AACT Herbal Dietary Supplement Section Abstracts March 2022

1. Secular Trends in Severe Idiosyncratic Drug Induced Liver Injury in North America: An Update from the ALFSG Registry. Rao A, Rule JA, Hameed B, Ganger D, Fontana RJ, Lee WM.

Am J Gastroenterol. 2022 Jan 25. doi: 10.14309/ajg.0000000000001655. Online ahead of print.

BACKGROUND: Idiosyncratic drug-induced liver injury (DILI) is the second-leading cause of acute liver failure (ALF) in the US. Our study aims were to characterize secular trends in the implicated agents, clinical features, and outcomes of adults with DILI ALF over a 20-year period. METHODS: Among 2,332 ALF patients enrolled in the Acute Liver Failure Study Group registry, 277 (11.9%) were adjudicated as idiosyncratic DILI ALF (INR ≥ 1.5 and hepatic encephalopathy) via expert opinion. The 155 cases in Era 1 (January 20, 1998-January 20, 2008) were compared to the 122 cases in Era 2 (January 21, 2008-January 20, 2018). RESULTS: Among 277 cases of DILI ALF, 97 different agents, alone or in combination, were implicated: Antimicrobials, n=118 (43%); Herbal/Dietary supplements (HDS), n=42 (15%); Central Nervous System agents/Illicit substances, n=37 (13%); Oncologic/Biologic agents, n=29 (10%); and Other, n=51 (18%). Significant trends over time included 1) an increase in HDS DILI ALF (9.7% vs 22%, p<0.01) and decrease in antimicrobial-induced DILI ALF (45.8% vs 38.5%, p=0.03) and 2) improved overall transplant-free survival (23.5% to 38.7%, p<0.01) while the number of patients transplanted declined (46.4% vs 33.6%, p<0.03). CONCLUSION: DILI ALF in North America is evolving, with HDS cases rising and other categories of suspect drugs declining. The reasons for a significant increase in transplant free survival and reduced need for liver transplantation over time remain unclear, but may be due to improvements in critical care, increased NAC utilization, and improved patient prognostication.

DOI: 10.14309/ajg.0000000000001655
PMID: 35081550

2. Herbal and Dietary Supplements-Induced Liver Injury in Latin America: Experience From the LATINDILI Network. Bessone F, García-Cortés M, Medina-Caliz I, Hernandez N, Parana R, Mendizabal M, Schinoni MI, Ridruejo E, Nunes V, Peralta M, Santos G, Anders M, Chiodi D, Tagle M, Montes P, Carrera E, Arrese M, Lizarzabal MI, Alvarez-Alvarez I, Caballano-Infantes E, Niu H, Pinazo J, Cabello MR, Lucena MI, Andrade RJ.

Clin Gastroenterol Hepatol. 2022 Mar;20(3):e548-e563. doi: 10.1016/j.cgh.2021.01.011. Epub 2021 Jan 9.

Comment in Clin Gastroenterol Hepatol. 2022 Jan;20(1):243-244.

BACKGROUND: Herbal and dietary supplements (HDS) consumption, a growing cause of hepatotoxicity, is a common practice among Latin-American populations. OBJECTIVES: To evaluate clinical, laboratory features and outcome in HDS-hepatotoxicity included in the Latin America-Drug Induced Liver Injury (LATINDILI) Network. METHODS: A total of 29 adjudicated cases of HDS hepatotoxicity reported to the LATINDILI Network from October 2011 through December 2019 were compared with 322 DILI cases due to conventional drugs and 16 due to anabolic steroids as well as with other series of HDS-hepatotoxicity. RESULTS: From 367 DILI cases, 8% were attributed to HDS. An increasing trend in HDS-hepatotoxicity was noted over time (p = .04). Camellia sinensis, Herbalife® products, and Garcinia cambogia, mostly used for weight loss, were the most frequently adjudicated causative agents. Mean age was 45 years (66% female). Median time to onset was 31 days. Patients presented typically with hepatocellular injury (83%) and jaundice (66%). Five cases (17%) developed acute liver failure. Compared to conventional medications and anabolic steroids, HDS hepatotoxicity cases had the highest levels of aspartate and alanine transaminase (p = .008 and p = .021, respectively), had more re-exposure events to the culprit HDS (14% vs 3% vs 0%; p = .026), and had more severe and fatal/liver transplantation outcomes (21% vs 12% vs 13%; p = .005). Compared to other DILI cohorts, less HDS hepatotoxicity cases in Latin America were hospitalized (41%). CONCLUSIONS: HDS-hepatotoxicity in Latin-America affects mainly young women, manifests mostly

with hepatocellular injury and is associated with higher frequency of accidental re-exposure. HDS hepatotoxicity is more serious with a higher chance of death/liver transplantation than DILI related to conventional drugs.

DOI: 10.1016/j.cgh.2021.01.011
PMID: 33434654 [Indexed for MEDLINE]

3. Evaluation of drug-induced liver injury as etiology for acute liver failure in Brazil. Santos G, Figueira ERR, D'Albuquerque LAC, Lisboa PB, de Almeida MD, Filgueira NA, Boin I, Porta G, da Silva RCMA, Viana CFG, Faria LC, Alvares-da-Silva MR, de Moraes ACP, Morsoletto DBG, Codes L, Paraná R.

Ann Hepatol. 2021 Jul-Aug;23:100310. doi: 10.1016/j.aohep.2021.100310. Epub 2021 Jan 27.

