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Review Article

Khat-associated Autoimmune Hepatitis: A Review with RUCAM Analysis

Rachael Hagen[1*] and George Y. Wu[2]

[1]*Department of Medicine, University of Connecticut Health Center, Farmington, CT, USA;* [2]*Division of Gastroenterology and Hepatology, Department of Medicine, University of Connecticut Health Center, Farmington, CT, USA*

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Abstract

Khat (*Catha edulis*) is a plant native to East Africa and the Arabian Peninsula, chewed for its stimulant effects by millions worldwide. Its sympathomimetic properties, primarily due to cathinone and other pyrrolizidine alkaloids, resemble those of amphetamine. Emerging reports have linked khat use to the development of autoimmune hepatitis, supported by elevated autoimmune markers, characteristic liver biopsy findings, and clinical resolution following khat cessation or a prompt response to corticosteroid therapy without recurrence. In this review, we aimed to update knowledge on both acute and chronic forms of khat-associated AIH. We discuss cathinone metabolism, pharmacokinetics, and proposed mechanisms of khat hepatotoxicity. We also provide an updated synthesis of published cases of khat-associated autoimmune hepatitis, including our calculated Roussel-Uclaf Causality Assessment Method analysis and the simplified Hennes AIH score where data were available. Case presentations, diagnostic criteria, histopathological findings, and treatment approaches are summarized to help guide management.

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Introduction

Khat (*Catha edulis*) is a plant chewed recreationally as a stimulant by over 20 million people worldwide.[1] Khat grows as a bush native to the Horn of Africa and the Arabian Peninsula. Consumption is primarily concentrated among these populations and is deeply ingrained in their cultural practices. The euphoric effects of khat are mostly attributed to cathinone, its main active component, along with other pyrrolizidine alkaloids to a lesser extent, such as cathidine and cathine.[1] These constituents are sympathomimetic with pharmacological properties similar to amphetamines, causing a similar central nervous system response by releasing dopamine and other catecholamines.[2–4] Mastication of khat leaves extracts alkaloids, which are absorbed by the buccal mucosa.[5] Fresh khat leaves, which contain a higher ratio of cathinone to cathine, are associated with greater toxicity than dried leaves.[5]

The alkaloid compounds in khat, particularly cathinone (aminopropiophenone), have been associated with numerous adverse health effects, including myocardial infarction, hypertension, anxiety, upper gastrointestinal cancers, impaired fetal growth,[6] and a range of psychiatric disorders, from psychosis to suicide.[7] Khat is also associated with acute hepatitis[8] and chronic liver disease (CLD), which may progress to cirrhosis and occasionally require liver transplantation.[3,9] Although khat ingestion and hepatotoxicity are fairly confined to geographic areas corresponding to regions where the plant grows abundantly, immigration and illegal importation can result in the presentation of hepatotoxicity in atypical locations.

Khat use has also been linked to autoimmune hepatitis (AIH), as evidenced by elevated autoimmune markers, biopsy findings consistent with AIH, and complete resolution with cessation of khat exposure, or prompt complete response to corticosteroids without recurrence after discontinuation.[1] This autoimmune-associated khat hepatotoxicity is not generally well appreciated. Therefore, our review aims to update knowledge on khat-associated AIH. We used the Roussel Uclaf Causality Assessment Method (RUCAM) to evaluate the causality of suspected drug-induced liver injury (DILI) and the simplified Hennes AIH score, incorporating autoimmune titers, IgG levels, histology, and hepatitis viral markers to assess concurrent AIH.[10,11] We applied these calculated RUCAM and AIH scores where data were available to assess presentations, diagnostics, and treatments to determine their association.

Epidemiology

The prevalence of khat use in East Africa has been reported to range from 16% to 90%. The highest rates of khat chewing were observed in Yemen, Somalia, and Ethiopia. In Yemen, 80% of people over 16 years old have chewed khat at least once.[12] Approximately 80% of Yemeni people chew khat daily.[13] Over 90% of Yemeni men chew khat daily compared to 50% of Yemeni women.[13] Additionally, most khat users are between 15 and 30 years old.[13]

Liver injury from khat use is likely underreported due to cultural perceptions of khat's benefits and its legal status in Africa. Additionally, detecting cathinones in standard drug

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[*]**Correspondence to:** Rachael Hagen, Department of Medicine, University of Connecticut Health Center, 263 Farmington Ave., Farmington, CT 06030, USA. ORCID: https://orcid.org/0009-0004-6988-6724. Tel: +1-941-250-4330, Fax: +1-860-679-6582, E-mail: rhagen@uchc.edu.

screenings is difficult, as cathinones are only detected within one day after chewing khat.[14,15] This limited detection window makes testing for khat use challenging.[16] Furthermore, only cathinones are specific to khat use, as other substances can also metabolize into cathine and cathinone derivatives. Liver injury from khat exposure primarily affects young men from these regions, the population with the most frequent use.[17] A retrospective study in Egypt reported that acute hepatitis from khat use accounted for 4% of DILI hospitalizations over one year.[18] A case-control study attributed 83.2% of cases of CLD in men to khat use, compared to only 1.9% in women.[19] This differs from typical AIH, which affects middle-aged women aged 40 to 70.[20]

Data on rates of acute and chronic AIH linked to khat are derived primarily from case reports. Khat-associated acute and chronic AIH have been reported beyond the Horn of Africa due to East African immigration to the United Kingdom, United States, and Australia.[1,4,21] With increasing migration, the spread of khat consumption globally and the incidence of khat-induced hepatotoxicity are expected to rise.[16] The widespread use of khat among men in East Africa and its growing global reach through migration make increased awareness and surveillance essential to recognize and manage khat-associated liver injury and AIH, especially in populations traditionally considered low-risk for AIH.

