AACT Herbal Dietary Supplement Section Abstracts September 2023

1. Notes from the Field: Online Weight Loss Supplements Labeled as Tejocote (Crataegus mexicana) Root, Substituted with Yellow Oleander (Cascabela thevetia) - United States, 2022. Berland N, Kababick J, Santos C, Calello DP.

MMWR Morb Mortal Wkly Rep. 2023;72(37):1016-1017. Published 2023 Sep 15. doi:10.15585/mmwr.mm7237a3

In the United States, dietary supplements are regulated by the Food and Drug Administration (FDA).* Regulations mandate that all ingredients used to manufacture dietary supplements be tested for identity and be free from reasonably anticipated contaminants. Despite these regulations, misbranded dietary supplements are frequently found to contain potentially dangerous substances (*1*). Tejocote (*Crataegus mexicana*) root, a supplement promoted online through social media for weight loss, is readily available from online retailers. Recent DNA fingerprinting of a product labeled as containing tejocote root under the brand name Alipotec determined that the product was 100% yellow oleander (*Cascabela thevetia*) (*2*). Yellow oleander contains the cardenolide thevetin B, which has the same clinical effects as other cardenolides, such as digoxin, and can be highly toxic.

DOI: 10.15585/mmwr.mm7237a3
PMID: 37708076

2. Weight Loss or Liver Loss: A Case Report on Fulminant Hepatic Failure Secondary to Garcinia cambogia Supplementation. Le D, Hydro BA, Jones CL, Beauchamp GA.

Cureus. 2023 Jul 12;15(7):e41778. doi: 10.7759/cureus.41778. eCollection 2023 Jul.

This case describes a 56-year-old man with a past medical history including sickle cell trait requiring blood transfusions, who presented to the emergency department (ED) with generalized weakness and fatigue following Garcinia cambogia supplementation. Initial laboratory abnormalities included: aspartate aminotransferase (AST) and alanine transaminase (ALT) 4,222 U/L and 4,664 U/L respectively, alkaline phosphatase 215 U/L, international normalized ratio (INR) 3.2, and his model for end-stage liver disease was 37. Creatinine, hemoglobin and hematocrit, and ferritin levels were all elevated. The differential diagnosis for his acute illness was broad ranging from hemochromatosis, anabolic steroid use, and portal venous thrombosis. The patient was started on N-acetylcysteine (NAC) and his liver function improved. He was discharged on hospital day 10 and instructed to discontinue his supplements and follow up for repeat blood work. This case explores the critical management of G. cambogia toxicity. The patient explored G. cambogia as an herbal supplementation resulting in weight loss, worsening generalized fatigue, and fulminant hepatic failure.

DOI: 10.7759/cureus.41778
PMCID: PMC10421402
PMID: 37575813

3. Interaction of Garcinia cambogia (Gaertn.) Desr. and Drugs as a Possible Mechanism of Liver Injury: The Case of Montelukast. Di Giacomo S, Di Sotto A, Percaccio E, Scuotto E, Battistelli C, Mazzanti G, Menniti-Ippolito F, Ippoliti I.

Antioxidants (Basel). 2023 Sep 16;12(9):1771. doi: 10.3390/antiox12091771.

Overweight and obesity prevalence has increased worldwide. Apart from conventional approaches, people also resort to botanical supplements for reducing body weight, although several adverse events have been

associated with these products. In this context, the present study aimed at evaluating the toxicity of Garcinia cambogia-based products and shedding light on the mechanisms involved. The suspected hepatotoxic reactions related to G. cambogia-containing products collected within the Italian Phytovigilance System (IPS) were examined. Then, an in vitro study was performed to evaluate the possible mechanisms responsible for the liver toxicity, focusing on the modulation of oxidative stress and Nrf2 expression. From March 2002 to March 2022, the IPS collected eight reports of hepatic adverse reactions related to G. cambogia, which exclusively involved women and were mostly severe. The causality assessment was probable in three cases, while it was possible in five. In the in vitro experiments, a low cytotoxicity of G. cambogia was observed. However, its combination with montelukast greatly reduced cell viability, increased the intracellular ROS levels, and affected the cytoplasmic Nrf2 expression, thus suggesting an impairment of the antioxidant and cytoprotective defenses. Overall, our results support the safety concerns about G. cambogia-containing supplements and shed light on the possible mechanisms underpinning its hepatotoxicity.

