Liver Injury Associated With Kratom (*Mitragyna speciosa*): A Systematic Review

Xavier Alexander Calicdan, BA, Anika Kopczynski, BS, Edwin Medina, BS, Samantha Singh, Diana Sotelo, BS, Alexander Chen Wu, BA, and Joji Suzuki, MD

Objectives: Kratom (*Mitragyna speciosa*) is a psychoactive herbal product increasingly used for pain, anxiety, and opioid withdrawal. Although marketed as a natural dietary product, concerns have emerged regarding adverse effects like cardiotoxicity, seizures, opioid-like physical dependence, and, particularly, liver toxicity.

Methods: We conducted a systematic review following PRISMA 2020 guidelines of all studies on kratom use and liver toxicity.

Results: Thirty-one studies were included, comprising 32 cases of kratom-associated liver injury. Most reports originated from the United States and were single-patient case reports. Most patients were adult males, with frequent co-occurrence of polysubstance use and comorbid conditions. Concomitant exposures were commonly reported but variably characterized across studies. Baseline liver disease was present in 3 patients (9%). Kratom dose, form, frequency, and duration were inconsistently reported. Only 7 cases (22%) provided complete exposure details, whereas the remainder lacked one or more elements. Kratom use was temporally associated with the onset of liver injury, commonly presenting with jaundice and elevations in liver enzymes. The patterns of injury were predominantly cholestatic. In most cases, liver enzymes and function improved after cessation of kratom use. In 4 cases, the patient's liver function did not improve and progressed to liver transplantation. Although formal causality assessments were inconsistently reported, many reports supported an association based on exclusion of alternative etiologies and, in some cases, rechallenge episodes.

Conclusions: Further research is needed to better characterize kratom's mechanisms of liver injury and to inform clinical decision-making and public health policy.

Key Words: kratom, mitragynine, liver injury

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Kratom (*Mitragyna speciosa*) is a tropical evergreen tree native to Southeast Asia. Traditionally, it has been used in the region for its stimulant properties at low doses and opioid-like analgesic and sedative effects at higher doses.[1] In recent years, kratom has gained popularity in Western countries, particularly in the United States, where it is widely available through smoke shops and online vendors, marketed as an herbal product.

Kratom contains over 40 different alkaloids, with the most abundant alkaloid being mitragynine.[2] Mitragynine undergoes hepatic metabolism into a variety of active alkaloids, such as 7-hydroxymitragynine, by cytochrome P450 3A4 (CYP3A4).[3] The opioid-like analgesic effects of kratom are primarily attributed to mitragynine's activity as a partial agonist at the mu-opioid and delta-opioid receptors, whereas 7-hydroxymitragynine seems to be a full agonist at the mu-opioid receptor and weaker antagonist activity at the kappa-opioid receptor.[4] Preclinical pharmacologic studies have shown that 7-hydroxymitragynine exhibits markedly greater opioid receptor potency, with ~13-fold higher potency than morphine and up to 46-fold higher potency than mitragynine.[5]

As kratom use continues to rise, recent nationally representative data provide important context for who uses kratom and why. A 2025 survey of US adults estimated a past-year prevalence of ~9.1% with the highest use among adults aged 30–50 years old.[6] Consistent with earlier findings from Grundmann's 2017 survey, pain relief was the most common reason for kratom use along with management of other chronic conditions including anxiety and depression.[7]

From the University of Toledo College of Medicine and Life Sciences, Toledo, OH (XAC); Department of Psychiatry, Brigham and Women's Hospital, Boston, MA (AK, SS, ACW, JS); University of Puerto Rico Medical Sciences Campus School of Medicine, San Juan, Puerto Rico (EM); Northeastern University, Boston, MA (SS); Texas Tech Health Sciences Center, Paul L. Foster School of Medicine, El Paso, TX (DS); and Harvard Medical School, Boston, MA (JS).

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Send correspondence and reprint requests to Joji Suzuki, MD, Department of Psychiatry, Brigham and Women's Hospital, 60 Fenwood Rd, Boston, MA 02115. E-mail: jsuzuki2@bwh.harvard.edu.