Pharmacokinetics and Metabolism of Cathinones

Fresh khat leaves (100 g) are reported to contain an average of 36 mg of cathinones.[22] Cathinone metabolism occurs faster in the liver than in other organs, including the lungs, kidneys, heart, brain, and serum, which may partially explain the increased rates of liver toxicity compared to other organ involvement.[23] Mean fractional oral absorption has been reported to be 59 ± 21% for cathinone and 84 ± 6% for cathine. Peak plasma concentrations occurred at approximately 127 m for cathinone, 183 m for cathine, and 200 m for norephedrine.[24] The half-life of cathinone has been reported to range from 1.5 ± 0.8 h to about 4 h after khat ingestion, while the half-life of cathine was approximately 5.2 ± 3.4 h.[25]

Cathinones are eliminated by glucuronidation and urinary excretion of their glucuronide conjugates.[26] However, only 0.6% to 7.0% of cathinones are excreted in the urine, while the majority undergo metabolism, illustrating the significant metabolic burden placed on the liver following khat ingestion.[24,27] Acidified urine enhances cathinone elimination, suggesting that lowering urinary pH could assist in cathinone excretion and may be beneficial in managing khat toxicity.[26] Further studies should explore the potential of urinary acidification as a treatment strategy for khat toxicity.

Cathinones are primarily metabolized in the liver by cytochrome P450 enzymes, especially CYP2D6.[28,29] Khat has been shown to inhibit CYP2D6 activity significantly,[30] likely due to competitive inhibition by cathinone. This may alter the metabolism of other CYP2D6 substrates, potentially resulting in increased plasma levels of these drugs and enhanced effects or toxicity.

Genotype-dependent inhibition of CYP2C19 and CYP1A2 can contribute to differential metabolism of pyrrolizidine alkaloids between individuals and, therefore, varying hepatotoxic effects. Inhibition of CYP2C19 can result in the accumulation of toxic metabolites due to decreased metabolism of the latter. Because CYP2C19 activity varies by genotype, the extent of enzyme inhibition and subsequent pyrrolizidine alkaloid metabolite accumulation can contribute to observed differences in hepatotoxicity between individuals.

Notably, lower CYP2D6 activity is seen in individuals of Ethiopian descent living in Ethiopia compared to those living in Sweden, despite sharing the same CYP2D6 genotypes, suggesting an environmental component, such as khat use, involved in CYP2D6 activity.[31] Furthermore, the frequency of CYP2D6 duplication coincides with regions with the highest rates of khat use.[30] Thus, individuals with lower CYP2D6 enzyme activity are likely to be at an increased risk of drug reactions with khat ingestion. This is particularly concerning in patients taking pharmaceuticals metabolized by CYP2D6, such as antidepressants, antipsychotics, antimalarials, beta blockers, antiarrhythmics, opioids, and antiemetics, among others.[30,32] Thus, khat abstinence should be strongly advised in these patients.

Khat metabolism is also regulated by glucuronidation, facilitated by UDP-glucuronosyltransferases (UGT), particularly UGT1A and UGT2B. UGTs aid in excretion by converting lipophilic substances into hydrophilic forms, increasing solubility and renal excretion.[28,29,33] Due to the interaction between CYP enzymes and UGTs, inhibition of CYP2D6 by khat can lead to a compensatory increase in UGT activity, facilitating the elimination of unmetabolized khat components.[34,35] This relationship highlights the need to consider both phase I (CYP-mediated) and phase II (UGT-mediated) metabolic pathways when evaluating potential drug interactions induced by khat. Similar to CYPs, UGT enzymes are variably expressed due to genetic polymorphisms inhibiting or inducing UGTs, altering the pharmacokinetics and pharmacodynamics of other medications,[36] requiring monitoring and potential dose adjustments when khat is used concurrently with other drugs.[37]

These findings underscore the complex metabolic interplay between CYP2D6 and UGT enzymes in khat users, highlighting the potential for genotype-dependent variations in liver toxicity and drug interactions. This emphasizes the need for caution and personalized treatment strategies, particularly in individuals with altered CYP2D6 or UGT activity and patients taking medications metabolized by these pathways.

Proposed pathogenetic mechanisms of khat-associated AIH

CD4 and CD8 levels

Cathinones stimulate the immune system by inducing pro-inflammatory cytokine release. Elevated $CD4^+$ and $CD8^+$ T lymphocytes are accompanied by an increase in cytokine production, such as interleukin (IL)-2,[38] TNF-alpha, and IFN-gamma, which result in hepatic inflammation.[39] Proinflammatory cytokines have been reported to increase proportionally with khat exposure, indicating the presence of underlying tissue damage.[40] One study reported a hepatocellular pattern of hepatitis induced by khat, associated with an increase in IL-2, IL-6, and TNF-alpha in a dose-dependent manner. Other cytokines, such as IL-1beta and IL-4, increased as the dosage increased.[40] These findings suggest that direct measurement of these cytokines could help predict the severity of khat-related hepatotoxicity. Despite no significant gender differences, TNF-alpha, IL-6, IL-2, IL-4, and IL-1beta levels were higher in male rats.[40] This gender difference may help explain why khat-induced AIH is more prevalent in males, due to higher levels of these cytokines. A higher bacterial burden in the lungs of khat-addicted individuals may also contribute to khat's immune modulation, although this likely plays a smaller role than other mechanisms.[41]

An Ethiopian study suggested that khat stimulates the immune system, as $CD4^+$ counts were 62% higher in khat

chewers and rose in a dose-dependent manner, independent of cigarette smoking or parasitic infections. Additionally, lymphocyte counts were significantly higher in male khat chewers.[42] Increased lymphocyte counts could signify hepatic inflammation, but this remains unclear and non-specific, as subjects were not screened for liver disease. Some studies show that low doses of khat are immune-enhancing, while high doses of khat are immune-suppressing.[43] Therefore, it is also possible that the doses of khat administered in these studies were too low to demonstrate an immunosuppressive effect. This highlights the importance of dose in determining the immunological impact of khat.