INTRODUCTION AND OBJECTIVES: Little is known about the etiology of acute liver failure (ALF) in Latin America. The objective of this paper is to investigate the main etiologies of ALF in Brazil, including Drug Induced Liver Injury (DILI) using stringent causality criteria. PATIENTS OR MATERIAL AND METHODS: All the cases of individuals who underwent liver transplantation (LT) in 12 centers in Brazil for ALF were reviewed. When DILI was stated as the cause of ALF, causality criteria were applied on site by the main investigator in order to rule out other etiologies. RESULTS: 325 individuals had ALF mainly for unknown reasons (34%), DILI (27%) and AIH (18%). Reassessment of the 89 cases of DILI, using stringent causality criteria, revealed that in only 42 subjects could DILI be confirmed as the cause of ALF. Acetaminophen (APAP) toxicity (n = 3) or DILI due to herbal and dietary supplements (HDS) (n = 2) were not commonly observed. CONCLUSIONS: Undetermined etiology and DILI are the main causes of ALF in Brazil. However, APAP toxicity and DILI due to HDS are mostly uncommon.

DOI: 10.1016/j.aohep.2021.100310
PMID: 33508520 [Indexed for MEDLINE]

4. Impact of Prior Drug Allergies on the Risk, Clinical Features, and Outcomes of Idiosyncratic Drug-Induced Liver Injury in Adults. Yeboah-Korang A, Memon A, Patel N, Portocarrero-Castillo A, Osman A, Kleesattel D, Lopez C, Louissaint J, Sherman K, Fontana R.

Dig Dis Sci. 2022 Feb 4. doi: 10.1007/s10620-022-07403-0. Online ahead of print.

BACKGROUND: Prior drug allergies are common and may increase susceptibility to adverse medication effects. The aim of this study was to compare the frequency, clinical features, and outcomes of DILI among patients with and without a history of prior drug allergy. METHODS: The EMR at a large liver referral center was searched for all DILI encounters using ICD-10 T-codes for drug poisoning/toxicity and K-71 codes for toxic liver injury between 10/1/2015 and 9/30/2019. Clinically significant liver injury was identified using predefined laboratory criteria, and cases were adjudicated using a 5-point expert opinion scale: 1/2/3 = probable DILI and 4/5 = non-DILI. Drug allergy was defined as a history of anaphylaxis, hives, rash, or pruritus after drug exposure. RESULTS: Among 766,930 patient encounters, 127 unique patients met inclusion criteria with 72 (56.7%) cases adjudicated as probable DILI and 55 (43.3%) as non-DILI. In the probable DILI group, the most frequent suspect drug classes were: antimicrobials (41.9%), herbal and dietary supplements (9.5%), and antineoplastics (8.1%). Twenty-three of the 72 DILI patients (31.9%) had a history of drug allergy before the DILI episode compared to 16 (29.1%) of the 55 non-DILI cases ($p = 0.89$). However, none of the allergy drugs and suspect DILI drugs were the same although many were in the same drug class. DILI patients with a prior drug allergy were more likely to be female (73.9% vs. 44.9%, $p = 0.04$) and have lower serum bilirubin (4.0 vs. 7.8, $p = 0.08$) and INR (1.1 vs. 1.6, $p = 0.043$) levels at presentation. The likelihood of death or liver transplantation among probable DILI cases with prior drug allergy was lower than those without prior drug allergy (0% vs. 8.2%, $p = 0.35$). The suspect drug was subsequently documented in the "Drug Allergy" section of the EMR in only 23 (31.9%) of the 72 probable DILI patients, and these patients were more likely to present with a rash (7% vs. 2%, $p = 0.006$) and higher serum bilirubin levels (10.5 vs. 4.7, $p = 0.008$) compared to those in whom the suspect drug was not listed as "drug allergy." CONCLUSION: A prior drug allergy history was not associated with a greater likelihood of developing DILI compared to other causes of acute liver injury. However, the probable DILI patients with a history of prior drug allergy tended to have less severe liver injury and clinical outcomes. The low rate of suspect drug documentation in the "Drug Allergy" section of EMR after a DILI episode is of concern and could lead to avoidable harm from inadvertent suspect drug re-challenge.

DOI: 10.1007/s10620-022-07403-0
PMID: 35122190

5. A system for reporting and evaluating adverse drug reactions of herbal medicine in Taiwan from 1998 to 2016. Chang HH, Chiang SY, Chen PC, Tsai CH, Yang RC, Tsai CL, Wu TH, Hsieh YW, Lin YC, Kuo YT, Chen KC, Chu HT.

Sci Rep. 2021 Nov 2;11(1):21476. doi: 10.1038/s41598-021-00704-w.

The Taiwan Adverse Drug Reaction Reporting System for Herbal Medicine (TADRRS-HM) has systematically documented suspected adverse events from adverse drug reaction (ADR) reports from 1998 (prior to its formal establishment in 2001) and evaluates safety profiles of herbal medicines. This article describes findings from 2079 ADR reports filed between 1998 and 2016: 941 reports involved single herbs and 87 involved folk herbals; 842 were generated from clinical trials, while 209 ADR reports involving foods, health foods, dietary supplement foods and herbal cuisine were grouped as Other. Severity assessments using the Modified Hartwig and Siegel scale classified 72.4% of ADRs as mild, 17.4% as moderate and 6.5% as severe. System Organ Class classification of the ADRs identified gastrointestinal system disorders as the most common (33.4%), followed by skin and subcutaneous tissue disorders (21.2%). The TADRRS-HM records indicate that herbal medicines may cause a wide range of ADRs. Aconiti Radix, Xiao-Qing-Long-Tang, and Datura suaveolens were the most commonly reported single herb, herbal formula, and folk herbal, respectively. The data indicate that herbal medicines may cause a wide range of ADRs. This system will confer long-term benefits for the development of Taiwan's herbal medicines adverse reaction database and facilitate epidemiological analysis.

