Characterization of a Liver Injury Outbreak in 2022 After Ingestion of the Frozen French Lentil and Leek Crumble (FLLC) Food Product

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Introduction

In April 2022, FLLC, a new frozen food, was introduced online as part of a meal subscription plan. Soon thereafter, widespread anecdotal reports of acute gastrointestinal symptoms with liver injury were reported, leading to its voluntary withdrawal in June 2022, after shipment of 28,000 preparations. FDA reported 393 adverse illness events and 133 hospitalizations related to this product.[1]

Methods and Materials

Analysis of patients enrolled in the DILIN prospective study in 2022 with suspected FLLC associated liver injury. A total of 11 cases were adjudicated: 5 cases definite, 5 cases highly likely, and 1 case probable. Since removal of the product from the market, no further subjects have been enrolled into the DILIN.

Results

Demographics:
A total of 17 patients were enrolled. The mean age was 41 years, 76% female, mean BMI of 24kg/m^2, and all were Caucasian without underlying liver disease.

Clinical presentation:
The median latency to onset was 5 days with 18 days to resolution. In some cases, abdominal pain proportional to the amount of FLLC consumed was observed. At presentation, 29% had jaundice, 35% nausea, 29% fever, 41% abdominal pain, 35% itching, and none had rash. The median initial serum ALT was 369 U/L, AST 117 U/L, alkaline phosphatase 176 U/L, and total bilirubin 2.7 mg/dL (**Table 1**). The mean time to peak injury was 2 days. 53% had a hepatocellular pattern of liver injury at presentation as determined by R value, with the rest mixed or cholestatic. 24% of patients were hospitalized and there were no fatalities or liver transplants.

Histopathology:
Liver biopsy in one subject revealed mild ductular reaction, mild lymphocytic and eosinophilic portal inflammation with preserved bile ducts and no interface hepatitis. There was mild lobular necroinflammation without steatosis, granulomatous reaction or cholestasis, consistent with acute hepatitis of unknown etiology (**Fig 1**).

Chemical analysis:
Four FLLC samples underwent chemical analysis and no amatoxins, phallotoxins, aflatoxins, microcystins, or pyrrolizidine alkaloids were identified within limits of detection (10-25 ppb) and the heavy metals (As, Pb, Hg, Cr, Cd) were within acceptable limits. Phylogenetic analysis confirmed the presence of *Tara spinosa*, the source of Tara flour.

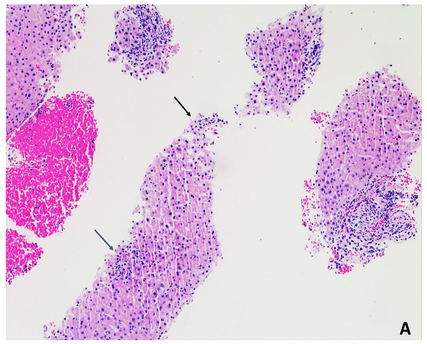
Table 1. Clinical features and presentation.

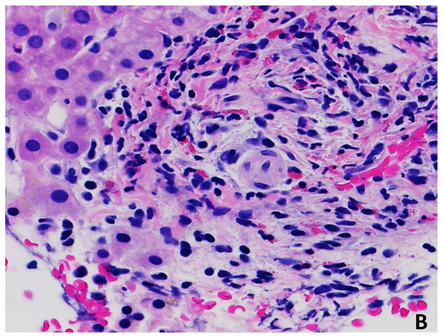
	N = 17
Mean Age	41 (28-55)
Gender (Female)	76%
Mean BMI	24 (18-31)
Race/Ethnicity	
White	100%
Black	0
Asian	0
Latino	0
Injury at Onset (median)	
Latency (days)	5 (2-8)
ALT (IU)	369 (262-485)
AST (IU)	117 (80-432)
ALK (U/L)	176 (138-258)
Tile (mg/dL)	2.7 (1.4-4.3)
Symptoms	
Jaundice	29%
Nausea	35%
Fever	29%
Abdominal pain	41%
Itching	35%
Rash	0
Outcomes	
Hospitalized	24%
Liver death	0
Transplantation	0
Chronic injury	0

Study supported by NIDDK U01/U24 grants. See DILIN website https://urldefense.com/v3/__https://dilin.org/publications__;!!F9wkZZsI-LA!BDmHYqYLPXZz96s3hJhnYR7bHZN-jWC9LjOGAcvw-wNZbnA12s-wHvT8XWjGdXKhxvIFacnjbmQ-hfqbZmjHbbp_l_SzcBFh$ [dilin[.]org] for a complete listing of funding sources, sites, investigators, co-investigators, coordinators, and staff.

References

[1]Chittiboyina AG, et al. Chem Res Toxicol. 2023 Jun 19;36(6):818-821





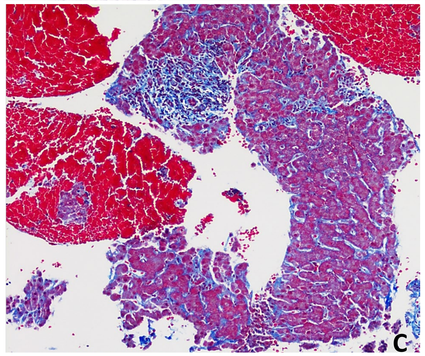


Figure 1: Liver Histopathology

Fig 1a. Liver biopsy specimen in one subject, obtained through endoscopic ultrasound revealed fragmented liver tissue with foci of parenchymal necroses.

Fig 1b. Only a few complete portal tracts were present, showing focal fibrosis, mild lymphocytic and eosinophilic infiltration, mild ductular reaction and no interface hepatitis without steatosis, granulomatous reaction or cholestasis.

Fig 1c. Trichrome stain confirms focal portal fibrosis without fibrous septum formation.

Discussion

Recent study revealed that Baikiain, a non-protein amino acid, is present at high levels in FLLC from the *Tara spinosa* flour. Upon ingestion, we hypothesize that Baikiain could be metabolize into reactive intermediates such as 4,5-epoxy pipecolic acid (via CYP-mediated oxidation) or 4- or 5-hydroxy pipecolic acids (via hydration) that induce glutathione depletion, oxidant stress, and inactivation of detoxifying enzymes.[1] This may result in adverse events in both the intestine and liver, which are dependent on both the amount consumed and potentially genetic variants in metabolic pathways that may predispose to injury..[1]

Conclusions

Hepatotoxicity resulting from FLLC might be the result of Tara flour containing the non-protein amino acid Baikiain. Ongoing studies seek to identify host factors, including potential genetic variants, which may predispose to liver injury.