

Liver Injury Associated with Turmeric—A Growing Problem: Ten Cases from the Drug-Induced Liver Injury Network [DILIN]



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ABSTRACT

BACKGROUND: Turmeric is a commonly used herbal product that has been implicated in causing liver injury. The aim of this case series is to describe the clinical, histologic, and human leukocyte antigen (HLA) associations of turmeric-associated liver injury cases enrolled in the US Drug-Induced Liver Injury Network (DILIN).

METHODS: All adjudicated cases enrolled in DILIN between 2004 and 2022 in which turmeric was an implicated product were reviewed. Causality was assessed using a 5-point expert opinion score. Available products were analyzed for the presence of turmeric using ultra-high-performance liquid chromatography. Genetic analyses included HLA sequencing.

RESULTS: Ten cases of turmeric-associated liver injury were found, all enrolled since 2011, and 6 since 2017. Of the 10 cases, 8 were women, 9 were White, and median age was 56 years (range 35-71). Liver injury was hepatocellular in 9 patients and mixed in 1. Liver biopsies in 4 patients showed acute hepatitis or mixed cholestatic-hepatic injury with eosinophils. Five patients were hospitalized, and 1 patient died of acute liver failure. Chemical analysis confirmed the presence of turmeric in all 7 products tested; 3 also contained piperine (black pepper). HLA typing demonstrated that 7 patients carried *HLA-B*35:01*, 2 of whom were homozygous, yielding an allele frequency of 0.450 compared with population controls of 0.056-0.069.

CONCLUSION: Liver injury due to turmeric appears to be increasing in the United States, perhaps reflecting usage patterns or increased combination with black pepper. Turmeric causes potentially severe liver injury that is typically hepatocellular, with a latency of 1 to 4 months and strong linkage to *HLA-B*35:01*.

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INTRODUCTION

Turmeric is a widely used herbal product derived from the roots of *Curcuma longa*, a perennial plant belonging to the ginger family. Extracts of the rhizomes of turmeric contain curcuminoids, such as curcumin, which are believed to be the active components.¹ Turmeric is promoted as a dietary

supplement for a variety of conditions, including arthritis, respiratory infections, liver disease, aging, and more recently, for prevention of coronavirus disease 2019 (COVID-19).² Recently, turmeric has been implicated in rare cases of clinically apparent acute liver injury.³⁻⁶

Trials of turmeric in humans have not shown toxic effects,⁷⁻¹⁰ and curcumin is reported to be safe orally at the dose of 6 grams per day for 4 to 7 weeks.¹¹ One reason given for its safety is that curcumin is poorly absorbed orally. Indeed, it is unclear whether there is adequate systemic exposure to achieve any of the purported beneficial or adverse effects of oral turmeric or curcumin.^{12,13} However, recently marketed turmeric supplements often include piperine (black pepper), which can substantially increase its systemic bioavailability. For example, only 20 mg of piperine taken with turmeric is reported to increase its bioavailability 20-fold in serum.¹² Conceivably, the enhanced bioavailability could potentiate liver injury.

The US Drug-Induced Liver Injury Network (DILIN) has prospectively enrolled cases of liver injury due to medications and herbal and dietary supplements since 2004.¹⁴⁻¹⁸ Patients with suspected drug-induced liver injury undergo testing to exclude other causes of liver injury, and expert opinion is used to assess whether the liver injury is due to a medication or herbal and dietary supplements.¹⁵ The aims of this case series were 1) to describe the clinical phenotype of turmeric-associated hepatotoxicity, 2) conduct chemical analysis of products to confirm the presence of turmeric, and 3) perform genetic analyses to identify possible human leukocyte antigen (HLA) associations.