DOI: 10.1038/s41598-021-00704-w
PMCID: PMC8564513
PMID: 34728662 [Indexed for MEDLINE]

6. Adverse effects associated with use of specific dietary supplements: The US Military Dietary Supplement Use Study. Knapik JJ, Trone DW, Steelman RA, Farina EK, Lieberman HR.

Food Chem Toxicol. 2022 Mar;161:112840. doi: 10.1016/j.fct.2022.112840. Epub 2022 Jan 31.

Dietary supplements (DSs) are used by 50% of Americans and 70% of United States military service members (SMs); some have adverse effects (AEs). This cross-sectional investigation examined AEs associated with specific DSs. A stratified random sample of SMs from the Air Force, Army, Marine Corps, and Navy was obtained. Volunteers completed a questionnaire reporting AEs for 96 generic and 62 specific DSs. The highest prevalence (≥1 AE) in specific DS categories was 35% prohormones, 33% weight loss supplements, 26% pre/post workout supplements, 14% herbal products, 12% multivitamin/multiminerals, 11% protein/amino acids, 9% muscle building supplements, 7% other DSs, 6% joint health products, and 5% individual vitamins/minerals. Specific DSs of concern (with proportion reporting AEs) included: Libido Max® (35%), Hydroxycut Hardcore® (33%), OxyElite® (33%), Roxylean® (31%), Growth Factor 9® (30%), Super HD® (29%), Hydroxycut Advanced® (29%), Lipo 6® (28%), The Ripper® (27%), Test Booster® (27%), Xenadrine Xtreme Thermogenic® (27%), C4 Extreme® (26%), and C4 Original® (25%). Products marketed for weight loss, use before/after workout, and prohormones had the highest AE prevalence. DSs can contain substances with independent/additive AEs and/or interact with other ingredients or prescribed medications. Methods described here could provide a continuous surveillance system detecting dangerous DSs entering the market.

DOI: 10.1016/j.fct.2022.112840
PMID: 35093428 [Indexed for MEDLINE]

7. A Threat to Military Combat Power: Dietary Supplements. Whaley D, Sylvester JE, Deuster PA.

Am J Med. 2021 Dec;134(12):1560-1563. doi: 10.1016/j.amjmed.2021.07.026. Epub 2021 Aug 16.

BACKGROUND: The use of dietary supplements by young warfighters is pervasive and comes with a readiness cost, especially in the deployed setting. Predatory targeting and marketing by various unscrupulous companies put this population at risk for a higher than baseline risk for adverse events. METHODS: We

report on 6 serious adverse events experienced by warfighters while deployed in Kuwait and Afghanistan. Presented is a discussion of current practice gaps and solutions, as well as details regarding how polypharmacy contributes to the seriousness of the threat posed by problematic supplements. RESULTS: The morbidity associated with the 6 cases of dietary supplement adverse events compromised mission readiness and was costly in terms of health and health care expenditures. CONCLUSION: The military dietary supplement issue needs exposure, review, and action at the highest levels of government.

DOI: 10.1016/j.amjmed.2021.07.026
PMID: 34411520 [Indexed for MEDLINE]

8. Sports nutrition supplements and adverse events - a meta-epidemiological study of case reports specifically addressing causality assessment. Zeijlon R, Hantelius V, Wallerstedt SM, Holmqvist L.

Eur J Clin Pharmacol. 2022 Jan;78(1):1-9. doi: 10.1007/s00228-021-03223-9. Epub 2021 Oct 2.

PURPOSE: This meta-epidemiological study aimed to systematically review case reports regarding sports nutrition supplements and adverse events (AEs), specifically addressing the issue of causality assessments.METHODS: Through a systematic literature search we identified all published case reports of AEs associated with sports nutrition supplements between 1 January 2008 and 1 March 2019. Data regarding AEs, suspected supplements, relevant causality assessment factors and the reporting of clinical reasoning and/or systematic causality assessment methods were extracted. RESULTS: In all, 72 publications were included, reporting 134 supplements and 37 different AEs in 97 patients (85% males; median age: 30 years [range: 14-60]). Information regarding previous health and regular prescription drugs was not presented in 30% (29/97) and 46% (45/97) of cases, respectively. In 23% (22/97) of the cases, no alternative cause was mentioned. Clinical reasoning was identified in 63% (61/97), and in 13% (8/61) of these, a systematic causality assessment method was applied. In cases with clinical reasoning, a theoretic rationale (92% vs 78%, P = 0.05), a description of previous cases (90% vs 72%, P = 0.021) and body fluid analysis (18% vs 3%, P = 0.027) were reported to a greater extent. Among cases with clinical reasoning, the application of a systematic causality assessment method captured additional important aspects: use of medication (100% vs 55%, P = 0.015), alcohol use (88% vs 43%, P = 0.020) and illicit drug use (88% vs 40%, P = 0.011). CONCLUSIONS: In published case reports where sports nutrition supplements were suspected to have caused AEs, essential factors for causality assessment were left out in a non-negligible proportion. Clinical reasoning was identified in most cases whereas a systematic causality assessment method was applied in a minority. Factors of importance for causality assessment were reported to a greater extent in cases including clinical reasoning, and the application of a systematic causality assessment method captured additional aspects of importance.

