AACT Herbal Dietary Supplement Section Abstracts

September 2024

1. **Elemental impurities (heavy metals) in kratom products: an assessment of published individual product analyses. Caroti KS, Joseph A, Sapowadia A, White CM**

Clinical Toxicology, 2024. https://doi.org/10.1080/15563650.2024.2395552

Introduction Kratom is commonly used by consumers, and the elemental impurity exposure that consumers would have at different kratom ingestion doses has been determined.
Methods: This assessment used original data from independent third-party laboratory testing of kratom products to identify the percentage of products that exceeded permissible daily exposure limits for lead (5 µg/day), nickel (200 µg/day), arsenic (15 µg/day), and cadmium (5 µg/day), the interim reference level for lead in adults (12.5 µg/day), and the tolerable upper intake level for manganese (11 mg/day) and nickel (1 mg/day). We assessed all products regardless of type and then evaluated non-extract products, extract products, and a soda preparation separately for elemental impurities.
Results Three assessments of elemental impurities in kratom products have been published, totaling 68 products. Assessing all products and assuming a 3 g daily dose of kratom, 7.4% would exceed the permissible daily exposure limits for lead, 0% for nickel, 3.1% for arsenic, and 0% for cadmium. At a kratom dose of 25 g daily, 70.6% would exceed the permissible daily exposure limits for lead, 20.6% for nickel, 9.4% for arsenic, and 0% for cadmium. The interim reference level for lead would be exceeded by 1.5% of products at a kratom daily dose of 3 g and 33.8% of products at 25 g. The tolerable upper intake level for manganese would be exceeded by 12.5% of products at a kratom daily dose of 3 g and 41.7% of products at 25 g. Non-extract products generally contain greater concentrations of elemental impurities than extract products or the soda preparation.
Discussion Apart from their concentrations in a gram of product, assessing the amount of exposure to elemental impurities at different kratom ingestion doses is also important. Elemental impurities exceeding regulatory permissible concentrations for many products, especially with greater daily kratom ingestion doses, may impact human health.
Conclusions Some kratom products contain excessive concentrations of elemental impurities of toxicological concern, such as lead and arsenic. Non-extract products (powders, capsules, tablets) generally contain greater concentrations of elemental impurities than extract products or the soda preparation. Daily use of these products can result in exposures exceeding regulatory thresholds and adverse health effects.

DOI https://doi.org/10.1080/15563650.2024.2395552

2. **Kratom regulatory trends and poison control calls with serious outcomes: a national analysis.** Comstock G, Gulotta A, Rein L, Brazauskas R, Feldman R.

   Clinical Toxicology, 62 (sup2):1-174 [NACCT 2024, abstract 22)

   Background: Kratom is a plant from Southeast Asia (Mitragyna speciosa) containing the psychoactive compounds mitragynine and 7-hydroxymitragynine. It is currently widely available in many U.S. states and reported uses of kratom include treatment of pain, anxiety, and depression. As use within the U.S. rises, adverse effects from use have been reported, including seizure, withdrawal, respiratory depression, and death. Currently kratom is not federally scheduled and regulation is determined by individual states. State level kratom policies range from complete ban to heterogeneous regulatory bundles termed Kratom Consumer Protection Acts (KCPA) to full unrestricted access. The impact of these policies on public health is unknown. The intent of this study is to compare kratom exposures reported to poison centers (PC) between states with differing regulatory statuses. Methods: This was a retrospective cohort study of kratom expo-sures reported to National Poison Data System (NPDS) from 2010to 2023. Both single and multiple substance exposures were included. The number of annual exposures per state was modeled using Poisson regression. The model included year and the state's kratom regulatory status as predictor variables. States were grouped by their kratom regulatory status separately foreach year into the following five categories: unrestricted, KCPA, age restricted, KCPA and age restricted, or fully banned. The model used an offset term for the log of the state population to control for population size within each group. Exposures from states in which kratom is regulated at local or county levels were excluded. Primary outcome was rates of kratom exposures reported to PCs, and secondary outcomes were rates of patients evaluated in healthcare facility, hospitalizations, and serious medical outcomes defined as cases coded as moderate and major effects and deaths, per America's Poison Center coding definitions. Event rate comparisons between regulatory categories are presented as incidence rate ratios (IRR) over the study period of 2010–2023. Results: A total of 8,933 exposures were reported during the study period, including 3,284 (37%) healthcare evaluations, 1,185(13%) hospitalizations, and 4,389 (49%) serious outcomes. States with "fully banned" regulatory status had fewer exposures, healthcare evaluations, hospital admissions, and serious medical outcomes when compared to states with any other regulatory status ($p < 0.001$). Pairwise comparisons of IRR for the restricted regulatory status with the KCPA, age restricted, and KCPA with age restriction showed no difference in per population exposure rate, exposure healthcare assessment rate, exposure hospitalization rate ($p > 0.05$).Conclusions: In this study, which assessed rates of exposure by state regulatory status, a full kratom ban is associated with reduced exposures, healthcare utilization, hospital admissions, and serious medical outcomes. No other regulation (KCPA, age restriction, or both) appeared to reduce rates of negative out-comes. The lack of federal regulation and heterogeneous legislation at the state level creates a complex public health issue. Further research is needed to understand the long-term effects of kratom and develop a comprehensive regulatory framework.

