negative tests for APAP, hepatitis A, B, C, HIV. Normal ceruloplasmin and AAT. Serum mitragynine 47.8 ng/mL, and detectable metabolite 7-hydroxymitragynine Ultrasound normal
Mousa et al. 2018 [31]	A 31-year-old male used kratom tea for 2 weeks and presented with 4 days of dark urine and malaise. He was treated with 18 doses of NAC (140 mg/kg load then 70 mg/kg every 4 h) and discharged on day 4	Initial bilirubin total 2.2, ALP 191, ALT 578, AST 191. Negative viral hepatitis panel and ANA, unremarkable abdominal CT and ultrasound (Mousa MS, personal communication, 20 June 2019)

Table 1 (continued)

Article	Description	Diagnostics
Mackenzie and Thompson, 2018 [49] De Francesco et al. 2019 [50]	A 27-year-old male ingested kratom powder purchased online. Several weeks after using it multiple times weekly, typically 3–4 tablespoons, the patient had 2 days of 'heavy' alcohol consumption, then developed vomiting, diarrhea, and epigastric pain. The next 3 days he ingested APAP 4 g/day, then presented with liver injury. On day 5 of admission, a liver transplant was performed	Initial bilirubin total 0.98, ALP 109, ALT 330, AST 1,431, APAP 2.6 µg/mL. Liver tests peaked 48 h later, with bilirubin total 11.2, ALP 162, ALT 6969, AST > 14,000, INR 8.8. Comprehensive urine toxicology screen was negative, except APAP and caffeine. Blood culture grew *Salmonella javiana*. Negative tests for viral hepatitis, Wilson disease, and extensive unspecified other causes. Biopsy found extensive hepatocellular necrosis with extracellular cholestasis. Gas chromatography–mass spectrometry of two of the kratom bags found mitragynine, paynantheine, and speciogynine (mitragynine isomer), without chemical adulterants. The kratom was confirmed to have *S. javiana*
Antony and Lee 2019 [32]	A 70-year-old male used kratom twice daily for 4 days and 2–3 weeks later presented with jaundice, nausea, and a 9-kg weight loss, as well as hepatitis that improved. He was readmitted 3 days later for worsening pruritis, melena, and syncope. At that time, Hgb was 4.8, creatinine was 2.9, and the patient had a red blood cell transfusion. Kidney injury of unclear etiology was thought to be as a result of acute tubular necrosis due to pigment nephropathy from hyperbilirubinemia. Three months later, laboratory tests normalized, except creatinine 1.8	Unclear documentation of laboratory test timing between admissions. Bilirubin total 27, ALP 230, ALT 59, AST 53, creatinine 2.27, BUN 80. Negative viral hepatitis, negative for 'various liver diseases', and unremarkable CT and MR cholangiography
Fernandes et al. 2019 [34]	A 52-year-old male used APAP 800 mg twice daily plus kratom for 2 months. He used kratom 1 teaspoon of crushed leaf initially twice daily for a few days, then daily for 2 months. Approximately 2 weeks after starting kratom, scleral icterus and jaundice began that slowly progressed. 16 days after stopping kratom, the patient presented with jaundice. He was treated with ursodiol for 1 month, at which time bilirubin improved but was not normal, and transaminases were rising. Not followed further	Initial bilirubin total 23.2 (peaked 10 days later at 28.9), ALP 255, ALT 66, AST 55, INR normal. MRI showed patent biliary ducts. Negative unknown work-up for alternate causes of liver disease. Biopsy showed acute cholestatic injury Laboratory tests on day 27 (last follow-up) showed bilirubin total 4, AST 71, ALT 78, ALP 183
Osborne et al. 2019 [33]	A 47-year-old male used kratom capsules for 3 weeks, not daily, then developed a few days of dark urine, pruritis, chills, and nausea. He took APAP < 3 g/day for symptoms, and denied any other new drugs, including herbals. The patient was managed as an outpatient. At 16 days, laboratory tests were still slightly abnormal; at 58 days, the only abnormality was ALT 60, possibly from underlying nonalcoholic fatty liver disease given obesity, dyslipidemia 9 months later, the patient presented again with 2 days of pruritis and anorexia, after rechallenge with kratom powder for 1 day. Bilirubin total 3.2, AST 185, ALT 566, ALP 211, and laboratory tests "trended toward normal 3 weeks following re-challenge"	Initial bilirubin total 5.8 (direct 4.3), ALP 170, ALT 265, AST 108. Laboratory tests peaked on day 2 then started downtrending. Undetectable serum APAP, negative EBV and viral hepatitis, normal AAT and ceruloplasmin levels, negative ANA. CMV IgM antibody index 1.7. Ultrasound showed steatosis (in the setting of obesity)
Ricardo et al. 2019 [42]	A 33-year-old female used kratom tea 1–2 small cups for 1 month; she had a history of chronic hepatitis C. The patient presented with 3 days of abdominal pain, jaundice, pruritis, and dark urine. Occasional alcohol use (unquantified). The patient was discharged after 3 days, when jaundice resolved and liver tests downtrended (unknown to what degree)	Initial bilirubin total 5.1 (direct 4.4), ALP 387, ALT 1134, AST 4624, normal INR. Undetectable APAP, ultrasound normal. Hepatitis C antibody reactive, hepatitis C RNA 31,100 IU/mL (Ricardo J, personal communication, 24 June 2019)

Table 1 (continued)