MATERIALS AND METHODS

The DILIN Prospective Study (ClinicalTrials.gov Identifier: NCT00345930) is an ongoing multicenter observational study conducted at 6 centers throughout the United States. Its design and inclusion and exclusion criteria have been described previously in detail.¹⁵ Suspected cases of drug-induced liver injury presenting within 6 months of injury onset meeting predefined laboratory criteria are prospectively enrolled in DILIN at clinical study sites. Eligibility criteria include total bilirubin ≥ 2.5 mg/dL or international normalized ratio (INR) > 1.5 and any elevation in alanine or aspartate aminotransferase (ALT or AST) or alkaline phosphatase (Alk P) levels; or elevations of ALT or AST above 5 times the upper limit of normal (ULN) or Alk P above 2 times ULN on 2 consecutive measurements at least 24 hours apart. A systematic approach is used to exclude nondrug or nonherbal and dietary supplement causes for the liver injury.¹⁵

A standardized protocol assesses the causal relationship between the use of a medication or herbal and dietary supplements and liver injury.¹⁵ Causality is graded by expert consensus opinion as either definite ($> 95\%$ likelihood), highly likely (75%-95%), probable (50%-74%), possible (25%-49%), or unlikely ($< 25\%$). The pattern of liver injury is categorized using the *R*-value, where $R = [\text{ALT/ULN}] \div$

$[\text{Alk P/ULN}]$; hepatocellular being defined by an $R \geq 5$, cholestatic ≤ 2 and "mixed" between 2 and 5. A 5-point scale is used to define severity, ranging from 1 (mild, anicteric), 2 (moderate, jaundiced), 3 (moderate and hospitalized), 4 (severe, evidence of hepatic failure), and 5 (death or liver transplantation due to drug-induced liver injury within 6 months of onset).

For the current study, only high confidence cases of herbal and dietary supplement-related liver injury (causality graded as definite, highly likely, or probable) were assessed for demographic, clinical, biochemical,

and histologic features. Descriptive statistics were computed for demographic and patient characteristics by median (lowest, highest) for continuous variables and as frequency (%) for categorical variables.

In herbal and dietary supplement suspected cases, attempts were made to retrieve the product taken by the patient for inclusion in a supplement repository. Products were then sent to the National Center for Natural Products Research (University of Mississippi, University Park), where they were tested using high-performance liquid chromatography and mass spectroscopy to verify that the ingredients matched the product label, and to search for contaminants and common hepatotoxins. In patients who gave consent for genetic testing, DNA was extracted from whole blood at a central sample repository and aliquots were sent to the Vanderbilt University Medical Center Immunogenomics, Microbial Genetics, and Single Cell Technologies core for high resolution HLA Class I and II gene sequencing. Available liver biopsies were sent to and reviewed by a single expert hepatic histopathologist (DEK). The biopsies were scored for multiple histological features as well as an overall pattern of liver injury without knowledge of the clinical information.¹⁹

Descriptive statistics were computed to describe the study cohorts, using median and range for continuous variables and frequency and percentage for categorical variables. Comparisons of the allele or carriage frequency of *HLA-B*35:01* between groups were assessed by Fisher's exact test. All analyses were carried out in SAS version 9.4 (SAS Institute Inc, Cary, NC). All authors had full access to the study data and reviewed and approved the final manuscript.

The DILIN Prospective Study was registered with ClinicalTrials.gov (NCT # 00345930). All patients provided

CLINICAL SIGNIFICANCE

- Turmeric is a widely used herbal product promoted as a dietary supplement for a variety of conditions.
- Liver injury due to turmeric appears to be increasing, reflecting usage patterns and combination with black pepper, which increases its absorption.
- The pattern of turmeric-related liver injury is typically hepatocellular, with a latency of 1 to 4 months and linkage to *HLA-B*35:01*.

written informed consent for enrollment, and all details of the study protocol were reviewed and approved by institutional review boards at each site as well as by a Data Safety and Monitoring Board appointed by the National Institute of Diabetes and Digestive and Kidney Diseases.

RESULTS

A total of 2392 cases of suspected drug-induced liver injury were enrolled in the DILIN Prospective Study between September 2004 and March 2022. Of this total, 2278 had undergone formal adjudication for causality and 1798 were scored as definite, highly likely, or probable (high confidence). Of the high confidence cases, 345 (19%) were attributed to an herbal and dietary supplement, 10 (3%) of which were attributed to turmeric. All turmeric cases were enrolled during or after 2011, and 6 since 2017 (Figure 1).