Elevated $CD4^+$ levels induced by cathinones stimulate a T cell-dependent humoral response, promoting B cell differentiation into plasma cells.[38] Khat and cathinones stimulate humoral (IgG and IgM) immunity, cellular immune responses, and antibody titer production. These substances also enhance the phagocytic activity of the reticuloendothelial system in a dose-dependent manner. At lower doses of khat (50–100 mg/kg), significantly higher delayed-type hypersensitivity was observed, which diminished at higher doses (200 mg/kg).[43]

Furthermore, human studies report that khat chewing is associated with significantly higher levels of high-sensitivity C-reactive protein and IL-6in khat chewers. These results suggest that frequent khat ingestion leads to a chronic inflammatory state, resulting in hepatitis. Therefore, measurement of high-sensitivity C-reactive protein and IL-6 in khat users may be beneficial in predicting underlying inflammation. Khat has also been shown to increase IL-6 gene expression.[44] Studies in mice models exposed to khat also show that pro-inflammatory cytokines are upregulated, including TNF-alpha and IL-6.[45,46] These findings support the role of proinflammatory cytokines, especially CD4 and CD8, in the development of khat-associated hepatotoxicity.

Animal studies

Researchers theorized that increased IgG and IgM anti-sheep red blood cell titers result from direct B cell interaction with antigens or indirect activation by type 2 T helper (Th) cells.[43] The increased phagocytic activity of the reticuloendothelial system and increased delayed-type hypersensitivity observed in mice treated with khat and cathinones indicated that $CD4^+$ T cells may further differentiate into Th cells. Furthermore, khat and cathinones modulate the immune system by stimulating Th1 and Th2 cytokines. Th1 cells promote cytotoxic responses, while Th17 cells mediate tissue inflammation. Th1 cells drive hepatocyte damage by secreting interferon-gamma, activating macrophages, which phagocytose intracellular pathogens and recruit $CD8^+$ T cells.[47] Th17 cells produce IL-17, recruiting neutrophils and contributing to chronic inflammation and liver injury.

Additionally, other components of khat, such as flavonoids, contribute to immune regulation. For instance, flavonoids activate immune cells, while alkaloids suppress T cell proliferation and the production of Th1, Th2, and Th3 cytokines.[48] Therefore, the chemical makeup of the khat strain chewed likely dictates its immune effects. These results from animal studies support the involvement of khat in the development of hepatoxicity through the modulation of immune responses, particularly involving Th cells.

Hepatic sinusoidal obstruction syndrome (HSOS)

HSOS is a condition in which liver sinusoids become obstructed due to endothelial injury from toxins such as pyrrolidine alkaloids. These alkaloids are found in certain plants, such as *Senecio brasiliensis*, which is used to make herbal teas.

Unlike *Senecio*, khat plants contain cathine, cathidine, and cathinone. These are pyrrolizidine alkaloids, which are structurally and functionally different from pyrrolidine alkaloids because they possess a double bond between C1 and C2. Cleavage of this bond can generate reactive free radicals through the action of cytochromes, particularly CYP2A6, CYP3A4, and CYP3A5.[49] Free radical damage is thought to result primarily in hepatocyte damage. Pyrrolidine alkaloids have not been described in khat extracts, and currently, no data definitively support an association between khat use and the development of HSOS.

Idiosyncratic DILI

DILI is classified as either intrinsic or idiosyncratic. Intrinsic DILI is dose-dependent and predictable, with hepatotoxicity typically developing within days of exposure, as lipophilic drugs readily cross hepatocyte membranes.[50] In contrast, idiosyncratic DILI is unrelated to dose, unpredictable in onset, and varies in severity from spontaneous recovery to acute liver failure.[51,52] It is less common and occurs in susceptible individuals, likely reflecting an adaptive immune-mediated mechanism.[53] Idiosyncratic DILI represented 78.6% of acute and 90.9% of chronic cases of khat-associated AIH cases presented here. Intrinsic DILI accounted for 21.4% of the acute cases and 9.1% of the chronic cases.

Several studies have linked specific human leukocyte antigen alleles to idiosyncratic DILI, implicating these alleles as risk factors for genetically mediated drug-induced AIH.[54,55] This predisposition may explain why some individuals experience spontaneous resolution of khat-induced liver injury, referred to as clinical adaptation, while others progress to AIH requiring treatment.[56] Although human leukocyte antigen variants likely influence susceptibility to khat-related DILI, their exact role in khat-induced AIH has not been defined.

Acute khat-associated AIH

Many case reports have linked long-term khat use with AIH, resulting in acute liver injury (Table 1).[1,8,9,17,21,57–62] Our review identified 18 case reports with khat-associated acute AIH, although some cases were not biopsy-confirmed. There was a case series involving 420 patients; however, no biopsies were obtained. The strongest evidence in favor of khat-associated AIH came from cases with high RUCAM and AIH scores, along with positive serology, high aminotransferase levels, histopathology findings consistent with AIH, and a positive response to steroids.[1] Furthermore, complete resolution upon cessation of khat or a complete response to immunosuppression without recurrence supported a diagnosis of khat-associated AIH. Among 11 acute AIH cases with sufficient data, 27.3% met criteria for highly probable AIH and 72.7% for probable AIH (Table 1).

Emerging evidence describes four major idiosyncratic DILI subtypes.[63] One of these DILI subtypes is drug-induced AIH, defined by a combination of high RUCAM scores and AIH criteria such as seropositive autoimmune markers, elevated IgG, and a favorable steroid response. However, when the offending agent is an herbal substance, such as khat, the term "herb-induced autoimmune hepatitis (HIAIH)" is more appropriate. Accordingly, cases meeting both elevated RUCAM and AIH scores should be classified as HIAIH.

Our calculated RUCAM scores ranged from four to eleven among cases with sufficient data for calculation. One-third of patients had a RUCAM score of at least 5, indicating a probable (22.2%) or highly probable (11.1%) causal rela-

