AACT Herbal Dietary Supplement Section Abstracts

November 2024

1. **DRESS syndrome associated with a hemophagocytic lympho-histiocytosis: A rare presentation of DILI induced by a nutritional supplement.** Lemmens T, Sebagh M, De Martin E

   Clin Res Hepatol Gastroenterol. 2024 Oct;48(8):102455. doi: 10.1016/j.clinre.2024.102455. Epub 2024 Aug 26.

   Boswellia Serrata is a dietary supplement used for its anti-inflammatory properties by indirect inhibition of leukotrienes. Reported adverse effects are nausea, diarrhoea (5–20 %) and dermatitis (6–10 %), but no hepatitis [3]. DRESS-syndrome develops 2–6 weeks after the introduction of a new drug or substance with generalized maculopapular erythematous skin eruption, fever, lymphadenopathy, flu-like symptoms, eosinophilia and systemic involvement.

   DOI: 10.1016/j.clinre.2024.102455
   PMID: 39197740 [Indexed for MEDLINE]

2. **From garden to madness: herbal products and psychotic experiences.** Şair YB, Yılmaz Yıldırım E, Zeybek RE, Şallı Başaran G, Sevinçok L.

   Neurocase. 2024 Nov 29:1-6. doi: 10.1080/13554794.2024.2436217. Online ahead of print.

   Psychotic symptoms, characterized by hallucinations, delusions, and cognitive disturbances, are associated with various psychiatric and neurological disorders. This manuscript explores two cases of acute psychotic episodes triggered by the regular consumption of herbal products. The cases highlight the need for increased awareness of the potential toxic side effects of herbal products. The impact of herbal ingredients like maca and matcha on neurotransmitter activity is explored, shedding light on the underlying mechanisms leading to psychosis. The manuscript highlights the need to report both the benefits and risks of herbal products, challenging the misconception that they are inherently safe.

   DOI: 10.1080/13554794.2024.2436217
   PMID: 39611748

3. **Fitness and Dietary Supplements: A Cross-Sectional Study on Food Practices and Nutrivigilance**. Galman A, Chikhaoui M, Bouhrim M, Eto B, Shahat AA, Herqash RN, Lotfi R, Belamgharia H, Daoudi D, Kaddouri M, Dlimi C, Alahyane H, Liba H, Reda Kachmar M, Boutoial K.

   Nutrients. 2024 Nov 18;16(22):3928. doi: 10.3390/nu16223928.

   Background/Objectives: The use of dietary supplements (DSs) has become common among fitness enthusiasts, aiming to enhance performance, recovery, and overall well-being.
   Methods: A cross-sectional study was conducted in the city of Beni Mellal from April to July 2024, assessed dietary practices, motivations for supplement use, and associated adverse effects among 420 survey participants.
   Results: The majority of dietary supplement users were aged 25-64 and had higher education levels. Colopathy (67.38%) was the most common eating disorder, followed by digestive 59.46%), inflammatory, and rheumatic diseases (53.50%). Dietary supplementation prevalence was 88.1%, with proteins (60.81%), medicinal plants (45.13%), and vitamins (42.70%) being the most consumed. Key motivations included supporting muscle, bone, and joint strength (musculoskeletal) (83.78%) and enhancing heart and lung function for cardiorespiratory health (82.43%). However, 28% of protein users experienced adverse effects, such as myalgia, gastralgia, palpitations, and insomnia. Multivariate linear regression indicated a significant negative association of creatine with effectiveness ($\beta = -0.485$, $p = 0.001$).
   Conclusions: Overall, while the benefits of dietary and sports practices are evident, the adverse effects associated with protein supplements highlight the necessity for enhanced nutrivigilance and nutritional education to ensure safe supplements.

   DOI: 10.3390/nu16223928
   PMCID: PMC11597613
   PMID: 39599714 [Indexed for MEDLINE]

4. **Hepatotoxic Medicinal Plants in Weight Loss Formulations Sold at Ver-o-Peso Market, Amazon Region, Brazil.** Borges JPA, Silva BBD, Fernandes RM, Uchôa TLDA, Lopes TRM, Vieira JLF.

   J Med Food. 2024 Nov 8. doi: 10.1089/jmf.2024.0188. Online ahead of print.