The 10 cases included 8 female and 2 male patients; 9 were White and 1 was Black (Table 1). The median age was 56 years (range 35 to 71), and median BMI 26.7 kg/m² (range, 14.7 to 39.5). Seven patients used alcohol, but none to excess, and none had a history of underlying liver disease.

The 3 most common reasons reported by patients for turmeric use were arthritis, pain relief, and general health or well-being. Turmeric was used for a median of 86 days prior to onset of injury with laboratory abnormalities (range 38-429 days). At presentation, 9 patients were symptomatic, and the most common symptoms were jaundice, nausea, and abdominal pain. None had fever or rash noted on presentation, and itching was not prominent. Initial median ALT was 1140 U/L (range 328-2245), Alk P 164 U/L (41-441), total bilirubin 2.5 mg/dL (0.7-13.9), and INR 1.0 (0.9-1.2). Five patients developed jaundice, and median

serum total bilirubin peaked at 4.0 mg/dL (0.8-26) and INR 1.1 (1.0-2.5). Liver injury pattern was initially hepatocellular in 9 patients and mixed in 1 patient (median *R* = 13.9; range 3.4-42.8). Five patients were hospitalized, and one patient died of acute liver failure. No patient underwent liver transplantation, and none of 9 patients had evidence of chronic liver injury when seen 5 or more months after onset.

Five patients had antinuclear antibody (1:160 to 1:640), and 2 had low levels of smooth muscle antibody (1:20 and 1:80). However, immunoglobulin levels were normal or only modestly elevated (immunoglobulin G 769-1840 mg/dL) in the 7 patients in whom they were measured, and only one patient was treated with corticosteroids (and for 6 days only). Extrahepatic manifestations such as rash, thrombocytopenia, neutropenia, or other manifestations of acute drug hypersensitivity were not seen. A history of drug allergies was reported by 7 patients, but none had a history of liver injury from a medication.

Five patients underwent liver biopsies, 4 of which were available for central review (Figure 2). Three biopsies were obtained within 30 days of injury onset, while the fourth was done approximately 8 months later. Of the 3 biopsies performed within 30 days of onset, 2 showed acute hepatitis with moderate to severe inflammatory activity and the third showed a cholestatic hepatitis with mild inflammation and moderate cholestasis in zone 3. The cases showing acute hepatitis histologically both had increased numbers of eosinophils. One of the cases with severe hepatic injury also had clusters of plasma cells and both confluent and bridging necrosis, mimicking autoimmune hepatitis. All 3 cases showed duct injury and varying degrees of hepatocyte apoptosis. No biopsy had advanced fibrosis, although the one case with severe hepatic injury did show portal fibrotic

Cases of Turmeric Hepatotoxicity

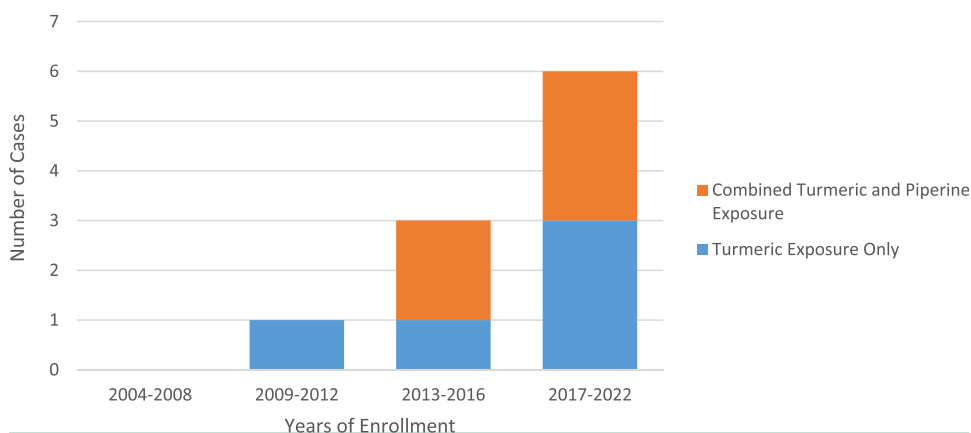


Figure 1 Year of presentation of 10 cases of turmeric liver injury. Shown are the years of the clinical presentation of 10 cases of turmeric liver injury reported in the Drug-Induced Liver Injury Network Prospective Study. Cases with turmeric exposure only are shown in blue; those with combined turmeric and piperine exposure (based upon product label and chemical analysis) are shown in orange.