Table 1. Cases of acute khat-associated AIH

Pt	Age	Sex	Country of origin	Total Bili (NR: 0.1–1.2 mg/dL)	AST (NR: 10–40 U/L)	ALT (NR: 7–56 U/L)	ALP (NR: 40–130 U/L)	IgG (NR: 6.0–16.0 g/L)	ANA (NR: Neg)	ASMA (NR: Neg)	RUCAM score	RUCAM interpretation	AIH score	AIH score Interpret.	Intrin. or Idios. DILI?	Treatment	Ref.
1	25	M	Somalia	20	1,129	1,142	NA	NA	1:1,280	AAA elevated*	11	Highly probable	5	Probable	Idios.	Prednisone	60
2	32	M	Somalia	14	1,620	1,880	161	NA	1:640	1:160^	10	Highly probable	6	Probable	Idios.	Cessation	21
3	70	F	Saudi Arabia	70	1,150	1,043	79	19	Pos*	Neg	6	Probable	CC	NA	Idios.	Prednisone	58
4	41	M	Somalia	14	NA	791	NA	NA	Neg	1:40	7	Probable	4	Probable	Idios.	Cessation	8
5	33	M	Somalia	30	NA	1,428	NA	NA	Neg	1:80	7	Probable	5	Probable	Intrin.	Cessation	8
6	26	M	Somalia	34	649	372	NA	NA	1:80	Neg	7	Probable	6	Probable	Intrin.	Transplant	9
7	41	M	Saudi Arabia	36	421	266	242	37	Neg	1:320	4	Possible	CC	NA	Idios.	Cessation	58
8	24–57*	M	Somalia	NA	NA	1,569	125	>2x ULN	Neg	Neg	4	Possible	6	Probable	Idios.	Prednisolone	1
9	24–57*	M	Somalia	NA	NA	1,223	170	WNL	Neg	Neg	4	Possible	4	Probable	Idios.	Prednisolone	1
10	24–57*	M	Somalia	NA	NA	1,957	187	>2x ULN	>1:80*	>1:80*	4	Possible	8	Highly prob	Idios.	Prednisolone	1
11	24–57*	M	Somalia	NA	NA	1,005	179	>2x ULN	~1:80*	~1:80*	4	Possible	8	Highly prob	Idios.	Prednisolone	1
12	24–57*	M	Somalia	NA	NA	1,052	298	>2x ULN	>1:80*	>1:80*	4	Possible	CC	NA	Idios.	Prednisolone	1
13	24–57*	M	Yemen	NA	NA	118	59	>1.5x ULN	Neg	Neg	4	Possible	8	Highly prob	Idios.	Prednisolone	1
14	25–40*	M	Saudi Arabia	20	1,291	1,148	NA	High	Pos*	NA	4	Possible	CC	NA	NA	Corticosteroids + AZA	62
15	25–40*	M	Saudi Arabia	35	1,115	610	NA	High	Pos*	NA	4	Possible	CC	NA	NA	Corticosteroids + AZA	62
16	25–40*	M	Saudi Arabia	19	605	232	NA	High	Pos*	NA	4	Possible	CC	NA	NA	Corticosteroids + AZA	62
17	25–40*	M	Saudi Arabia	10	1,098	830	NA	High	Pos*	NA	4	Possible	CC	NA	NA	Corticosteroids + AZA	62
18	33	M	Somalia	NA	NA	NA	NA	NA	NA	1:80	CC	NA	6	Probable	Intrin.	Transplant	61
19–189	NA	NA	Yemen	NA	High*	High*	NA	NA	Pos*	Neg	CC	NA	CC	NA	NA	Prednisone, ursochol, & Livbest	59
190–240	NA	NA	Yemen	NA	High*	High*	NA	NA	Pos*	Pos*	CC	NA	CC	NA	NA	Prednisone, ursochol, & Livbest	59
241–421	NA	NA	Yemen	NA	High*	High*	NA	NA	Neg	Pos*	CC	NA	CC	NA	NA	Prednisone, ursochol, & Livbest	59

AAA, anti-actin antibodies; AIH, autoimmune hepatitis; ALT, alanine aminotransferase; ALP, alkaline aminotransferase; ANA, anti-nuclear antibody; ASMA, anti-smooth muscle antibody; AST, aspartate aminotransferase; AZA, azathioprine; Bili., bilirubin; CC, cannot calculate due insufficient information; DILI, drug-induced liver injury; Idios., idiosyncratic; IgG, immunoglobulin G; Interpret., interpretation; Intrin., intrinsic; NA, no information available; Neg, negative; NR, normal range; Pos, positive; Pt, patient; Ref, references; RUCAM, Roussel Uclaf Causality Assessment Method score; ULN, upper limit normal; ^after one year; *level not specified.

tionship between khat and liver damage. Immunosuppression was required in two-thirds of cases. However, 22.2% of patients[8,21,58] responded to khat cessation alone. It is possible that patients did not require immunosuppressants due to the removal of the triggering agent in the early stages of the disease. Liver injury may have been reversible, due to milder disease severity, individual variations in immune response, spontaneous remission, or immunomodulatory effects of khat. Meanwhile, 61.1% of patients had RUCAM scores of 4, suggesting a possible association.

In all reported cases, IgG levels were elevated, while ANA was positive in 58.8% and ASMA was positive in 44.4% of acute khat-associated AIH cases. As expected from the demographics of khat users, nearly all (94.4%) reported cases involved male patients, with only one female case documented.[58] One study on khat-associated AIH (n = 420) reported that 40.4% of patients were ANA positive, 42.9% were ASMA positive, and 11.9% were positive for both ANA and ASMA (titers not specified).[59] However, the lack of important details, such as autoimmune serology titers, liver histopathology findings, and RUCAM scores, significantly weakens the diagnosis of khat-associated AIH. Therefore, while the data were included in the table for reference, they were excluded from our analysis discussed in this section.

One case reported a khat user with acute AIH marked by positive ANA (1:1,280), anti-actin antibodies (75 arbitrary units; normal <20), and biopsy confirmation. Our RUCAM score indicated a highly probable link to khat use. The patient initially showed improvement in ANA levels and liver function with khat abstinence, and immunosuppression further supported the diagnosis of AIH.[60] However, he later relapsed with a significant rise in liver enzymes with khat re-exposure. He again improved upon khat cessation. Anti-actin antibodies, which demonstrate higher sensitivity (74% vs. 34%) and comparable specificity to ASMA (98% vs. 99%), likely serve an equivalent diagnostic role.[64] Therefore, despite the absence of ASMA testing, the clinical presentation was consistent with a diagnosis of acute AIH.