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Given these trends in use, concerns regarding kratom's safety profile have continued to grow. In the United States, the Food and Drug Administration (FDA) has not approved kratom as an approved drug, dietary supplement, or food additive. The Drug Enforcement Administration (DEA) lists it as a Drug and Chemical of Concern.[8] Although some individuals report benefits with kratom use, a range of adverse effects has also been documented, including seizures, cardiotoxicity, addiction, and hepatotoxicity.[9] Published reports have described cases of kratom-associated liver injury, often presenting with elevated liver enzymes, jaundice, and a hepatocellular, cholestatic, or mixed pattern of liver injury. However, the underlying mechanisms remain poorly understood and are often confounded by polysubstance use, limited toxicological data, and limited rigorous research in humans.

As kratom continues to be widely used and largely unregulated in many regions, a systematic review of the literature is needed to help establish an association between kratom and liver toxicity. Previous reviews have summarized kratom-associated liver injury, including a comprehensive scoping review and an analysis of cases reported to the US Drug-Induced Liver Injury Network.[10,11] These studies provided important foundational insights into clinical presentation and causality assessment of kratom-associated liver injury. The present review builds upon this prior work by applying PRISMA 2020 methodology, incorporating a structured risk-of-bias assessment, and focusing exclusively on published case reports and case series with detailed clinical and exposure data. The objective, therefore, of this systematic review is to describe reported cases of liver toxicity associated with kratom use, characterize clinical and biochemical features, describe patterns of liver injury, and assess the quality and strength of causality in the existing literature.

METHODS

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines.[12]

Data Sources

The electronic databases searched for this review included PubMed, Embase, and Web of Science. The search was limited to studies published in English, but no restrictions were placed on the date or geographic location of publication. The search aimed to identify all published studies involving humans that examined the relationship between kratom and liver-related outcomes. Keywords and search terms included: "kratom", "mitragyna speciosa", "mitragynine", "7-hydroxymitragynine", "liver injury", "hepatotoxicity", "liver toxicity", "elevated liver enzymes", "bilirubin", "jaundice", "drug-induced liver injury", "ALT", "AST", and "ALP". The search was conducted on June 9th, 2025.

Eligibility Criteria

Published studies reporting cases of liver injury associated with kratom use were included. Eligible studies had to include sufficient clinical details to assess the association between kratom use and liver injury, including laboratory values (ALT, AST, ALP, and bilirubin), and, when available, markers for hepatic synthetic function (albumin, PT, and INR) or a diagnosis of a drug-induced liver injury (DILI).

Published studies identified through the selected electronic databases were imported into Covidence for systematic screening and data extraction. The screening process occurred in 2 stages. In the first stage, 2 independent reviewers screened titles and abstracts from imported studies. Studies were excluded if there was not a focus on kratom use or lacked sufficient detail of a liver-related outcome. Disagreements between reviewers at this stage were resolved by a third reviewer through discussion and consensus. In the second stage, full-text articles of potentially eligible studies were reviewed independently by 2 reviewers to determine final inclusion. Conflicts at this stage were similarly settled by a third reviewer.

Data Extraction

Data were extracted from all eligible studies by 2 independent extractors using a customized data extraction form. The extracted forms were compared, and a third extractor reviewed discrepancies to generate a final consensus data set.

The customized data extraction form was designed to collect a comprehensive set of variables from each study. Study characteristics such as country of origin and article type (eg, case report or case series) were recorded. Patient demographics, including age, sex, comorbidities, alcohol use, acetaminophen use, polysubstance use, and prescription medicines were abstracted as reported in original case descriptions. Information on alcohol, acetaminophen, and other substance use could be derived from patient self-report, documented medication lists, or toxicology testing. Details of kratom exposure were extracted, including the form of ingestion, dosage, frequency, duration, and reported reason for use. Liver-related laboratory values, including alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), total bilirubin, and direct bilirubin, were recorded when available. Albumin, prothrombin time (PT), and international normalized ratio (INR) values were also extracted when reported. The pattern of liver injury (hepatocellular, cholestatic, or mixed) was recorded from the cases. The use of a causality assessment of drug-induced liver injury was extracted. Lastly, patient outcomes were documented, along with any additional findings. Outcome terms such as 'resolved' or 'improved' reflected the original authors' descriptions in each case report and were not redefined for this review.