Article	Description	Diagnostics
Desai et al. 2019 [47]	A 36-year-old female used kratom for a few weeks, and was transferred for perinephric abscess. She drank a few beers weekly and used APAP < 10 g/week. ALT and AST more than doubled within a few hours. Started NAC intravenously. Liver enzymes improved to ALT < 300 and AST < 1000. NAC was stopped, but within 16 h, ALT/AST increased again therefore NAC was restarted. Peaked at ALT > 3800 and AST > 12,000; on discharge ALT was 352 and AST was 56. During admission, the perinephric abscess was drained and ciprofloxacin was administered (Desai P, personal communication, 25 November 2019)	Initial bilirubin total 2.4, ALP 239, ALT 592, AST 1482. Unremarkable viral hepatitis panel, ceruloplasmin, autoimmune antibodies, serum APAP, and ultrasound
Bøgevig et al. 2019 [43]	A 56-year old male used kratom powder 1 teaspoon daily. He had obstipation for 10 days and jaundice for 5 days, then presented 14 days after starting kratom. The patient had a history of mild 'liver enzyme' elevation that was normal 6 months prior, and no history of substance abuse, including ethanol. Bilirubin and ALT normalized in 3 weeks	Initial bilirubin total 17.3, ALP 392, ALT 887, AST unlisted. Negative viral hepatitis and CMV Gas chromatography–mass spectrometry of the kratom powder found mitragynine content 0.590 mg/g; there is no description of potential contaminant analysis
Aldyab et al. 2019 [35]	A 40-year-old female used kratom weekly for 1 month, then had abdominal pain and fever, and presented for care. The patient had also started a ketogenic diet 1 month before symptom onset. She had been taking an oral contraceptive and a nettle leaf supplement for a few years. She stopped kratom, contraceptives, and supplements, but started ursodiol, prednisone. The authors questioned if the discrepancy between cholestatic histology and hepatocellular biochemical tests may have been from prebiopsy corticosteroids that reduced lobular hepatitis more than bile duct injury	Initial bilirubin total 5.1, ALP 162, ALT 875, AST 462. Negative viral hepatitis, Wilson's disease, AAT deficiency, ANA, SMA, AMA. CT and MR cholangiopancreatography found mild periportal edema. Biopsy showed bile duct injury with few vague granulomas, and portal tract inflammation
Pronesti et al. 2019 [45]	A 30-year-old male used kratom powder with water for 4–6 weeks at night. He presented with 1 week of dark urine and pale stools, and one day of scleral icterus. The patient had a history of diabetes mellitus. No drug or APAP use. At 1 month, laboratory tests normalized	Bilirubin total 5.7, direct bilirubin 4.5, ALP 556, ALT 308, AST 125. Normal CT, hepatitis A, B, C, iron studies, ceruloplasmin, AAT, AMA, liver–kidney microsomal antibody, except ferritin 405 and SMA 1:20. Ultrasound found coarsened liver texture Biopsy showed inflammation with focal prominent eosinophils, and hepatocellular and canalicular cholestasis without fibrosis
Kaur et al. 2019 [46]	A 42-year-old female used kratom for 4 months, with the last use 4 weeks before presenting. One week before presenting, the patient had subjective fever, fatigue, nausea, anorexia, and dark urine (Kaur R, personal communication, 16 November 2019). No prior liver disease, alcohol use, or APAP use. Jaundice and AST/ALT improved at discharge, and at 1 month had normalized	Initial bilirubin total 3.3, ALP 298, ALT 371, AST 171, INR 0.97. ALT peaked at 606 Ultrasound found thickened gallbladder wall and normal liver. Negative autoimmune liver panel, viral hepatitis, HIV, EBV, CMV. Normal AAT, iron, ceruloplasmin
LiverTox Case 6972 [52]	A 29-year-old male used kratom powder daily, and 23 days after starting, the patient had jaundice, dark urine, pruritis, abdominal pain, and fever. He also used herbs Ma Huang (ephedra), kava kava, and *Sida cordifolia* for 2 days prior to starting kratom. The patient had a history of ethanol and injection drug use, and no history of liver disease. The illness was complicated by hemolysis and acute kidney injury	Initial bilirubin total 22.4, ALP 428, ALT 272, AST 70, INR 1.1. Negative viral hepatitis (including E) and ANA. CT and ultrasound found no biliary obstruction but showed gallbladder wall thickening and increased lymph nodes. Biopsy showed "cholestatic changes with mild necrosis and inflammation", but did not suggest chronic alcoholic liver disease or viral hepatitis

Table 1 (continued)

Article	Description	Diagnostics
LiverTox Case 8332 [53]	A 25-year-old male began using kratom every third day for five doses. 25 days after starting use, he developed jaundice, dark urine, pruritis, and abdominal pain. Documentation is conflicting on whether the patient had excess ethanol intake, but, in scoring, excess intake was used. The patient had no history of liver disease. He had started venlafaxine 3 months prior, and consumed a psilocybin mushroom once	Initial bilirubin total 5.6, ALP 218, ALT 126, AST 73, INR 0.9. Negative viral hepatitis (including E) and negative ANA. Ultrasound showed no biliary obstruction

AAT α-1-antitrypsin, *ALP* alkaline phosphatase, *ALT* alanine aminotransferase, *AMA* antimitochondrial antibodies, *ANA* antinuclear antibody, *APAP* acetaminophen, *AST* aspartate aminotransferase, *BUN* blood urea nitrogen, *CMV* cytomegalovirus, *CT* computed tomography, *EBV* Epstein–Barr virus, *Hgb* hemoglobin, *IgM* immunoglobulin M, *INR* international normalized ratio, *LFTs* liver function tests, *MR* magnetic resonance, *MRI* magnetic resonance imaging, *NAC* N-acetylcysteine, *SMA* smooth muscle antibody

Units are bilirubin, mg/dL; aminotransferases and alkaline phosphatase, units/L

the case with liver biopsy showing cholestatic injury. For one additional case, it was unclear whether the DILI criteria were met as ALP was 230 U/L but a reference range was not provided [32].

Six cases involved acetaminophen and although onset times were compatible for the RUCAM, reported doses were nontoxic and there was no suspected self-harm intent; therefore, as a concomitant drug, acetaminophen was considered not compatible with liver injury. One case used < 2 g/day × 3 days [39], one case used < 3 g/day for several days to treat symptoms of liver injury that were already present [33], one case used 1.6 g/day for 2 months [34], one case used 4 g/day for 3 days (and had serum acetaminophen 2.6 µg/mL [49], one case used < 10 g/week [47], and one case used acetaminophen 'occasionally' without quantification and the authors felt it was noncontributory [36]. Furthermore, Kesar et al. [39] and Fernandes et al. [34] had pure cholestatic patterns, which is inconsistent with acetaminophen toxicity. One case that used five doses of an unknown acetaminophen strength was excluded for lack of documentation [29]. It is unknown if therapeutic dosing of acetaminophen alters the risk for kratom liver injury.

A separate case was noteworthy for sonographic gallbladder wall thickening with pericholecystic fluid, in the absence of cholelithiasis or sludge [48]. The patient reported a single kratom use 2 weeks prior, but, based on serum mitragynine, likely used kratom more recently, and it is unclear to what extent the patient's ethanol use contributed. The patient recovered without cholecystectomy. One case was presented at two conferences, and a combination of the two abstracts was used to calculate the RUCAM [49, 50]. This case was notable for the positive *Salmonella javiana*, with liver failure requiring transplant. It is unclear to what extent kratom use was directly responsible, relative to *S. javiana* infection.

6 Human Reports in the Drug-Induced Liver Injury Network (DILIN)

Using data from 2004 to 2018, a study by Navarro et al. found eight cases of liver injury associated with kratom, out of 404 cases associated with herbal and dietary supplements [55]. There were two cases in 2008, one in 2016, and five in 2018. Rather than RUCAM, the DILIN uses a structured, expert opinion process for causality assessment. The expert opinion process determined a causal association in seven of eight cases, in which the median age was 46 years. The authors reported that "products were used for a median of 22 days (range 15–49) before onset of injury; 5 had jaundice, 6 itching, 5 abdominal pain, 3 fever, and none had rash" [55]. All cases had ethanol use. Hospitalization occurred for six of eight patients, and all recovered. The study did not describe whether NAC or other treatments were administered.

Table 2 Cases in FAERS [57]