Table 1 Clinical Features of 10 Patients with Acute Liver Injury Attributed to Turmeric

	Total (N = 10)	
Median age/years (range)	56 (35-71)	
Sex: female/male	8/2	
Race: White/African American	9/1	
Median BMI kg/m ² (range)	26.7 (14.7-39.5)	
Alcohol use/abuse	8/0	
	Onset	Peak
Median ALT, U/L (range)	1140 (328-2245)	1392 (470-2521)
Median Alk P, U/L (range)	164 (41-441)	168 (88-538)
Median total bilirubin, mg/dL (range)	2.5 (0.7-13.9)	4.0 (0.8-26)
Median INR (range)	1.0 (0.9-1.2)	1.1 (1.0-2.5)
ANA +	5 (50%)	
ASMA +	2 (20%)	
Median IgG, mg/dL (range)	1070 (769-1840)	
Median days from starting turmeric to symptoms (range)	84 (16-410)	
Median days from starting turmeric to DILI onset (range)	86 (38-429)	
Median days from onset to peak bilirubin	8 (0-19)	
Median days from peak bilirubin to <2.5 mg/dL	10.5	
Enzyme pattern at onset		
Cholestatic ($R \leq 2$)	0 (0%)	
Mixed ($R > 2$ and < 5)	1 (11%)	
Hepatocellular ($R > 5$)	9 (89%)	
Median R value at onset (range)	13.9 (3.4-42.8)	
Severity score		
Mild	5 (50%)	
Moderate	1 (10%)	
Moderate-hospitalized	3 (30%)	
Severe	0 (0%)	
Fatal	1 (11%)	
Chronic liver injury	0 (0%)	

Alk P = alkaline phosphatase; ALT = alanine aminotransferase; ANA = antinuclear antibody; ASMA = anti-smooth muscle antibodies; BMI = body mass index; IgG = immunoglobulin G; INR = international normalized ratio.

expansion. Two had mild macrovesicular steatosis. The biopsy taken at 8 months after onset showed minimal hepatitis with eosinophils and no fibrosis.

The turmeric products consumed by patients and implicated in injury were obtained from 7 patients. Chemical analysis confirmed the presence of turmeric in all 7; 3 also contained piperine (black pepper), and none contained green tea (*Camellia sinensis*), *Garcinia cambogia*, or *Polygonum multiflorum* (Fo-ti). Piperine was noted on the label of an additional patient's product that was not available for testing. No other common hepatotoxins were detected.

All 10 patients underwent HLA sequencing, and 7 were found to carry *HLA-B*35:01*, a class I HLA allele previously implicated in green tea, *Garcinia cambogia*, and *Polygonum multiflorum* hepatotoxicity.^{20,21} Two patients were homozygous, so that the allele frequency was 0.450 and carrier frequency 70%. The published allele frequencies of *HLA-B*35:01* in a large US population is 0.056 in Whites of European ancestry and 0.069 in Americans of African ancestry (allele frequencies.net: accessed August 11, 2022). There were minor differences in clinical and biochemical features of the 7 patients with *HLA-B*35:01* and the 3 without this allele, but the numbers of cases were too

few to make any firm conclusions (Table 2). The 3 subjects without *HLA-B*35:01* included the single Black patient (Case #2), the single case with mixed rather than hepatocellular liver injury (Case #7), and the single case of acute liver failure, which also was unusual in having a latency to onset of more than 1 year (Case #10).

