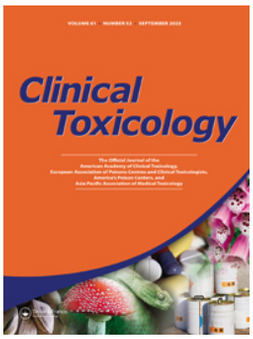

Clinical Toxicology

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/ictx20

A food product as a potential serious cause of liver injury

Stephanie E. Chan & Christopher A. Smith

To cite this article: Stephanie E. Chan & Christopher A. Smith (14 Sep 2023): A food product as a potential serious cause of liver injury, Clinical Toxicology, DOI: 10.1080/15563650.2023.2256469

To link to this article: https://doi.org/10.1080/15563650.2023.2256469

CLINICAL TOXICOLOGY
https://doi.org/10.1080/15563650.2023.2256469

Taylor & Francis
Taylor & Francis Group

SHORT COMMUNICATION

A food product as a potential serious cause of liver injury

Stephanie E. Chan and Christopher A. Smith

Department of Internal Medicine, Kingston General Hospital, Queen's University, Kingston, Canada

ABSTRACT

Introduction: Drug-induced liver injury can be challenging to diagnose, as it can develop following the use of many prescription and nonprescription medications, herbals, and dietary supplements. Food products may not be routinely considered as a potential cause of hepatotoxicity. We describe the clinical features of two cases of acute liver injury following consumption of a smoothie product.

Case presentations: Two patients independently presented to the hospital with epigastric pain and acute liver injury. Both patients had consumed a new smoothie product in the same month that they presented to the hospital, with a recurrence of acute liver injury with further consumption. A diagnosis of drug-induced liver injury was established after the evaluation excluded other causes of liver injury. It was thought that a natural ingredient in the smoothie, tara flour, was the cause of hepatotoxicity based on prior news reports. Both patients stopped drinking the smoothie product with subsequent normalization of liver enzyme activities and no further recurrence of epigastric pain.

Conclusion: The diagnosis of drug-induced liver injury largely relies on a compatible history and exclusion of other causes of liver injury. We demonstrate the importance of considering new food products in the differential diagnosis of acute liver injury.

ARTICLE HISTORY
Received 6 July 2023
Revised 28 August 2023
Accepted 1 September 2023

KEYWORDS
Hepatology; food toxicity; drug induced liver injury; hepatotoxicity; supplements

Introduction

Drug-induced liver injury (DILI) can be challenging to diagnose as it can clinically present as hepatocellular, cholestatic, or mixed injury, and can occur after exposure to many natural or manufactured compounds [1]. Diagnosis depends on obtaining a careful history and excluding other causes of liver injury, as there is no specific confirmatory test.

The National Institutes of Health maintains a searchable database of prescription and nonprescription medications, herbals, and dietary supplements that have been associated with DILI [2]; however, regulation of herbal and dietary supplements varies by country. In Canada, herbal and dietary supplements are required to provide evidence of safety and efficacy. This contrasts with food products containing natural ingredients, which are generally not subject to premarket review and assessment by Health Canada before they can be sold [3]. We demonstrate the importance of considering food products in the differential diagnosis of DILI, as they may contain new ingredients not previously known to be hepatotoxic.

Case presentations

Patient A

A 37-year-old female presented in May 2022 with epigastric pain, fatigue, jaundice, dark urine, and pale stools. Laboratory investigations showed a total bilirubin concentration of 52 μmol/L (3.0 mg/dL), aspartate aminotransferase (AST) activity of 256 U/L, alanine aminotransferase (ALT) activity of 768 U/L, and alkaline phosphatase (ALP) activity of 199 U/L (Figure 1). Paracetamol concentration, antinuclear antibodies, anti-extractable nuclear antigens, and viral hepatitis serology were negative. She consumed one to two alcoholic beverages per week. Medication review indicated that azithromycin had been taken two days prior to presentation, and her acute liver injury was attributed to azithromycin. The episode was resolved with supportive care.

Her epigastric pain and jaundice recurred in June 2022 for three days. She denied any new prescription or non-prescription medications. Liver function tests are shown in Figure 1. The bilirubin concentration was within the normal range. Magnetic resonance cholangiopancreatography showed small-volume sludge with no intra or extrahepatic biliary dilatation or choledocholithiasis. Her presentation was initially attributed to biliary sludge. However, further history revealed that the patient had consumed a new smoothie in May and June 2022 containing tara flour, a natural ingredient that has been linked to liver enzyme elevation [4,5]. In May, she began to feel unwell after consuming a whole smoothie and was found to have elevated liver enzymes two days later. In June, she had consumed another whole smoothie the day before her symptoms recurred. She was advised to stop consuming the smoothie, and since then has had no further episodes of liver injury.