DOI: 10.3390/antiox12091771
PMID: 37760074

4. Liver Injury Associated with Turmeric-A Growing Problem: Ten Cases from the Drug-Induced Liver Injury Network [DILIN]. Halegoua-DeMarzio D, Navarro V, Ahmad J, et al.

Am J Med. 2023;136(2):200-206. doi:10.1016/j.amjmed.2022.09.026

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 the in 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*.

DOI: 10.1016/j.amjmed.2022.09.026
PMID: 36252717

5. Severe Drug-Induced Liver Injury in the Military: A Retrospective Review. Ordway S, Sadowski B, Driggers KE, Kwok R.

Mil Med. 2023 May 16;188(5-6):e991-e996. doi: 10.1093/milmed/usab445.

OBJECTIVES: Drug-induced liver injury (DILI) is a significant cause of morbidity and mortality. Establishing a diagnosis is challenging due to the broad differential diagnosis of liver injury. We retrospectively reviewed patients with severe idiosyncratic DILI at Walter Reed National Military Medical Center in order to define the scope and patterns of injury in the military population. METHODS: Using the military health database, we identified a total of 110 patients who had an International Classification of Disease (ICD)-10 code for toxic liver injury in the electronic medical record at Walter Reed National Military Medical Center between 2016 and 2019. Each patient record was reviewed, and all pertinent data for included patients were recorded into a database for analysis. RESULTS: Twenty-seven out of 110 patients with a diagnostic code for toxic liver injury met inclusion criteria for severe idiosyncratic DILI. Nine cases were caused by supplements, including 5 active duty service members using synthetic anabolic steroids or preworkout supplements. The majority of patients were men and one-third were serving on active duty. The ranges of liver enzyme elevation and patterns of liver injury widely varied. CONCLUSION: Military service

members are at particularly high risk for DILI given the frequent use of over-the-counter and other unregulated strength- and performance-enhancing supplements. These injuries not only have significant medical consequences but can profoundly impact military readiness and mission capability. Diagnosis of DILI among active duty service members requires a strong index of suspicion, and inquiry regarding all ingestions is crucial. Educating physicians, providers, and policy makers on the risks of supplement-induced liver injury among service members is crucial. These data will facilitate additional studies exploring susceptibility to severe idiosyncratic DILI among the military population.

DOI: 10.1093/milmed/usab445
PMID: 34697623 [Indexed for MEDLINE]

6. Herb-Induced Liver Injury by Ayurvedic Ashwagandha as Assessed for Causality by the Updated RUCAM: An Emerging Cause. Bokan G, Glamočanin T, Mavija Z, Vidović B, Stojanović A, Björnsson ES,Vučić V.

Pharmaceuticals (Basel). 2023 Aug 10;16(8):1129. doi: 10.3390/ph16081129.

Herb-induced liver injury (HILI) caused by herbal supplements, natural products, and products used in traditional medicine are important for differential diagnoses in patients with acute liver injury without an obvious etiology. The root of Withania somnifera (L.) Dunal, commonly known as ashwagandha, has been used in Ayurvedic medicine for thousands of years to promote health and longevity. Due to various biological activities, ashwagandha and its extracts became widespread as herbal supplements on the global market. Although it is generally considered safe, there are several reported cases of ashwagandha-related liver injury, and one case ended with liver transplantation. In this paper, we review all reported cases so far. Additionally, we describe two new cases of ashwagandha hepatotoxicity. In the first case, a 36-year-old man used ashwagandha capsules (450 mg, three times daily) for 6 months before he developed nausea, pruritus, and dark-colored urine. In the second case, a 30-year-old woman developed pruritus after 45 days of using ashwagandha capsules (450 mg). In both cases, serum bilirubin and liver enzymes (aspartate transaminase (AST), alanine transaminase (ALT), and alkaline phosphatase (ALP) were increased. The liver injury pattern was hepatocellular (R-value 11.1) and mixed (R-value 2.6), respectively. The updated Roussel Uclaf Causality Assessment Method (RUCAM) (both cases with a score of seven) indicated a "probable" relationship with ashwagandha. Clinical and liver function improvements were observed after the discontinuation of ashwagandha supplement use. By increasing the data related to ashwagandha-induced liver injury, these reports support that consuming ashwagandha supplements is not without its safety concerns.

