AACT Herbal Dietary Supplement Section Abstracts September 2021

1. Eight fold increase in the dietary supplement related liver failure leading to transplant waitlisting over the last quarter century in the US. Ghabril M, Ma J, Patidar KR, Nephew L, Desai AP, Orman E, Vuppalanchi R, Kubal S, Chalasani N.

Liver Transpl. 2021 Jul 31. doi: 10.1002/lt.26246. Online ahead of print.

INTRODUCTION: We investigated the trends in listing and outcomes of drug induced acute liver failure (DIALF) over the last quarter century in the United States using the United Network for Organ Sharing (UNOS) database. METHODS: We examined waitlisted patients in the UNOS database between 1995 and 2020 with a diagnosis of DIALF, and assessed trends in etiologies, demographic and clinical characteristics, and outcomes over 3 periods, 1995-2003, 2004-2012 and 2013-2020. Patients with DIALF and cirrhosis were classified as drug induced acute on chronic liver failure (DI-ACLF). Implicated agents including acetaminophen (APAP) and herbal or dietary supplements (HDS) were ascertained. RESULTS: There were 2146 individuals with DIALF during the study period. The observed demographic trends between the earliest and latest period included fewer pediatric patients (19% to 13%), but with increasing male gender in non-APAP DIALF (32% to 41%), and increased racial diversity in APAP DIALF. Antimicrobials remained the most common non-APAP agents across all periods, but antiepileptics, propylthiouracil and mushroom poisoning decreased, while HDS markedly increased from 2.9% to 24.1% of all non-APAP DIALF. The overall 5-year post liver transplant (LT) patient survival improved significantly over the 3 periods (69.9% to 77.4% to 83.3%) and was evident for both APAP and non-APAP DIALF. DISCUSSION: Over the last quarter century, there has been an eight-fold increase in HDS related liver failure necessitating waitlisting for liver transplantation in the US. There are other important temporal trends during the study period, including improved survival following LT among both APAP and non-APAP DIALF.

DOI: 10.1002/lt.26246
PMID: 34331346

2. Drug-induced liver injury in Australia, 2009-2020: the increasing proportion of non-paracetamol cases linked with herbal and dietary supplements. Nash E, Sabih AH, Chetwood J, Wood G, Pandya K, Yip T, Majumdar A, McCaughan GW, Strasser SI, Liu K.

Med J Aust. 2021 Jul 17. doi: 10.5694/mja2.51173. Online ahead of print.

OBJECTIVE: To compare the characteristics and outcomes of drug-induced liver injury (DILI) caused by paracetamol and non-paracetamol medications, particularly herbal and dietary supplements. DESIGN: Retrospective electronic medical record data analysis. SETTING, PARTICIPANTS: Adults admitted with DILI to the Gastroenterology and Liver Centre at the Royal Prince Alfred Hospital, Sydney (a quaternary referral liver transplantation centre), 2009-2020. MAIN OUTCOME MEASURES: 90-day transplant-free survival; drugs implicated as causal agents in DILI. RESULTS: A total of 115 patients with paracetamol-related DILI and 69 with non-paracetamol DILI were admitted to our centre. The most frequently implicated non-paracetamol medications were antibiotics (19, 28%), herbal and dietary supplements (15, 22%), anti-tuberculosis medications (six, 9%), and anti-cancer medications (five, 7%). The number of non-paracetamol DILI admissions was similar across the study period, but the proportion linked with herbal and dietary supplements increased from 2 of 13 (15%) during 2009-11 to 9 of 19 (47%) during 2018-20 (linear trend: P = 0.011). Despite higher median baseline model for end-stage liver disease (MELD) scores, 90-day transplant-free survival for patients with paracetamol-related DILI was higher than for patients with non-paracetamol DILI (86%; 95% CI, 79-93% v 71%; 95% CI, 60-82%) and herbal and dietary supplement-related cases (59%; 95% CI, 34-85%). MELD score was an independent predictor of poorer 90-day transplant-free survival in both paracetamol-related (per point increase: adjusted hazard ratio [aHR], 1.19; 95% CI, 1.09-3.74) and non-paracetamol DILI (aHR, 1.24; 95% CI, 1.14-1.36). CONCLUSION: In our

single centre study, the proportion of cases of people hospitalised with DILI linked with herbal and dietary supplements has increased since 2009. Ninety-day transplant-free survival for patients with non-paracetamol DILI, especially those with supplement-related DILI, is poorer than for those with paracetamol-related DILI.