CONTACT Stephanie E. Chan 0sec8@queensu.ca Department of Internal Medicine, Queen's University Kingston General Hospital, 76 Stuart Street, Kingston, Canada ON.

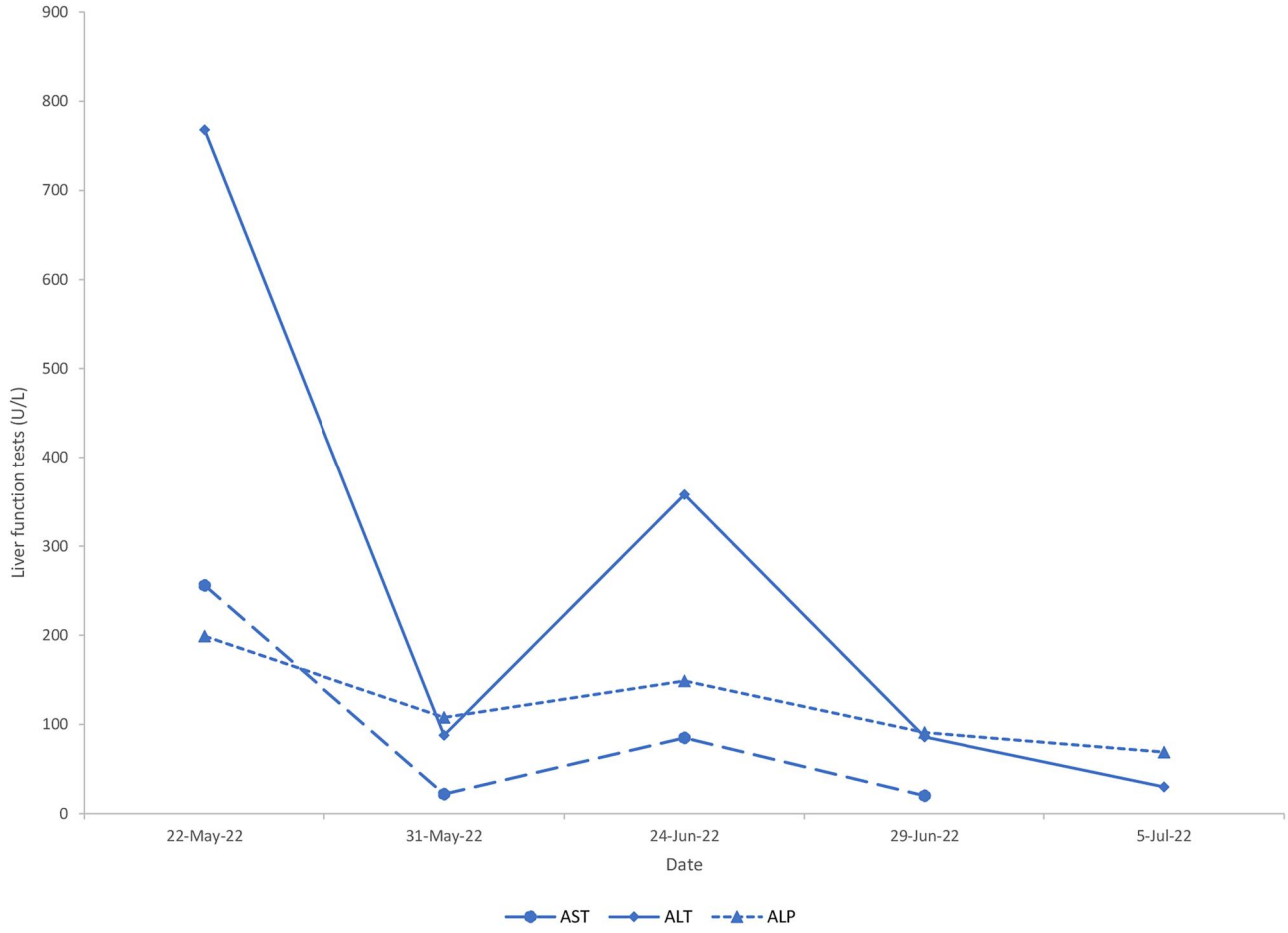

Figure 1. Case 1: Time course of selected liver function tests (LFTs) in the days following consumption of a smoothie product in May 2022 and June 2022. AST: asparate aminotransferase; ALT: alanine aminotransferase; ALP: alkaline phosphatase. Normal values for LFTs in our institution: AST - 8-40 U/L, ALT 8-40 U/L; ALP 48-110 U/L

Patient B

A 37-year-old female presented in June 2022 with epigastric pain, nausea, vomiting, and mixed acute liver injury (Figure 2). Doppler ultrasound showed no biliary duct dilation or cholelithiasis, and magnetic resonance cholangiopancreatography was normal. Investigations for hepatitis B and C, cytomegalovirus, Epstein-Barr virus, hemochromatosis, Wilson's disease, and autoimmune hepatitis were negative. Her symptoms resolved with conservative management, with the presumed diagnosis of passed biliary stones. Her liver function tests normalized after two months.