   DOI:10.1080/15563650.2024.2370671

3. **Increasing incidence of kratom-associated series adverse effects in medical toxicology patients.** Weiss S, Culbreth R, Falise A, Aldy K, Smith K, Wax P, Campleman S, Brent J.

Clinical Toxicology, 62 (sup2):1-174 [NACCT 2024, abstract 31)

Background: “Kratom” refers to preparations derived from the Southeast Asian tree Mitragyna speciosa, which contains dozens of psychoactive alkaloids. Kratom has been reported to have both opioid-like and stimulant effects. While most kratom use is not associated with serious adverse effects, cases of kratom-associated toxicity and death have been anecdotally reported to poison centers and in published case reports. To date, there has been no prospective systematic data collection on serious adverse effects associated with kratom use. Methods: This is a prospective, descriptive registry sub analysis that included all single-agent or multiple-agent kratom-related cases seen by attending medical toxicologists and reported to the Toxicology Investigators Consortium (ToxIC) Core Registry from 1 January 2013 through 31 December 2023. Clinical and patient information was recorded using uniform a priori data col-lection fields entered into a secure REDCap database. These included patient demographic characteristics, reason for kratom exposure, clinical presentation, and case outcome. No hypothesis testing was undertaken, but the increase in entered kratom cases from 2013 to 2023 was analyzed using linear regression. Because all ToxIC Core Registry cases required a medical toxicology consultation or admission to a medical toxicology service, all were classified as serious exposures. Results: Eighty-nine cases met our inclusion criteria, of which 75were from the United States and 14 were from Thailand. There has been a significant time-trend of increasing kratom cases entered into the ToxIC Core Registry yearly since 2013 (b ¼ 1.16,SE ¼0.26, $p < 0.01$). Most patients were non-Hispanic White, adults (18), and males. Most cases involved other substances in addition to kratom. Tachycardia was the most common vital sign abnormality, occurring in 15.7% of patients. However, the most common adverse effects were neurological, occurring in 85.4% of the cases. These were primarily agitation (31.5%), central nervous system depression (27.0%), delirium/toxic psychosis (19.1%), hallucinations (14.6%), and seizures (12.4%). Other significant findings included 24.7% of patients with cardiovascular effects and16.9% of patients with respiratory depression. Notably, only 5.6%of the kratom cases entered in the ToxIC Core Registry presented with an opioid toxidrome. Patient outcomes were mostly good, with 88 patients surviving and one death. Conclusions: Reports of serious adverse effects associated with kratom use in patients cared for by a medical toxicologist increased over the eleven-year period of this study. This trend likely parallels the overall increase in kratom use by the general population over this same time period, as well as increasing patient and clinician awareness of kratom and the possible toxicities associated with its use. Consistent with the known psychoactive effects of kratom alkaloids and previously reported clinical observations, the most common serious adverse effects were neurological, and tachycardia was the most commonly reported cardiovascular effect. However, despite the strong mu opioid receptor agonism of the kratom alkaloid metabolite 7-hyroxymitragynine, an opioid toxidrome was uncommon in this patient population

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4. **Beneficial and adverse health effects of kratom (Mitragyna speciosa): A critical review of the literature**. Heywood J, Smallets S, Paustenbach D.

   Food Chem Toxicol. 2024 Oct;192:114913. doi: 10.1016/j.fct.2024.114913. Epub 2024 Aug 0.

   Used in Southeast Asia for generations, kratom gained popularity in the United States and elsewhere over the past several decades. Derived from Mitragyna speciosa, kratom preparations including leaves, teas, powders, capsules, and extracts may yield stimulant, analgesic, and opioid-like effects that occur dose-dependently based on concentrations of kratom's key alkaloids, mitragynine and 7-hydroxymitragynine. Such effects are responsible for kratom's potential as a reduced-harm alternative to opiates and as a withdrawal treatment. But these properties are also associated with tolerance development and addictive potential. Given mitragynine and 7-hydroxymitragynine activity on cytochrome P450 isoforms and opioid receptors, adverse effects among polysubstance users are a concern. Current literature on the toxicology of kratom is reviewed, including product alkaloid concentrations, in vitro and in vivo data, epidemiological evidence, and human case data. The potential harms and benefits of kratom products are discussed within an exposure assessment framework, and recommendations for industry are presented. Current evidence indicates that kratom may have therapeutic potential in some persons and that products present few risks with typical, non-polysubstance use. However, few studies identified alkaloid doses at which adverse effects were expected in humans or animals. Such research is needed to inform future assessments of kratom's risks and benefits.

   DOI: 10.1016/j.fct.2024.114913
   PMID: 39134135 [Indexed for MEDLINE]

5. **Critical tachyarrhythmia related to berberine use.** Mesmin M, Tweet M, Fulks T.