DOI: 10.1007/s00228-021-03223-9
PMCID: PMC8724217
PMID: 34599661 [Indexed for MEDLINE]

9. Strychnine poisoning due to traditional Chinese medicine: a case series. Tong HF, Chan CY, Ng SW, Mak TW.

F1000Res. 2021 Sep 15;10:924. doi: 10.12688/f1000research.73072.2. eCollection 2021.

Background: Strychnine poisoning is rare but possibly fatal. The most reported sources of strychnine poisoning include rodenticides and adulterated street heroin. Here we report a case series of an unusual cause of strychnine poisoning - Strychni semen, a herb known as "maqianzi" in traditional Chinese medicine (TCM). Methods: All cases of strychnine poisoning confirmed by the Hospital Authority Toxicology Reference Laboratory (HATRL, the highest-level clinical toxicology laboratory in Hong Kong) between May 2005 and May 2018 were reviewed. Results: Twelve cases of strychnine poisoning were recorded, and Strychni semen was the exclusive source. Ten (83%) patients presented with muscle spasms, and four (33%) developed typical conscious convulsions. The poisoning was severe in two (17%) patients, moderate in three (25%) and mild in eight (58%). No case fatality was recorded. Three (25%) patients were TCM practitioners and two (17%) were laymen who bought the herb themselves without a proper prescription. Conclusion: The practice of TCM is becoming popular in different parts of the world amid the COVID-19 pandemic. The spectrum of clinical features of strychnine poisoning secondary to Strychni semen are similar to those arising from different origins. Eliciting a history of TCM use, apart from exposure to rodenticides and drugs of

abuse, may allow timely diagnosis in patients with compatible clinical features. Enhancement of TCM safety could minimize the hazard.

DOI: 10.12688/f1000research.73072.2
PMCID: PMC8817065
PMID: 35169461 [Indexed for MEDLINE]

10. Cutaneous mercury granulomas, hyperpigmentation and systemic involvement: A case of mercury toxicity following herbal medication for psoriasis. Jagadeesan S, Duraisamy P, Panicker VV, Anjaneyan G, Sajini L, Velayudhan S, Thomas J.

Indian J Dermatol Venereol Leprol. 2021 Nov-Dec;87(6):892. doi: 10.25259/IJDVL_888_20.

DOI: 10.25259/IJDVL_888_20
PMID: 34623046 [Indexed for MEDLINE]

11. Abdominal pain caused by lead toxicity due to over the counter herbal medicines: A case series. Jain AK, Singh A, Joshi A, Pipawat R, Singh SK, Sircar S, Chatterjee D.

Indian J Gastroenterol. 2022 Feb 22. doi: 10.1007/s12664-021-01183-7. Online ahead of print.

In the last three decades, the use of herbal medications has been increasing for the treatment of various chronic disorders. Studies in the past have shown that many of these medicines could contain high levels of heavy metals, including lead. Therefore, we planned this study to evaluate the possibility of lead toxicity as the underlying cause in patients consuming these unnamed herbal medicines among patients presenting with significant abdominal pain. (Unexplained abdominal pain means pain in abdomen in which no etiology could be ascertained after all possible routine and specialized investigations including computerized axial tomography [CT] of the abdomen and upper gastrointestinal [UGI] endoscopy/colonoscopy). This is an observational case series of prospectively maintained data of all patients having unexplained abdominal pain and found to have an elevated blood lead level from 2011 to 2019. Lead toxicity was diagnosed when its blood lead level was >25 µg/dL. Total sixty-six patients with unexplained abdominal pain from 2011 to 2019 were recruited. Out of the sixty-six patients, seventeen had elevated blood lead levels. All seventeen patients had a history of ingestion of herbal medicines for more than 6 months. Among the seventeen patients, eight were taking it for infertility and sexual dysfunction, six for diabetes, two for arthritis and one for hypertension. Basophilic stippling was seen in one patient. Fourteen patients had low hemoglobin with a median value of 9.7 g/dL. Mean serum blood lead level was 87.1 µg/dL. None of them required anti-chelating agent. Lead toxicity owing to herbal medicine is not uncommon cause of unexplained abdominal pain. Most of these patients do not require a chelating agent for treatment. There is a need to bring these herbal medicines under strict regulations for displaying its constituents and their concentrations.

DOI: 10.1007/s12664-021-01183-7
PMID: 35192187

12. Are Ayurvedic medications store house of heavy metals? Bhalla A, Pannu AK.

Toxicol Res (Camb). 2022 Jan 15;11(1):179-183. doi: 10.1093/toxres/tfab124. eCollection 2022 Feb.