   Obesity represents a significant global public health challenge. Various therapeutic strategies for weight reduction are available, including formulations containing medicinal plants, which are favored due to their availability and low cost. The efficacy and safety of these formulations must be evaluated as they can lead to adverse reactions, including severe hepatic injuries. Despite their widespread usage, particularly among residents of the Amazon, there is a considerable gap in knowledge regarding the species of medicinal plants used in these formulations. This study evaluated the labels of natural weight loss products sold from January to October 2022 at the Ver-o-Peso market in Belém, Brazil. A subsequent review of databases was performed to identify plants listed on the labels that were associated with hepatic injuries. In total, 54 plants were identified in these products, primarily in mixed formulations. None of the labels adhered to current legislative standards. Furthermore, nine of these plants were

documented in the literature as having hepatotoxic effects, either through in vivo or in vitro studies. The presence of medicinal plants that can cause liver injury on the labels of weight loss compounds is a relevant issue requiring rigorous health surveillance intervention.

DOI: 10.1089/jmf.2024.0188
PMID: 39514333

5. **Developing a screening strategy to identify hepatotoxicity and drug interaction potential of botanicals**. Roe, AL, Krzykwa, J, Calderón, AI, Bascoul, C, Gurley, BJ, Koturbash, I et al.

Journal of Dietary Supplements. 25 Oct 2024 doi.org/10.1080/19390211.2024.2417679

Botanical supplements, herbal remedies, and plant-derived products are used globally. However, botanical dietary supplements are rarely subjected to robust safety testing unless there are adverse reports in post-market surveillance. Botanicals are complex and difficult to assess using current frameworks designed for single constituent substances (e.g. small molecules or discrete chemicals), making safety assessments costly and time-consuming. The liver is a primary organ of concern for potential botanical-induced hepatotoxicity and botanical-drug interactions as it plays a crucial role in xenobiotic metabolism. The NIH-funded Drug Induced Liver Injury Network noted that the number of botanical-induced liver injuries in 2017 nearly tripled from those observed in 2004–2005. New approach methodologies (NAMs) can aid in the rapid and cost-effective assessment of botanical supplements for potential hepatotoxicity. The Hepatotoxicity Working Group within the Botanical Safety Consortium is working to develop a screening strategy that can help reliably identify potential hepatotoxic botanicals and inform mechanisms of toxicity. This manuscript outlines the Hepatotoxicity Working Group's strategy and describes the assays selected and the rationale for the selection of botanicals used in case studies. The selected NAMs evaluated as a part of this effort are intended to be incorporated into a larger battery of assays to evaluate multiple endpoints related to botanical safety. This work will contribute to a botanical safety toolkit, providing researchers with tools to better understand hepatotoxicity associated with botanicals, prioritize and plan future testing as needed, and gain a deeper insight into the botanicals being tested.

PMID: 39450425
DOI: 10.1080/19390211.2024.2417679

6. **A Case of Drug-Induced Liver Injury Caused by Mushroom Gummy Ingestion.** Antony I, Farhoud A, Lin MV.

American Journal of Gastroenterology. 119(10S):p S2837-S2839, October 2024. DOI: 10.14309/01.ajg.0001047140.41596.dd

Introduction: Drug-induced liver injury (DILI) is used to describe any injury to the liver caused by medications or supplements. The diagnosis of DILI relies on the exclusion of other etiologies of liver disease as specific biomarkers are still lacking. We report a case of DILI from a mushroom gummy supplement which was treated successfully with N-acetylcysteine (NAC).

Case Description/Methods: A 32-year-old man with a history of alcohol use disorder and necrotizing pancreatitis presented to an outside hospital (OSH) with jaundice and pruritis over 2.5 weeks. He denied any history of liver disease or abnormal liver enzymes. He started a mushroom gummy last month. He reported his last alcohol drink was 5 years ago. He denied any history of blood transfusion, IV drug use,

tattoos, new medications, or antibiotics. At the OSH, he was noted to have an elevated AST and ALT at 688 U/L and 1080 U/L respectively, and elevated T Bilirubin at 10.1 mg/dL. The patient was transferred 5 days later to our center for management. Table 1 lists all the drug, serological, and autoimmune workups done at admission. RUQUS showed mild CBD dilation. MRCP showed mild biliary ductal dilation with abrupt tapering at the pancreatic neck most likely due to an inflammatory stricture related to repetitive pancreatitis with no evidence of biliary obstruction. Poison control was contacted, and he was treated with NAC for 4 days with LFTs improving. Follow-up LFTs in a month showed normalization of AST, ALT, and T Bilirubin. Figure 1 notes the LFT trend from admission to our center till outpatient follow-up.