   Clinical Toxicology, 62 (sup2):1-174 [NACCT 2024, abstract 31)

   Background: This report explores the case of a 92-year-old male patient who developed recurrent critical tachyarrhythmia after adding berberine supplements to his medication regimen to better manage his diabetes. Case Report: Patients have long explored the integration of herbal supplements into their medication regimen and this practice is rising in popularity. Berberine is a plant-based alkaloid that has been suggested to help manage diabetes by improving insulin sensitivity among other anti-hyperglycemic mechanisms. Our patient had a history of type 2 diabetes mellitus and hypertension for which he takes lisinopril. He added berberine to his regimen for improved glucose control in addition to metformin. He presented to our emergency department with chief complaints of tremors, urinary incontinence, and brief episodes of unresponsiveness approximately 2 weeks after starting berberine. In the emergency department the patient had multiple episodes of polymorphic ventricular tachycardia with pulselessness requiring immediate defibrillation with a rapid return to baseline between episodes. Amiodarone and lidocaine were started; however, despite this, he continued to have persistent episodes. Finally, the episodes resolved after starting isoproterenol in the ICU. The patient’s workup was notable for QTc prolongation (QTc 616ms [normal male QTc <430ms]). His cardiac workup was otherwise normal, including a normal ejection fraction on echocardiogram. Withholding berberine and supportive management

resulted in an improved QTc. After three days, the QTc was 454ms. The patient had a short inpatient admission and was discharged without any further episodes. Discussion: Berberine has been shown to cause bradycardia and prolong the QTc interval. Cardiology suspected the patient's episodes of polymorphic ventricular tachycardia were attributed to the R-on-T phenomenon secondary to bradycardia and prolonged QTc interval. This case is an example of the combination of bradycardia and QTc prolongation inducing a high-risk arrhythmogenic state contrary to the purported theory that berberine has antiarrhythmic effects. Conclusion: More studies will be helpful to better characterize risks and benefits of berberine use due to its multiple drug interactions and varied physiologic effects to form best practice recommendations regarding its use.

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6. **Alpha lipoic acid: a not so jolly green giant mystery.** Moore E, Edelen K, Epperson L, Banner W.

Clinical Toxicology, 62 (sup2):1-174 [NACCT 2024, abstract 31)

Background: Alpha-lipoic acid (ALA) is a naturally occurring necessary fatty acid and common ingredient in many over-the-counter (OTC) dietary supplements. ALA is crucial for mitochondrial function through the pyruvate dehydrogenase enzyme complex and the regeneration of endogenous antioxidants such as vitamins A and C, and glutathione. Despite gaining attention in recent years for its antioxidant, antidiabetic, anti-inflammatory, and antiaging effects, there is a paucity of human data documenting ALA toxicity with only nine other published cases found. We present a pediatric case with initially unrecognized alpha-lipoic acid toxicity resulting in metabolic acidosis, seizure-like activity, and asystole. Case report: An 11-year-old female presented to the Emergency Department 7 hours after reported ingestion of five unknown strength OTC acetaminophen (APAP) tablets and an unknown liquid substance. The patient was somnolent, hypokalemic, had neon green vomitus, and a high anion gap (AG) metabolic acidosis (venous pH of 7.13, HCO3 of 15 mEq/L, AG of 19 mEq/L, osmolar gap of 5.29 mOsmol/L); although the family reported having only orange antifreeze in the home, the patient was initially worked up for toxic alcohol ingestion and given a dose of fomepizole. APAP toxicity and diabetic ketoacidosis were ruled out, and the patient, becoming increasingly acidotic (venous pH of 6.9, HCO3 of 10 mEq/L, AG of 20 mEq/L, osmolar gap of −0.12mOsmol/L, lactate 3.6 mmol/L) and developing seizure-like activity, was admitted to the pediatric intensive care unit and fomepizole was continued. Within 24 hours of initial presentation, the patient was intubated and sedated and had three episodes of bradycardia and asystole responsive to epinephrine. Other notable clinical effects observed in this patient were hyperglycemia(333 mg/dL) and rhabdomyolysis (peak creatinine kinase of 3527units/L). After extubation 28 hours later, the patient's acidosis was improving (lactate 0.48 mmol/L) and she admitted to taking an unknown amount of Nervive, a green dietary supplement containing 600 mg ALA, 1.2 mg thiamine, 1.7 mg pyridoxine,2.4 mg cyanocobalamin, 27 mg calcium, turmeric, and ginger. The patient was clinically stable and back to baseline six days after presentation. Discussion: Clinical effects reported after large ingestions of ALA include vomiting, tachycardia, agitation, metabolic acidosis, coma, seizures, rhabdomyolysis, thrombocytopenia, disseminated intravascular coagulation, elevated hepatic enzymes, multi-organ failure and death. In this case, our patient presented with rapid onset of unusual neon

green-colored vomitus and a high AG metabolic acidosis and later developed asystole. Several well-established causes of acidosis were ruled out and the true toxin was not readily apparent until the patient admitted to it. Conclusions: While several clinical trials demonstrated that moderate doses of ALA (up to 2400 mg/day in adults) were well-tolerated, this case contributes to the growing literature reporting significant toxicity following ALA overdose. Given its increasing popularity and accessibility, clinicians should include ALA intoxication in their differential for patients with acidosis, seizures, and multi-organ failure of unknown origin and be prepared for rapid deterioration of these patients. Further research is necessary to establish a toxic dose in both adult and pediatric patients

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7. **Vitamin A-containing dietary supplements from German and US online pharmacies: market and risk assessment**. Rathmann AM, Seifert R.

Naunyn Schmiedebergs Arch Pharmacol. 2024 Sep;397(9):6803-6820. doi: 10.1007/s00210-024-03050-6. Epub 2024 Mar 28.