DOI: 10.3390/ph16081129
PMCID: PMC10459262
PMID: 37631044

7. Ashwagandha-induced liver injury-A case series from India and literature review. Philips CA, Valsan A, Theruvath AH, Ravindran R, Oommen TT, Rajesh S, Bishnu S, Augustine P; Liver Research Club India.

Hepatol Commun. 2023 Sep 27;7(10):e0270. doi: 10.1097/HC9.0000000000000270. eCollection 2023 Oct 1.

BACKGROUND: Ashwagandha herb is commonly used in Ayurveda and a "fad" dietary supplement for a host of indications based on low levels of evidence. Recently, ashwagandha was implicated in multiple reports of herb-induced liver injury (HILI), mainly from the United States. We present the first, and currently largest, series of ashwagandha-HILI from multiple centers in India. METHODS: We retrospectively analyzed the respective institutional electronic medical records for ashwagandha-HILI. Patients consuming ashwagandha as part of multiherbal formulations or along with other known hepatotoxic supplements or medicines were excluded. All patients underwent a detailed diagnostic workup to exclude competing causes reasonably. Where possible, the implicated herbal formulation was retrieved and subjected to chemical analysis. RESULTS: Out of 23 patients with liver injury from ashwagandha (January 2019 to December 2022), we report 8 patients with single-ingredient formulation-related HILI. Study cohort was male predominant, and cholestatic hepatitis was the commonest presentation. Five patients had underlying chronic liver disease; 3 presented with acute-on-chronic liver failure, and all 3 died on follow-up. In others, the liver injury was prolonged, nonetheless self-limiting. Liver biopsy revealed cholestatic features predominantly with hepatocellular necrosis and lymphocyte/eosinophil predominant portal-based inflammation. One patient

progressed to chronic HILI. Chemical analysis revealed only natural phytochemicals without adulteration or contamination. CONCLUSIONS: Ashwagandha-HILI presents with cholestatic hepatitis and can lead to the syndrome of acute-on-chronic liver failure with high mortality in those with pre-existing liver disease. Educating the public on avoiding the use of potentially toxic and unrecommended herbal supplements can help mitigate the avoidable liver disease burden in the community.

DOI: 10.1097/HC9.0000000000000270
PMCID: PMC10531359
PMID: 37756041

8. Nomenclature, diagnosis and management of drug-induced autoimmune-like hepatitis (DI-ALH): An expert opinion meeting report. Andrade RJ, Aithal GP, de Boer YS, Liberal R, Gerbes A, Regev A, Terziroli Beretta-Piccoli B, Schramm C, Kleiner DE, De Martin E, Kullak-Ublick GA, Stirnimann G, Devarbhavi H, Vierling JM, Manns MP, Sebode M, Londoño MC, Avigan M, Robles-Diaz M, García-Cortes M, Atallah E, Heneghan M, Chalasani N, Trivedi PJ, Hayashi PH, Taubert R, Fontana RJ, Weber S, Oo YH, Zen Y, Licata A, Lucena MI, Mieli-Vergani G, Vergani D, Björnsson ES; IAIHG and EASL DHILI Consortium.

J Hepatol. 2023 Sep;79(3):853-866. doi: 10.1016/j.jhep.2023.04.033. Epub 2023 May 8.