DOI: 10.5694/mja2.51173
PMID: 34272737

3. Herbal and dietary supplement-induced liver injury in Taiwan: comparison with conventional drug-induced liver injury. Huang YS, Chang TT, Peng CY, Lo GH, Hsu CW, Hu CT, Huang YH.

Hepatol Int. 2021 Aug 11. doi: 10.1007/s12072-021-10241-3. Online ahead of print.

BACKGROUND AND AIMS: Whether herbal and dietary supplements (HDS) are safer than Western conventional drugs is controversial. The aim of this study was to explore the characteristics and risk factors for HDS-induced liver injury (HILI) in Taiwan. METHODS: This is a 9-year multi-center prospective study conducted in Taiwan from 2011 to 2019. Patients with HILI were compared to those with conventional drug-induced liver injury (CILI). RESULTS: A total of 1,297 patients were enrolled, of whom 285 (22.0%) had HILI and 1,012 (78.0%) had CILI. Compared to the CILI group, the HILI group had higher initial serum alanine aminotransferase, alkaline phosphatase (ALP), peak ALP and bilirubin levels, and higher rates of jaundice, ascites, encephalopathy, coagulopathy, sepsis and acute liver failure. In addition, the HILI group had a higher mortality rate than the CILI group (12.6 vs. 8.0%, p = 0.016). Hepatitis B carrier status, elevated baseline liver biochemical tests and the use of crude herbs (without processing) were associated with an increased risk of HILI-related mortality (adjusted hazard ratios [95% confidence intervals]: 2.90 [1.43-5.99], 2.40 [1.01-5.68] and 2.94 [1.45-5.97], respectively). CONCLUSIONS: HDS are popular and incriminated in more than one-fifth of drug-induced liver injuries in Taiwan. The patients with HILI were more severe than those with CILI in terms of liver biochemical tests, complications and mortality. Hepatitis B carriers, those with elevated baseline liver tests and crude herb users may have a higher risk of HILI-related mortality. The prudent use of HDS is suggested in these high-risk subjects.

DOI: 10.1007/s12072-021-10241-3
PMID: 34382132

4. Garcinia Cambogia, Either Alone or in Combination with Green Tea Causes Moderate to Severe Liver Injury. Vuppalanchi R, Bonkovsky HL, Ahmad J, Barnhart H, Durazo F, Fontana RJ, Gu J, Khan I, Kleiner DE, Koh C, Rockey DC, Phillips EJ, Li YJ, Serrano J, Stolz A, Tillmann HL, Seeff LB, Hoofnagle JH, Navarro VJ; Drug-Induced Liver Injury Network.

Clin Gastroenterol Hepatol. 2021 Aug 13:S1542-3565(21)00871-5. doi: 10.1016j.cgh.2021.08.015. Online ahead of print.

BACKGROUND: Garcinia cambogia, either alone or with green tea, is commonly promoted for weight loss. Sporadic cases of liver failure from G. cambogia have been reported, but its role in liver injury is controversial. METHODS: Among 1418 patients enrolled in the Drug-Induced Liver Injury Network (DILIN) from 2004 to 2018, we identified 22 cases (adjudicated with high confidence) of liver injury from G. cambogia either alone (n=5) or in combination with green tea (n=16) or Ashwagandha (n=1). Control groups consisted of 57 patients with liver injury from herbal and dietary supplements (HDS) containing green tea without G. cambogia and 103 patients from other HDS. RESULTS: Patients who took G. cambogia were between 17 to 54 years, with liver injury arising 13 to 223 days (median = 51) after the start. One patient died, one required liver transplantation, and 91% were hospitalized. The liver injury was hepatocellular with jaundice. Although the peak values of aminotransferases were significantly higher (2001 ± 1386 U/L) in G. cambogia group (p <0.018), the median time for improvement in total bilirubin (TB) was significantly lower compared to the control groups (10 vs. 17 and 13 days, p = 0.03). The presence of HLA-B*35:01 allele was significantly higher in the G. cambogia containing HDS (55%) compared to patients due to other HDS (19%) (p = 0.002) and those with acute liver injury from conventional drugs (12%) (p = 2.55x10-6). CONCLUSIONS: The liver injury caused by G. cambogia and green tea is clinically indistinguishable. The possible association with HLA-B*35:01 allele suggests an immune-mediated mechanism of injury.

DOI: 10.1016/j.cgh.2021.08.015
PMID: 34400337

5. The Dietary Supplement Health And Education Act: are we healthier and better informed after 27 years? Sissung TM, Cordes LM, Figg WD.

Lancet Oncol. 2021 Jul;22(7):915-916. doi: 10.1016/S1470-2045(21)00084-X.