Case no	Description	Diagnostics
15346316	A 24-year-old male used kratom 15 capsules on back-to-back days, 1 week apart (total of 4 days). The patient had an unknown pre-existing liver disease. He went to a hospital for routine liver biopsy, diagnosed with unknown staphylococcus infection, determined he would need a liver transplant. FAERS report by the patient's mother, who said his liver failure was thought to be from kratom	No diagnostics listed
14367521	A 25-year-old male used kratom two times on different days, and presented with hepatotoxicity 8 days after the initial use. No past medical history	Initial bilirubin total 4.2, ALP 141, ALT 684, AST 449
14180919	A 26-year-old male used kratom tea for 2 weeks, and had jaundice and lethargy. No past medical history. Treated with N-acetylcysteine	Initial bilirubin total 5.8, ALP 297, ALT 466, AST 214
14345738	A 35-year-old male used kratom for 3 weeks, and had jaundice, dark urine, and pruritis. No other drugs or herbs, 'drinks socially'. No past medical history. The patient was admitted and treated by discontinuing kratom	ALT 461, AST 189
15680525	A 35-year-old male used kratom two to three times over 1 month. The patient had severe abdominal pain. He was treated with N-acetylcysteine and transaminases normalized; surgery for potential cholecystitis was deferred	'Elevated LFTs' with no further laboratory results. Radiographic findings of cholecystitis
15346315	A 35-year-old male developed yellow skin when withdrawing from 2 years of significant daily kratom use, however it was unclear if this was jaundice	No diagnostics listed
15561348	A 45-year-old male presented for a few weeks of malaise, myalgias, and fatigue. He had pneumonia, acute kidney injury, and liver injury. His family found bags of kratom and thought he may have used it for 2–3 months. The patient had a history of hepatitis C and alcohol abuse, and had recent use of over-the-counter cold and flu products. FAERS report by the patient's sibling	ALT 300, AST 1900 at an unclear point in the illness. Undetectable acetaminophen. Thrombocytopenia. Creatinine 2.1. Ammonia 135 (unknown unit)
14347379	A 46-year-old male used kratom for a 'few weeks', and presented with 1 week of jaundice, lethargy, and confusion. He had a history of presumed alcoholic cirrhosis without decompensated events. Per family, no heavy ethanol intake for 1.5 years. Prior laboratory tests showed normal bilirubin, ALT, and AST. Medications were citalopram, lisinopril, metoprolol. Liver failure progressed to death	Initial bilirubin total 12.8, ALT 2426, AST 2609 Last laboratory tests were bilirubin total 24.6, ALT 1162, AST 802, INR 5.4
15373449	A 54-year-old female used an unknown amount of kratom powder. Two days later, the patient presented for unstated reasons. She used kratom once several months prior without effect. She had a history of hepatitis C, tobacco use, myocardial infarct, dilated cardiomyopathy, hypertension, dyslipidemia, and methadone dependence. Medications were aripiprazole, escitalopram, mirtazapine, lorazepam, methadone, aspirin, atorvastatin, losartan, and metoprolol	Initial ALP 114, ALT 2747, AST 3062. CT showed normal liver size/morphology. Ammonia reached 110 µmol/L
15744592	A male of unknown age used kratom tea for an unknown period. He presented for hematuria and bleeding with shaving. The patient was not receiving anticoagulants, gets regular testosterone injections, and the only new medication was meloxicam for 1 month	INR 12. Unremarkable mixing studies and fibrinogen, and factor X, II, and V levels. No other diagnostics

ALP alkaline phosphatase, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *CT* computed tomography, *FAERS* US FDA Adverse Event Reporting System, *LFTs* liver function tests, *INR* international normalized ratio
Units are bilirubin, mg/dL; aminotransferases and alkaline phosphatase, units/liter

The following cases were reviewed and considered unlikely to be kratom-induced liver injury: 14212085, 14356493, 14554619, 14995024, 14554565

7 Human Reports to the US FDA

A total of 25 cases of kratom hepatotoxicity have been reported to the FDA, which maintains the Center for Food Safety and Applied Nutrition Adverse Event Reporting System (CAERS) as a database of adverse event reports for food, dietary supplements, and cosmetics. A related database, the FDA Adverse Event Reporting System (FAERS), collects adverse event reports on drugs.

CAERS was queried from 2004 through June 2018, using the terms 'kratom', 'Mitragyna', and 'mitragynine'. This yielded 132 cases, of which 15 were related to liver injury [56]. This attribution was based on reports of 'acute hepatitis', 'drug-induced liver injury', 'acute liver/hepatic failure', 'hepatotoxicity', etc. Case details are unknown and causality was not estimated.

FAERS was queried from 2008 through March 2019, and a total of 408 reports under 'Mitragynine/Herbals' were identified [57]. Of these, 15 were considered potential hepatotoxicity, and case details were obtained from the FDA. Reviewing case notes excluded a further five cases as unlikely to be kratom liver injury. The remaining 10 cases are described in Table 2 and are of varying quality. Some are unlikely to be from kratom, but the lack of documentation prevented this determination.

FAERS has several potential drawbacks, including incomplete reports and lack of information verification. Case overlap between CAERS and FAERS is possible, however there is no overlap of ages between included CAERS and FAERS cases, or of case details between FAERS and LiverTox or published case reports and abstracts.

8 Human Reports in Internet Forums

The internet has numerous drug user forums, with intent ranging from risk reduction to high enhancement. Reports of kratom hepatotoxicity were queried on two popular harm reduction websites—Erowid and Bluelight—from the earliest available through March 2019 [58, 59]. Erowid allows for user posts but is curated by the website's operators, while Bluelight is a traditional user forum. Notably, although the first case report of kratom hepatotoxicity was published in 2011, these two websites have reports from 2004, 2007, 2008, and 2009. This underscores the value of user communities in detecting and reporting potential toxicity prior to identification by the medical community. A total of 27 posts were identified that are suggestive of kratom hepatotoxicity, listed in abbreviated form in Table 3. The reports vary in quality, with some listing specific test results and timeframes, while others omit important information. Given the number of online venues for drug use discussion, these 27 posts likely represent a fraction of online user-generated kratom hepatotoxicity reports. Reports include differing kratom formulations such as powdered kratom and concentrated extract, with frequency of use spanning from daily to weekly or less, and with variable intervals to hepatotoxicity onset. Diagnostic testing included three liver biopsies, and there were no reported deaths (although the majority are self-reports). Causality for user reports was not formally evaluated with RUCAM due to the high rate of omitted information. Despite limitations inherent to data from non-medical user forums, this adjunctive data source has value in demonstrating variations in formulations, time to onset, and frequency of use.

9 Human Biopsies

Twelve human liver biopsies have been described in case reports, not inclusive of internet forums. Kapp et al. found pure cholestatic injury without hepatocellular damage, with bile precipitations and canalicular cholestasis [27]. Kesar et al. found cholestasis, lobular inflammation, and increased eosinophils in sinusoids [39]. Drago et al. noted histology that was "entirely consistent with cholestatic liver injury" [37]. Shah et al. found intrahepatic cholestasis [41], and Bernier et al. found cholestatic overload with discrete destruction of interlobular bile ducts [40]. One of two cases in the LiverTox database showed "cholestatic changes with mild necrosis and inflammation" [52]. Riverso et al. found normal lobular architecture, mild portal tract inflammatory infiltrate with predominantly eosinophils, mild bile duct injury with rare apoptotic bodies and lymphocytic infiltration, and mild duct proliferation [29]. There was also focal steatosis and focal hepatocyte dropout, with mild centrilobular hepatocellular and canalicular cholestasis. Fernandes et al. found marked canalicular cholestasis, portal tract inflammatory infiltrate with lymphocytes, eosinophils, and some neutrophils, and bile duct injury with epithelial disarray [34]. Lobules showed injury with mild sinusoidal mononuclear infiltrate and Kupffer cell hyperplasia, and rare spotty necrosis without steatosis. Aldyab et al. found portal tract inflammatory infiltrate with predominantly nonplasma cells, bile duct injury, and scattered ballooned hepatocytes and endotheliitis [35]. Also noted were a few vaguely formed granulomas encasing interlobular bile ducts. Lastly, Pronesti et al. showed inflammation with focal prominent eosinophils, and hepatocellular and canalicular cholestasis without fibrosis [45]. Two biopsies performed in the DILIN (below) showed cholestasis.