Drug-induced liver injury (DILI) can mimic almost all other liver disorders. A phenotype increasingly ascribed to drugs is autoimmune-like hepatitis (ALH). This article summarises the major topics discussed at a joint International Conference held between the Drug-Induced Liver Injury consortium and the International Autoimmune Hepatitis Group. DI-ALH is a liver injury with laboratory and/or histological features that may be indistinguishable from those of autoimmune hepatitis (AIH). Previous studies have revealed that patients with DI-ALH and those with idiopathic AIH have very similar clinical, biochemical, immunological and histological features. Differentiating DI-ALH from AIH is important as patients with DI-ALH rarely require long-term immunosuppression and the condition often resolves spontaneously after withdrawal of the implicated drug, whereas patients with AIH mostly require long-term immunosuppression. Therefore, revision of the diagnosis on long-term follow-up may be necessary in some cases. More than 40 different drugs including nitrofurantoin, methyldopa, hydralazine, minocycline, infliximab, herbal and dietary supplements (such as Khat and Tinospora cordifolia) have been implicated in DI-ALH. Understanding of DI-ALH is limited by the lack of specific markers of the disease that could allow for a precise diagnosis, while there is similarly no single feature which is diagnostic of AIH. We propose a management algorithm for patients with liver injury and an autoimmune phenotype. There is an urgent need to prospectively evaluate patients with DI-ALH systematically to enable definitive characterisation of this condition.

DOI: 10.1016/j.jhep.2023.04.033
PMID: 37164270 [Indexed for MEDLINE]

9. Sex disparity and drug-induced liver injury. Floreani A, Bizzaro D, Shalaby S, Taliani G, Burra P; Special Interest Group Gender in Hepatology of the Italian Association for the Study of the Liver (AISF).

Dig Liver Dis. 2023 Jan;55(1):21-28. doi: 10.1016/j.dld.2022.06.025. Epub 2022 Jul 15.

Drug-induced liver injury (DILI) is a potentially serious clinical condition that remains a major problem for patients, physicians and those involved in the development of new drugs. Population and hospital-based studies have reported incidences of DILI varying from 1.4 to 19.1/100.000. Overall, females have a 1.5- to 1.7-fold greater risk of developing adverse drug reactions and the female/male ratio increases after the age of 49 years, suggesting a clear susceptibility of DILI after menopause. Sex differences in pharmacokinetics and pharmacodynamic, sex-specific hormonal effects or interaction with signalling molecules that can influence drug efficacy and safety and differences in abnormal immune response following drug exposure are the main probable causes of the higher vulnerability observed among female patients. A novel phenotype of autoimmune-mediated DILI following the use of check-point inhibitors in oncology and haematology has been recently described. Finally, there have been increasing reports of DILI associated with use of herbal and dietary supplements that is more frequently reported in women.

DOI: 10.1016/j.dld.2022.06.025
PMID: 35843842 [Indexed for MEDLINE]

10. Evaluation of the Herb-Drug Interaction Potential of Commonly Used Botanicals on the US Market with Regard to PXR- and AhR-Mediated Influences on CYP3A4 and CYP1A2. Haron MH, Dale O, Martin K, et al.

J Diet Suppl. 2023;20(5):763-776. doi:10.1080/19390211.2022.2110351

In this study, hydroethanolic extracts of 30 top-selling botanicals (herbs) commonly used as ingredients of herbal dietary supplements in the US were screened for their potential to activate the human pregnane X receptor (hPXR) and human aryl hydrocarbon receptor (hAhR) and to increase the activities of hPXR- and hAhR-regulated drug metabolizing cytochrome P450 enzymes (i.e., CYP3A4 and CYP1A2, respectively). Of the 30 botanicals tested, 21 induced PXR and 29 induced AhR transcriptional activities. Out of the 21 botanicals that induced hPXR transcriptional activity, 14 yielded >50% induction in CYP3A4 activity at concentrations ranging from 6 to 60 µg/mL and 16 out of the 29 botanicals that activated hAhR yielded >50% induction in CYP1A2 activity at concentrations ranging from 3 to 30 µg/mL. Moreover, eight botanicals (*G. gummi-gutta* [garcinia], Hemp [low and high CBD content], *H. perforatum* [St. John's wort], *M. vulgare* [horehound], *M. oleifera* [moringa], *O. vulgare* [oregano], *P. johimbe* [yohimbe] and *W. somnifera* [ashwagandha]) yielded >50% induction in both CYP3A4 and CYP1A2 activity. Herbal products are mixtures of phytoconstituents, any of which could modulate drug metabolism. Our data reveals that several top-selling botanicals may pose herb-drug interaction (HDI) risks *via* CYP450 induction. While *in vitro* experiments can provide useful guidance in assessing a botanical's HDI potential, their clinical relevance needs to be investigated *in vivo*. Botanicals whose effects on hPXR/CYP3A4, and hAhR/CYP1A2 activity were most pronounced will be slated for further clinical investigation.