Ayurvedic formulations are widely used and perceived as safer medicine and subjected to be self-prescribed. However, recent reports have demonstrated adulterating these drugs with toxic quantities of heavy metals. To study the magnitude of the problem in Indian-manufactured Ayurvedic medications, we randomly collected common over-the-counter Ayurvedic preparations from the licensed Ayurvedic shops in the local markets of Chandigarh in 2017. The samples were analyzed to identify and quantify eight metal ions, including mercury, arsenic, lead, cadmium, zinc, iron, copper, and chromium, using inductively coupled plasma mass spectrometry in Postgraduate Institute of Medical Education and Research, Chandigarh. The permissible limit set by the Food and Agriculture Organization/World Health Organization (FAO/WHO) for herbal medicines was followed to define the high metal concentrations. Out of 43 Ayurvedic preparations, 42 were analyzed. Heavy metals were detected in all formulations. The median (range) concentrations (in µg/g or mg/kg) of the metals were quantified as follows- mercury, 13.52 (0.00-61 095.99); arsenic, 0.00 (0.00-1038.83); lead, 1.40 (0.00-57.09); zinc, 84.2200 (26.48-22 519.03); iron, 1356.21 (128.24-136 835.25); copper, 17.1450 (0.00-12 756.86) and chromium, 20.9050 (0.00-2717.58). The metal contents above the FAO/WHO-

mandated limit for zinc, mercury, arsenic, and lead were detected in 35, 29, 6, and 2 formulations, respectively. All medications contained detectable quantities of zinc and iron. Copper was detected in all except one. Cadmium was not found in any sample. Ayurvedic medications have a high prevalence of heavy metals. An evaluation of the sources of contamination and the necessary drug safety regulations are required.

DOI: 10.1093/toxres/tfab124
PMCID: PMC8882783
PMID: 35237422

13. Khat, a Cultural Chewing Drug: A Toxicokinetic and Toxicodynamic Summary.
Silva B, Soares J, Rocha-Pereira C, Mladěnka P, Remião F, On Behalf Of The Oemonom Researchers.

Toxins (Basel). 2022 Jan 20;14(2):71. doi: 10.3390/toxins14020071.

Khat (Catha edulis) is a recreational, chewed herbal drug that has been used as a psychostimulant for centuries in East Africa and the Arabian Peninsula, namely in Somalia, Ethiopia, and Yemen. However, the growing worldwide availability of khat has produced widespread concern. The plant comprises a large number of active substances, among which cathinone, cathine, and norephedrine are the main constituents, which can be included in the group of sympathomimetics of natural origin. In fact, these compounds are amphetamine analogues, and, as such, they have amphetamine-like nervous system stimulant effects. Chewing the leaves gives people a sensation of well-being and increases energy, alertness, and self-confidence. The chronic use of khat is, however, associated with severe cardiac, neurological, psychological, and gastrointestinal complications. The psychological dependence and withdrawal symptoms of khat are the reasons for its prolonged use. The aim of this paper is to review current knowledge on the khat plant with toxicokinetic and toxicodynamic perspectives. Namely, this review paper addresses in vitro, in vivo, and human studies. The models used, as well as the concentrations and doses with the respective biological effects, are discussed. Additionally, the main drug interactions involved with khat are described.

DOI: 10.3390/toxins14020071
PMCID: PMC8875844
PMID: 35202099 [Indexed for MEDLINE]

14. Multistate Outbreak of Melioidosis Associated with Imported Aromatherapy Spray. Gee JE, Bower WA, Kunkel A, Petras J, Gettings J, Bye M, Firestone M, Elrod MG, Liu L, Blaney DD, Zaldivar A, Raybern C, Ahmed FS, Honza H, Stonecipher S, O'Sullivan BJ, Lynfield R, Hunter M, Brennan S, Pavlick J, Gabel J, Drenzek C, Geller R, Lee C, Ritter JM, Zaki SR, Gulvik CA, Wilson WW, Beshearse E, Currie BJ, Webb JR, Weiner ZP, Negrón ME, Hoffmaster AR.

N Engl J Med 2022; 386:861-868, DOI: 10.1056/NEJMoa2116130

Melioidosis, caused by the bacterium Burkholderia pseudomallei, is an uncommon infection that is typically associated with exposure to soil and water in tropical and subtropical environments. It is rarely diagnosed in the continental United States. Patients with melioidosis in the United States commonly report travel to regions where melioidosis is endemic. We report a cluster of four non-travel-associated cases of melioidosis in Georgia, Kansas, Minnesota, and Texas. These cases were caused by the same strain of B. pseudomallei that was linked to an aromatherapy spray product imported from a melioidosis-endemic area.

DOI: 10.1056/NEJMoa2116130
PMID: 35235727 [Indexed for MEDLINE]

15. Oleandrin: A Systematic Review of its Natural Sources, Structural Properties, Detection Methods, Pharmacokinetics and Toxicology. Zhai J, Dong X, Yan F, Guo H, Yang J.

Front Pharmacol. 2022 Feb 21;13:822726. doi: 10.3389/fphar.2022.822726. eCollection 2022.

Oleandrin is a highly lipid-soluble cardiac glycoside isolated from the plant Nerium oleander (Apocynaceae) and is used as a traditional herbal medicine due to its excellent pharmacological properties. It is widely applied for various disease treatments, such as congestive heart failure. Recently, oleandrin has attracted widespread attention due to its extensive anti-cancer and novel anti-viral effects. However, oleandrin has a narrow therapeutic window and exhibits various toxicities, especially typical cardiotoxicity, which is often

fatal. This severe toxicity and low polarity have significantly hindered its application in the clinic. This review describes natural sources, structural properties, and detection methods of oleandrin. Based on reported poisoning cases and sporadic animal experiments, the pharmacokinetic characteristics of oleandrin are summarized, so as to infer some possible phenomena, such as enterohepatic circulation. Moreover, the relevant factors affecting the pharmacokinetics of oleandrin are analyzed, and some research approaches that may ameliorate the pharmacokinetic behavior of oleandrin are proposed. With the toxicology of oleandrin being thoroughly reviewed, the development of safe clinical applications of oleandrin may be possible given potential research strategies to decrease toxicity.