Another case involved a khat user of three months who presented with a week of jaundice, hepatocellular hepatitis, and biopsy-confirmed AIH. The RUCAM score of 10 indicated a highly probable relationship between khat and liver injury. Positive serology included ANA 1:640 initially, and ASMA 1:160 after one year.[21] Although treatment was not required, the patient exhibited many hallmark features of AIH. Repeat biopsy after 12 months revealed fibrosis progression, raising concerns for ongoing AIH.[21] Similarly, Someili *et al*. reported a patient who maintained abstinence, was treated with steroids, and achieved liver enzyme normalization within three months, with no subsequent recurrences.[58] Overall, the evidence supports a causal association between khat use and acute AIH, although the quality and consistency of reporting were limited in some cases.

Steroid response and recurrence of khat-associated acute AIH

Complete resolution of symptoms with khat cessation or a rapid, sustained response to steroids without recurrence supports a diagnosis of khat-associated AIH. Of the six total acute khat-induced AIH cases with probable RUCAM scores, five either had a prompt response to steroids if administered (50%)[58,60] or rapid improvement with cessation (33.3%),[8,21] while one patient underwent an emergent transplant for acute liver failure.[9] Among six patients with possible acute khat-induced AIH based on their RUCAM score, all abstained from khat without re-exposure or recurrence. One patient initially improved with khat abstinence but later developed recurrences of hepatitis with the development of ASMA titers after one year.[21] Four showed prompt improvement in liver enzymes following immunosuppression and khat cessation, while one achieved full resolution. The prevalence of AIH in this population is higher than would be expected for the same population in the Middle East without khat.[65,66] Conversely, some patients improved with khat cessation alone, without experiencing recurrences, arguing against khat-induced AIH.[8,58] Another patient progressed to acute liver failure and ultimately required liver transplantation without ever receiving steroids.[9] The prompt resolution observed in several cases with immunosuppressive therapy supported a diagnosis of khat-induced AIH.

Acute liver failure from khat-associated acute AIH: Acute liver failure due to acute khat-associated AIH was reported in two patients who developed a prolonged INR and jaundice. One patient required transplantation, while the other died from variceal hemorrhage.[8] Due to limited details, the cases are not included in Table 1. Roelandt *et al*. also described a case of acute liver failure from khat, characterized by encephalopathy, significantly elevated liver enzymes, and impaired synthetic liver function, ultimately requiring transplantation.[9] This is the only case of probable khat-AIH that has led to acute liver failure. Other reports have documented acute liver failure associated with khat use, but without an autoimmune component.[3,67] These cases highlight the potential for khat to cause acute liver failure in the context of AIH and underscore the need for greater clinical awareness.

Chronic khat-associated AIH

Chronic khat-associated AIH has been observed in patients presenting with AIH features, including positive autoimmune serologies, laboratory abnormalities, and histological findings, within the context of chronic liver injury. Our review identified 14 cases consistent with khat-associated chronic AIH (Table 2).[4,8,12,57,58,68–71] Half of these patients responded to immunosuppressive therapy, while 29% of patients died due to complications of AIH,[6,8,61,68] and one required transplantation.[8] These outcomes reflect the worse prognosis and more severe progression of chronic compared to acute AIH. Among the eight chronic AIH patients, 62.5% had scores consistent with highly probable AIH, while 37.5% fell within the probable range (Table 2). Cases with both high RUCAM and AIH scores are classified as HIAIH.[63] Some patients lacked biopsy data, but several had AIH scores of 6, suggesting they would qualify as highly probable AIH if histology were available.[12,58]

Our RUCAM scores were ≥5, indicating a probable or highly probable association with khat, in 57.1% of cases. Among these, six demonstrated biopsy-confirmed AIH, while biopsy was precluded in two due to coagulopathy. Of the patients with at least probable RUCAM scores, 62.5% responded to steroid therapy. Among the remaining cases, one recovered promptly with khat cessation alone, one underwent transplantation, and one died of liver failure, outcomes still consistent with a diagnosis of khat-AIH.

All reported cases of chronic khat-associated AIH involved male patients with hepatitis and hypergammaglobulinemia. RUCAM scoring could not be applied in 42.9% of cases due to incomplete data, which weakens the overall strength of the evidence. Nonetheless, the findings support an association between chronic khat use and the development of chronic AIH, particularly in repeat users, as demonstrated by over half of the cases described progressing to chronic AIH.

Recurrence of hepatitis after initial improvement with steroids, despite reported khat abstinence, raises doubt about

Table 2. Cases of chronic khat-associated AIH

Pt	Age	Sex	Country of origin	Total Bili. (NR: 0.1–1.2 mg/dl)	AST (NR: 10–40 U/L)	ALT (NR: 7–56 U/L)	ALP (NR: 40–130 U/L)	IgG (NR: 6.0–16.0 g/L)	ANA (NR: Neg)	ASMA (NR: Neg)	RU-CAM score	RU-CAM interpretation	AIH score	AIH score Interpret.	Intrin. or Idios. DILI?	Treatment	Ref.
1	34	M	Yemen	16	689	935	209	26	Neg	~1:160′	10	Highly prob	8	Highly prob	Idios.	Prednisone	4
2	28	M	Somalia	23	NA	820	NA	NA	1:40	1:160	7	Probable	5	Probable	Idios.	Died	8
3	33	M	Somalia	9	NA	896	NA	NA	Neg	Neg	7	Probable	3	Probable	Idios.	Transplant	8
4	21	M	Yemen	14	326	164	208	25	1:640	Strongly pos*	7	Probable	CC	NA	Idios.	Prednisolone + AZA	12
5	37	M	Yemen	NA	NA	NA	NA	32	1:40	1:1,280	6	Probable	8	Highly prob	Idios.	Corticosteroids + AZA	12
6	21	M	Yemen	32	713	517	260	34	1:640	Strongly pos*	4	Probable	CC	NA	Idios.	Prednisone + AZA	12
7	31	M	Yemen	4	321	375	245	24	Neg	1:40	6	Probable	7	Highly prob	Idios.	Cessation	69
8	25	M	Saudi Arabia	24	1,723	1,745	113	17	1:80	1:160	6	Probable	7	Highly prob	Idios.	Prednisone + AZA	58
9	NA	M	Yemen	NA	High*	High*	NA	NA	1:80	1:40	CC	NA	CC	NA	Idios.	Cessation	70
10	47	M	Ethiopia	21	395	196	200	30	Pos*	Strongly pos*	CC	NA	8	Highly prob	NA	Died	68
11	38	M	Somalia	35	1,232	196	200	29	Pos*	Pos*	CC	NA	CC	NA	NA	Corticosteroids + AZA	68
12	17	M	Somalia	25	2,584	1,192	42	23	Pos*	Pos*	CC	NA	CC	NA	NA	Corticosteroids + AZA	68
13	28	M	Somalia	NA	NA	NA	NA	NA	NA	1:160	CC	NA	5	Probable	Idios.	Died	57
14	34	M	Somalia	NA	NA	NA	NA	NA	NA	NA	CC	NA	CC	NA	Intrin.	Died	71