Vitamin A supplements are used by many people, and the number of newly registered dietary supplements is continuously increasing. The preparations fall under food law and are not subject to the strict controls of pharmaceuticals. Risk indications and maximum quantity recommendations, e.g., from the Bundesinstitut für Risikobewertung (BfR) and the U.S. Food and Drug Administration (FDA) are not binding, which means that overdoses and potentially serious health problems can easily occur. The hepatotoxicity and teratogenicity of vitamin A are well documented, and other negative effects of high doses of vitamin A are also being discussed. Nevertheless, preparations with exorbitantly high doses are freely available for sale and unrestricted. In this study, 75 supplements containing vitamin A available in Germany and 26 available in the USA were critically examined on the basis of various parameters such as the recommended daily dose according to the manufacturer, daily therapy costs (DTC), the presence of warnings about overdose, use during pregnancy and breastfeeding, and information on adverse effects/interactions. The aim was to gain insights into their risk potential and to examine the need for closer monitoring and stricter guidelines for these preparations. The results show some considerable country-specific differences. Overall, there are serious deficiencies in compliance with the labeling requirements for both the German and the US preparations, and the dosages are often far too high in view of the applicable expert recommendations. Overall, these deficits can pose a risk for consumers that is difficult to assess in its entirety, especially for vulnerable consumer groups. It should be noted that the US preparations perform better overall than the German preparations. This suggests better regulation of dietary supplements in the US market. Based on the available data and literature research, it is doubtful whether the intake of vitamin A-containing preparations, without a diagnosed vitamin A deficiency, has a positive health benefit. Furthermore, it should be examined whether vitamin A should continue to be offered over-the-counter as a food supplement.

DOI: 10.1007/s00210-024-03050-6
PMID: 38546747

8. **Acute Liver Failure Induced by Provitalize: A Menopause Supplement Concocted From Herbs & Probiotics.** Patel R, Hassan A, Scanlan H, Everwine M, Ren Z, Snyder C, ElGenaidi H.

   ACG Case Rep J. 2024 Sep 20;11(9):e01509. doi: 10.14309/crj.0000000000001509. eCollection 2024 Sep.

   Drug-induced liver injury is one of the most common causes of acute liver failure in the Western world. Despite discontinuation of the offending agent, it can still tax a grim prognosis. We describe a case of a menopausal woman taking a herbal supplement called "Provitalize" to relieve hot flashes and bloating. This is the first case report of liver injury from this supplement. She initially presented with mild jaundice and elevated transaminases. Unfortunately, she rapidly progressed to encephalopathy, experienced multiorgan failure, and then died.

   DOI: 10.14309/crj.0000000000001509
   PMCID: PMC11415125
   PMID: 39310049

9. **Berberine potentiates liver inflammation and fibrosis in the PI*Z hAAT transgenic murine model**. Lu Y, Mohammad NS, Lee J, Aranyos AM, Serban KA, Brantly ML.

   PLoS One. 2024 Sep 19;19(9):e0310524. doi: 10.1371/journal.pone.0310524. eCollection 2024.

   BACKGROUND: Alpha-1 antitrypsin deficiency (AATD) is an inherited disease, the common variant caused by a Pi*Z mutation in the SERPINA1 gene. Pi*Z AAT increases the risk of pulmonary emphysema and liver disease. Berberine (BBR) is a nature dietary supplement and herbal remedy. Emerging evidence revealed that BBR has remarkable liver-protective properties against various liver diseases. In the present study, we investigated the therapeutic effects and toxicities of BBR in Pi*Z hepatocytes and Pi*Z transgenic mice. METHODS: Huh7.5 and Huh7.5Z (which carries the Pi*Z mutation) cells were treated with different concentrations of BBR for 48 hours. MTT was performed for cell viability assay. Intracellular AAT levels were evaluated by western blot. In vivo studies were carried out in wild type, native phenotype AAT (Pi*M), and Pi*Z AAT transgenic mice. Mice were treated with 50 mg/kg/day of BBR or solvent only by oral administration for 30 days. Western blot and liver histopathological examinations were performed to evaluate therapeutic benefits and liver toxicity of BBR. RESULTS: BBR reduced intracellular AAT levels in Huh7.5Z cells, meanwhile, no Pi*Z-specific toxicity was observed. However, BBR did not reduce liver AAT load but significantly potentiated liver inflammation and fibrosis accompanying the activation of unfolded protein response and mTOR in Pi*Z mice, but not in wild type and Pi*M mice. CONCLUSIONS: BBR exacerbated liver inflammation and fibrosis specifically in Pi*Z mice. This adverse effect may be associated with the activation of unfolded protein response and mTOR. This study implicates that BBR should be avoided by AATD patients.

   DOI: 10.1371/journal.pone.0310524
   PMCID: PMC11412680

10. **Pirfenidone-induced liver injury, a case report of a rare idiosyncratic reaction**. Fortunati F, Froidure A, Baldin P, Horsmans Y, Lanthier N, Dahlqvist G, Delire B.

    Ther Adv Drug Safety. 2024 Sep 14;15:20420986241270866.
    doi: 10.1177/20420986241270866. eCollection 2024.