DOI: 10.3389/fphar.2022.822726
PMCID: PMC8902680
PMID: 35273501

16. Hypertensive Emergency Caused by Sexual Enhancement Supplements. Abenoza N, Stoner K.

WMJ. 2021 Dec;120(4):330-332.

INTRODUCTION: In the United States, major depression ranks second among all diseases and injuries as a cause of disability and 40% of patients using antidepressants experience sexual dysfunction. CASE PRESENTATION: A 41-year-old woman with past history of depression and anxiety presented with hypertensive urgency after ingesting a sexual enhancement supplement-BioXgenic-for the first time. Shortly after, computed tomography showed a basal ganglia hemorrhage. After many weeks of rehabilitation, some cognitive deficits remained. DISCUSSION: The US Food and Drug Administration (FDA) does not regulate supplements. The sexual enhancement supplement ingested had monoamine oxidase inhibitor properties and precipitated a hypertensive emergency with an intracerebral hemorrhage. Reducing medication dosage, switching medication, using drug holidays, and changing the time of administration may help alleviate sexual side effects. CONCLUSION: Physicians should inquire about dietary supplements and warn about the risks, encourage patients to report adverse effects with the FDA, and refer to the FDA's Tainted Supplements database for known adulterated supplements.

PMID: 35025185 [Indexed for MEDLINE]

17. Toxic hepatitis-associated aplastic anaemia after dual homeopathic remedies and Gymnema sylvestre use. Philips CA, Theruvath AH, Ravindran R.

BMJ Case Rep. 2022 Mar 22;15(3):e247867. doi: 10.1136/bcr-2021-247867.

Hepatitis-associated aplastic anaemia (HAAA) is a rare condition characterised by onset of acute hepatitis which is followed by development of severe pancytopenia due to bone marrow failure within 6 months. This syndrome can be precipitated by acute viral infections, but the aetiology remains unknown in the majority. Drug-induced HAAA is extremely rare and has been reported with nutritional and dietary supplements in current literature. We report the first cases of ayurvedic herbal and homeopathic remedies-associated HAAA in two patients which proved fatal in both. Evaluation of patients with acute hepatitis and severe pancytopenia must include a detailed evaluation for complementary and alternative medicine use.

DOI: 10.1136/bcr-2021-247867
PMID: 35318201

18. Drug-induced hepatocellular injury due to herbal supplement ashwagandha. Ireland PJ, Hardy T, Burt AD, Donnelly MC.

J R Coll Physicians Edinb. 2021 Dec;51(4):363-365. doi: 10.4997/JRCPE.2021.409.

A 39-year-old female presented with a one-week history of jaundice and nausea after taking an over-the-counter herbal supplement containing ashwagandha root extract. Initial investigations revealed a hepatocellular pattern of liver enzyme abnormality with jaundice. Investigations, including viral serology, liver specific autoantibodies and an ultrasound scan of the abdomen, were unremarkable. Liver biopsy showed an acute cholestatic hepatitis with confluent necrosis but no features of chronicity. These histopathological findings differ to that of a previously reported case. Review of recent literature revealed that some clinical features and the time course of liver injury were similar to previous reports of

ashwagandha drug-induced liver injury (DILI). The patient received treatment with ursodeoxycholic acid. We compare this case to previous reported cases of ashwagandha DILI and discuss the biochemical and histopathological features of ashwagandha DILI, therapeutic strategies and the importance of recognising herbal supplements as a possible cause of DILI.

DOI: 10.4997/JRCPE.2021.409
PMID: 34882134 [Indexed for MEDLINE]

19. Probable Drug-Induced Liver Injury Caused by Tinospora species: A Case Report. Gupta S, Dhankhar Y, Har B, Agarwal S, Singh SA, Gupta AK, Saigal S, Jadaun SS.

J Clin Exp Hepatol. 2022 Jan-Feb;12(1):232-234. doi: 10.1016/j.jceh.2021.10.002. Epub 2021 Oct 27.

DOI: 10.1016/j.jceh.2021.10.002
PMCID: PMC8766687
PMID: 35068807

20. Colonic Bluish-Black Patches in a 57-Year-Old Woman with Crohn's Disease. Le PH, Kuo CJ, Wu RC.

Gastroenterology. 2021 Sep;161(3):e10-e11. doi: 10.1053/j.gastro.2021.02.034. Epub 2021 Feb 18.

DOI: 10.1053/j.gastro.2021.02.034
PMID: 33609507 [Indexed for MEDLINE]

21. Acute interstitial nephritis associated with ingestion of Achyranthes japonica extract: a case report. Jang HN, Jung S, Lee S, Chang SH, Lee TW, Bae E, Park DJ.

BMC Nephrol. 2021 Apr 7;22(1):121. doi: 10.1186/s12882-021-02326-w.