Table 3 Self-reports through March 2019 in the Erowid Experience Vaults and Bluelight forum [58, 59]

Year	Post title (Author); website	Description
2004	Kratom—First time–Another Kratom Success (m#########n); Bluelight	Male used kratom for 3 weeks, and, over 1 week, developed jaundice, weakness, nausea, and dark urine; he suspected it was from kratom. Unknown if he stopped kratom use, it improved. History of prior significant ethanol use
2007	Extreme abdominal pain (PB); Erowid	Male used kratom weekly for several months, then had abdominal pain, malaise, and dark urine. Resolved 1 day later. Used kratom again 2 weeks later with identical symptoms. Not medically evaluated
2008	Kratom-induced hepatotoxicity (Sly); Erowid	25-year-old male used kratom extract every other day. After dose number 4, the patient had abdominal pain, dark urine, and jaundice. He was diagnosed with cholestatic hepatitis, which resolved in 2 weeks
2009	Kratom Health Issues (M#####h); Bluelight	Used kratom 10 g two to three times per week; after an unclear interval, the patient had jaundice, ALP 447–570, AST 375–460, ALT 685–834, urine bilirubin 6
2011	Kratom-induced hepatitis? (nlogn); Erowid	22-year-old female used crushed leaf almost daily for 2 weeks; had jaundice and pruritis. Previously healthy, no heavy ethanol use. Peak ALT 1400, AST 300, Tbili 6, ALP unknown. Ruled out viral and autoimmune hepatitis
2011	Kratom and liver damage (K################e); Bluelight	On day 1 used 10 × kratom extract 2.5 g and that night had abdominal pain. Over the next 2 weeks, the patient had jaundice and pruritis. On day 15, the patient went to hospital and was diagnosed with liver failure. Many tests were performed, including liver biopsy, and the patient was diagnosed with drug-induced cholestasis. Five weeks later, the patient was improving but had not returned to baseline
2012	Trip to the ER (SobeDog); Erowid	A 37-year-old male used kratom extract for first time, then the next day had abdominal pain and malaise that lasted 1 week. Two weeks later, he used kratom extract again, and awoke that night with abdominal pain and went to hospital. ALT 340, AST 250, unknown bilirubin and ALP. Liver tests trended down the next day, and normalized in 3 weeks
2012	Kratom-induced liver issues (Mark); Erowid	A 38-year-old female used kratom then had dyspnea and chest discomfort. In the Emergency Department, she had elevated liver function tests and was discharged. Over the next 5 days, the patient had progressive jaundice and pruritis
2013	Liver issues after very little use of kratom (l#####r); Bluelight	"I developed hepatitis around the same time I was taking kratom fairly often"
2013	Liver issues after very little use of kratom (a########l); Bluelight	Used kratom extract six times over 2 weeks (daily for 3 days, then three times in 1.5 weeks). 1 week after starting, the patient had nausea, and, 1 week after stopping, the patient had jaundice, pruritis, and dark urine, and was admitted. Liver enzymes, which were previously normal, were elevated. Negative hepatitis C. Ultrasound deferred. Previously healthy, no other drug use in 1.5 years, including OTC. Diagnosed as drug-induced cholestasis, which doctors thought was from kratom. Jaundice and pruritis improved but were still present 2 weeks after the last dose. Two years later, the patient used kratom again a few times over 1 week and 'liver symptoms' started returning. The patient stopped immediately, and was not medically evaluated
2013	Liver issues after very little use of kratom (J##########n); Bluelight	Used kratom 9 g daily for 2 weeks. After 1 week, the patient had dark urine, went to hospital, and had ALT > 500, "with other enzymes elevated as well". The patient stopped kratom and urine gradually normalized at the time of the online post; awaiting repeat tests. "I personally think that is [53] was the kratom, but given the other medicines I was taking to ease the [suboxone] withdrawal, I can't be sure."
2013	A warning to new Kratom users (J##########m); Bluelight	Used kratom approximately six times, then had jaundice; unclear timeline. The first four times were 3–10 g, the fifth time was 10 g; the patient had fever and nausea. The patient took an additional 10 g that night, and the next day had jaundice and pale stools. The patient had "elevated liver enzymes that of 6–8 times the normal levels". Further unknown tests were performed. The patient had also recently started the anabolic steroid methylepitiostanol

Table 3 (continued)

Year	Post title (Author); website	Description
2013	Kratom-induced liver injury? (s#########r); Bluelight	A 26-year-old male used powdered kratom 3 g, then a further few grams a few days later. Three weeks later, he drank kratom tea, and a few nights later repeated it. Over the next 2 weeks, he used kratom 5 times, 10 g each time, but never more than once in 2 days. He woke with emesis, went to the doctor, and "liver enzymes were through the roof". He was discharged, but a few days later had jaundice, pruritis, and dark urine, and was admitted. He had "extensive blood tests and several ultrasounds, I tested negative for all common liver diseases and showed no signs of gallstones, bile duct obstruction or anything else likely to cause such a reaction". He had detectable serum mitragynine. In addition, 18 months prior, he had a history of elevated liver enzymes for 3 weeks, which resolved and was attributed to acetaminophen. He used ethanol but not heavily, and marijuana was the only other drug used in this period. "Samples of the powdered kratom showed no obvious contaminants". The patient was diagnosed with "drug-induced hepatic injury causing severe biliary cholestasis", which doctors thought was from kratom. One month later, jaundice resolved, with residual fatigue and elevated liver enzymes
2013	Kratom-induced liver injury? (W######1); Bluelight	Began using daily kratom 1–3 teaspoons of crushed leaf. Five weeks later, the patient had abdominal pain, pruritis, and mild flu-like symptoms. One week later, the patient had scleral icterus, and tests showed "liver enzymes through the roof". The patient was admitted for 4 days, "no infection was detected, had many blood tests and abdominal ultrasound. Doctors thought from kratom". Diagnosed with drug-induced hepatitis. No other drugs were used, drinks "a couple of glasses of wine" in an evening, and abstains at least two nights weekly. 10 weeks later, the patient was back to baseline, and was awaiting repeat tests at the time of the online post
2013	A warning to new Kratom users (M####m); Bluelight	Used kratom daily for 1.5 weeks. The patient had vomiting and was admitted since "enzymes were severely elevated"; discharged after several days. One month later "enzyme levels were only a few points above normal". The patient then used kratom again for 1 week and had identical symptoms. The patient stopped use, did not seek medical care, and improved
2014	Hepatitis-like jaundice (FakeName); Erowid	Used kratom daily for 1 week, then had malaise, jaundice, pale stools, and very elevated 'liver enzymes'. Viral hepatitis tests were negative. Liver biopsy showed "blockage of the bile duct". started ursodiol, resolved over 1.5 months
2014	Killing my liver (happygent1236); Erowid	A male used kratom daily for several months, then suddenly had chills and jaundice. He was diagnosed with 'liver toxicity'. Previously healthy, no ethanol use
2014	Hard to Ignore: Kratom is extremely dangerous for some users (b################t); Bluelight	Used kratom for 3–4 weeks, 2–3 teaspoons of powder once daily. The patient had fever, abdominal pain, and dark urine, then scleral icterus and vomiting. The patient had leukopenia and "enzymes elevated to six times a normal level" with 'intrahepatic cholestasis'. No other hepatotoxic drug use, no pre-existing liver condition or hereditary concern. Doctors thought from kratom. Three weeks after being admitted, liver enzymes fell to slightly above normal. Symptoms gradually improved, starting 8 h after the last dose
2014	Hard to Ignore: Kratom is extremely dangerous for some users (C#######c); Bluelight	Used tramadol for 1 year and stopped, then started kratom six capsules daily. The patient had gradual pruritis, abdominal pain, and 3–4 weeks later stopped kratom. After 2–3 days of stopping, the symptoms resolved. The patient tried kratom again and severe symptoms returned. Did not seek medical care either time
2015	Almost Destroyed My Liver (sammers); Erowid	A 26-year-old previously healthy male (unclear duration of kratom use) awoke with nausea, and outpatient "liver enzymes were through the roof". Several days later, he had worse jaundice, no alternate etiology based on ultrasound, and "extensive blood tests". He was admitted for 1 week, and jaundice resolved over 1 month, with liver tests gradually improving but still elevated at the time of the online post