AAA, anti-actin antibodies; AIH, autoimmune hepatitis; ALT, alanine aminotransferase; ALP, alkaline aminotransferase; ANA, anti-nuclear antibody; ASMA, anti-smooth muscle antibody; AST, aspartate aminotransferase; AZA, azathioprine; Bili., bilirubin; CC, cannot calculate due insufficient information; DILI, drug-induced liver injury; Idios., idiosyncratic; IgG, immunoglobulin G; Interpret., interpretation; Intrin., intrinsic; NA, no information available; Neg, negative; NR, normal range; Pos, positive; Pt, patient; Ref, references; RUCAM, Roussel Uclaf Causality Assessment Method score; ULN, upper limit normal; *level not specified; ′measured as 53 U/ml which corresponds to ~1,160.

a khat-induced AIH diagnosis and may suggest an alternative etiology or undisclosed re-exposure to khat. In one case, hepatitis recurred three months after initial improvement, requiring escalation of immunotherapy before resolution.[58] Another patient achieved normalization of liver enzymes after three months but developed recurrence of hepatitis six months later, necessitating increased immunosuppression for remission. His steroid responsiveness favors an autoimmune process, but recurrent disease is not typical for khat-associated AIH,[12] as most cases demonstrate sustained improvement following khat cessation and steroid initiation.[69]

Histological evaluation in cases of chronic khat-associated AIH revealed varying degrees of fibrosis. One case described chronic hepatitis with stage III-IV focal fibrosis and sporadic bridging fibrosis.[4] Two additional cases, using the Ishak scoring system, reported portal fibrosis (score of 3/6) and advanced fibrosis (score of 4/6).[69] Stuyt *et al*. reported one patient with F2 fibrosis and another two with F3 fibrosis, with ascites and encephalopathy.[68] Additionally, two patients had biopsy-confirmed cirrhosis, though further details were not provided, limiting our understanding of cirrhosis in khat-induced chronic AIH.[8] Unfortunately, many cases did not specify fibrosis staging, representing a key limitation. Our review indicates that progression of khat-AIH to CLD is almost always due to persistent use of khat. A lack of response to immunosuppressive therapy suggests misdiagnosis or typical (non-khat induced) AIH.

Diagnosis of khat-associated AIH

Autoimmune serological markers

Khat-associated AIH is diagnosed based on high RUCAM scores and clinical and histological characteristics that resemble AIH, with no other cause of hepatitis in patients who regularly use khat. Autoimmune markers such as ANA and ASMA are considered defining features of AIH, while the presence of liver-kidney microsomal, anti-soluble liver antigen, and anti-actin antibodies also support the diagnosis. Hypergammaglobulinemia and elevated IgG levels are well-recognized hallmarks of AIH. The revised AIH scoring system includes serum IgG levels that exceed twice the normal value. The combination of serologic markers, elevated IgG levels, and high RUCAM scores in the absence of other causes of AIH strengthens the diagnosis of khat-associated AIH, highlighting the importance of comprehensive clinical, laboratory, and histological evaluation in khat users who develop elevated liver enzymes.

Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels

Khat-induced hepatotoxicity manifests with hepatocellular hepatitis.[58] A retrospective, cross-sectional study in Yemen separated khat users by the presence of liver injury.[72] Among those with liver injury, 88% (127) had elevated liver enzymes, and 62% (89) had abnormal ultrasound findings. ALT (52.93 vs. 22.30) and AST (34.71 vs. 21.59) were both significantly elevated in khat users.[72] Older age was associated with increased hepatotoxicity, while there was no relationship between body mass index and ALT levels. Additionally, 40% of patients with a normal body mass index showed liver damage, indicating that khat exposure rather than obesity was the primary cause.[72]

Khat appears to cause duration-related hepatic injury. Ramzy *et al*. concluded that while transient khat consumption does not affect liver function, prolonged use causes hepatic injury. ALT elevations were more pronounced in individuals with a longer history of exposure (23.8% in patients with a 10-year chewing history vs. 11.2% with a less than 10-year chewing history), though the difference was not statistically significant.[73] Khat chewers without other signs of liver disease often have subclinical hepatocellular hepatitis. For example, a case-control study comparing 50 khat users to 50 non-khat users found statistically significant increases in ALT (43.09 vs. 39.90) and AST (39.37 vs. 35.02).[70] Similarly, in a case-control study of 20 Yemeni women, khat users had significantly higher levels of ALT (60 vs. 15) and AST (55 vs. 20), despite showing no other signs of liver disease.[74] Overall, studies indicate that khat causes liver inflammation related to both the duration and amount of exposure, evidenced by a hepatocellular pattern of liver injury. Elevated AST and ALT levels are a consistent and prominent finding across nearly all reported cases of khat-associated AIH.