Discussion: Amanita phalloides have been widely noted as a cause of DILI but mushroom supplements have rarely been reported as a cause. This case reflects on the increasing DILI from nutritional supplements seen around the world. Approximately half the United States adult population consumes herbals and dietary supplements, and the proportion of supplement-related DILI cases has doubled from 7%–9% in 2004–2007 to 19%–20% in 2010–2014. The time to onset or latency of DILI varies and ranges between 5 days and 3 months, which correlates with the latency of our case. Time to recovery takes weeks to months after cessation of medication as seen in our case. The utilization of management of DILI with NAC in this case aligns with its current use with non-acetaminophen toxicity with data showing improved overall survival, transplant-free survival, and decreased length of hospital stay

DOI: 10.14309/01.ajg.0001047140.41596.dd

7. **A Case of Herbs and Dietary Supplements-Drug-Induced Liver Injury From Unripe Ackee Fruit!** Paladiya RD, Zhao D, Vaziri H

The American Journal of Gastroenterology 119(10S):p S2951, October 2024. | DOI: 10.14309/01.ajg.0001048012.02809.5c

Introduction: Herbs and dietary supplements-Drug-induced liver injury (HDS-DILI) ranges from self-limited acute liver injury to acute liver failure, necessitating orthotopic liver transplantation or leading to mortality. We present a case of acute liver injury from ingestion of Ackee fruit (Blighia sapida), a national fruit of Jamaica known to cause “Jamaican vomiting sickness”.
Case Description/Methods: A 25-year-old healthy male presented to the ED with 10 days of jaundice and diffuse, non-radiating abdominal pain that started 2 weeks after visiting Jamaica for vacation. He reported subjective fevers, chills, nausea, postprandial non-bloody emesis, anorexia, dark urine, and scleral icterus. His friends also experienced self-resolving diarrhea during the trip. He reported consuming seafood, local Ackee fruit, and only 1 alcoholic beverage. He denied any recent medications, supplements, tobacco, or recreational drugs. Vital signs were normal. Examination showed jaundice and a soft nontender abdomen. He was not encephalopathic. Blood work showed AST 1949 U/L, ALT 4330 U/L, ALP 160 U/L, Total bilirubin 13.7 mg/dL, Direct bilirubin 10 mg/dL, ASMA 1:20, Acetaminophen level , 17.4 ug/mL and negative alcohol level. Rest of the serologic workup was negative except positive hepatitis C antibody. Imaging showed stomach wall thickening (CT scan), with no portal vein thrombosis (abdominal Doppler USG), or biliary obstruction (MRCP). He was empirically treated with N-acetylcysteine, sofosbuvir, and velpatasvir with transfer to liver transplant center. The liver biopsy showed active cholestatic hepatitis. He had gradual improvement in liver enzymes and symptoms. Hep C RNA was negative and the medications were discontinued upon discharge. Liver enzymes normalized after 4 months. Discussion: The edible portion of the ackee fruit, aril, contains water-soluble toxins, hypoglycin A and B. As the fruit ripens, their concentration drops to safe levels. These toxins impair gluconeogenesis and beta-oxidation of fatty acids, resulting in hypoglycemia. However, the exact mechanism of idiosyncratic hepatotoxicity remains unknown. Our patient’s HDS-DILI was presumed due to the temporal relationship of unripe ackee fruit exposure with elevated liver enzymes, jaundice and liver biopsy findings along with remission on discontinuation of exposure. The fruit is only available in canned forms with import restrictions. We aim to highlight its potential toxicity and heighten clinical suspicion in relevant contexts (see Figure 1).

DOI: 10.14309/01.ajg.0001048012.02809.5c

8. **LC-MS/MS confirmation of 11-nor-9-carboxy-tetrahydrocannabinol (Δ8, Δ9, Δ1°) and hexahydrocannabinol (HHC) metabolites in authentic urine specimens.** Patton AL, Muir L, Seither JZ, Walterscheid JP, Karschner EL.