Risk of Bias Assessment

The quality of included studies was assessed using a custom quality assessment form based on the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for case reports and case series.[13] The risk of bias was determined based on authors report of patient demographics, clinical history, presenting condition, diagnostic test, kratom exposure, adverse liver outcome, causality assessment, follow-up, and lessons discussed. Quality assessment was performed by 2 independent reviewers, and discrepancies were resolved through discussion and consensus of a third reviewer.

Data Synthesis

Extracted data were summarized using descriptive statistics, and a narrative synthesis was used to describe clinical patterns, laboratory findings, patterns of liver injury, and outcomes.

RESULTS

Study Selection and Characteristics

A total of 759 records were identified through database searches, including 365 from Embase, 199 from Web of Science, and 195 from PubMed. After the removal of 547 duplicates (546 identified by Covidence and 1 removed manually), 212 records were screened by title and abstract. Of these, 153 studies were excluded for not meeting basic relevance criteria. A total of 59 full-text articles were assessed for eligibility. Twenty-eight studies were excluded, which yielded 31 studies that met inclusion criteria and were included in the final review. A detailed summary of the study selection process is illustrated in the PRISMA flow diagram (Fig. 1).

The publication dates of the 31 included studies ranged from 2011 to 2025. Of the included studies, the majority were single-patient case reports (n = 30) with one case series (n = 1). Several studies described not only initial presentations of kratom-associated liver injury but also rechallenge events (n = 3). Across all studies, a total of 32 individual cases of liver injury associated with kratom use were identified. Most studies originated from the United States (n = 26), with additional cases reported from countries such as Canada (n = 1), Denmark (n = 1), Germany (n = 1), Switzerland (n = 1), and Thailand (n = 1).

Patient and Clinical Characteristics

Across the 32 cases, the median age was 36 years (range: 18–70 y), with a mean age of ~38 years. The majority of patients were male (n = 21, 65.6%), whereas female patients accounted for the remainder (n = 11, 34.4%). Alcohol use was reported in 34.4% of cases, whereas 40.6% of patients denied alcohol use and 25.0% had no alcohol information reported. Acetaminophen (APAP) use was present in 21.9% of cases, whereas 50.0% denied APAP use or had undetectable or normal serum levels, and 28.1% had no APAP information reported. Non-APAP polysubstance use was documented in 43.8% of patients and included cannabinoids, benzodiazepines, and opioids. The use of additional substances along with kratom further introduces potential confounding in causality assessments and may influence the severity or pattern of liver injury. Comorbid conditions were present in 63% of patients and varied widely, including metabolic syndrome, psychiatric disorders, and opioid use disorder. Baseline liver disease was documented in 3 patients (9%), including hepatic steatosis, chronic hepatitis C, and biliary stricture. As most reports did not include baseline liver laboratory values, premorbid liver function could not be clearly characterized in the remaining cases.

The reported reasons for kratom use by patients were varied and included self-treatment for chronic pain, opioid withdrawal, and anxiety. Reporting of kratom exposure characteristics was inconsistent across studies. Among the 32 cases, the form of kratom used was described in 23 (72%), dose in 15 (47%), frequency in 23 (72%), and duration in 30 (94%). Three cases (9%) mentioned a strain or product label, but none reported quantitative potency or alkaloid concentration data. Only 7 cases (22%) provided complete exposure details, including form, dose, frequency, and duration, whereas one or more of these elements were missing in the remaining reports. Among the cases that reported use, daily use was the most frequently described pattern, with exposures ranging from one-time ingestion to chronic daily use over weeks to years. Reported forms of kratom included powders, teas, capsules, tablets, leaves, and combination preparations.

Laboratory Findings and Injury Patterns

Liver laboratory values were reported in all included cases, although some data points were incomplete due to unreported values in the case reports. In cases involving a rechallenge event, laboratory values were reported separately, resulting in a total of 35 distinct laboratory profiles across 32 patients. Both initial presentation values and peak values were recorded when available. Peak values were noted separately for each liver value rather than part of a full laboratory panel. The clinical presentation and peak laboratory values for each case are presented in Tables 1 and 2, respectively.

Patterns of liver injury were classified as hepatocellular, cholestatic, or mixed, based on the reported interpretation. Among the cases including rechallenge events, the most observed pattern of injury was cholestatic (n = 18, 51%), followed by hepatocellular (n = 9, 26%) and mixed (n = 8, 23%).