DOI: 10.1080/19390211.2022.2110351
PMID: 36017806

11. Assessment of Herb-Drug Interaction Potential of Five Common Species of Licorice and Their Phytochemical Constituents. Haron MH, Avula B, Ali Z, et al.

J Diet Suppl. 2023;20(4):582-601. doi:10.1080/19390211.2022.2050875

The dried roots and rhizomes of *Glycyrrhiza* species (*G. glabra, G. uralensis* and *G. inflata*), commonly known as licorice, have long been used in traditional medicine. In addition, two other species, *G. echinata* and *G. lepidota* are also considered "licorice" in select markets. Currently, licorice is an integral part of several botanical drugs and dietary supplements. To probe the botanicals' safety, herb-drug interaction potential of the hydroethanolic extracts of five *Glycyrrhiza* species and their key constituents was investigated by determining their effects on pregnane X receptor, aryl hydrocarbon receptor, two major cytochrome P450 isoforms (CYP3A4 and CYP1A2), and the metabolic clearance of antiviral drugs. All extracts enhanced transcriptional activity of PXR and AhR (>2-fold) and increased the enzyme activity of CYP3A4 and CYP1A2. The highest increase in CYP3A4 was seen with *G. echinata* (4-fold), and the highest increase in CYP1A2 was seen with *G. uralensis* (18-fold) and *G. inflata* (16-fold). Among the constituents, glabridin, licoisoflavone A, glyasperin C, and glycycoumarin activated PXR and AhR, glabridin being the most effective (6- and 27-fold increase, respectively). Licoisoflavone A, glyasperin C, and glycycoumarin increased CYP3A4 activity while glabridin, glyasperin C, glycycoumarin, and formononetin increased CYP1A2 activity (>2-fold). The metabolism of antiretroviral drugs (rilpivirine and dolutegravir) was increased by *G. uralensis* (2.0 and 2.5-fold) and its marker compound glycycoumarin (2.3 and 1.6-fold). The metabolism of dolutegravir was also increased by *G. glabra* (2.8-fold) but not by its marker compound, glabridin. These results suggest that licorice and its phytochemicals could affect the metabolism and clearance of certain drugs that are substrates of CYP3A4 and CYP1A2.Supplemental data for this article is available online at https://doi.org/10.1080/19390211.2022.2050875.

DOI: 10.1080/19390211.2022.2050875
PMID: 35302913

12. Drug Interactions and Safe Prescription Writing for Liver Transplant Recipients. Mathew JS, Philips CA.

J Clin Exp Hepatol. 2023 Sep-Oct;13(5):869-877. doi: 10.1016/j.jceh.2023.03.011. Epub 2023 Apr 1.

Immunosuppression optimization is central to graft function in liver transplant recipients. Post-transplantation patients develop new onset or worsening metabolic syndrome, are prone to atypical infections, and are at higher risk of developing cardiac and brain-related clinical events. In this context, liver transplant recipients are at risk of using multiple comedications alongside immunosuppressants. It is imperative for the transplant physician to understand the various drug-drug interactions that potentially reduce or promote toxicity of immunosuppression, as well as associated synergistic or antagonistic effects on extrahepatic organ systems. This comprehensive review discusses drug-drug interactions in liver transplant recipients and the impact and role of complementary and alternative medicines among individuals on immunosuppression.

DOI: 10.1016/j.jceh.2023.03.011
PMCID: PMC10483006
PMID: 37693257

13. Weight Loss Supplements. Dini I, Mancusi A.

Molecules. 2023 Jul 12;28(14):5357. doi: 10.3390/molecules28145357.