Histopathology

Histopathology of khat-associated acute AIH exhibits features of khat hepatotoxicity combined with histological features of AIH. Features of khat hepatotoxicity alone have been described to include ballooning degeneration of hepatocytes and lymphocytic infiltrate in the lobular and portal regions.[21] Features of khat-associated AIH reflect characteristics seen in other forms of AIH, including interface hepatitis and plasmacytic infiltration on histology.[4,17,75]

The hepatic regions most frequently affected in khat-associated AIH include the periportal (zone 1)[8,21] and perivenous (zone 3) areas,[8,21,60] reported in three cases each. Biopsies from patients with khat-associated acute AIH and frequent khat use revealed hallmark features of AIH in the eleven cases with full pathology reports, including lymphoplasmacytic infiltration (54.5%),[1,8,21,62] interface hepatitis (54.5%),[1,21] and liver cell rosetting (36.4%) (Table 3).[1,8,9,21,58–62] Fibrosis was observed in the majority (70%) of cases of khat-associated chronic AIH.[4,58,61,68,69] The extent of fibrosis ranged from bridging fibrosis in 30% of cases[4] to periportal fibrosis in 20%.[58,68]

In contrast, fibrotic septa were visualized in one case of khat-associated acute AIH. However, the extent of fibrosis was not specified. The findings were consistent with acute toxic hepatitis (Table 4).[4,8,12,57,58,60,68–71] Early histopathological changes in khat-associated AIH, such as apoptosis and inflammation, typically precede the development of fibrosis over time with chronic khat exposure.[21] These findings suggest that histopathological features associated with khat use vary based on the duration and amount of exposure. Fibrosis is a hallmark of chronic AIH, resulting from progressive liver injury, and is rarely observed in acute cases.[8,12,21,58] Cirrhosis has also been confirmed on biopsy in patients with khat-induced AIH.[8,68]

Management of khat-associated AIH

Treatment begins with cessation of khat use and monitoring of liver enzymes,[58] but typically requires corticosteroids. The most frequently reported dose was prednisolone 0.5 mg/kg/day, which was effective in one-third of patients with khat-associated acute AIH (Table 1).[1] Other patients responded to prednisone 40 mg daily.[58] One study reported that after three months of treatment with prednisone (0.5 mg/kg/day), ursochol (10 mg/kg/day), and Livbest (two tablets twice daily), 75% of patients with khat-associated AIH (n = 420) recovered, while 6% of patients remained ANA or ASMA positive.[59]

Prednisone is rarely effective for khat-associated chronic AIH (Table 2) due to the established nature of the condition.[4]

Table 3. Pathology results of khat-associated acute AIH cases

Pt	AST (NR: 10–40 U/L)	ALT (NR: 7–56 U/L)	ANA (NR: Neg)	ASMA (NR: Neg)	RU-CAM score	RUCAM interpre-tation	Biopsy findings	Treatment	Ref.
1	1,129	1,142	1:1,280	AAA elevat-ed*	11	Highly probable	Cholestatic hepatocytes in zone 3 and mild lobular and portal tract inflammation with fibrotic septa	Prednisone	60
2	1,620	1,880	1:640	1:160^	10	Highly probable	Portal and lobular hepatitis with plasma cells, eosinophils, neutrophils and lymphocytes, mild interface hepatitis and no fibrosis	Cessation	21
3	1,150	1,043	Pos*	Neg	6	Probable	NA	Prednisone	58
4	NA	791	Neg	1:40	7	Probable	Hepatocellular injury in zones 1 and 3, no fibrosis	Cessation	8
5	NA	1,428	Neg	1:80	7	Probable	Hepatocellular injury in zones 1 and 3, no fibrosis	Cessation	8
6	649	372	1:80	Neg	7	Probable	Acute necroinflammatory hepatitis, bridging necrosis, prominent Krt7+ ductular reaction	Transplant	9
7	421	266	Neg	1:320	4	Possible	NA	Cessation	58
8	NA	1,569	Neg	Neg	4	Possible	Interface hepatitis, lymphoplasmacyt-ic infiltrates, rosetting of liver cells	Prednisolone	1
9	NA	1,223	Neg	Neg	4	Possible	Interface hepatitis, lymphoplasmacyt-ic infiltrates, rosetting of liver cells	Prednisolone	1
10	NA	1,957	>1:80*	>1:80*	4	Possible	Interface hepatitis, lymphoplasmacyt-ic infiltrates, rosetting of liver cells	Prednisolone	1
11	NA	1,005	~1:80*	~1:80*	4	Possible	Interface hepatitis, rosetting of liver cells	Prednisolone	1
12	NA	1,052	>1:80*	>1:80*	4	Possible	NA	Prednisolone	1
13	NA	118	Neg	Neg	4	Possible	Interface hepatitis, lymphoplasmacyt-ic infiltrates, rosetting of liver cells	Prednisolone	1
14	1,291	1,148	Pos*	NA	4	Possible	Mild hepatitis with lymphocytic infiltra-tion, quantity of plasma cells not reported	Corticosteroids + AZA	62
15	1,115	610	Pos*	NA	4	Possible	Refused	Corticosteroids + AZA	62
16	605	232	Pos*	NA	4	Possible	Refused	Corticosteroids + AZA	62
17	1,098	830	Pos*	NA	4	Possible	NA	Corticosteroids + AZA	62
18	NA	NA	NA	1:80	CC	NA	No fibrosis (0/6)	Transplant	61
19–189	High*	High*	Pos*	Neg	CC	NA	NA	Prednisone, urso-chol, and Livbest	59
190–240	High*	High*	Pos*	Pos*	CC	NA	NA	Prednisone, urso-chol, and Livbest	59
241–421	High*	High*	Neg	Pos*	CC	NA	NA	Prednisone, urso-chol, and Livbest	59

AAA, anti-actin antibodies; AIH, autoimmune hepatitis; ALT, alanine aminotransferase; ANA, anti-nuclear antibody; ASMA, anti-smooth muscle antibody; AST, aspartate aminotransferase; AZA, azathioprine; CC, cannot calculate due insufficient information; NA, no information available; Neg, negative; NR, normal range; Pos, positive; Pt, patient; Ref, references; RUCAM, Roussel Uclaf Causality Assessment Method score; ^after one year; *level not specified.

