AACT Herbal Dietary Supplement Section Abstracts March 2023

1. Toxicities of herbal abortifacients. Feng C, Fay KE, Burns MM.

Am J Emerg Med. 2023 Mar 7;68:42-46. doi: 10.1016/j.ajem.2023.03.005. Online ahead of print.

BACKGROUND: In the post-Roe era, barriers to facility-based abortions may lead to an increased incidence of self-managed abortions. While misoprostol-based medication abortions have significant literature supporting its safety profile, there is a knowledge deficit within the medical community regarding the toxicities of commonly used herbal abortifacients. METHODS: This is a narrative review, based on a MEDLINE and HOLLIS database search, of self-managed abortion methods with herbal abortifacients and their associated toxicities. RESULTS: Common herbal abortifacients with significant morbidity and mortality implications include pennyroyal, blue cohosh, rue, and quinine. Other commonly reported abortifacients considered to be less toxic also are discussed in brief. Special considerations for hepatic, cardiac, renal, and hematologic toxicities are important in patients with significant exposures to these herbal substances. CONCLUSION: There is an anticipated increase in the utility of herbal xenobiotics for self-managed abortions with post-Roe restrictions to standard mifepristone-misoprostol protocols. Frontline providers should be aware of the associated toxicities and have special considerations when treating a poisoned patient in this population.

DOI: 10.1016/j.ajem.2023.03.005
PMID: 36924751

2. Pseudo Hyperaldosteronism Secondary to Herbal Medicine Use. Khan O, Hashim M, Lu T, Raashid S, Uddin SMM, Shapiro J, Seitillari A, Kaur A, Vasudevan S.

J Community Hosp Intern Med Perspect. 2022 Nov 7;12(6):116-118. doi: 10.55729/2000-9666.1118. eCollection 2022.

Glycyrrhizic acid, better known as licorice, is commonly found in various food and cosmetic products. Excessive consumption is known to cause a syndrome of apparent mineralocorticoid excess or pseudo hyperaldosteronism. Patients typically present with resistant hypertension and hypokalemia mimicking symptoms of primary hyperaldosteronism however laboratory workup will reveal low or normal levels of plasma renin and aldosterone in the serum. While diagnosis of licorice toxicity is relatively straight forward, the challenge lies in determining the culpable agent. We report the case of a Chinese man who initially presented with resistant hypertension and hypokalemia refractory to therapy and was later diagnosed with pseudo hyperaldosteronism secondary to licorice toxicity.

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PMCID: PMC9924636
PMID: 36816162

3. A Licorice-Flavored Edema: A Case Report of Glycyrrhizic Acid Toxicity From Chronic Licorice Root Consumption. Blanpain JS.

Cureus. 2023 Jan 31;15(1):e34425. doi: 10.7759/cureus.34425. eCollection 2023 Jan.

This article presents a case study of a 49-year-old patient who was admitted to the emergency department with hypertension, edema, and intense fatigue caused by excessive consumption for three weeks of licorice herbal teas purchased on the internet. The patient was only taking antiaging hormonal treatment. The examination revealed bilateral edema of the face and lower limbs, and blood tests showed discrete hypokalemia (3.1 mmol/L) and low aldosterone levels. The patient revealed that she had been consuming large amounts of licorice herbal teas to compensate for the lack of sweetness in her low-sugar diet. This case study highlights that although licorice is widely used for its sweet taste and has medicinal properties, it can also have a mineralocorticoid-like activity that can lead to apparent mineralocorticoid excess (AME) when consumed in excess. The main component of licorice responsible for these symptoms is glycyrrhizic acid, which increases the availability of cortisol by decreasing its catabolism and has a mineralocorticoid effect through the inhibition of the enzyme 11-β-hydroxysteroid dehydrogenase (11-β-HSD) type 2. The case also discusses the clinical effects of licorice consumption, such as sodium retention and potassium excretion, leading to potential cardiovascular complications, as well as a differential diagnosis of similar clinical presentations mainly based on laboratory findings including aldosterone level and plasma renin activity (PRA). The potential dangers of consuming excessive amounts of licorice are well established, and we advocate stricter regulations and increased awareness and education for both the general public and the medical profession about these negative side effects and suggest that physicians should consider licorice consumption in their approach to patients' lifestyles and diets.