    Nearly all medications carry the risk of drug-induced liver injury (DILI). Idiosyncratic reactions are rare and poorly predictable, and the mechanisms are not always well understood. Pirfenidone is an oral antifibrotic drug used to treat idiopathic pulmonary fibrosis. While elevation of liver enzymes is a common adverse reaction during therapy, it rarely leads to discontinuation or reduction of the drug. Although isolated cases of liver damage or liver failure have been reported, they are infrequent. This report presents the case of a 70-year-old woman with known idiopathic pulmonary fibrosis, depression, hypothyroidism, and hypercholesterolemia who presented at our emergency department with jaundice, anorexia, and asthenia. The patient's medication regimen included lamotrigine, simvastatin, levothyroxine, and pirfenidone, which had been introduced 6 months prior. Laboratory testing revealed elevated liver enzyme levels consistent with acute hepatocellular hepatitis. Following a medical workup, which included anamnesis, laboratory testing, iconographic investigations, and liver biopsy, we concluded that the patient had suffered from pirfenidone-induced liver injury. Pirfenidone was withdrawn, and liver tests gradually improved. The purpose of this clinical case report is to highlight this rare adverse reaction and to make clinicians aware of its assessment and management. In 2018, only one other case of severe liver failure leading to the death of the patient was reported. Early detection of potential DILI during the workup is crucial to discontinue the suspected medication promptly. Any drug-induced hepatitis must be reported for registration.

    DOI: 10.1177/20420986241270866
    PMCID: PMC11403680
    PMID: 39286238

11. **Regular Consumption of Green Tea as an Element of Diet Therapy in Drug-Induced Liver Injury (DILI)**.Winiarska-Mieczan A, Jachimowicz-Rogowska K, Kwiecień M, Borsuk-Stanulewicz M, Tomczyk-Warunek A, Stamirowska-Krzaczek E, Purwin C, Stryjecka M, Tomaszewska M.

    Nutrients. 2024 Aug 24;16(17):2837. doi: 10.3390/nu16172837.

    The liver is a highly metabolically active organ, and one of the causes of its dysfunction is the damage caused by drugs and their metabolites as well as dietary supplements and herbal preparations. A common feature of such damage is drugs, which allows it to be defined as drug-induced liver injury (DILI). In this review, we analysed available research findings in the global literature regarding the effects of green tea and/or its phenolic compounds on liver function in the context of protective action during prolonged exposure to xenobiotics. We focused on the direct detoxifying action of epigallocatechin gallate (EGCG) in the liver, the impact of EGCG on gut microbiota, and the influence of microbiota on liver health. We used 127 scientific research publications published between 2014 and 2024. Improving the effectiveness of DILI detection is essential to enhance the safety of patients at risk of liver

damage and to develop methods for assessing the potential hepatotoxicity of a drug during the research phase. Often, drugs cannot be eliminated, but appropriate nutrition can strengthen the body and liver, which may mitigate adverse changes resulting from DILI. Polyphenols are promising owing to their strong antioxidant and anti-inflammatory properties as well as their prebiotic effects. Notably, EGCG is found in green tea. The results of the studies presented by various authors are very promising, although not without uncertainties. Therefore, future research should focus on elucidating the therapeutic and preventive mechanisms of polyphenols in the context of liver health through the functioning of gut microbiota affecting overall health, with particular emphasis on epigenetic pathways.

DOI: 10.3390/nu16172837
PMCID: PMC11396919
PMID: 39275155 [Indexed for MEDLINE]

12. **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 Sep 16:e243045. doi: 10.1001/jamapediatrics.2024.3045. Online ahead of print.

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 active 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 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
PMCID: PMC11406456
PMID: 39283619

13. **Herbal abortion: Non-toxic method, dangerous representation.** Dutton-Kenny M, Horner D.

    Am J Emerg Med. 2024 Sep 10:S0735-6757(24)00451-0. doi: 10.1016/j.ajem.2024.09.012. Online ahead of print.

    Letter: paragraph one:
    Since the Dobbs decision in 2022, there is a renewed interest in talking about herbal abortion, particularly in mainstream outlets. As herbalists and midwives who study, publish and practice utilizing herbal medicine in all phases of pregnancy, we bear witness with regularity how herbal medicine is tremendously helpful in our client's experience of their pregnancies, can be distorted in scientific literature, and then echoed through other information outlets. The article “Toxicities of herbal abortifacients” published in the American Journal of Emergency Medicine in March 2023 details three plants and their potential bodily toxicity when misused as herbal abortifacients. The article is aimed at emergency room physicians, asserting that the changing status of legal abortion may result in more emergency room visits due to herbal abortions and clinicians should understand treatment protocols. Unfortunately, this framework continues the legacy of herbal misrepresentation and demonstrates a lack of knowledge of how herbal medicine works by the medical establishment at large.
    DOI: 10.1016/j.ajem.2024.09.012
    PMID: 39271399

14. **A case of infant aristolochic acid nephropathy caused by Radix Aristolochiae.** Gao CL, Fang X, Yao J, Zhang XD, Shi KL, Fu MZ, Zhang P. Zhonghua Er Ke Za Zhi.

    2024 Sep 2;62(9):890-892. doi: 10.3760/cma.j.cn112140-20240405-00241.

    The patient was a 2-month-old boy who visited the Department of Pediatrics of Jinling Hospital Affiliated to Nanjing University Medical School because of "high serum creatinine for more than one month". The patient had a history of ingestion of the Chinese herbal medicine Aristolochic acid, and the renal pathology results showed acute tubulo-interstitial injury combined with mild chronic lesions, with exposed tubular basement membranes. The aristolochic acid A content of Aristolochic acid herbal medicine Aristolochic acid was determined by high-performance liquid chromatography to be 39.95 mg/g, and aristolochic acid nephropathy was diagnosed. Infant aristolochic acid nephropathy is mainly manifested by acute kidney injury, with a poor prognosis and requires long-term follow-up. (Abstract translation from Chinese.)