Causality Assessment

Causality between kratom use and liver injury was evaluated based on the information reported in each study. Including initial and rechallenge episodes as separate events, formal causality assessment tools were applied in 12 of the 35 cases (34%), 2 of which were a rechallenge event. Among the 12 cases, the most frequently used tool was the Roussel Uclaf Causality Assessment Method (RUCAM), used in 6 cases (50%). Other tools included the Naranjo Adverse Drug Reaction Probability Scale (n = 3, 25%), the Revised Electronic Causality Assessment Method (RECAM) (n = 1, 8.3%), and the World Health Organization-Uppsala Monitoring Centre (WHO-UMC) system (n = 1, 8.3%). One case reported the use of a causality assessment without specifying the method (n = 1, 8.3%). In the remaining cases (n = 23, 66%), causality was assumed based on expert clinical reasoning, such as temporal association with kratom use, exclusion of alternative liver injury causes, and improvement after cessation.

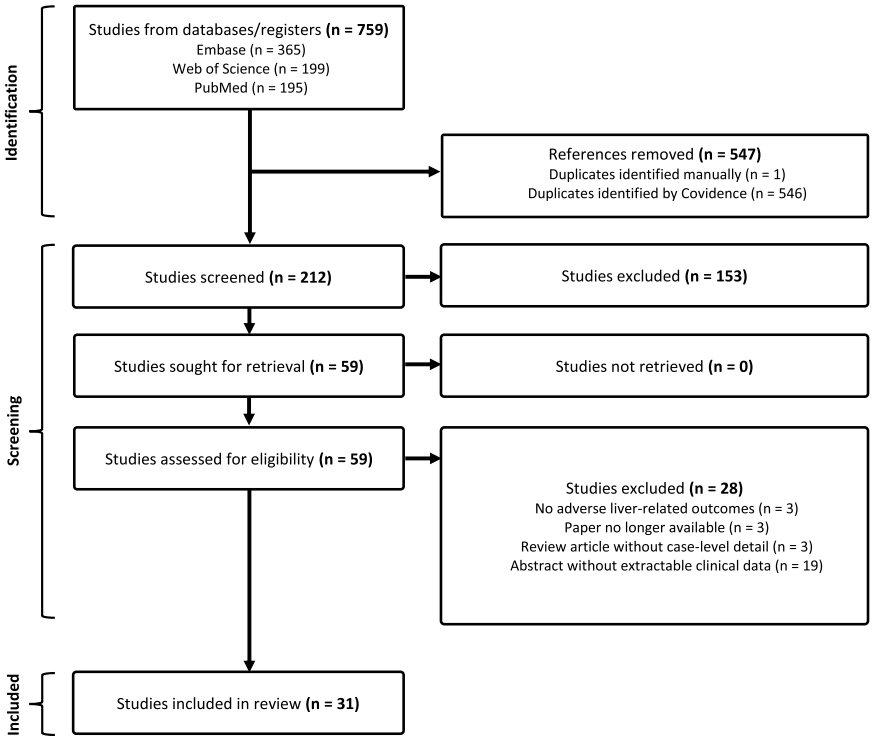

FIGURE 1. PRISMA flowchart.

Outcomes and Additional Findings

Clinical outcomes were reported in nearly all cases. Rechallenge was attempted in 3 cases, all of which demonstrated recurrence of liver injury after re-exposure. Of the 35 cases, including initial and rechallenge episodes, the majority (n = 24, 69%) experienced resolution of laboratory abnormalities and symptoms after cessation of kratom use. The time to resolution varied widely, with most patients recovering within a few weeks, although exact timelines were often not specified. Seven cases (20%) showed partial improvement in clinical and laboratory findings by the time of discharge, but full resolution was not explicitly reported. Four cases (11%) progressed to liver transplantation. No fatalities were reported in any of the included cases, although the severity of liver injury varied substantially. A detailed summary of individual case outcomes, associated findings, and causality assessments is provided in Table S1, Supplemental Digital Content 1, http://links.lww.com/JAM/A781

Risk of Bias

Most studies demonstrated low risk of bias across core domains such as patient demographics, clinical history, presenting condition, and diagnostic testing. The clearest limitations were observed in the reporting of kratom, mitragynine, or 7-hydroxymitragynine exposure (domain 5), performance of a formal causality assessment (domain 7), and adequacy of follow-up descriptions (domain 8). A detailed summary of the risk of bias across the studies included is provided in Figure 2.