   J Anal Toxicol. 2024 Nov 26:bkae091. doi: 10.1093/jat/bkae091. Online ahead of print.

   Recently, tetrahydrocannabinol (THC) isomers and other semi-synthetic cannabinoids have been introduced into the consumer market as alternatives to botanical cannabis. To assess the prevalence of these potential new analytical targets, a liquid chromatography-tandem mass spectrometry confirmation method was developed for the quantitation of seven cannabinoid metabolites and the qualitative identification of four others in urine. The validated method was applied to authentic urine specimens that screened positive by immunoassay (50 ng/mL cutoff; n=1300). The most commonly observed analytes were 11-nor-9-carboxy-Δ8- and Δ9-THC (Δ8- and Δ9-THCCOOH), with the combination of the two seen as the most prominent analyte combination found. In addition to these metabolites, Δ1°-THCCOOH was observed in 77 specimens. This is the first study to report Δ1°-THCCOOH in authentic urine specimens, with this analyte always appearing in combination with Δ9-THCCOOH. Cross-reactivity studies were performed for (6aR,9R)-Δ1°-THCCOOH using the Beckman Coulter Emit® II Plus Cannabinoid immunoassay and demonstrated cross reactivity equivalent to the Δ9-THCCOOH cutoff, providing added confidence in the reported prevalence and detection patterns. Additionally, 11-nor-9(R)-carboxy-hexahydrocannabinol (9(R)-HHCCOOH) was the most abundant stereoisomer (n=12) in specimens containing HHC metabolites alone (n=14). This is in contrast to 9(S)-HHCCOOH, which was the predominant stereoisomer in specimens containing Δ8- and/or Δ9-THCCOOH. Although HHC and Δ1°-THC metabolites are emerging toxicology findings, based on these specimens collected between April 2022 and May 2024, an analytical panel containing Δ8- and Δ9-THCCOOH appears to be sufficient for revealing cannabinoid exposure within workplace monitoring and deterrence programs.

   DOI: 10.1093/jat/bkae091
   PMID: 39586679

9. **Fatal aconite poisoning in a rural Nepali traditional healer: clinical challenges and management strategies.** Adhikari P.

   INTRODUCTION AND IMPORTANCE: Aconite, also known as Aconitum spp., is a group of highly toxic flowering plants used historically in traditional medicine despite their potent neurotoxic and cardiotoxic effects. In rural Nepal, where traditional healing practices are prevalent, accidental ingestion of Aconite remains a significant public health concern due to its resemblance to medicinal herbs.
   CASE PRESENTATION: The authors present a case of severe Aconite poisoning in a 45-year-old male traditional healer from rural Nepal. Following ingestion of a homemade herbal tea containing Aconitum species, the patient developed rapid-onset symptoms, including paresthesia around the mouth, severe abdominal pain, and progressive weakness. Upon admission, he exhibited signs of cardiovascular compromise and metabolic acidosis. Despite aggressive management, including gastric lavage, fluid resuscitation, and symptomatic treatment, the patient succumbed to cardiovascular collapse within 12 h of admission.

CLINICAL DISCUSSION: Aconite poisoning manifests with early neurological symptoms and progresses to severe gastrointestinal and cardiovascular complications. Its toxicity is attributed to aconitine, which disrupts cellular function by binding to voltage-gated sodium channels. Management focuses on supportive care and symptomatic treatment, given the absence of a specific antidote and challenges in rural healthcare settings.
CONCLUSION: This case underscores the critical need for awareness among healthcare providers and the public regarding the dangers of Aconite. Improved education, healthcare infrastructure, and early intervention are essential in mitigating the morbidity and mortality associated with Aconite poisoning in resource-limited settings.

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PMCID: PMC11444581
PMID: 39359847

10. **Aristolochic acid-induced dyslipidemia and hepatotoxicity: The potential role ofFXR and AHR receptors.** Ma Y, Du C, Liu Y, Feng M, Shou Y, Yu D, Jin Y.

Ecotoxicol Environ Saf. 2024 Nov 15;287:117266. doi: 10.1016/j.ecoenv.2024.117266. Epub 2024 Nov 6.