DOI: 10.7759/cureus.34425
PMCID: PMC9981224
PMID: 36874748

4. An evaluation of adverse drug reactions and outcomes attributed to kratom in the US Food and Drug Administration Adverse Event Reporting System from January 2004 through September 2021. Li X, Ndungu P, Taneja SB, Chapin MR, Egbert SB, Akenapalli K, Paine MF, Kane-Gill SL, Boyce RD.

Clin Transl Sci. 2023 Mar 2. doi: 10.1111/cts.13505. Online ahead of print.

Kratom is a widely used Asian botanical that has gained popularity in the United States due to a perception that it can treat pain, anxiety, and opioid withdrawal symptoms. The American Kratom Association estimates 10-16 million people use kratom. Kratom-associated adverse drug reactions (ADRs) continue to be reported and raise concerns about the safety profile of kratom. However, studies are lacking that describe the overall pattern of kratom-associated adverse events and quantify the association between kratom and adverse events. ADRs reported to the US Food and Drug Administration Adverse Event Reporting System from January 2004 through September 2021 were used to address these knowledge gaps. Descriptive analysis was conducted to analyze kratom-related adverse reactions. Conservative pharmacovigilance signals based on observed-to-expected ratios with shrinkage were estimated by comparing kratom to all other natural products and drugs. Based on 489 deduplicated kratom-related ADR reports, users were young (mean age 35.5 years), and more often male (67.5%) than female patients (23.5%). Cases were predominantly reported

since 2018 (94.2%). Fifty-two disproportionate reporting signals in 17 system-organ-class categories were generated. The observed/reported number of kratom-related accidental death reports was 63-fold greater than expected. There were eight strong signals related to addiction or drug withdrawal. An excess proportion of ADR reports were about kratom-related drug complaints, toxicity to various agents, and seizures. Although further research is needed to assess the safety of kratom, clinicians and consumers should be aware that real-world evidence points to potential safety threats.

DOI: 10.1111/cts.13505
PMID: 36861661

5. Update on Cannabidiol Clinical Toxicity and Adverse Effects: a Systematic Review. Madeo G, Kapoor A, Giorgetti R, Busardò FP, Carlier J.

Curr Neuropharmacol. 2023 Mar 22. doi: 10.2174/1570159X21666230322143401. Online ahead of print.

BACKGROUND: Compelling evidence from preclinical and clinical studies supports the therapeutic role of cannabidiol (CBD) in several medical disorders. We reviewed the scientific evidence on CBD-related toxicity and adverse events (AEs) in 2019, at the beginning of the spike in clinical studies involving CBD. However, CBD safety remained uncertain. OBJECTIVE: With the benefit of hindsight, we aimed to provide an update on CBD-related toxicity and AEs in humans. METHODS: A systematic literature search was conducted following PRISMA guidelines. PubMed, Cochrane, and Embase were accessed in October 2022 to identify clinical studies mentioning CBD-related toxicity/AEs from February 2019 to September 2022. Study design, population characteristics, CBD doses, treatment duration, co-medications, and AEs were compiled. RESULTS: A total of 51 reports were included. Most studies investigated CBD efficacy and safety in neurological conditions, such as treatment-resistant epilepsies, although a growing number of studies are focusing on specific psychopathological conditions, such as substance use disorders, chronic psychosis, and anxiety. Most studies report mild or moderate severity of AEs. The most common AEs are diarrhea, somnolence, sedation, and upper respiratory disturbances. Few serious AEs have been reported, especially when CBD is co-administered with other classes of drugs, such as clobazam and valproate. CONCLUSIONS: Clinical data suggest that CBD is well tolerated and associated with few serious AEs at therapeutic doses both in children and adults. However, interactions with other medications should be monitored.

DOI: 10.2174/1570159X21666230322143401
PMID: 36946485

6. 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, Avula B, Barnhart H, Barritt AS, Bonkovsky HL, Fontana RJ, Ghabril MS, Hoofnagle JH, Khan IA, Kleiner DE, Phillips E, Stolz A, Vuppalanchi R.

Am J Med. 2023 Feb;136(2):200-206. doi: 10.1016/j.amjmed.2022.09.026. Epub 2022 Oct 14.

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
PMCID: PMC9892270
PMID: 36252717 [Indexed for MEDLINE]

7. A Case Report of Acute Hepatitis Involving the Medicinal Herb Tinospora cordifolia Along with Other Variables. May K, Jeitler M, Murthy V, Stapelfeldt E, Kessler CS.

J Integr Complement Med. 2023 Mar 17. doi: 10.1089/jicm.2022.0755. Online ahead of print.