    DOI: 10.3760/cma.j.cn112140-20240405-00241
    PMID: 39192450 [Indexed for MEDLINE]

15. **Drug Interactions between Traditional Chinese Medicines and Cardiovascular Drugs.** Shen Q, Chen W, Wang W, Kang S, Du Y, Shi J, Yao L, Li W.

    Eur J Drug Metab Pharmacokinet. 2024 Sep;49(5):559-582. doi: 10.1007/s13318-024-00905-4. Epub 2024 Jul 15.

    Cardiovascular disease (CVD) is one of the leading causes of death worldwide, and its internal medicine treatments are mostly single/few-target chemical drugs. Long-term use of cardiovascular drugs for complex chronic diseases may lead to serious adverse drug reactions. Traditional Chinese medicine (TCM) has been used to treat heart diseases for thousands of years, helping to ease symptoms and prolong patients' lifespan in ancient China. TCM has the pharmacological characteristics of being multi-component, multi-target and multi-pathway, and the combined application of TCM and western medicine can be an alternative treatment for chronic and intractable diseases with high safety levels. This article reviewed the interactions and synergistic effect of TCM and cardiovascular drugs. In the treatment of arrhythmia, TCM combined with western medicine can more effectively regulate patients' cardiac electrophysiological characteristics, reduce the onsets of premature beat and heart rate variability, lower the levels of QT interval dispersion and serum inflammatory factors, alleviate clinical symptoms and TCM syndromes, and improve cardiac function with good safety levels. In the treatment of hypertension, integrative medicine can more steadily reduce blood pressure and levels of serum inflammatory factors and improve hemodynamic indexes and exercise tolerance, and it has high safety levels, especially for pregnant women. As for coronary heart disease, the combination of TCM and antiplatelet drugs may promote the absorption of each other. However, the interaction risk of pharmacokinetic mechanism between them is low at the dose of efficacy. Integrative medicine can reduce the level of N-terminal pro-brain natriuretic peptide, delay cardiac remodeling and improve heart function and quality of life for patients with heart failure with high safety levels.

    DOI: 10.1007/s13318-024-00905-4
    PMID: 39008006 [Indexed for MEDLINE]

16. **Mass aconite poisoning from a contaminated spice product**. Kent J, Sathya A, Juurlink D, Austin E, Thompson M, Pakes B, Gollob M

    Clinical Toxicology, 62 (sup2):1-174 [NACCT 2024, abstract 31)

    Background: Aconite (Aconitum spp.) contains aconitine, an alkaloid capable of causing profound toxicity due to its sodium channel opening properties. Aconite poisoning is uncommon, with most reported cases involving the improper processing of traditional Chinese medicine. We describe the first reported instance of a mass poisoning event in which aconite, mistaken for sand ginger, was added to a chicken dish at a local restaurant. Case series: Over an 8-hour period, 12 patients presented to two hospitals in Toronto, Ontario, with symptoms beginning shortly after consuming a chicken dish at an Asian restaurant. Initial symptoms included perioral paresthesias and gastrointestinal upset. In hospital, the spectrum of illness varied from volume contraction requiring only intravenous fluids to refractory ventricular dysrhythmias managed with infusions of sodium bicarbonate, amiodarone, and vasopressors. Two patients received mechanical ventilation for 48 hours. No patients died. Given the

similarity and acuity of the presentations, the local poison center was contacted for diagnostic clarification and management advice. The rapid onset of classic neurologic symptoms, in the absence of another causative agent, suggested possible aconite toxicity. Recommendations for support-vie care were given and consultation with Public Health authorities was suggested. Public health officials immediately began an investigation, visiting the restaurant, sampling the powder common to the dish eaten by those affected, and removing the suspected product from local retail outlets and the distribution facility. Over the following week, aconite contamination was confirmed based on testing of the product by the Canadian Food Inspection Agency and the clinical samples by the Centre of Forensic Sciences. No further cases were identified beyond this cluster. Discussion: The expanding global marketplace increases the opportunity for exposure to contaminated food items and health products. In this case, the restaurant purchased spices directly from Guangdong province, China, where aconite was mistakenly labeled as sand ginger. While aconite is used in traditional Chinese medicine, as little as one gram of unprocessed plant can be lethal, necessitating careful processing prior to consumption. After ingesting small amounts of unprocessed aconite present in the chicken dish, restaurant patrons developed symptoms suggestive of aconite toxicity. Those who reported consuming larger amounts experienced profound cardiotoxicity requiring intensive care admission. Involvement of the poison centre was critical, not only to facilitate identification and management of aconite poisoning, but also to serve as a link to public health for confirmatory testing and dissemination of accurate information to the public. Conclusions: This case series demonstrates the potential for mass poisoning through contaminated foodstuffs, and the critical role of poison centres for public health surveillance and response in such events. With the increasing availability of internationally sourced herb and spice products, such events are likely to recur, emphasizing the importance of educational initiatives focusing on multidisciplinary communication between emergency physicians, medical toxicologists and public health officials.