She was represented in January 2023 with similar symptoms. Laboratory investigations showed a total bilirubin concentration of 72 µmol/L (4.2 mg/dL) and raised enzyme activities (Figure 2). Albumin, international normalized ratio, prothrombin time, and lipase were within normal limits. Repeat imaging was negative for cholelithiasis, choledocholithiasis, or biliary duct dilatation, and her liver function tests improved with supportive care.

A careful history was taken. It was found that the patient had consumed the same smoothie as patient A in June 2022 and in January 2023. She had consumed a whole smoothie about 8 h prior to experiencing symptoms in both instances and had not consumed the product in the interim. After stopping, she had no recurrence of her features.

Discussion

Key elements in the history for establishing causality include substance exposure preceding liver injury (although the latency period can be anywhere from 1 to 4 months), exclusion of other causes, improvement following discontinuation of the drug, and rapid recurrence following re-challenge [6]. Exposure to a drug with a known history of DILI in other patients should also raise the index of suspicion. Several scoring systems have been developed to assess the causality of drug toxicity using objective criteria, including the Roussel-Uclaf Causality Assessment Method scale [1] and the World Health Organization Uppsala Monitoring Centre scale [7]. The offending drug should be immediately discontinued, with a favorable prognosis for most patients.

Case reports of food products leading to DILI are uncommon, with our search finding a case series of acute liver failure from consuming fried rice contaminated with Bacillus cereus toxin [8]. Our patients had consumed a fruit smoothie that contained tara flour, a natural product manufactured from the seeds of the South American tree *Tara spinosa* with limited data on safety and efficacy [5]. There have been reports of liver injury associated with a different company's product (Daily Harvest's French Lentil and Leek Crumbles) which had identified tara flour as the cause of hepatotoxicity [4,5]. A recent study identified baikiain, a nonprotein amino