Being overweight or obese can predispose people to chronic diseases and metabolic disorders such as cardiovascular illnesses, diabetes, Alzheimer's disease, and cancer, which are costly public health problems and leading causes of mortality worldwide. Many people hope to solve this problem by using food supplements, as they can be self-prescribed, contain molecules of natural origin considered to be incapable of causing damage to health, and the only sacrifice they require is economic. The market offers supplements containing food plant-derived molecules (e.g., primary and secondary metabolites, vitamins, and fibers), microbes (probiotics), and microbial-derived fractions (postbiotics). They can control lipid and carbohydrate metabolism, reduce appetite (interacting with the central nervous system) and adipogenesis, influence intestinal microbiota activity, and increase energy expenditure. Unfortunately, the copious choice of products and different legislation on food supplements worldwide can confuse consumers. This review summarizes the activity and toxicity of dietary supplements for weight control to clarify their potentiality and adverse reactions. A lack of research regarding commercially available supplements has been noted. Supplements containing postbiotic moieties are of particular interest. They are easier to store and transport and are safe even for people with a deficient immune system.

DOI: 10.3390/molecules28145357
PMCID: PMC10384751
PMID: 37513229 [Indexed for MEDLINE]

14. Ephedrae Herba: A Review of Its Phytochemistry, Pharmacology, Clinical Application, and Alkaloid Toxicity. Tang, S.; Ren, J.; Kong, L.; Yan, G.; Liu, C.; Han, Y.; Sun, H.; Wang, X.-J.

Molecules 2023, 28, 663. https://doi.org/10.3390/molecules28020663

Ephedrae Herba (*Ephedra*), known as “MaHuang” in China, is the dried straw stem that is associated with the lung and urinary bladder meridians. At present, more than 60 species of *Ephedra* plants have been identified, which contain more than 100 compounds, including alkaloids, flavonoids, tannins, sugars, and organic phenolic acids. This herb has long been used to treat asthma, liver disease, skin disease, and other diseases, and has shown unique efficacy in the treatment of COVID-19 infection. Because alkaloids are the main components causing toxicity, the safety of *Ephedra* must be considered. However, the nonalkaloid components of *Ephedra* can be effectively used to replace ephedrine extracts to treat some diseases, and reasonable use can ensure the safety of *Ephedra*. We reviewed the phytochemistry, pharmacology, clinical application, and alkaloid toxicity of *Ephedra*, and describe prospects for its future development to facilitate the development of *Ephedra*.

doi: 10.3390/molecules28020663
PMID: 36677722
PMCID: PMC9863261

15. Alpha Lipoic Acid Toxicity: The First Reported Mortality in an Adult Patient After Multiorgan Failure. Halabi Z, El Helou C, Al Balushi H, Gittinger M, Steck AR, Kaakour A, Abu-Alfa A, El Zahran T.

J Emerg Med. 2023 Feb;64(2):190-194. doi: 10.1016/j.jemermed.2022.12.016. Epub 2023 Feb 18.

BACKGROUND: Alpha lipoic acid (ALA) is an anti-oxidant found in many over-the-counter supplements and is used in treatments for diabetes, hypertension, and obesity. Although it is a safe oral molecule, there have been eight cases of ALA toxicity reported. Three reported cases were among adult patients and five were among pediatric patients. A 14-year-old girl died after ingestion of 6 g of ALA leading to multi-organ failure. CASE REPORT: A 42-year-old woman presented to the emergency department 4 h after an intentional overdose of 10 tablets of ALA 600 mg each (6 g, 92.3 mg/kg). She developed refractory seizures, metabolic acidosis, thrombocytopenia, rhabdomyolysis, depressed cardiac contractility, kidney injury, and supraventricular tachycardia. Her condition deteriorated and she developed multi-organ failure. The patient was started on dual pressors, anti-epileptic medications, high-dose insulin and euglycemia protocol, and methylene blue (1 mg/kg). Despite aggressive resuscitation, she required intubation and died. WHY SHOULD AN EMERGENCY PHYSICIAN BE AWARE OF THIS?: This was the ninth case and the first reported adult mortality from ALA toxicity with multi-organ failure. Our case shared some similar findings with previously reported cases, including refractory seizures, metabolic acidosis, thrombocytopenia, and rhabdomyolysis. Refractory supraventricular tachycardia and severe agitation have not been reported with ALA toxicity previously. The range of toxicity of ALA is not well established. A reported dose of 6 g caused death in a pediatric patient as well as our patient, but others survived doses of 6 g and 18 g. Toxicologists and emergency physicians should be prepared for clinical deterioration and consider aggressive resuscitation in severe ALA toxicity.