Table 3 (continued)

Year	Post title (Author); website	Description
2015	Induced hepatoxicity? (EkbatDeSebat); Erowid	A 26-year-old female used kratom once, then a few weeks later began daily use for 2 weeks. She had nausea, dark urine, and pale stools. ALT was approximately 400, Tbili 4.6, ALP unknown. She was admitted for a few days until laboratory tests downtrended. She had a CT scan, HIDA scan, ultrasound, and blood tests. The patient had a history of heavy ethanol use, with unclear frequency
2015	Kratom—Second time–hepatotoxic, ER with liver problems (h##########n); Bluelight	Used kratom once previously, then 2–3 teaspoons twice daily. The patient had abdominal pain, but continued to use for 1–2 days, then stopped use. The patient went to hospital and was diagnosed with hepatitis; had negative viral hepatitis tests. A repeat test showed downtrending liver enzymes. Abdominal pain peaked 2 days after stopping kratom, and improved within 1 week of abstinence. Repeat liver tests showed normalization
2017	Kratom and liver damage (H##########n); Bluelight	A few days after starting kratom, the patient had jaundice, pruritis, lower extremity edema, and vomiting. No other drugs were used in this time. The patient stopped kratom for an unknown period. There was no other drug use during this time, including OTC. The patient began using kratom again 2 weeks later, at a lower dose (1 teaspoon), but redeveloped vomiting and lower extremity edema. Did not seek medical care either time
2018	Bilirubin levels were through the roof (San Salvador); Erowid	A 23-year-old previously healthy male with no heavy ethanol use, used kratom for the first time. He awoke that night with abdominal pain, dark urine, and jaundice. A clinic said he had "drug-induced hepatoxicity and that my bilirubin levels were through the roof"
2018	Shooting liver pains and two trips to the ER (actual_ carrot); Erowid	A 20-year-old female used kratom for first time, but later that night had nausea and malaise. She suspected viral illness. 2 weeks later, she used kratom again, and awoke that night with chills, abdominal pain, and pale stools that progressed over 1 week. CT scan showed hepatomegaly, Tbili 3.9, elevated ALT. Negative viral hepatitis tests and ultrasound, and no heavy ethanol use. Bilirubin normalized over 2 weeks, and symptoms resolved over 2 months
2018	Kratom and liver damage (M########s); Bluelight	A male used kratom and had severe pruritis and elevated liver enzymes for 3 weeks. He also had liver biopsy. No further details are available
2019	Kratom, drug interactions prescription/OTC (a####n); Bluelight	Used kratom concurrent with ethanol, and developed 'severe hepatitis', but recovered

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ALP alkaline phosphatase, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *CT* computed tomography, *ER* emergency room, *HIDA* hepatobiliary iminodiacetic acid, *OTC* over-the-counter, *Tbili* total bilirubin

10 Animal Studies

While the majority of animal studies have had neurobehavioral or other focuses, numerous animal studies have evaluated hepatotoxicity. In 1972, Macko et al. conducted the first mitragynine animal toxicity studies, in rats and dogs [60]. Biochemical parameters of liver injury were not tested, however hepatic changes were found on sacrifice. Liver weight actually decreased overall in rats administered mitragynine 5 or 50 mg/kg/day most days per week for 6 weeks. In dogs administered 20 mg/kg/day most days of the week, 3/4 developed diffuse increased sinusoidal cellularity, which did not occur at 5 mg/kg/day.

In a 2010 rat study by Harizal et al. of acute kratom toxicity, methanolic *M. speciosa* extract was ingested at 100, 500, or 1000 mg/kg over 14 days [61]. A positive control group ingested high-dose morphine, and a negative control group received 1% methanol. All three experimental groups and the positive control group had higher mean transaminases versus negative controls, while total bilirubin and γ-glutamyltransferase (GGT) did not differ. Rats in the highest-dose experimental group and the positive control group

also developed severe sinusoidal congestion, centrilobular necrosis, lipid accumulation, hepatocyte hemorrhage, and Kuppfer cells.

In 2012, Kamal et al. administered a single oral dose of *M. speciosa* extract to rats at 175–2000 mg/kg [62]. When measured at 14 days, there was no significant change in ALP or ALT compared with controls; however, histology demonstrated steatosis in all treatment groups, and the 2000 mg/kg group had centrilobular necrosis.

In a 2013 study by Sabetghadam et al. rats received oral mitragynine at 1, 10, or 100 mg/kg for 28 days [63]. A control group received vehicle alone (propylene glycol, Tween-80, water). There was no difference in transaminases versus controls at mitragynine 1 or 10 mg/kg, but the 100 mg/kg group had significantly higher mean transaminases, with higher mean relative liver weights. Bilirubin was not assessed. Histology in the 10 and 100 mg/kg mitragynine groups demonstrated hepatocyte hypertrophy, hemorrhage, and sinusoidal dilation. Centrilobular necrosis and inflammatory cell infiltration were absent in all groups.

In 2013, Fakurazi et al. administered mitragynine at 15 and 25 mg/kg intraperitoneally to mice with and without morphine [64]. There was no change from controls in AST, ALT, or GGT among treatment groups, with the exception of elevated ALT in the mitragynine 25 mg/kg group.

In a 2014 study by Sakaran et al. 32 rats were administered either control 15% Tween-80 on an acute or subacute basis, or administered *M. speciosa* methanolic extract [65]. The two *M. speciosa* groups received either a single oral dose of 1000 mg/kg for 14 days (acute group), or repeated doses of 500 mg/kg daily for 28 days (subacute group). The control groups had normal liver parenchyma. The acute *M. speciosa* group developed hypertrophy of hepatocytes with mild cytoplasmic vacuolation and sinusoidal congestion, while the subacute group demonstrated severe hepatocyte hypertrophy with numerous vacuoles and severe sinusoidal congestion.

A 2014 study by Ali et al. administered oral *M. speciosa* chloroform-methanolic extract to 70 rats, at doses of 10, 30, or 100 mg/kg [66]. One group of rats was additionally exposed to immobilization stress conditions for 2 h daily, and there was also a placebo group. On liver histology, slight and moderate hyperemia were noted in the 100 mg/kg non-stressed and 30 mg/kg stressed groups, respectively.

A 2015 rat study by Ilmie et al. administered oral methanolic *M. speciosa* extract for 28 days at 100, 200, or 500 mg/kg, while controls received water [67]. There was no difference in ALT between groups. Compared with controls, mean AST was significantly higher in the 100 mg/kg group only (lowest dose). The authors noted that "total bilirubin … showed statistically significant differences when compared to the control group", but this data is not provided. Histology in the 200 mg/kg group showed portal inflammation and bile duct proliferation.

In 2018, Haslan et al. investigated *Piper betle* as a hepatoprotective herb in rats with kratom [68]. Controls received oral 15% Tween-80 *or P. betle* methanolic extract dissolved in Tween-80. Experimental groups received *M. speciosa* methanolic extract 500 mg/kg/day in Tween-80 for 28 days, or *M. speciosa* extract with *P. betle* extract. Control groups demonstrated normal liver histology. The *M. speciosa* group developed severe sinusoidal congestion with disrupted central veins, scattered focal necrosis with inflammatory cell infiltrate, 'drop out' lesions, and acidophilic bodies. Some hepatocytes had ballooning degeneration and microvesicular steatosis, and a few areas showed fibrous portal expansion and bridging fibrosis. The *M. speciosa* group with *P. betle* had minimal focal necrotic and acidophilic bodies, and only a few portal triads with fibrous portal expansion. The authors concluded *P. betle* reduced *M. speciosa* liver injury in this animal model.