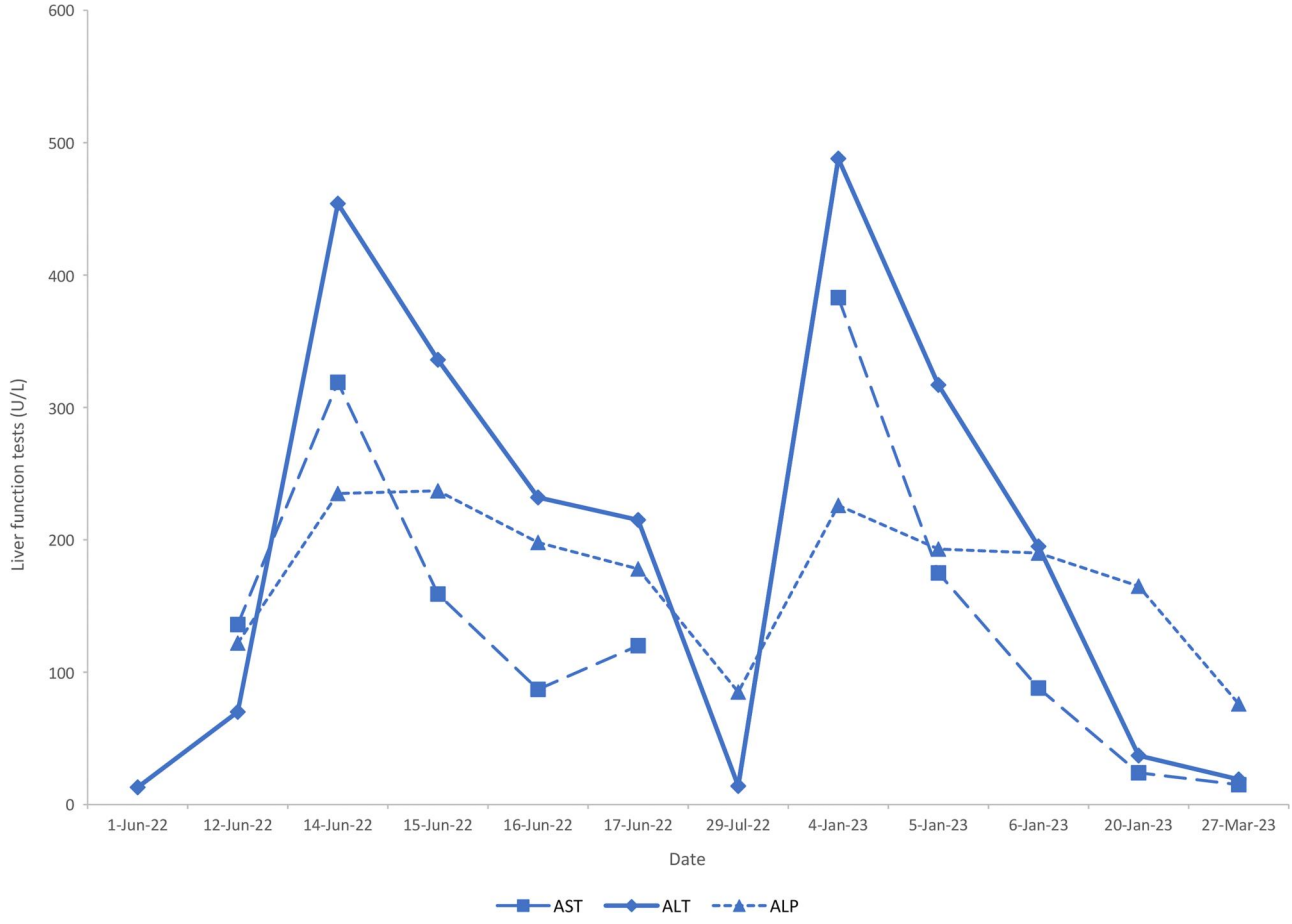

Figure 2. Case 2: Time course of selected liver function tests (LFTs) in the days following consumption of a smoothie product in June 2022 and January 2023. AST: asparate aminotransferase; ALT: alanine aminotransferase; ALP: alkaline phosphatase. Normal values for LFTs in our institution: AST - 8-40 U/L, ALT 8-40 U/L; ALP 48-110 U/L

acid, in tara as a potential compound of interest, as administration of baikiain in mice led to a statistically significant increase in ALT activity and a reduction in liver glutathione concentration [5]. There have been no conclusions or recommendations made by a national regulatory agency with regard to tara flour as of July 2023. Our patients have submitted a report to the Canadian Food Inspection Agency, which is currently undergoing investigation.

Conclusion

In conclusion, we report a case series of DILI most likely precipitated by an ingredient in a smoothie product. We demonstrate the importance of a compatible history in arriving at the diagnosis, as our patients had developed hepatotoxicity shortly after consuming the same product, which resolved when the exposure was stopped and recurred when the product was taken again. Our observations highlight the importance of reporting cases of DILI to regulatory bodies for further evaluation, as early recognition could reduce unnecessary testing or investigative burden for patients.

Disclosure statement

No potential conflict of interest was reported by the authors.

Funding

The authors reported there is no funding associated with the work featured in this article.

ORCID

Stephanie E. Chan http://orcid.org/0000-0001-7165-945X

References

[1] Chalasani NP, Maddur H, Russo MW, et al. ACG clinical guideline: diagnosis and management of idiosyncratic drug-induced liver injury. Am J Gastroenterol. 2021;116(5):878–898. doi: 10.14309/ajg.0000000000001259.

[2] LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Bethesda (MD): National institute of diabetes and digestive and kidney diseases; 2012-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK547852/.

[3] General Questions – Regulation of Natural Health Products - Canada.ca [Internet]. [cited 2023 Mar 25]. Available from: https://www.canada.ca/en/health-canada/services/drugs-health-products/natural-non-prescription/frequently-asked-questions/general-questions-regulation.html.

[4] Daily Harvest. | One-Step-Prep, Chef-crafted Food Built on Organic Ingredients. Delivered to You. Food that Takes Care of You. [Internet]. [cited 2023 Mar 25]. Available from: https://www.daily-harvest.com/content/french-lentil-leek-crumbles-advisory.

[5] Chittiboyina AG, Ali Z, Avula B, et al. Is Baikiain in Tara flour a causative agent for the adverse events associated with the recalled frozen french lentil & leek crumbles food product? - a working hypothesis. Chem Res Toxicol. 2023; 36(6):818–821. https://pubmed.ncbi.nlm.nih.gov/37255213/. doi: 10.1021/acs.chemrestox.3c00100.

[6] Navarro VJ, Senior JR. Drug-related hepatotoxicity. N Engl J Med. 2006;354(7):731–739. doi: 10.1056/NEJMra052270.

[7] The Uppsala Monitoring Centre: The use of the WHO-UMC system for standardised case causality assessment. [Internet]. Available from https://www.who.int/docs/default-source/medicines/pharmacovigilance/whocausality-assessment.pdf.

[8] Schreiber N, Hackl G, Reisinger AC, et al. Acute liver failure after ingestion of fried rice balls: a case series of Bacillus cereus food poisonings. Toxins. 2021;14(1):12. doi: 10.3390/toxins14010012.