Aristolochic acids (AAs) represent a class of nitrophenanthrene carboxylic acids naturally existing or accidentally mixed in herbal medicines or crops, which have long been recognized for causing nephropathy. Recently, the linkage between AAs and liver injury has become a concern; however, the current understanding of the mechanism or mode of action (MOA) is limited. In the present study, we investigated nuclear receptor-mediated MOA associated with AAs-induced liver injury including dyslipidemia and hepatotoxicity. Bioinformatic analysis of AAI-interacting genes indicated nuclear receptor-mediated metabolizing pathways; Transcriptomic profiling of AAs-exposed rats with liver injury suggested FXR-, NRF2-, and AHR- mediated pathways in the injured livers of the rats. Mechanistic investigation using HepG2 cells indicated AAI-induced hepatic lipid accumulation by elevating Triglyceride (TG) through inhibition of the FXR. In addition, AAI-induced hepatocellular damage by activating the AHR pathway, which further generated ROS and activated the NRF2 pathway. Together, these results provided new clues for esearchers who are interested in chemical-induced liver injury.

DOI: 10.1016/j.ecoenv.2024.117266
PMID: 39509784 [Indexed for MEDLINE]

11. **Cannabinoids Used for Medical Purposes in Children and Adolescents: A Systematic Review and Meta-Analysis.** Chhabra M, Ben-Eltriki M, Mansell H, Lê ML, Huntsman RJ, Finkelstein Y, Kelly LE.

JAMA Pediatr. 2024 Nov 1;178(11):1124-1135. doi: 10.1001/jamapediatrics.2024.3045.

IMPORTANCE: Cannabinoids are increasingly used for medical purposes in children. Evidence of the safety of cannabinoids in this context is sparse, creating a need for reliable information to close this knowledge gap.OBJECTIVE: To study the adverse event profile of cannabinoids used for medical purposes in children and adolescents.DATA SOURCES: For this systematic review and meta-analysis, MEDLINE, Embase, PsycINFO, and the Cochrane Library were searched for randomized clinical trials published from database inception to March 1, 2024, for subject terms and keywords focused on cannabis and children and adolescents. Search results were restricted to human studies in French or English.STUDY SELECTION: Two reviewers independently performed the title, abstract, and full-text review, data extraction, and quality assessment. Included studies enrolled at least 1 individual 18 years or younger, had a natural or pharmaceutical cannabinoid used as an intervention to manage any medical condition, and had an ctive comparator or placebo.DATA EXTRACTION AND SYNTHESIS: Two reviewers performed data extraction and quality assessment independently. The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guideline and PRISMA-S guideline were used. Data were pooled using a random-effects model. MAIN OUTCOMES AND MEASURES: The primary outcome was the incidence of withdrawals, withdrawals due to adverse events, overall adverse events, and serious adverse events in the cannabinoid and control arms. Secondary outcomes were the incidence of specific serious adverse events and adverse events based on organ system involvement.RESULTS: Of 39 175 citations, 23 RCTs with 3612 participants were included (635 [17.6%] female and 2071 [57.3%] male; data not available from 2 trials); 11 trials (47.8%) included children and adolescents only, and the other 12 trials (52.2%) included children, adolescents, and adults. Interventions included purified annabidiol (11 [47.8%]), nabilone (4 [17.4%]), tetrahydrocannabinol (3 [13.0%]), cannabis herbal extract (3 [13.0%]), and dexanabinol (2 [8.7%]). The most common indications were epilepsy (9 [39.1%]) and chemotherapy-induced nausea and vomiting (7 [30.4%]). Compared with the control, cannabinoids were associated with an overall increased risk of adverse events (risk ratio [RR], 1.09; 95% CI, 1.02-1.16; I2 = 54%; 12 trials), withdrawals due to adverse events (RR, 3.07; 95% CI, 1.73-5.43; I2 = 0%; 14 trials), and serious adverse events (RR, 1.81; 95% CI, 1.21-2.71; I2 = 59%; 11 trials). Cannabinoid-associated adverse events with higher RRs were diarrhea (RR, 1.82; 95% CI, 1.30-2.54; I2 = 35%; 10 trials), increased serum levels of aspartate aminotransferase (RR, 5.69; 95% CI, 1.74-18.64; I2 = 0%; 5 trials) and alanine aminotransferase (RR, 5.67; 95% CI, 2.23-14.39; I2 = 0%; 6 trials), and somnolence (RR, 2.28; 95% CI, 1.83-2.85; I2 = 8%; 14 trials). CONCLUSIONS AND RELEVANCE: In this systematic review and meta-analysis, cannabinoids used for medical purposes in children and adolescents in RCTs were associated with an increased risk of adverse events. The findings suggest that long-term safety studies, including those exploring cannabinoid-related drug interactions and tools that improve adverse event reporting, are needed.