DISCUSSION

The experience in DILIN reported here with turmeric-associated liver injury suggests that this phenomenon may be increasing in the United States, at least since 2017. Additionally, a reliable description of the clinical presentation, laboratory features, liver histology, and outcomes of turmeric-associated liver injury are provided from these prospectively enrolled and well-characterized cases. Of note, no other drug or herbal and dietary supplement product was implicated in these cases. Specifically, the typical injury occurs in women using turmeric for arthritis, pain relief, or general health. Patients present with a hepatocellular pattern of injury after a latency of 1 to 4 months. Autoantibodies such as antinuclear antibody and smooth muscle antibody are frequent but with normal immunoglobulin levels. Most cases are self-limited, with rapid improvement in

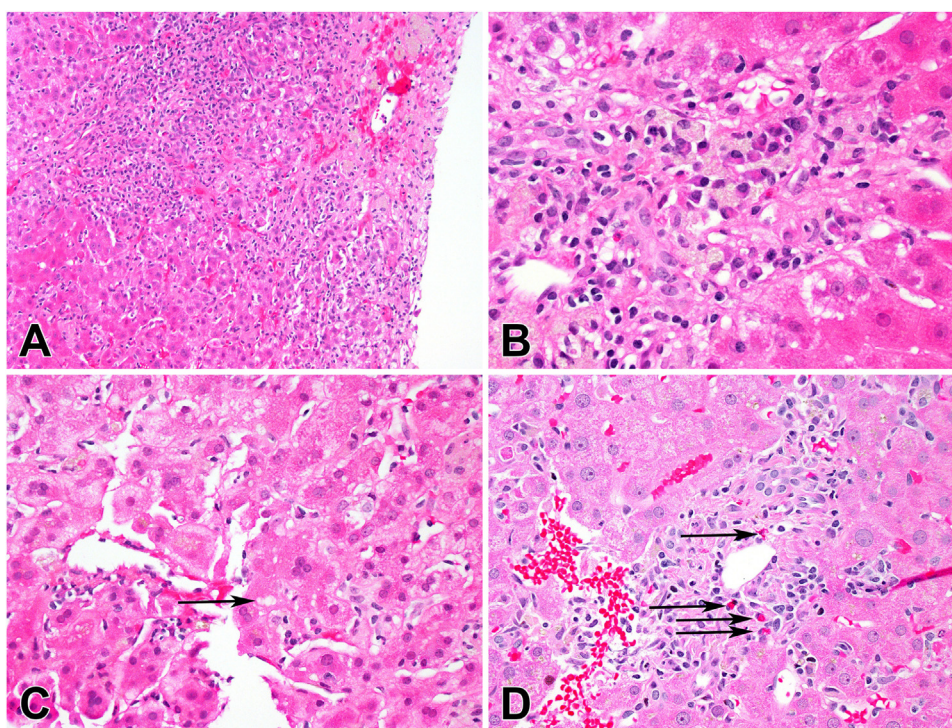


Figure 2 Histological changes associated with turmeric liver injury. (A) Case 3: Severe acute hepatitis with bridging necrosis spanning between a portal area and a central vein (hematoxylin & eosin [H&E] 200 \times). (B) Case 3: Higher magnification shows clusters of plasma cells at the portal-parenchymal interface (H&E 600 \times). (C) Case 4: Canalicular cholestasis (arrow) with mild lobular hepatitis (H&E 400 \times). (D) Case 5: Moderate hepatitis with increased numbers of eosinophils (arrows) in the portal area (H&E 400 \times).

liver tests on discontinuing turmeric. Rarely, the injury can be severe and result in death.

Like many herbal products, turmeric has a long history of safe use in traditional medicine, and as a culinary ingredient (curry). Turmeric has been claimed to be beneficial for multiple conditions, from aging to arthritis, and for prevention or amelioration of COVID-19.^{2,7-10} The increasing popularity of turmeric over the last 5 years appears to mirror the increase in reported cases collected in the DILIN Prospective Study.²¹⁻²³

Chemical analysis confirmed the presence of turmeric in all 7 products tested. Moreover, the detection of piperine in several of the more recent cases raises the possibility that it increased bioavailability, and thus, toxic exposure was the cause of hepatotoxicity. However, no cases of hepatotoxicity secondary to piperine ingestion alone have been reported, making the latter possibility less likely. Thus, it stands to reason that the addition of piperine could enhance direct toxicity of the turmeric product. Other approaches to increase bioavailability have also been adopted recently, including use of lecithin and packaging turmeric in nanoparticles.