This is a 54-year-old woman from Germany of central European origin who developed an acute hepatitis while orally taking Ayurvedic herbal remedies, among those was the medicinal herb Tinospora cordifolia. She took the plant powders from July 1, 2021, to October 1, 2021, with the intention of relieving the symptoms of her subjectively irritated gastrointestinal tract. The patient's main symptoms of acute hepatitis were progressively increasing general fatigue, nausea, and exhaustion. During an inpatient hospital admission from November 4, 2021, to November 9, 2021, she was under clinical observation, but no specific therapeutic measures were deemed necessary; however, blood chemistry showed an acute toxic hepatitis. There was no clinical or laboratory evidence of acute liver failure. Aminotransferase values decreased to normal values on December 14, 2021, by themselves. This case report contributes to the ongoing discussion about the potential risks of triggering an acute hepatitis due to the intake of herbal remedies from the Tinospora genus in rare cases, differentiating other involved risk factors. The case also shows that causality assignments are not trivial in the context of multivariate clinical scenarios. In the case of known hepatic metabolism-associated risk factors, T. cordifolia should be used with more caution based on available case reports. At the same time, no hasty and exaggerated prejudgments should be made about this medicinal herb, which has been very successfully used in traditional South Asian systems of medicine for many centuries.

DOI: 10.1089/jicm.2022.0755
PMID: 36930784

8. Herb-Induced Liver Injury by Ayurvedic Medicine With Severe Lactic Acidosis: A Case Report. Sharma DS, Ahmed A, Razak AA, Sharma P.

Cureus. 2023 Feb 8;15(2):e34761. doi: 10.7759/cureus.34761. eCollection 2023 Feb.

Lactate is the basic blood parameter in the arsenal of an intensivist when managing a critically ill patient. A 62-year-old male presented with nausea and vomiting. He had been using an Ayurvedic medication, Insulin Management Expert (IME-9), for his type 2 diabetes mellitus and was found to have severe lactic acidosis that was resistant to initial fluid resuscitation and Ayurvedic medicine-induced liver injury. He required admission to critical care for organ support and ultimately recovered. Because current literature on the adverse effects of this Ayurvedic medication, particularly hepatotoxicity, is limited, causality was determined using the adverse drug association tool Roussel Uclaf Causality Assessment Method (RUCAM), which determined this as a probable cause with a strong score of seven. As a result, our case adds a vital gear to the wheel of current research literature.

DOI: 10.7759/cureus.34761
PMCID: PMC9999305
PMID: 36909122

9. Liver Dangers of Herbal Products: A Case Report of Ashwagandha-Induced Liver Injury. Lubarska M, Hałasiński P, Hryhorowicz S, Mahadea DS, Łykowska-Szuber L, Eder P, Dobrowolska A, Krela-Kaźmierczak I.

Int J Environ Res Public Health. 2023 Feb 22;20(5):3921. doi: 10.3390/ijerph20053921.

In recent years, cases of liver damage caused by ashwagandha herbal supplements have been reported from different parts of the world (Japan, Iceland, India, and the USA). Here, we describe the clinical phenotype of suspected ashwagandha-induced liver injury and the potential causative mechanism. The patient was admitted to the hospital because of jaundice. In the interview, it was reported that he had been taking ashwagandha for a year. Laboratory results showed an increase in total bilirubin, alanine transaminase (ALT), aspartate transaminase (AST), (gamma-glutamyl transpherase (GGT), alkaline phosphatase (ALP), total cholesterol, triglycerides, and ferritin. Based on clinical symptoms and additional tests, the patient was diagnosed with acute hepatitis and referred to a facility with a higher reference rate to exclude drug-induced liver injury. An R-value was assessed, indicative of hepatocellular injury. The result of the 24 h urine collection exceeded the upper limit of normal for copper excretion in urine twice. The clinical condition improved after intensive pharmacological treatment and four plasmapheresis treatments. This case is another showing the hepatotoxic potential of ashwagandha to cause cholestatic liver damage mixed with severe jaundice. In view of several documented cases of liver damage caused by ashwagandha and the unknown metabolic molecular mechanisms of substances contained in it, attention should be paid to patients reporting the use of these products in the past and presenting symptoms of liver damage.

DOI: 10.3390/ijerph20053921
PMCID: PMC10002162
PMID: 36900932 [Indexed for MEDLINE]

10. A toxic shrub turned therapeutic: The dichotomy of Nerium oleander bioactivities. Sharma R, Singh S, Tewari N, Dey P.