DOI: 10.1016/j.jemermed.2022.12.016
PMID: 36806430 [Indexed for MEDLINE]

16. A case of fatal overdose involving both hydromorphone and kratom. Shi T, Shea JL.

J Forensic Sci. 2023 Sep 27. doi: 10.1111/1556-4029.15394. Online ahead of print.

Kratom is a plant originating in Southeast Asia that has been used for its dose-dependent stimulant and opioid effects. The main active compound in kratom is mitragynine, an alkaloid with affinity for the mu-opioid receptor. Toxicity and fatalities related to kratom use have increased substantially in recent years. In this case report, we describe a 44-year-old man who was found deceased in bed. The only significant finding at autopsy was abdominal distension with >4 L of ascites. Toxicology testing was performed on femoral blood which showed 79 ng/mL of hydromorphone, 560 ng/mL of mitragynine, and 240 ng/mL of olanzapine. In addition, creatinine and urea in vitreous humor were significantly elevated, consistent with renal impairment. Death was attributed to hydromorphone toxicity with mitragynine being a contributing factor.

DOI: 10.1111/1556-4029.15394
PMID: 37753815

17. A Case of Pseudo-Hematochezia from Beet Supplement Ingestion. Oscherwitz M, Tamayo RM, Heudebert A, Centor R.

Am J Med. 2023 Sep;136(9):e177-e178. doi: 10.1016/j.amjmed.2023.04.017. Epub 2023 May 5.

Pseudo-hematochezia is frequently described in pediatrics but is more rarely seen in the adult population, typically in the setting of significant ingestion of offending dietary ingredients (often beets). Here we describe a case of pseudo-hematochezia in the setting of beet supplement ingestion, adding a new facet to the complete history of hematochezia.

DOI: 10.1016/j.amjmed.2023.04.017
PMID: 37150494 [Indexed for MEDLINE]

18. Trends in the incidence of urothelial carcinoma in Taiwan after the ban on aristolochic acid-containing Chinese herbal preparations, 2001-2018: a national population-based cohort study. Liao CI, Fang HC, Lee PT, Hsu CY, Chen CL, Huang CW, Chen XY, Ou SH, Tsai CT, Chou KJ.

J Cancer Res Clin Oncol. 2023 Sep;149(11):8201-8211. doi: 10.1007/s00432-023-04771-6. Epub 2023 Apr 15.

PURPOSE: Urothelial carcinoma (UC) of the bladder (BUC) and the upper urinary tract (UTUC) are the two most common UCs. The incidence of UTUC in Taiwan is the highest worldwide. Aristolochic acid (AA) was identified as the main cause of UTUC in Taiwan. To explore trends in the incidence of UC in Taiwan after the ban on Chinese herbal preparations containing AA in 2003. METHODS: We used data from the Taiwanese National Health Insurance Research Database-linked Taiwanese National Cancer Registry for 2001-2018. UC was defined in accordance with the International Classification of Disease for Oncology. The age-standardized incidence was calculated on the basis of the World Health Organization standard population. Trends in the incidence were calculated as the annual percent change (APC) by using the Joinpoint regression program. RESULTS: Over the investigated period, the incidence of UC decreased at an average annual percent change (AAPC) of - 1.19% (95% CI - 1.47 ~ - 0.91, P < 0.001). However, the incidence in UTUC significantly increased, with the AAPC being 1.47% (95% CI 1.03 ~ 1.90, P < 0.001). In contrast, the incidence of BUC significantly decreased, with the overall AAPC being - 1.92% (95% CI - 2.3 ~ - 1.54, P < 0. 001). From 2001 to 2018, the overall incidence of UCs and BUC decreased in Taiwan, but the incidence of UTUC significantly increased. CONCLUSION: We suggest to apply the same review standards of new drug development process to herbal preparations and incorporate them into the adverse drug reaction or poison surveillance system. Most importantly, raise public awareness of the potential toxicity of phytotherapy.

DOI: 10.1007/s00432-023-04771-6
PMID: 37061628 [Indexed for MEDLINE]

19. Cannabidiol safety considerations: Development of a potential acceptable daily intake value and recommended upper intake limits for dietary supplement use. Henderson RG, Vincent M, Rivera BN, Bonn-Miller MO, Doepker C.