The small sample size of this case series limited the genetic analysis. However, it is notable that 7 of the 10 patients carried *HLA-B*35:01*, a class I HLA allele previously implicated in green tea (*Camellia sinensis*),

Garcinia cambogia, and *Polygonum multiflorum* hepatotoxicity.^{18,20,21} Genetic studies performed by our group and others suggest that there is a common susceptibility link in persons carrying *HLA-B*35:01*, making them sensitive to multiple polyphenols.^{20,21} Therefore, carriage of this allele may be a risk factor for liver injury from several herbal components.

Consumers in the United States spent an estimated \$11.261 billion on herbal and dietary supplement sales in 2020, according to the American Botanical Council's 2020 Herb Market Report, marking the first time total annual sales surpassed \$10 billion.²² Turmeric was noted to be one of the top 10 ingredients in sold herbal and dietary supplements.^{23,24} Despite broad claims for potential benefits of turmeric to treat multiple conditions, clinical trials published so far have not yet produced evidence of significant efficacy and it is not an approved therapeutic agent.^{13,24}

The small number of cases and DILIN's non-population-based approach to enrollment limit confidence in a statement that the frequency of turmeric-associated liver injury is increasing. Yet, the observation of increased frequency in the DILIN cohort coupled with the growing popularity of the product and its being touted as a treatment or prevention from COVID-19 lead to a reasonable presumption of a growing incidence of attributable hepatotoxicity. Therefore, practitioners should be aware of the risk of liver injury

Table 2 Clinical Features of Patients with Turmeric Induced Liver Injury With or Without *HLA-B*35:01*

Feature	<i>HLA-B*35:01</i> Positive (n = 7)	<i>HLA-B*35:01</i> Negative (n = 3)
Female sex	5 (72%)	3 (100%)
White race	7 (100%)	2 (67%)
Age [years], median (range)	55 (35-71)	62 (37-63)
Latency to symptom onset [days]	52 (16-99)	104 (76-410)
Latency to lab onset	70 (38-107)	109 (83-429)
Initial ALT [U/L]	1425 (328-2245)	581 (470-1230)
Initial Alk P [U/L]	125 (41-250)	329 (164-441)
Initial bilirubin [mg/dL]	0.8 (0.5-13.9)	2.5 (1.6-6.0)
Initial R value	13.7.1 (9.3-42.8)	8.5 (3.4-13.9)
Peak ALT [U/L]	2014 (1140-2521)	581 (470-1360)
Peak Alk P [U/L]	138 (88-306)	333 (164-538)
Peak bilirubin [mg/dL]	1.9 (0.8-26.0)	6.0 (1.6-23.6)
Peak INR	1.1 (1.0-1.4)	1.1 (0.9-2.5)
ANA or SMA positivity	5 (71%)	1 (33%)
Enzyme pattern		
Hepatocellular	6 (100%)	2 (67%)
Mixed or cholestatic	0	1 (33%)
Severity		
Mild (1+)	4 (57%)	1 (33%)
Moderate (2+ and 3+)	3 (43%)	1 (33%)
Severe or fatal (4+ and 5+)	0 (0%)	1 (33%)

Median (range) for continuous variables and frequency (%) for categorical variables.

Alk P = alkaline phosphatase; ALT = alanine aminotransferase; ANA = antinuclear antibody; INR = international normalized ratio; SMA = smooth muscle antibody.

associated with turmeric. Studies of the potential for additive or synergistic hepatotoxicity of turmeric when combined with piperine are needed to better understand the potential mechanism of liver injury.

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SUPPLEMENTARY DATA

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.amjmed.2022.09.026>.

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