Toxicon. 2023 Mar 1;224:107047. doi: 10.1016/j.toxicon.2023.107047. Epub 2023 Jan 25.

Nerium oleander L. is a medicinal plant, used for the treatment of cancers and hyperglycemia across the world, especially in Indian sub-continent, Turkey, Morocco, and China. Although clinical studies supporting its pharmacological effects remain critically underexplored, accidental and intentional consumption of any part of the plant causes fatal toxicity in animals and humans. While the polyphenolic fraction of oleander leaves has been attributed to its pre-clinical pharmacological activities, the presence of diverse cardiac glycosides (especially oleandrin) causes apoptosis to cancer cells in vitro and results in clinical signs of oleander poisoning. Thus, the dual pharmacological and toxicological role of oleander is a perplexing dichotomy in phytotherapy. The current investigative review, therefore, intended to analyze the intrinsic and extrinsic factors that likely contribute to this conundrum. Especially by focusing on gut microbial diversity, abundance, and metabolic functions, oleander-associated pharmacological and toxicological studies have been critically analyzed to define the dual effects of oleander. Electronic databases were extensively screened for relevant research articles (including pre-clinical and clinical) related to oleander bioactivities and toxicity. Taxonomic preference was given to the plant N. oleander L. and synonymous plants as per 'The World Flora Online' database (WCSP record #135196). Discussion on yellow oleander (Cascabela thevetia (L.) Lippold) has intentionally been avoided since it is a different plant. The review indicates that the gut microbiota likely plays a key role in differentially modulating the pharmacological and toxicological effects of oleander. Other factors identified influencing the oleander bioactivities include dose and mode of treatment, cardiac glycoside pharmacokinetics, host-endogenous glycosides, plant material processing and phytochemical extraction methods, plant genotypic variations, environmental effects on the phytochemical quality and quantity, gene expression variations, host dietary patterns and co-morbidity, etc. The arguments proposed are also relevant to other medicinal plants containing toxic cardiac glycosides.

DOI: 10.1016/j.toxicon.2023.107047
PMID: 36706925 [Indexed for MEDLINE]

11. Ephedrae herba: A comprehensive review of its traditional uses, phytochemistry, pharmacology, and toxicology. Zheng Q, Mu X, Pan S, Luan R, Zhao P.

J Ethnopharmacol. 2023 May 10;307:116153. doi: 10.1016/j.jep.2023.116153. Epub 2023 Jan 11.

ETHNOPHARMACOLOGICAL RELEVANCE: Ephedrae herba (called Mahuang in China) is the dried herbaceous stem of Ephedra sinica Stapf, Ephedra intermedia Schrenk et C. A. Mey., and Ephedra equisetina Bge. Ephedrae herba has a long history of use as an herb, and it was originally recorded in Sheng Nong's herbal classic. Ephedrae herba has also been widely used as both medicine and food. In the clinic, Ephedrae herba is commonly used for treating colds, bronchial asthma, nasal congestion, and other diseases. AIM OF REVIEW: This review aims to provide a systematic summary on the traditional use, chemical constituents, pharmacological effects, clinical applications, quality control, toxicology, and pharmacokinetics of Ephedrae herba to provide a theoretical basis for further reasonable development of Ephedrae herba in clinical practice and creation of new drugs. MATERIALS AND METHODS: Information on Ephedrae herba was gathered from various sources, including the scientific databases including CNKI, PubMed,

SciFinder and ScienceDirect, classical books on traditional Chinese herbal medicine, Ph.D. and M.Sc. dissertations; Baidu Scholar; and from different professional websites. RESULTS: Ephedrae herba is distributed in regions of China and other areas. Ephedra and its compound preparations can be used for colds, bronchial asthma, nasal congestion and other diseases. Approximately 281 chemical constituents have been isolated from Ephedrae herba, including alkaloids, flavonoids, tannins, polysaccharides, volatile oils, organic acids, and other compounds. Among these constituents, alkaloids and volatile oils are the most abundant and represent the major bioactive constituents. Ephedrae herba possesses multiple pharmacological activities, including diuretic effect, anti-allergic effect, blood pressure regulatory, anti-inflammatory effect, anti-oxidation effect and anti-viral effects. Ephedrine hydrochloride and pseudoephedrine hydrochloride are generally selected as indicators for the quantitative determination of Ephedrae herba. The maximum dosage of Ephedrae herba should not exceed 10 g. If overused, adverse reactions such as palpitations, sweating, irritability and insomnia will occur. CONCLUSIONS: Ephedrae herba is an ancient herbal medicine with a broad spectrum of pharmacological activities that has been used for thousands of years in China. It is one of the most commonly used herbal components of the TCM formulas. Hydrochloride and pseudoephedrine are the major bioactive constituents. However, there is a need to further understand the mechanisms of active components of Ephedrae herba. Future studies should perform an in-depth analyses of the pharmacokinetics and mechanisms of toxicity of Ephedrae herba. Quality standards should be developed to correspond to the various application methods to ensure the efficacy of drugs in actual treatment.