A 2019 mouse study by Guenther et al. administered oral kratom tea at varying doses, found increased liver size on day 11 in the kratom tea group compared with controls [69]. Kratom was then discontinued and, at 4 weeks after kratom cessation, liver size was similar in the kratom-treated mice and controls. However, after 4 weeks of cessation, the kratom-treated group was noted to have adhesions of the liver to adjacent intraperitoneal organs. Biochemical parameters of liver injury were not measured, and the authors concluded kratom can cause reversible hepatomegaly in as few as 10 days in a murine model.

Overall, animal studies tend to show increased histologic and biochemical marker effects of liver injury at higher doses, however this is not consistent. Pathohistological patterns have included centrilobular necrosis and bile duct proliferation, among other findings. Most studies used *M. speciosa* methanolic extract at doses far higher than typical users are exposed to.

11 Mechanisms of Kratom Hepatotoxicity

Kratom metabolism is primarily hepatic, but its effects on hepatic transporters and enzymes remain poorly studied. Based on current evidence, we propose a multifactorial pathophysiologic mechanism involving pregnane X receptor (PXR) activation and cytotoxicity, but this is likely an incomplete model. The effects on UDP glucuronosyltransferases (UGTs), glutathione S-transferases (GSTs), and P-glycoprotein (PgP) may also play a role. These mechanisms may also reduce the threshold for hepatotoxicity from other substances.

PXR is a nuclear ligand-gated transcription factor that upregulates hepatic expression and activity of multiple

drug-metabolizing enzymes and transporters [70]. PXR activation has been linked to DILI, and postulated mechanisms involve either increased toxic metabolite formation due to upregulated drug-metabolizing enzymes and transporters, or altered homeostasis leading to increased endogenous toxic substances [71]. In general, drugs with significant hepatic metabolism cause DILI at a rate higher than other drugs, likely by generation of local toxic metabolites [72]. A single study has examined the in vitro effect of kratom on PXR. It found that at 0.37 μM for 48 h, mitragynine increased PXR activity 1.2-fold and several other *M. speciosa* alkaloids had increased effect [70]. This in vitro concentration must be considered in the context of plausible human plasma concentrations. A single study examined maximum concentration (C_{max}) in human volunteers and found the highest C_{max} was 0.105 μg/mL (0.26 μM) [73]. This study administered varying concentrations and volumes of kratom tea to regular kratom users, and the highest C_{max} was reached in the subject taking the largest loading dose of 23 mg. In rats, C_{max} has been reported as 1–1.8 μM [74]. Kratom in vitro studies are challenging to extrapolate clinically. Human C_{max} may reach higher levels since those using kratom recreationally often consume doses larger than those reported by Trakulsrichai et al.; however, free mitragynine is likely much lower, since the authors measured total mitragynine, which does not account for high protein binding [74]. Additionally, users often consume kratom for a longer duration than the 48 h studied in vitro by Manda et al. [70].

Cytotoxicity may play a role in kratom liver injury, causing hepatocellular injury or selectively damaging canalicular membranes, with specific pathways unelucidated. Saidin et al. found *M. speciosa* extract and mitragynine cytotoxic in vitro to human neurons, and cytotoxicity was enhanced by cytochrome P450 (CYP) 2E1 [75]. Separately, cytotoxicity and genotoxicity of mitragynine and methanolic *M. speciosa* extract were tested in vitro on human intestinal epithelial and neuronal cells after 4 and 6 h [76]. There was concentration-dependent reduced viability in both intestinal and neuronal cells. Genotoxicity was noted from extract but not pure mitragynine, suggesting it may be mediated by non-mitragynine plant constituents.

Kratom undergoes metabolism by several phase I CYP450 enzymes, in addition to phase II sulfation and glucuronidation [74, 77]. Kratom has been variably shown to affect UGTs, GSTs, and CYP450 enzymes, however these effects lack a clear link to hepatotoxicity, unless there is a resultant increase in an unidentified toxic metabolite.

Mitragynine affects several CYP450 enzymes, particularly CYP1A2, CYP2D6, and CYP3A4. Findings on whether induction or inhibition occurs, and the concentration at which it occurs, have varied among studies [74]. Similar to phase II enzyme inhibition, these effects may reduce the ability of the liver to detoxify metabolites or endogenous substances.

UGTs perform glucuronidation. A 2013 study found *M. speciosa* extracts weakly inhibited UGT activity in vitro, at concentrations too high for clinical relevance [78]. The same study administered *M. speciosa* extract to rats for 2 weeks, and UGT activity actually increased, possibly from an unidentified mechanism not present in the in vitro system. Another in vitro study assessed the effects of mitragynine and 7-hydroxymitragynine on human liver microsomes expressing recombinant human UGTs, and found inhibition only at concentrations too high for clinical relevance [79]. Separately, GST inhibition was demonstrated in rat liver cytosol in vitro by high concentration *M. speciosa* extract, yet the same study found, in rats, an in vivo trend toward GST induction rather than inhibition [80]. The cause for the discrepancy is unclear and may relate to *M. speciosa* metabolites only present in vivo.

Lastly, it is unknown if the effects on PgP may contribute to kratom hepatotoxicity. Mitragynine is not a PgP substrate and has been found to inhibit PgP in three studies and to induce PgP in one study [74, 81].

Several transport proteins strongly implicated in cholestatic liver injury have not been studied with kratom and future research should focus on the bile salt export pump, multidrug resistance proteins 2 and 3, and farnesoid X receptor [82, 83]. Further research may reveal a single protein effect as the dominant pathophysiologic mechanism.

12 Clinical Course

Due to the small number of cases described, the clinical course of kratom liver injury is unclear. There have been no clear deaths from kratom liver injury and a single case in the FAERS database died without sufficient exclusion of alternate etiologies and with likely underlying alcoholic cirrhosis. Hepatic coagulopathy has not been described; one case in the FAERS database had severe coagulopathy, but no conclusions could be drawn due to poor documentation. Hepatic encephalopathy grade I was described in a single case report [28] and two cases in the FAERS database had elevated serum ammonia with no documentation of encephalopathy. Kidney injury was described in two cases, but one had unclear chronicity and was complicated by a duodenal ulcer requiring transfusion [32], and the other in the FAERS database was likely from hemolysis of unknown etiology.

Latency to onset of liver injury is unclear. Several case reports and online self-reports had seemingly fast onset within 1 day. However, some of these may have been re-exposure cases, with subclinical liver injury from prior use that increased to a clinically apparent threshold after re-use [51]. Some reports of liver injury occurred after varying

periods of regular use, while others developed without regular use [38, 39, 51]. The cases in this review had a median latency of 20.6 days (range 2–49), and these findings are similar to the seven-patient series by the DILIN. The cause for latency to clinical manifestations may relate to the half-life of the parent compound and metabolites. This may be supported by Kapp et al. [27] noting detectable urine mitragynine 2 weeks after cessation of use, and by the finding that many cases have laboratory abnormalities that peak following initial tests.

13 Management

Optimal management of kratom liver injury remains unstudied. The majority of cases resolved with discontinuation, and it is unknown if the treated cases would have self-resolved without intervention. Several cases utilized antihistamines for symptomatic treatment of cholestatic pruritis.