DOI:10.1080/15563650.2024.2370671

17. **Multiple Lactobacillus Infections Caused by Probiotics at Pediatric and Adult Academic Medical Centers.** Samuel AM, Lammers MG, Nachreiner J, Bogenschutz MC, Koffarnus K, Schulz L, Shadman KA, McBride JA.

WMJ. 2024 Sep;123(4):272-277.

BACKGROUND: Probiotics are synthetic oral supplements containing live bacterial and fungal species hypothesized to help with various gastrointestinal conditions. However, they can cause infection if the organism spreads outside of the gastrointestinal tract. The aim of this study was to identify and describe patients who experienced systemic infections caused by probiotic use. METHODS: This study was a retrospective chart review of pediatric and adult patients at academic medical centers who received probiotics and subsequently developed positive cultures from a sterile site for probiotic-related species. Two individuals completed the chart reviews to determine if the probiotic was the true cause of the infection. RESULTS: Lactobacillus, Bifidobacterium, and Saccharomyces cultures were reviewed, with a total of 71, 8, and 2 cultures isolated from sterile sites for each organism, respectively. Further review revealed 23 Lactobacillus cultures from 13 unique patients who were taking

Lactobacillus-containing probiotics. Four patients without gastrointestinal tract compromise were included in the final analysis, including 1 patient whose culture was confirmed as identical to the probiotic. Types of infections included meningitis and bacteremia. Targeted antimicrobial therapy included ampicillin, ampicillin-sulbactam, and piperacillin-tazobactam, with total durations of therapy ranging from 10 to 22 days. No patients had mortality attributed to Lactobacillus infection. CONCLUSIONS: Probiotics are not harmless supplements as they come with risk of serious infection as demonstrated in this review. Before use, the risks of probiotics should be considered carefully for each individual patient. Clinicians should consider avoiding probiotics in hospitalized patients, especially those with vascular or extra-ventricular access devices.

PMID: 39284085 [Indexed for MEDLINE]

18. **Acute manganese toxicosis related to joint health supplement ingestion in two dogs**. Jaffey JA, Chamberlin T, Hu J.

    Top Companion Anim Med. 2024 Jul-Aug;61:100877. doi: 10.1016/j.tcam.2024.100877. Epub 2024 May 23.

    Two unrelated dogs residing in the same house including an 11-year-old, female spayed, mixed breed dog and a 7-year-old, female spayed, mixed breed dog ingested approximately 75 capsules of a human joint health supplement (Ligaplex I; Standard Process, WI, USA). A total of 2,062 mg of manganese was ingested between both dogs. Dog 1 developed acute fulminant liver failure and a severe coagulopathy that led to hepatic fractures and exsanguination from hemoabdomen. The estimated maximum time from ingestion of the joint health supplement to death was 36 to 48 h. Histologic examination revealed severe periportal hepatic necrosis with mild evidence of preexisiting liver disease and renal tubular epithelial necrosis. Manganese concentrations in liver and kidney tissue were severely increased. Dog 2 developed a severe acute liver injury and was hospitalized for 6 days. Therapies provided during hospitalization included intravenous fluids, maropitant, pantoprazole, N-acetylcysteine, vitamin C, S-adenosylmethionine, and silybin. The dog was treated long-term with S-adenosylmethionine, silybin, ursodiol, and vitamin C. Clinical and biochemical resolution occurred on the recheck examination that took place on day 44. The veterinary literature is comprised of only 2 reports containing 3 dogs that describe acute manganese intoxication. Here, we provide a detailed description of 2 dogs that developed manganese-induced toxicosis after ingestion of a human joint health supplement.

    DOI: 10.1016/j.tcam.2024.100877
    PMID: 38788832 [Indexed for MEDLINE]

19. **Challenges in herbal-induced liver injury identification and prevention.** Halegoua-DeMarzio D, Navarro V.

    Liver Int. 2024 Aug 13. doi: 10.1111/liv.16071. Online ahead of print.

    Herbal and dietary supplements (HDS) are being used worldwide at an increasing rate. Mirroring this trend, HDS-induced liver injury, also known as HDS-induced liver injury (HILI), has increased significantly over the past three decades in the Drug-Induced Liver Injury Network (DILIN), now accounting for 20% of cases of drug-induced liver injury (DILI). There are significant challenges in the identification and prevention of HILI due to varying presentations, ability to make clear diagnosis, identification of the responsible ingredient, lack of treatment, and lack of regulatory oversight of HDS products to confirm their ingredients and ensure safety. The major implicated agents include anabolic steroids, green tea extract, garcinia cambogia, kratom, ashwagandha, turmeric and multi-ingredient nutritional supplements. Fortunately, with the formation of major DILI consortiums across the world, the last decade has seen advances in the identification of at-risk genetic phenotypes, the use of chemical analysis on multi-ingredient nutritional supplements, and the publication of data/injury patterns of potentially risky HDS.

    DOI: 10.1111/liv.16071
    PMID: 39136211

20. **Estimated Exposure to 6 Potentially Hepatotoxic Botanicals in US Adults**. Likhitsup A, Chen VL, Fontana RJ.
    JAMA Netw Open. 2024 Aug 1;7(8):e2425822. doi: 10.1001/jamanetworkopen.2024.25822.