BACKGROUND: The Japanese chaff flower, Achyranthes japonica, is used as complementary medicine to control degenerative arthritis. Although commonly used in South Korea, there has been no report of side effects. We report the first case of acute interstitial nephritis (AIN) that occurred in a woman who ingested A. japonica extract for 4 months. CASE PRESENTATION: A 56-year-old Korean woman was admitted for deterioration of renal function. She had general weakness and nausea for 1 month. Her initial blood urea nitrogen and serum creatinine levels were 26.3 mg/dL and 3.2 mg/dL, respectively. She acknowledged ingesting A. japonica extract for the past 4 months. Renal histology demonstrated AIN represented by immune cell infiltration into the interstitium, tubulitis, and tubular atrophy, but the glomeruli were intact. A. japonica was discontinued immediately and conservative management was started. Renal function was nearly restored to the baseline level without medication after 13 months. CONCLUSION: This is a rare case report of AIN associated with a pure A. japonica extract. In the case of unknown etiology of AIN, physicians should ask about the use of herbal medicines, nutraceuticals, and traditional folk medicines including A. japonica.

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PMCID: PMC8028177
PMID: 33827472 [Indexed for MEDLINE]

22. Creatine promotes cancer metastasis through activation of Smad2/3. Zhang L, Zhu Z, Yan H, Wang W, Wu Z, Zhang F, Zhang Q, Shi G, Du J, Cai H, Zhang X, Hsu D, Gao P, Piao HL, Chen G, Bu P.

Cell Metab. 2021 Jun 1;33(6):1111-1123.e4. doi: 10.1016/j.cmet.2021.03.009. Epub 2021 Apr 2.

Comment in: Cell Metab. 2021 Jun 1;33(6):1065-1067.

As one of the most popular nutrient supplements, creatine has been highly used to increase muscle mass and improve exercise performance. Here, we report an adverse effect of creatine using orthotopic mouse models, showing that creatine promotes colorectal and breast cancer metastasis and shortens mouse survival. We show that glycine amidinotransferase (GATM), the rate-limiting enzyme for creatine synthesis, is upregulated in liver metastases. Dietary uptake, or GATM-mediated de novo synthesis of creatine, enhances

cancer metastasis and shortens mouse survival by upregulation of Snail and Slug expression via monopolar spindle 1 (MPS1)-activated Smad2 and Smad3 phosphorylation. GATM knockdown or MPS1 inhibition suppresses cancer metastasis and benefits mouse survival by downregulating Snail and Slug. Our findings call for using caution when considering dietary creatine to improve muscle mass or treat diseases and suggest that targeting GATM or MPS1 prevents cancer metastasis, especially metastasis of transforming growth factor beta receptor mutant colorectal cancers.

DOI: 10.1016/j.cmet.2021.03.009
PMID: 33811821 [Indexed for MEDLINE]

23. Metabolic Activation and Hepatotoxicity of Furan-containing Compounds. Tian M, Peng Y, Zheng J.

Drug Metab Dispos. 2022 Jan 25:DMD-MR-2021-000458. doi: 10.1124/dmd.121.000458. Online ahead of print.

Furan-containing compounds are abundant in nature, of which many but not all have been found to be hepatotoxic and carcinogenic. The furan ring present in the chemical structures may be one of the domineering factors to bring about the toxic response resulting from the generation of reactive epoxide or cis-enedial intermediates which are of the potential to react with biomacromolecules. This review sets out to explore the relationship between the metabolic activation and hepatotoxicity of furan-containing compounds on the strength of scientific reports on several typical alkylated furans, synthetic pharmaceuticals and components extracted from herbal medicines. The pharmacological activities as well as concrete evidence of their liver injuries are described, and the potential toxic mechanisms were discussed partly based on our previous work. Efforts were made to understand the development of liver injury and seek solutions to prevention and interference of the adverse effects. Significance Statement This review mainly elucidates the vital role of metabolic activation in the hepatotoxicity of furan-containing compounds through several typical chemicals studied. The possible mechanisms involved in toxicities are discussed based on collective literatures as well as our work. Additionally, the structural features responsible for toxicities are elaborated to predict toxicity potentials of furan-containing compounds. This article may assist to seek solutions for the occurring problems, prevent and interfere the toxic effects of compounds with furan(s) in clinical practice.

DOI: 10.1124/dmd.121.000458
PMID: 35078805

24. Pyrrolizidine Alkaloid-Induced Hepatotoxicity Associated with the Formation of Reactive Metabolite-Derived Pyrrole-Protein Adducts. Ma J, Li M, Li N, Chan WY, Lin G.

Toxins (Basel). 2021 Oct 13;13(10):723. doi: 10.3390/toxins13100723.

Pyrrolizidine alkaloids (PAs) with 1,2-unsaturated necine base are hepatotoxic phytotoxins. Acute PA intoxication is initiated by the formation of adducts between PA-derived reactive pyrrolic metabolites with cellular proteins. The present study aimed to investigate the correlation between the formation of hepatic pyrrole-protein adducts and occurrence of PA-induced liver injury (PA-ILI), and to further explore the use of such adducts for rapidly screening the hepatotoxic potency of natural products which contain PAs. Aqueous extracts of Crotalaria sessiliflora (containing one PA: monocrotaline) and Gynura japonica (containing two PAs: senecionine and seneciphylline) were orally administered to rats at different doses for 24 h to investigate PA-ILI. Serum alanine aminotransferase (ALT) activity, hepatic glutathione (GSH) level, and liver histological changes of the treated rats were evaluated to assess the severity of PA-ILI. The levels of pyrrole-protein adducts formed in the rats' livers were determined by a well-established spectrophotometric method. The biological and histological results showed a dose-dependent hepatotoxicity with significantly different toxic severity among groups of rats treated with herbal extracts containing different PAs. Both serum ALT activity and the amount of hepatic pyrrole-protein adducts increased in a dose-dependent manner. Moreover, the elevation of ALT activity correlated well with the formation of hepatic pyrrole-protein adducts, regardless of the structures of different PAs. The findings revealed that the formation of hepatic pyrrole-protein adducts-which directly correlated with the elevation of serum ALT activity-was a common insult leading to PA-ILI, suggesting a potential for using pyrrole-protein adducts to screen hepatotoxicity and rank PA-containing natural products, which generally contain multiple PAs with different structures.