Seven cases were treated with NAC, five published cases [26, 31, 36, 39, 47] and two cases in the FAERS database. NAC has classically been used for acetaminophen hepatotoxicity, although it has multiple therapeutic mechanisms and has been used with varying success in other hepatic conditions [84]. In one case, NAC was discontinued due to anaphylaxis [36]. Its utility for kratom liver injury is unknown; however, given the low risk of harm, it may be a reasonable therapeutic option if the etiology in the setting of a hepatocellular injury pattern is unclear.

Three cases were treated with ursodiol (ursodeoxycholic acid) [34, 35, 39]. The mechanisms of ursodiol include protecting cholangiocytes from hydrophobic bile acid cytotoxicity, stimulating hepatobiliary secretion via insertion of transporters into the canalicular membrane, and protecting hepatocytes against apoptosis from bile acids [85]. Anticholestatic effects have been described in a number of conditions, and while there are no data on efficacy for kratom liver injury, ursodiol may be reasonable if a cholestatic pattern is not readily resolving with discontinuation.

Two cases were treated with glucocorticoids and their role in the management of kratom-induced liver injury is unknown [35, 38]. This treatment is occasionally used in severe cases of cholestatic pruritis. A single case underwent lier transplantation, however it is unclear to what extent liver failure was directly due to kratom use, relative to Salmonella infection [49, 50].

In cases of suspected kratom liver injury, after initial tests to exclude common alternate etiologies, pursuing outpatient management for select patients may be reasonable. This depends on the extent of hepatic injury, degree of symptomology, ability to tolerate oral hydration, and resources and follow-up capabilities. Outpatient management was followed by resolution in one case report [33] and for two patients in the DILIN [55]; several others had brief admissions followed by outpatient management.

14 Limitations

The available evidence has several limitations. The total number of cases remains a limited dataset relative to estimated prevalence of use. Furthermore, many of the case reports and abstracts lack the necessary information to calculate accurate RUCAM scores. These omissions range from nonreporting of known data, historical variables that were not asked of the patient, or diagnostic tests that were not performed. In several cases, the patient was not followed for a long enough period for biochemical parameters to improve to the degree dictated by the RUCAM. Many of the cases that did not score higher were due to a lack of information, such as lost to follow-up, laboratory tests not rechecked early enough, or unknown timing. Omitted information overall risks RUCAM scores underestimating causality, given the score penalty for lack of information. We contacted authors in an attempt to obtain instances of missing data.

Additionally, the RUCAM dictates that those receiving treatment for liver injury, such as ursodiol or corticosteroids, must receive a score of 0 for course (dechallenge period), since treatment may mask the natural course [17]. This resulted in a total of five cases each being penalized 2 points on the RUCAM.

Hepatotoxicity from a contaminant cannot be excluded but is less likely given the standardized extracts used in animal studies and the kratom gas chromatography–mass spectroscopy analysis in five cases [27, 49, 55].

R ratios were calculated based on initial laboratory testing when available, however some were based on laboratory testing later in the illness course. Due to variability in both patient presentation timing and report documentation, *R* ratio timing could not be standardized and may have changed during the illness course. This is a recognized drawback of the RUCAM, therefore using the initial values when available is recommended [17].

15 Discussion

This review identified 26 case reports and abstracts, in addition to 7 cases reported from the DILIN, 25 in FDA databases, and 27 in internet user forums. Although evaluation by clinical gestalt is an accepted method of judging causation, its lack of standardization or rigor should preclude its application to a wider cohort. Attributing causation in DILI and HILI is of paramount importance as it affects the drugs a patient can receive and informs policy decisions regarding drug availability. Determination of a substance's

Table 4 Calculation of RUCAM scores

	Liver injury type	Time to onset (days)	Risk factor (ethanol, pregnancy)	Age, years	Course	Concomitant drugs	Nondrug causes ruled out	Prior hepatotoxicity	Re-exposure response	Modified RUCAM
Kupferschmidt, 2011 [38]	R ratio 8.0 Hepatocellular	5–90 [+2]	Absent [0]	< 55 [0]	≥ 50% improved > 30 days [0]	None [0]	5–6 in group I [0]	Published, unlabeled [+1]	Unknown [0]	3
Kapp et al. 2011 [27]	R ratio 1.4 Cholestatic	5–90 [+2]	Absent [0]	< 55 [0]	≥ 50% improved in 180 days [+2]	None [0]	5–6 in group I [0]	Published, unlabeled [+1]	Unknown [0]	5
Rivera et al. 2011 [44]	No ALP for R ratio									Cannot calculate
Kesar et al. 2013 [39]	R ratio 0.5 Cholestatic	≤ 15 from last use [+1]	Absent [0]	< 55 [0]	Corticosteroid/ ursodiol [0]	None [0]	5–6 in group I [0]	Published, unlabeled [+1]	Unknown [0]	2
Dorman et al. 2015 [28]	R ratio 0.24 Cholestatic	1–90 for second exposure [+2]	Absent [0]	≥ 55 [+1]	Unknown [0]	Time incompatible [0]	5–6 in group I [0]	Published, unlabeled [+1]	Positive [+3]	7
Arens et al. 2015 [48]	R ratio 7.5 Hepatocellular	< 5 [+1]	Present [+1]	< 55 [0]	Unknown [0]	None [0]	5–6 in group I [0]	Published, unlabeled [+1]	Unknown [0]	3
Sullivan 2016 [51]	R ratio 3.4 Mixed	5–90 [+2]	Present [+1]	< 55 [0]	≥ 50% improved in 180 days [+2]	Time incompatible [0]	5–6 in group I [0]	Published, unlabeled [+1]	Unknown [0]	6
Drago et al. 2017 [37]	R ratio 2.7 Mixed	≤ 15 from last use [+1]	Absent [0]	< 55 [0]	≥ 50% improved in 180 days [+2]	None [0]	5–6 in group I [0]	Published, unlabeled [+1]	Unknown [0]	4
Bernier et al. 2017 [40]	R ratio 1.7 Cholestatic	≤ 15 from last use [+1]	Absent [0]	< 55 [0]	≥ 50% improved in 180 days [+2]	None [0]	Groups I and II [+2]	Published, unlabeled [+1]	Unknown [0]	6
Shah et al. 2017 [41]	R ratio 1.4 Cholestatic	Insufficient documentation								Cannot calculate
Riverso et al. 2018 [29]	R ratio 4.0 Mixed	Insufficient documentation								Cannot calculate
Griffiths et al. 2018 [30]	R ratio 4.8 Mixed	5–90 [+2]	Absent [0]	< 55 [0]	Unknown [0]	None [0]	5–6 in group I [0]	Published, unlabeled [+1]	Unknown [0]	3
Tayabali et al. 2018 [36]	R ratio 2.7 Mixed	Insufficient documentation								Cannot calculate
Mousa et al. 2108 [31]	R ratio 8.7 Hepatocellular	5–90 [+2]	Absent [0]	< 55 [0]	N-acetylcysteine [0]	None [0]	5–6 in group I [0]	Published, unlabeled [+1]	Unknown [0]	3
Mackenzie and Thompson, 2018 [49] De Francesco et al. 2019 [50]	R ratio 8.7 Hepatocellular	5–90 [+2]	Present [+1]	< 55 [0]	Liver transplant [0]	None [0]	5–6 in group I [0]	Published, unlabeled [+1]	Unknown [0]	4
Antony and Lee 2019 [32]	R ratio 0.7 Cholestatic	≤ 15 from last use [+1]	Absent [0]	≥ 55 [+1]	≥ 50% improved in 180 days [+2]	Time incompatible [0]	5–6 in group I [0]	Published, unlabeled [+1]	Unknown [0]	5
2019, Fernandes et al. 2019 [34]	R ratio 0.7 Cholestatic	5–90 [+2]	Absent [0]	< 55 [0]	Ursodiol [0]	None [0]	5–6 in group I [0]	Published, unlabeled [+1]	Unknown [0]	3