Table 4. Pathology results of khat-associated chronic AIH cases

Pt	AST (NR: 10–40 U/L)	ALT (NR: 7–56 U/L)	ANA (NR: Neg)	ASMA (NR: Neg)	RUCAM Score	RUCAM interpretation	Biopsy findings	Treatment	Ref.
1	689	935	Neg	~1:160′	10	Highly probable	Chronic hepatitis with grade IV inflammation and stage III-IV focal fibrosis and sporadic bridging fibrosis, inflammatory cell infiltration	Prednisone	4
2	NA	820	1:40	1:160	7	Probable	Hepatocellular affecting both zones 1 and 3	Died	8
3	NA	896	Neg	Neg	7	Probable	Hepatocellular affecting both zones 1 and 3	Transplant	8
4	326	164	1:640	Strongly pos*	7	Probable	Not obtained due to coagulopathy	Prednisolone + AZA	12
5	NA	NA	1:40	1:1,280	6	Probable	Chronic hepatitis with interface hepatitis and chronic inflammatory cells infiltration, mainly plasma cells and lymphocytes	Corticosteroids + AZA	12
6	713	517	1:640	Strongly pos*	4	Probable	Not obtained due to coagulopathy	Prednisone + AZA	12
7	321	375	Neg	1:40	6	Probable	Moderate interface hepatitis, spotty and focal confluent necrosis with mixed inflammatory infiltrate rich in plasma cells and eosinophils	Cessation	69
8	1,723	1,745	1:80	1:160	6	Probable	Chronic severe active hepatitis with severe portal, interface and lobular inflammation rich in plasma cells infiltrate with severe hepatocellular injury and areas of parenchymal drop-out. There was evidence of portal fibrosis with few septa (F2)	Prednisone + AZA	58
9	High*	High*	1:80	1:40	CC	NA	NA	Cessation	70
10	395	196	Pos*	Strongly pos*	CC	NA	Interface hepatitis, lobular hepatitis, cholestasis, ductular proliferation, F3 bridging fibrosis	Died	68
11	1,232	196	Pos*	Pos*	CC	NA	Interface hepatitis, lobular hepatitis, cholestasis, ductular proliferation, F3 bridging fibrosis	Corticosteroids + AZA	68
12	2,584	1,192	Pos*	Pos*	CC	NA	Interface hepatitis, cholestasis, ductular proliferation, F2 periportal fibrosis	Corticosteroids + AZA	68
13	NA	NA	NA	1:160	CC	NA	Significant fibrosis (6/6)	Died	57
14	NA	NA	NA	NA	CC	NA	NA	Died	71

AAA, anti-actin antibodies; AIH, autoimmune hepatitis; ALT, alanine aminotransferase; ANA, anti-nuclear antibody; ASMA, anti-smooth muscle antibody; AST, aspartate aminotransferase; AZA, azathioprine; Bili., bilirubin; CC, cannot calculate due insufficient information; NA, no information available; Neg, negative; NR, normal range; Pos, positive; Pt, patient; Ref, references; RUCAM, Roussel Uclaf Causality Assessment Method score; ‘measured as 53 U/mL which corresponds to ~1,160.

Azathioprine may be necessary during recurrent episodes, cases that are not adequately treated with steroids, or as patients develop tolerance to steroids.[12] Azathioprine was required in 22.2% of acute[62] and 42.8% of chronic[12,58,68] khat-associated AIH cases. Chronic AIH associated with khat use can lead to severe complications, including death either directly[61] or from complications of cirrhosis.[8,68] Transplantation was rarely required.[8,9,61] The efficacy of biologics and cyclosporins in managing acute and chronic khat-associated AIH has yet to be determined. These findings support khat cessation as the primary treatment for khat-associated chronic AIH combined with immunosuppression.

Outcomes

Early diagnosis and prompt cessation of khat use can decrease liver inflammation, potentially slowing or preventing fibrosis and the transition from acute to chronic AIH, ultimately improving patient outcomes. Early initiation of corticosteroids or immunosuppressants may help preserve liver function and reduce the risk of severe hepatitis. Delayed diagnosis may lead to fulminant hepatic failure requiring liver transplantation or progression to CLD or cirrhosis with associated complications.[8,68]

Patients with acute khat-associated AIH who respond to treatment may still be at risk of progression, particularly if they experience recurrent episodes, which may suggest a potential transition to chronic AIH. Additionally, fibrosis can develop despite clinical improvement, highlighting the potential for long-term disease progression. Although data remain limited, evidence suggests that in cases of acute AIH, the speed of response to treatment influences outcomes. Patients achieving biochemical remission within six months of treatment demonstrate a significantly lower risk of progression to cirrhosis or the need for transplantation.[76,77]

Similarly, individuals with chronic khat-associated AIH remain at risk of progression even after initial treatment. Some patients develop worsening fibrosis or cirrhosis despite immunosuppressive therapy, and cases of decompensated cirrhosis have been reported with continued khat use. Recurrent episodes of hepatitis, incomplete biochemical response, and persistent histological activity are likely associated with a higher risk of progression to cirrhosis or transplantation.[78,79]

Conclusions

High RUCAM scores (≥5) in many cases of acute and chronic AIH suggest a probable causal relationship between khat and liver injury. Furthermore, biopsy confirmation of AIH in nearly every case, particularly in those with high RUCAM and AIH scores, along with a complete response to cessation of khat or a prompt response to corticosteroids without recurrence, also strengthens the causal association.

However, significant limitations exist, including the inability to calculate RUCAM and AIH scores in seven (21.8%) cases due to insufficient data. Importantly, cases that resolved with khat cessation alone, without the need for immunosuppressive therapy, are less convincing as examples of khat-associated AIH. Some cases raise questions about the validity of the AIH diagnosis. It is possible that in these cases, the liver injury may have been a direct toxic effect of khat rather than a true autoimmune process. Also, some unreported cases may actually have been seronegative AIH.[79]

Our review of the cases with high RUCAM scores, autoimmune serology, liver histology, and steroid response strongly supports an association between khat use and the development of acute and chronic AIH. Furthermore, progression to cirrhosis or fulminant liver failure has been documented even with cessation of khat use. Khat cessation is strongly recommended to prevent progression, but most patients require immunosuppressive therapy for optimal management. Future studies should also investigate the immune processes related to khat-induced AIH using *in vitro* and *in vivo* models. A better understanding of these pathways could potentially guide treatments to alter the immunomodulatory effects of khat.

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Conflict of interest

GYW has been an Editor-in-Chief of the *Journal of Clinical and Translational Hepatology* since 2013. The other author has no conflict of interests related to this publication.

Author contributions

Data collection, drafting of the manuscript (RH), concept, and editing of the manuscript (GYW). All authors have approved the final version and publication of the manuscript.

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