DISCUSSION

This systematic review summarized 32 published cases of liver injury associated with kratom use, offering the most comprehensive synthesis to date of its hepatotoxic potential. Cases ranged from adults with no significant medical history to those with many comorbidities. Clinical recovery was achieved in most cases after kratom cessation, although all cases required hospitalization, and 4 progressed to liver transplantation, which demonstrates the potential severity of kratom-related hepatotoxicity. However, detection bias must be considered as only cases severe enough to warrant clinical evaluation and publication were captured. Mild or subclinical cases that resolved without hospitalizations, and severe cases that were unrecognized as kratom-related, were likely under-represented. Consequently, the true incidence and full clinical spectrum of kratom-associated liver injury remain uncertain. In addition, publication bias may have influenced the available literature. Earlier reports of kratom-associated liver injury were more likely to be published due to the novelty of the finding, whereas similar or milder cases in later years may not have been submitted or accepted for publication, leading to further under-representation of recent or less severe presentations.

These findings add to the concerns over kratom's safety profile as its use expands in the United States and globally. Although kratom is often marketed as a "natural" alternative for pain relief or opioid withdrawal, our

TABLE 1. Peak Liver Enzymes, Bilirubin Levels, and Synthetic Function Markers

References	ALT (IU/L)	AST (IU/L)	ALP (IU/L)	Total Bilirubin (mg/dL)	Direct Bilirubin (mg/dL)	Albumin (g/dL)	PT (S)	INR
Allison et al[14]	58	61	333	39.4	—	—	16.2	—
Botejue et al (case 1)[15]	404	345	115	1.3	—	—	"Normal"	"Normal"
Botejue et al (case 2)[15]	28	138	156	39.5	—	2.3		3
Fernandes et al[16]	34	41	301	28.9	—	—	—	"Normal"
Umbehr and Lukaszewicz[17]	1057	332	488	6.7	—	—	—	1.2
Roma et al[18]	168	64	265	10.7	—	—	10.9	1.04
Antony and Lee[19]	59	53	230	33.7	27	—	—	1.4
Thewjitcharoen et al[20]	1635	642	285	10.6	9.2	4.4	13.1	1.15
Riverso et al[21]	389	220	304	5.1	4	4.2	—	—
Khan et al[22]	230	310	648	11.3	7.8	—	—	1.6
Aldyab et al[23]	875	462	162	5.1	—	—	—	—
Gandhi et al[24]	591	385	839	19.5	—	—	—	—
Kapp et al[25]	94	66	173	30.9	28.6	—	—	1.15
Osborne et al (initial)[26]	265	108	170	5.8	—	3.5	"Normal"	"Normal"
Osborne et al (rechallenge)[26]	566	185	211	3.2	—	—	—	—
Tayabali et al[27]	365	222	391	6.3	—	"Normal"	"Normal"	"Normal"
Hairane and Weiss[28]	466	305	861	10.8	6.2	—	—	—
Schmitz et al (initial)[29]	677	348		16.9	11.4	—	—	—
Schmitz et al (rechallenge)[29]	420	650	—	5.4	—	—	—	—
Alias et al[30]	508	361	—	5.4	—	—	—	—
Fishburn and Mullins[31]	6528	1804	—	12	—	—	—	3.3
Pronesti et al[32]	308	125	556	5.7	4.5	—	—	—
Ricardo et al[33]	1134	4624	387	5.1	3.3	—	11	1.06
Bøgevig et al[34]	887	392	—	17.31	—	—	"Normal"	"Normal"
Mackenzie and Thomspon[35]	6969	14000	162	11.23	—	—	—	8.8
Kesar et al[36]	93	61	298	10.6	—	—	"normal"	"normal"
Kupferschmidt et al[37]	482	271	174	9.36	—	—	—	—
Books and Frederick[38]	1207	1125	143	5.4	—	—	19.9	1.9
Abushahin and Harris[39]	188	75	163	9.1	4.3	—	—	1.0
Dasgupta and Ye[40]	1023	—	—	70.6	—	—	—	—
Jensen et al[41]	586	173			—	"normal"	—	—
Mousa et al[42]	653	223	273	2.2	—	—	—	—
Griffiths et al[43]	319	294	193	2.86	—	4.3	14.1	1.09
Dorman et al (initial)[44]	79	—	270	9.7	—	—	—	1.0
Dorman et al (rechallenge)[44]	106	—	790	25.6	17.1	—	—	1.1

Reported peak liver enzyme, bilirubin, and synthetic function values in patients with kratom-associated liver injury. Peak values were noted separately for each analyte rather than as part of a complete laboratory panel.