Table 4 (continued)

	Liver injury type	Time to onset (days)	Risk factor (ethanol, pregnancy)	Age, years	Course	Concomitant drugs	Nondrug causes ruled out	Prior hepatotoxicity	Re-exposure response	Modified RUCAM
Osborne et al. 2019 [33]	R ratio 5.2 Hepatocellular	1–15 rechallenge [+2]	Absent [0]	< 55 [0]	> 50% improved in 30 days [+2]	None [0]	5–6 in group I [0]	Published, unlabeled [+1]	Positive [+3]	7
Ricardo et al. 2109 [42]	R ratio 8.4 Hepatocellular	5–90 [+2]	Absent [0]	< 55 [0]	Unknown [0]	None [0]	< 5 in group I [− 2]	Published, unlabeled [+1]	Unknown [0]	1
Desai et al. 2109 [47]	R ratio 7.1 Hepatocellular	5–90 [+2]	Absent [0]	< 55 [0]	*N*-Acetylcysteine [0]	None [0]	5–6 in group I [0]	Published, unlabeled [+1]	Unknown [0]	3
Bøgevig et al. 2019 [43]	R ratio 6.5 Hepatocellular	5–90 [+2]	Absent [0]	≥ 55 [+1]	> 50% improved in 30 days [+2]	None [0]	5–6 in group I [0]	Published, unlabeled [+1]	Unknown [0]	6
Aldyab et al. 2019 [35]	R ratio 10.4 Hepatocellular	5–90 [+2]	Absent [0]	< 55 [0]	Ursodiol [0]	Time incompatible [0]	5–6 in group I [0]	Published, unlabeled [+1]	Unknown [0]	5
Pronesti et al. 2019 [45]	R ratio 1.6 Cholestatic	5–90 [+2]	Absent [0]	< 55 [0]	≥ 50% improved in 180 days [+2]	Time incompatible [0]	5–6 in group I [0]	Published, unlabeled [+1]	Unknown [0]	5
Kaur et al. 2109 [46]	R ratio 3.6 Mixed	> 15 from last use								Cannot calculate
LiverTox Case 6972 [52]	R ratio 2.1 Mixed	Calculated by NIH LiverTox								5
LiverTox Case 8332 [53]	R ratio 2.1 Mixed	Calculated by NIH LiverTox								8

Interpretation: 9–10 highly probable, 6–8 probable, 3–5 possible, ≤ 0 excluded

Notes on scoring: for *R* ratios, upper limits of normal in the manuscript were used, but, if unavailable 40 was used for ALT and 115 was used for ALP. For Kapp et al. [27], serum mitragynine of 20 ng/mL at 12 days was not considered toxic due to the lack of reference ranges for toxicity. Griffiths et al. [30] describe common bile duct dilation, however 6.4 is within the normal limits. Antony and Lee [32] calculated RUCAM based on + 1 for alcohol risk factor, however the above calculation uses 0 because there was not excess ethanol consumption (Antony A, personal communication, 28 February 2019). For Osborne et al. [33], CMV hepatitis was unlikely given immunocompetency, but possible given + CMV IgM. For Ricardo et al. [42], the patient 'occasionally drank alcoholic beverages' that were unquantified, therefore the above calculation conservatively used ≤ 2 drinks/day (0 points). For nondrug causes, AST/ALT > 2 raised the possibility of alcoholic hepatitis, and hepatitis C RNA was moderately elevated, therefore hepatitis C flare is possible (Ricardo J, personal communication, 24 June 2019). Tayabali et al. [36] calculated a RUCAM score, however the latency period was unknown. In cases by Arens et al. [48] and Mackenzie and Thompson [49], ethanol is considered both a risk factor and a possible group I nondrug cause. For Kesar et al. [39] and Fernandes et al. [34], corticosteroid and/or ursodiol were administered, therefore although ≥ 50% improvement in 180 days would be [+2], the course had 0 points. For Mousa et al. [31], Aldyab et al. [35], and Desai et al. [47], N-acetylcysteine or ursodiol was administered, therefore although ≥ 50% improvement in 30 days would be [+2], the course had 0 points

ALP alkaline phosphatase, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *CMV* cytomegalovirus, *IgM* immunoglobulin M, *NIH* National Institutes of Health, *RUCAM* Roussel Uclaf Causality Assessment Method

hepatotoxicity based on pooling RUCAM scores has not been well-described but is instructive regarding the confidence in causation attribution. Among the 20 scorable case reports in this review, modified RUCAM scores had a median of 5 and a mean 4.5 (range 1–8) [Table 4]. Using the original RUCAM scoring criteria, the median was 6.0 and the mean was 6.0 (range 1–9). This difference is primarily due to the 2016 RUCAM modifications that emphasize Hepatitis E testing as only a single case report assessed hepatitis E beyond the two cases in the LiverTox database. Unless explicitly reported, it was assumed hepatitis E was not tested for. The updated RUCAM considers hepatitis E a group I nondrug cause due to a low percentage of cases previously attributed to DILI subsequently being attributed to hepatitis E [86, 87]. The 2016 modified RUCAM criteria are the current standard but have not undergone revalidation despite significant score changes due to the inclusion of hepatitis E.

The modified RUCAM scores suggest possible causality, while original RUCAM scores suggest probable causality. Overall, the above RUCAM scores likely underestimate causality, given the score penalty for lack of information, including testing and clinical course. Kratom likely causes liver injury based on the totality of low-quality human evidence in the form of case reports, FDA databases, and online user forums, and in the context of epidemiologic, animal, and mechanistic studies.

The R ratio assists in distinguishing cholestatic liver injury from hepatocellular liver injury, based on ALT and ALP. Determination of a substance's hepatotoxicity pattern by pooling R ratios is not well-described but informs classification in a standardized manner. Among 21 R ratios (Table 4) for which a RUCAM was calculated, the median was 3.4 and the mean was 4.6 (range 0.24–10.4). This result is similar to findings by the DILIN, which found a median R ratio at onset of 3.0 (range 0.9–3.2) [55]. This suggests kratom liver injury may be heterogenous or mixed, although, histologically, it seems predominantly cholestatic. Histology in animal studies was also heterogenous, including findings of both hepatocellular and cholestatic injury.

Kratom use is widespread and while kratom-induced liver injury is likely underreported, it is clear that many acute and chronic users, if not most, do not experience hepatotoxicity. It remains unclear which subgroups of users are at heightened risk and whether kratom liver injury is related to drug metabolizing enzyme polymorphisms (phase I or II) or use behaviors such as dose, frequency, or formulation. An idiosyncratic reaction should not be assumed until further pathophysiologic studies are conducted and the incidence is estimated.

16 Conclusions

Future research should focus on a more systematic investigation of the incidence of kratom-induced liver injury. Human case reports should include complete information to allow more accurate causality assessment, including hepatitis E serologies. Animal studies should utilize formulations and dosings that typical users are exposed to, rather than only methanolic extracts at often exceedingly high doses. Mechanistic underpinnings should be further explored by evaluating the effect of *M. speciosa* compounds on hepatic transporters strongly implicated in DILI, at biologically plausible concentrations.

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Compliance with ethical standards

Conflict of interest Jonathan Schimmel and Richard C. Dart declare no conflicts of interest.

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