DOI: 10.1016/j.jep.2023.116153
PMID: 36641108 [Indexed for MEDLINE]

12. ARDS, Diffuse Alveolar Hemorrhage and Pericardial Effusion due to Anabolic-Androgenic Steroids Consumption: Legal and Ethical Policy in Medical Education. Abdi M, Lotfolahi Z, Zareie M, Saeidi M, Amini K, Torkmandi H, Ghodrati S.

Tanaffos. 2022 Feb;21(2):239-248.

Anabolic-androgenic steroids (AAS) are one of the ingredients of herbal and dietary supplements that are popular among sports trainers. AAS abuse predisposes everyone to several complications. Reviews of the literature on AAS users have shown mainly skin, renal, and hepatic complications. In this case report, we presented a case with simultaneous complications, including diffuse alveolar hemorrhage (DAH), acute respiratory distress syndrome (ARDS), pericardial effusion, gastrointestinal bleeding (GIB), and acute kidney injury (AKI). Given the potential for lethal complications and the consequences of ethical, civil, and criminal law, it seems that specific policies will be considered for the use of bodybuilding drugs. It is also suggested that this approach be added as a new part of the medical curriculum. Also, ARDS and DAH are unreported side effects in other studies, which is suggested to be considered by specialists.

PMCID: PMC9985117
PMID: 36879726

13. Pharmacovigilance of herbal medicines: Concerns and future prospects. Choudhury A, Singh PA, Bajwa N, Dash S, Bisht P.

J Ethnopharmacol. 2023 Jun 12;309:116383. doi: 10.1016/j.jep.2023.116383. Epub 2023 Mar 12.

ETHNOPHARMACOLOGICAL RELEVANCE: The use of herbal medicines for prophylaxis, prevention, and treatment of various ailments is rising throughout the world because they are thought to be safer than allopathic treatments, which they are. However, several investigations have documented the toxicity and adverse drug reactions (ADR) of certain formulations and botanicals if not consumed wisely. AIM OF THE STUDY: The goal of the current study is to address herbal medication pharmacovigilance (PV) modeling and related considerations for improved patient safety. Also, focus is laid on the comprehensive and critical analysis of the current state of PV for herbal medications at the national and international levels. MATERIALS AND METHODS: Targeted review also known as focused literature review methodology was utilized for exploring the data from various scientific platforms such as Science Direct, Wiley Online Library, Springer, PubMed, Google Scholar using "pharmacovigilance, herbal medicine, traditional medicine, ADR, under reporting, herb toxicity, herb interactions" as keywords along with standard literature pertaining to herbal medicines that is published by the WHO and other international and national organizations etc. The botanical names mentioned in the present article were authenticated using World Flora Online database. RESULTS: The historical developments paving the way for PV in regulatory setup were also discussed, along with various criteria's for monitoring herbal medicine, ADR of herbs, phytoconstituents, and traditional medicines, herb-drug interactions, modes of reporting ADR, databases for reporting ADR's, provisions of PV in regulatory framework of different nations, challenges and way forward in PV are discussed in detail advocating a robust drug safety ecosystem for herbal medicines. CONCLUSION: Despite recent efforts to encourage the reporting of suspected ADRs linked to herbal medicines, such as expanding the programme and adding community pharmacists and other healthcare professionals as recognized reporters, the number of herbal ADR reports received by the regulatory bodies remains comparatively low. Since users often do not seek professional advice or report if they have side effects, under-reporting, is anticipated to be significant for herbal medications. There are inadequate quality control methods, poor regulatory oversight considering herbs used in food and botanicals, and unregulated distribution channels. In addition, botanical identity, traceability of herbs, ecological concerns, over-the-counter (OTC) herbal medicines, patient-physicians barriers requires special focus by the regulatory bodies for improved global safety of herbal medicines.

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