ALP indicates alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; INR, international normalized ratio; PT, prothrombin time.

review highlights that "natural" is not without risks. The pathophysiology underlying kratom-induced liver injury remains poorly understood. Metabolism of mitragynine through CYP3A4 may generate reactive metabolites, and potential idiosyncratic or immune-mediated injury mechanisms have been proposed.[45] Because 7-hydroxymitragynine is one of the key active metabolites of mitragynine, its pharmacologic properties have been of interest when considering potential toxicity. Preclinical studies indicate that 7-hydroxymitragynine is a much more potent opioid agonist than mitragynine, but existing human and animal data do not clearly distinguish whether these alkaloids differ in their contribution to hepatotoxicity. None of the included case reports quantified 7-hydroxymitragynine levels, which prevented assessment of whether greater 7-hydroxymitragynine exposure was associated with more severe liver injury. When provided, histopathologic findings revealed bile duct injury, cholestasis, or mixed inflammatory infiltrates, suggesting heterogeneous mechanisms of liver damage.

Prior reviews by Schimmel and Dart and Ahmad and colleagues first characterized kratom-associated liver injury through descriptive and registry-based analyses. The current synthesis expands on these findings by incorporating more recently published cases and providing updated summaries of clinical presentation, exposure patterns, and outcomes. Taken together, these collective data offer a clearer picture of the evolving clinical spectrum and potential severity of kratom-related hepatotoxicity.

This systematic review has several strengths. It follows PRISMA guidelines, incorporates structured data extraction and bias assessment, and provides a broad international synthesis of published cases.

However, there are numerous limitations to this review. Definitive conclusions cannot be drawn with reliance on case reports alone, which are inherently prone to bias. Included cases did not routinely use causality as-

TABLE 2. Presentation Liver Enzymes, Bilirubin Levels, and Synthetic Function Markers

Study ID	ALT (IU/L)	AST (IU/L)	ALP (IU/L)	Total Bilirubin (mg/dL)	Direct Bilirubin (mg/dL)	Albumin (g/dL)	PT (S)	INR
Allison et al[14]	58	61	220	34.3	—	—	16	—
Botejue et al (case 1)[15]	404	345	115	1.3	—	—	"Normal"	"Normal"
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Fernandes et al[16]	62	48	259	22.8	—	—	—	"Normal"
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Riverso et al[21]	389	220	304	5.1	4	4.2	—	—
Khan et al[22]	565	564	335	4.1	3.6	—	—	1.0
Aldyab et al[23]	875	462	162	5.1	—	—	—	—
Gandhi et al[24]	578	455	672	10.3	—	—	—	—
Kapp et al[25]	94	66	173	30.9	28.6	—	—	1.15
Osborne et al (initial)[26]	265	108	170	5.8	—	3.5	"Normal"	"Normal"
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Hairane and Weiss[28]	466	305	861	10.8	6.2	—	—	—
Schmitz et al (initial)[29]	677	348	—	16.9	11.4	—	—	—
Schmitz et al (rechallenge)[29]	420	650	—	5.4	—	—	—	—
Alias et al[30]	287	164	315	5.4	—	—	—	—
Fishburn and Mullins[31]	6528	1804	—	12	—	—	—	3.3
Pronesti et al[32]	308	125	556	5.7	4.5	—	—	—
Ricardo et al[33]	1134	4624	387	5.1	3.3	—	11	1.06
Bøgevig et al[34]	887	392	392	17.31	—	—	"Normal"	"Normal"
Mackenzie and Thomspon[35]	330	1431	109	0.98	—	—	—	8.8
Kesar et al[36]	93	61	298	10.6	—	—	"Normal"	"Normal"
Kupferschmidt et al[37]	482	271	174	9.36	—	—	—	—
Books and Frederick[38]	1207	1125	143	5.4	—	—	19.9	1.9
Abushahin and Harris[39]	217	122	161	4.5	2.8	—	—	1.0
Dasgupta and Ye[40]	—	—	1023	70.6	—	—	—	—
Jensen et al[41]	586	173	—	—	—	"normal"	—	—
Mousa et al[42]	578	191	191	2.2	—	—	—	—
Griffiths et al[43]	319	294	193	2.86	—	3.7	—	—
Dorman et al (initial)[44]	79	—	270	9.7	—	—	—	—
Dorman et al (rechallenge)[44]	106	—	790	25.6	17.1	—	—	1.1