Regul Toxicol Pharmacol. 2023 Aug 25:105482. doi: 10.1016/j.yrtph.2023.105482. Online ahead of print.

Consumer use of hemp-derived products continues to rise, underscoring the need to establish evidence-based safety guidance. The present study sought to develop recommendations for oral upper intake limits of cannabidiol (CBD) isolate. Sufficiently robust and reliable data for this purpose were identified from published human clinical trials and guideline-compliant toxicity studies in animal models. Based on the metrics used in this assessment, a potential Acceptable Daily Intake (ADI) value of 0.43 mg/kg-bw/d (e.g., 30 mg/d for 70-kg adult) was determined for the general population based on liver effects in human studies. This value applies to the most sensitive subpopulations, including children, over a lifetime of exposure and from all sources, including food. For dietary supplements with adequate product labeling intended for use by healthy adults only, a potential Upper Intake Limit (UL) of 70 mg/d was determined based on reproductive effects in animals. For healthy adults, except those trying to conceive, or currently pregnant or lactating, a conservative dietary supplement UL of 100 mg/d was identified based on liver effects; however, as the target population excludes individuals at risk for liver injury, an alternative dietary supplement UL of 160 mg/d for this population can also be considered.

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20. Plant identification applications do not reliably identify toxic and edible plants in the American Midwest. Long K, Townesmith A, Overmiller A, Applequist W, Scalzo A, Buchanan P, Bitter CC.

Clin Toxicol (Phila). 2023 Jul;61(7):524-528. doi: 10.1080/15563650.2023.2237282.

INTRODUCTION: Exposure to potentially toxic plants is a global problem, resulting in thousands of calls to poison centers and emergency department visits annually and occasional deaths. Persons with limited botanical knowledge may be tempted to rely on smartphone applications to determine if plants are safe to forage. This study evaluated the reliability of several popular smartphone applications to identify foraged foods and distinguish them from potentially toxic plants in the Midwestern United States. METHODS: Sixteen plant species were selected based on local availability, attractiveness as foraged food, and potential for misidentification. Of the 16 species, five are edible, three are potentially toxic if improperly harvested or prepared, and eight are considered to be toxic. Plant specimens were identified by graduate-level botanists and photographed during multiple stages of their growth cycles. LeafSnap, PictureThis, Pl@ntNet and PlantSnap were used to identify the plants. RESULTS: Overall accuracy of the applications in identifying

plant genus was 76% (95% confidence interval: 73-79, range 96% for PictureThis to 53% for PlantSnap). Accuracy for identification of plant species was 58% (95% confidence interval 55-62%, range 94% for PictureThis to 34% for PlantSnap). Five of eleven potentially toxic species were identified as an edible species by at least one application. CONCLUSION: Accuracy of the smartphone applications varies, with PictureThis outperforming other apps. At this time, apps cannot be used to safely identify edible plants. Foragers must have adequate botanical knowledge to ensure safe harvesting of wild plants.

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21. Pharmacopeial Standards for the Quality Control of Botanical Dietary Supplements in the United States. Sarma N, Upton R, Rose U, et al.

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Botanicals are among the fastest growing segments of the dietary supplement industry in the U.S. The Dietary Supplement Health and Education Act (DSHEA; Public Law 103-417 [Oct. 25, 1994]) provided a regulatory classification for the trade of numerous botanicals and botanically-derived products as dietary supplements. The global supply chain, the adoption of many botanicals that are also recognized as traditional medicines around the world as dietary supplement ingredients, and the differing recognition of the national and international pharmacopeias as sources for voluntary or mandatory quality standards present challenges in ensuring the quality of the ingredients and products. The complexity of quality assurance by compliance with pharmacopeial standards is illustrated in this article with a brief history of pharmacopoeias including their official recognition in national laws, their approaches to the science behind the standards, the use of reference standards for quality assessment and regulatory compliance, the use of pharmacopeial standards by the industry and regulators within the DSHEA framework in the United States, and a discussion of the global supply chain. Pharmacopeial standards can help regulators and the industry adapt to the new technologies that present both opportunities and challenges.

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