DOI: 10.1001/jamapediatrics.2024.3045
PMID: 39283619 [Indexed for MEDLINE]

12. **Synthetic cannabinoid identification in cases associated with blue lotus and valerian root vaping products.** Seither JZ, Karschner EL, Jackson KR, Deakin A, Roper SH, Walterscheid JP.

    J Anal Toxicol. 2024 Oct 28;48(8):557-565. doi: 10.1093/jat/bkae065.

    Synthetic cannabinoids emerged in the early 21st century and have continued to evolve and flourish to present day. Like other novel psychoactive substances (NPS), synthetic cannabinoids have been sold under the guise of legitimate products. Some examples include "potpourri," "incense," and herbal material. Between May 2020 and December 2023, the United States Army Criminal Investigation Laboratory, Drug Chemistry Division (USACIL) received 29 seized drug cases mentioning "blue lotus" or "valerian root." In 90% of these cases, at least one exhibit contained one or more synthetic cannabinoids. During the same timeframe, the Armed Forces Medical Examiner System, Division of Forensic Toxicology received 65 toxicology cases that contained synthetic cannabinoids and/or their corresponding metabolites where case history mentioned "blue lotus." The most frequently observed synthetic cannabinoids between laboratories were 5F-MDMB-PICA, ADB-BUTINACA, and MDMB-4en-PINACA. Innocuous branding and marketing may deceive law enforcement, investigators, and healthcare providers into believing that the adverse effects of erratic behavior, sedation, slurred speech, and hallucinations are a result of toxicity from botanical extracts (e.g. apomorphine and nuciferine in blue lotus). Due to the dangerous nature of these NPS, synthetic cannabinoid screening is recommended for all cases where there is suspected use of vaping products suggested to contain "blue lotus" or "valerian root" as vendors continue to conceal the presence of these compounds.

    DOI: 10.1093/jat/bkae065
    PMID: 39082147 [Indexed for MEDLINE]

13. **Examining the hepatotoxic potential of cannabidiol, cannabidiol-containing hemp extract, and cannabinol at consumer-relevant exposure concentrations in primary human hepatocytes.** Striz A, Zhao Y, Sepehr E, Vaught C, Eckstrum K, Headrick K, Yourick J, Sprando R.J Appl Toxicol. 2024 Oct;44(10):1595-1605. doi: 10.1002/jat.4646. Epub 2024 Jun 26.

    Hemp extracts and consumer products containing cannabidiol (CBD) and/or other phytocannabinoids derived from hemp have entered the marketplace in recent years. CBD is an approved drug in the United States for the treatment of certain seizure disorders. While effects of CBD in the liver have been well characterized, data on the effects of other cannabinoids and hemp extracts in the liver and methods for studying these effects in vitro are limited. This study examined the hepatotoxic potential of CBD, CBD concentration-matched hemp extract, and cannabinol (CBN), at consumer-relevant concentrations determined by in silico modeling, in vitro using primary human hepatocytes. Primary human hepatocytes exposed to between 10-nM and 25-μM CBD, CBN, or hemp extract for 24 and 48 h were evaluated by measuring lactate dehydrogenase release, apoptosis, albumin secretion, urea secretion, and mitochondrial membrane potential. Cell viability was not significantly affected by CBD, CBN, or the hemp extract at any of the concentrations tested.

Exposure to hemp extract induced a modest but statistically significant decrease in albumin secretion, urea secretion, and mitochondrial membrane potential at the highest concentration tested whereas CBD only induced a modest but statistically significant decrease in albumin secretion compared with vehicle control. Although this study addresses data gaps in the understanding of cannabinoid hepatoxicity in vitro, additional studies will be needed to determine how these results correlate with relevant consumer exposure and the biological effects of cannabinoids in human liver.

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