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PMCID: PMC8540779

PMID: 34679016 [Indexed for MEDLINE]

25. Analytical Challenges and Metrological Approaches to Ensuring Dietary Supplement Quality: International Perspectives. Durazzo A, Sorkin BC, Lucarini M, Gusev PA, Kuszak AJ, Crawford C, Boyd C, Deuster PA, Saldanha LG, Gurley BJ, Pehrsson PR, Harnly JM, Turrini A, Andrews KW, Lindsey AT, Heinrich M, Dwyer JT.

Front Pharmacol. 2022 Jan 11;12:714434. doi: 10.3389/fphar.2021.714434. eCollection 2021.

The increased utilization of metrology resources and expanded application of its' approaches in the development of internationally agreed upon measurements can lay the basis for regulatory harmonization, support reproducible research, and advance scientific understanding, especially of dietary supplements and herbal medicines. Yet, metrology is often underappreciated and underutilized in dealing with the many challenges presented by these chemically complex preparations. This article discusses the utility of applying rigorous analytical techniques and adopting metrological principles more widely in studying dietary supplement products and ingredients, particularly medicinal plants and other botanicals. An assessment of current and emerging dietary supplement characterization methods is provided, including targeted and non-targeted techniques, as well as data analysis and evaluation approaches, with a focus on chemometrics, toxicity, dosage form performance, and data management. Quality assessment, statistical methods, and optimized methods for data management are also discussed. Case studies provide examples of applying metrological principles in thorough analytical characterization of supplement composition to clarify their health effects. A new frontier for metrology in dietary supplement science is described, including opportunities to improve methods for analysis and data management, development of relevant standards and good practices, and communication of these developments to researchers and analysts, as well as to regulatory and policy decision makers in the public and private sectors. The promotion of closer interactions between analytical, clinical, and pharmaceutical scientists who are involved in research and product development with metrologists who develop standards and methodological guidelines is critical to advance research on dietary supplement characterization and health effects.

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PMCID: PMC8787362
PMID: 35087401

26. KCNQ Potassium Channels as Targets of Botanical Folk Medicines. Redford KE, Abbott GW.

Annu Rev Pharmacol Toxicol. 2022 Jan 6;62:447-464. doi: 10.1146/annurev-pharmtox-052120-104249. Epub 2021 Sep 13.

Since prehistory, human species have depended on plants for both food and medicine. Even in countries with ready access to modern medicines, alternative treatments are still highly regarded and commonly used. Unlike modern pharmaceuticals, many botanical medicines are in widespread use despite a lack of safety and efficacy data derived from controlled clinical trials and often unclear mechanisms of action. Contributing to this are the complex and undefined composition and likely multifactorial mechanisms of action and multiple targets of many botanical medicines. Here, we review the newfound importance of the ubiquitous KCNQ subfamily of voltage-gated potassium channels as targets for botanical medicines, including basil, capers, cilantro, lavender, fennel, chamomile, ginger, and Camellia, Sophora, and Mallotus species. We discuss the implications for the traditional use of these plants for disorders such as seizures, hypertension, and diabetes and the molecular mechanisms of plant secondary metabolite effects on KCNQ channels.

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PMID: 34516289 [Indexed for MEDLINE]

27. The real Theriac - panacea, poisonous drug or quackery? Raj D, Pękacka-Falkowska K, Włodarczyk M, Węglorz J.

J Ethnopharmacol. 2021 Dec 5;281:114535. doi: 10.1016/j.jep.2021.114535. Epub 2021 Aug 17.

ETHNOPHARMACOLOGICAL RELEVANCE: Theriac is considered the most popular cure-all multi-ingredient medicine and has been used for more than two millennia. It has also been used as one of the most important anti-epidemic drugs up to the 19th c., treated as an emergency medicine in case of e.g. bubonic

plague. AIM OF THE STUDY: Until now, no reliable information regarding the pharmacological effect of the treacle was available, including its possible toxic or narcotic properties. In order to change the state of knowledge in this matter we have selected the Theriac recipe that had been actually used for producing the treacle in 1630, which was confirmed by the official municipal documents of the time. METHODS: The recipe was written in Latin, with the use of pre-Linnean nomenclature and then apothecary common names, which required translation into the modern scientific language in order to get reliable pharmacological conclusions. The information from historical sources has been compiled with the pharmacological data concerning the most potent compounds, which for the first time made it possible to calculate the amounts of active compounds in the doses taken by then patients. RESULTS: Only two species included in Theriac can be harmful in humans: poppy and sea squill, but in both cases the calculated quantity of morphine and cardiac glycosides, respectively, were below toxic level. There are no indications, both from the historical and pharmacological point of view, for Theriac being toxic or narcotic in patients, when used as prescribed. CONCLUSIONS: As for now, the most probable is that the treacle owed its postulated efficacy in the main indications to the placebo effect. Still, the results should be further confirmed by reconstructing the actual Theriac and subjecting it to modern tests and analyses.

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