Presentation liver enzyme, bilirubin, and synthetic function values in patients with kratom-associated liver injury. Values reflect laboratory findings at the time of presentation.

ALP indicates alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; INR, international normalized ratio; PT, prothrombin time.

sessment tools, with only a third utilizing formal tools such as RUCAM and Naranjo. Concurrent alcohol and other substance use, incomplete diagnostic lab values, and lack of standardized kratom exposure data further limit the ability to establish definitive causality. Moreover, documentation of alcohol and acetaminophen exposure was inconsistent across cases. Although many reports specified whether these exposures were present or denied, several provided no information and did not indicate whether alcohol or acetaminophen use was explicitly queried or analytically assessed. Given that both substances are common hepatotoxins, the absence of clear documentation introduces uncertainty and may lead to under-recognition of potential confounders. Sparse documentation of baseline liver status adds an additional limitation.

The limited reporting of kratom form, daily dose, frequency of ingestion, and duration of exposure further constrains efforts to identify potential dose-response relationships. Without consistent quantitative exposure data, it is not possible to determine whether higher daily intake, repeated consumption throughout the day, or prolonged use increased the likelihood of liver injury. These gaps also hinder comparison with other well-characterized hepatotoxins such as alcohol and acetaminophen.[46,47] The absence of standardized exposure reporting across published case reports, therefore, remains a major barrier to defining toxicity thresholds and evaluating exposure toxicity patterns.

There was also a lack of analytical and quantitative confirmation of kratom alkaloids, specifically mitragynine and 7-hydroxymitragynine. Because kratom is not subject to standardized manufacturing or regulatory oversight, variability in purity and composition is common. Prior analyses have identified commercial kratom products adulterated with artificially elevated concentrations of 7-