    IMPORTANCE: Use of herbal and dietary supplements (HDSs) accounts for an increasing proportion of drug hepatotoxicity cases. Turmeric or curcumin, green tea extract, Garcinia cambogia, black cohosh, red yeast rice, and ashwagandha are the most frequently reported hepatoxic botanicals, but their prevalence and reasons for use in the general population are unknown. OBJECTIVE: To assess the prevalence and clinical characteristics of adult consumers of 6 potentially hepatoxic botanicals. DESIGN, SETTING, AND PARTICIPANTS: This survey study analyzed nationally representative data from the National Health and Nutrition Examination Survey (NHANES), a nationally representative, cross-sectional survey of the general US population. Prescription drug and HDS exposure data in the past 30 days were analyzed, and 2020 US Census data were used for population estimates. Data were analyzed July 1, 2023, to February 1, 2024. EXPOSURES: Adult NHANES participants enrolled between January 2017 and March 2020. MAIN OUTCOMES AND MEASURES: Baseline weighted characteristics of HDS users and users of 6 potentially hepatotoxic botanical products were compared with non-HDS users. Multivariable analysis was undertaken to identify factors associated with HDS use or at-risk botanical use. RESULTS: Among 9685 adults enrolled in this NHANES cohort, the mean (SE) age was 47.5 (0.5) years, and 51.8% (95% CI, 50.2%-53.4%) were female. The overall prevalence of HDS product use was 57.6% (95% CI, 55.9%-59.4%), while the prevalence of using the 6 botanicals of interest was 4.7% (95% CI, 3.9%-5.7%). Turmeric-containing botanicals were most commonly used (n = 236), followed by products containing green tea (n = 92), ashwagandha (n = 28), Garcinia cambogia (n = 20), red yeast rice (n = 20), and black cohosh

(n = 19). Consumers of these 6 botanicals were significantly older (adjusted odds ratio [AOR], 2.36 [95% CI, 1.06-5.25]; P = .04 for 40-59 years of age and AOR, 3.96 [95% CI, 1.93-8.11]; P = .001 for ≥60 years of age), had a higher educational level (AOR, 4.78 [95% CI, 2.62-8.75]; P < .001), and were more likely to have arthritis (AOR, 2.27 [95% CI, 1.62-3.29]; P < .001) compared with non-HDS users. An estimated 15 584 599 (95% CI, 13 047 571-18 648 801) US adults used at least 1 of the 6 botanical products within the past 30 days, which was similar to the estimated number of patients prescribed potentially hepatotoxic drugs, including simvastatin (14 036 024 [95% CI, 11 202 460-17 594 452]) and nonsteroidal anti-inflammatory drugs (14 793 837 [95% CI, 13 014 623-16 671 897]). The most common reason for consuming turmeric and green tea was to improve or maintain health. CONCLUSIONS AND RELEVANCE: In this survey study, an estimated 15.6 million US adults consumed at least 1 botanical product with liver liability within the past 30 days, comparable with the number of people who consumed nonsteroidal anti-inflammatory drugs and a commonly prescribed hypolipidemic drug. Given a lack of regulatory oversight on the manufacturing and testing of botanical products, clinicians should be aware of possible adverse events from consumption of these largely unregulated products.

DOI: 10.1001/jamanetworkopen.2024.25822
PMCID: PMC11301549
PMID: 39102266 [Indexed for MEDLINE]

21. **Silent Destruction: Fulminant Hepatitis and the Hidden Danger of Weight Loss Drugs.**
de Ataide EC, Perales SR, Bento APN, Teramoto FD, Lima MTF, Cunha-Silva M, Moisés CB, Kawamoto do Nascimento LF, Aguiar V, Sevá-Pereira T, Garcia A, Boin ISFSF.

Transplant Proc. 2024 Jun;56(5):1096-1097. doi: 10.1016/j.transproceed.2024.05.003. Epub 2024 Jul 5.

INTRODUCTION: The use of natural products for therapeutic purposes is a common practice throughout the world, in part, due to the global obesity epidemic and the search for products with appetite suppression and weight loss properties, which include nutritional supplements, vitamins and minerals to herbal products. It is known that such products may be associated with various adverse health effects. Thus, the objective of this study is to report a series of cases of patients, who presented fulminant liver failure (HFI) requiring liver transplantation (LT), related to the consumption of products used for weight loss. MATERIAL AND METHODS: This is a retrospective cohort based on the evaluation of patients listed for LT due to IHF at the Hospital das Clínicas of the Universidade Estadual de Campinas, between 1991 and 2022, with patients who had confirmed consumption of products with the aim of loss being selected. RESULTS: During the studied period, 92 patients were listed for HT due to IHF according to the Kings College criteria, with 5 cases being selected with proven consumption of herbal products for weight loss, and other causes that could explain the IHF were excluded. Four (80%) of the patients were female, with a mean age of 40.5 years, and 40% of the cases died. DISCUSSION AND CONCLUSIONS: Unlike traditional pharmaceutical medicines, in most countries, the commercialization of these products is not conditioned on clinical and safety evidence or prior approval by regulatory bodies. Hepatoxicity can be related to several factors, such as the presence of toxins naturally found in plants, the presence of heavy metals, contamination during obtaining or processing and

the addition of substances omitted from the labels. The use of weight loss products can evolve with IHF, a fact that deserves attention, due to ease of access and growing demand, and it is important to regulate the trade of these products and raise public awareness about the risks of use without professional supervision and guidance.

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PMID: 38969610 [Indexed for MEDLINE]