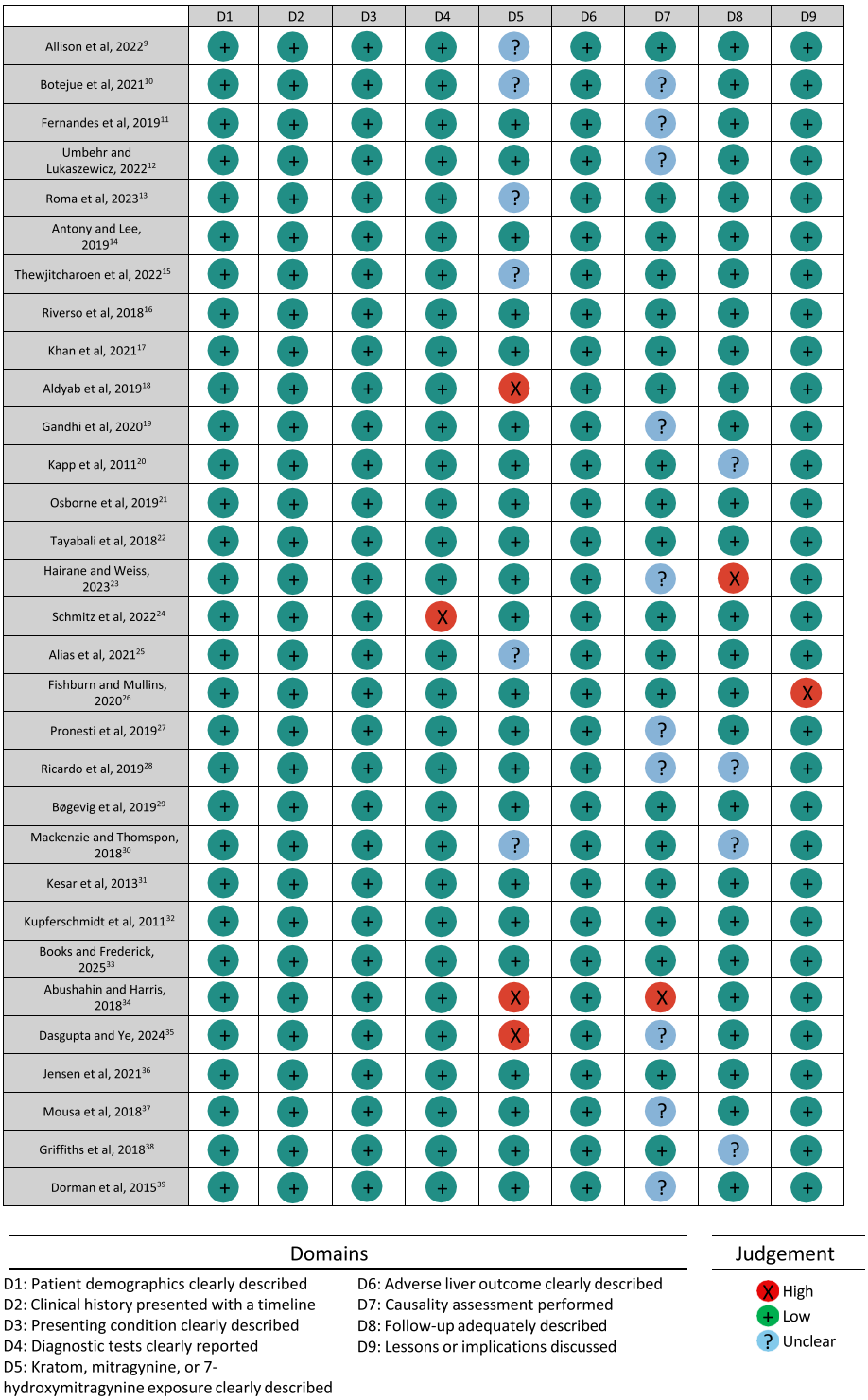

FIGURE 2. Risk of bias domain.

hydroxymitragynine and related synthetic analogs, which may increase toxicity risk.[48,49] In addition, contamination of kratom products with *Salmonella* has been confirmed in a multistate outbreak investigation.[50] These findings highlight that adulterants and contaminants may contribute to adverse effects reported in clinical cases.

At a broader population level, important gaps remain in our understanding of kratom-associated liver

injury. Existing case reports provide valuable clinical details but cannot estimate how often liver injury occurs among kratom users or what factors influence risk. Given that the national survey data indicate that potentially millions of adults in the United States use kratom, including many who report regular or prolonged use, answering these questions is increasingly important for public health. Clarifying whether kratom contributes directly to liver injury or acts as a risk-associated factor in susceptible individuals will be important for informing clinical decision-making and potential regulatory or labeling considerations. Future large-scale studies that systematically track kratom exposure and follow users over time would help determine incidence, identify risk factors, and clarify whether kratom independently contributes to liver injury.

Despite these limitations, the repeated documentation of liver injury temporally associated with kratom use across independent cases strengthens the plausibility of hepatotoxicity. In addition to temporality, other features supporting causality include consistency of findings across geographically diverse reports, biological plausibility given the known metabolism of mitragynine through hepatic CYP3A4, and experimental evidence from positive rechallenge cases demonstrating recurrence of liver injury after re-exposure. The causal relationship, therefore, seems highly probable in select cases.

CONCLUSIONS

Given the increasing prevalence of kratom use and its unregulated availability, health care providers should be aware of its potential to cause liver injury. A thorough history that includes inquiring about kratom use is essential in the evaluation of unexplained liver injuries. Because many published cases did not report exposure details such as form, dose, frequency, or duration, improving the consistency of exposure documentation will be important for clarifying potential liver toxicity, particularly when kratom is used with other hepatotoxins such as acetaminophen or alcohol. More consistent reporting of kratom exposure will also help facilitate the data needed for future prospective and registry-based studies to better define dose-related risk, long-term effects, and severe outcomes such as transplantation or death. In addition, future studies should aim to systematically document kratom exposure through analytic confirmation, use standardized causality tools, and explore mechanistic pathways of toxicity.

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