DOI: 10.1016/S1470-2045(21)00084-X
PMID: 34197743 [Indexed for MEDLINE]

6. Drug-induced liver injury caused by herbal and dietary supplements: where to next? Freeman E, Roberts SK.

Med J Aust. 2021 Aug 12. doi: 10.5694/mja2.51223. Online ahead of print.

DOI: 10.5694/mja2.51223
PMID: 34386975

7. Utilizing Big Data to Identify Tiny Toxic Components: Digitalis. Hunter ES, Literman R, Handy SM.

Foods. 2021 Aug 3;10(8):1794. doi: 10.3390/foods10081794.

The botanical genus Digitalis is equal parts colorful, toxic, and medicinal, and its bioactive compounds have a long history of therapeutic use. However, with an extremely narrow therapeutic range, even trace amounts of Digitalis can cause adverse effects. Using chemical methods, the United States Food and Drug Administration traced a 1997 case of Digitalis toxicity to a shipment of Plantago (a common ingredient in dietary supplements marketed to improve digestion) contaminated with Digitalis lanata. With increased accessibility to next generation sequencing technology, here we ask whether this case could have been cracked rapidly using shallow genome sequencing strategies (e.g., genome skims). Using a modified implementation of the Site Identification from Short Read Sequences (SISRS) bioinformatics pipeline with whole-genome sequence data, we generated over 2 M genus-level single nucleotide polymorphisms in addition to species-informative single nucleotide polymorphisms. We simulated dietary supplement contamination by spiking low quantities (0-10%) of Digitalis whole-genome sequence data into a background of commonly used ingredients in products marketed for "digestive cleansing" and reliably detected Digitalis at the genus level while also discriminating between Digitalis species. This work serves as a roadmap for the development of novel DNA-based assays to quickly and reliably detect the presence of toxic species such as Digitalis in food products or dietary supplements using genomic methods and highlights the power of harnessing the entire genome to identify botanical species.

DOI: 10.3390/foods10081794
PMCID: PMC8391216
PMID: 34441571

8. Deep learning approaches for extracting adverse events and indications of dietary supplements from clinical text. Fan Y, Zhou S, Li Y, Zhang R.

J Am Med Inform Assoc. 2021 Mar 1;28(3):569-577. doi: 10.1093/jamia/ocaa218.

OBJECTIVE: We sought to demonstrate the feasibility of utilizing deep learning models to extract safety signals related to the use of dietary supplements (DSs) in clinical text. MATERIALS AND METHODS: Two tasks were performed in this study. For the named entity recognition (NER) task, Bi-LSTM-CRF (bidirectional long short-term memory conditional random field) and BERT (bidirectional encoder representations from transformers) models were trained and compared with CRF model as a baseline to recognize the named entities of DSs and events from clinical notes. In the relation extraction (RE) task, 2 deep learning models, including attention-based Bi-LSTM and convolutional neural network as well as a random forest model were trained to extract the relations between DSs and events, which were categorized into 3 classes: positive (ie, indication), negative (ie, adverse events), and not related. The best performed NER and RE models were further applied on clinical notes mentioning 88 DSs for discovering DSs adverse events and indications, which were compared with a DS knowledge base. RESULTS: For the NER task, deep learning models achieved a better performance than CRF, with F1 scores above 0.860. The attention-based Bi-LSTM model performed the best in the RE task, with an F1 score of 0.893. When comparing DS event

pairs generated by the deep learning models with the knowledge base for DSs and event, we found both known and unknown pairs. CONCLUSIONS: Deep learning models can detect adverse events and indication of DSs in clinical notes, which hold great potential for monitoring the safety of DS use.

DOI: 10.1093/jamia/ocaa218
PMCID: PMC7936508
PMID: 33150942 [Indexed for MEDLINE]

9. Toxicity From Blue Lotus (Nymphaea caerulea) After Ingestion or Inhalation: A Case Series. Schimpf M, Ulmer T, Hiller H, Barbuto AF.

Mil Med. 2021 Aug 4:usab328. doi: 10.1093/milmed/usab328. Online ahead of print.

Plant extracts and other novel psychoactives can be ingested, vaped, injected, or insufflated. This includes products such as extracts from the blue lotus flower (Nypmhaea caerulea), which is known to produce euphoria and hallucinations at high doses. Blue lotus is sold in several forms, including dried plant material, teas, and extracts for use in electronic cigarettes. Because newer generations of electronic cigarettes can deliver a variety of substances, practitioners need to be mindful of toxicity from a growing number of psychoactives, some of which are not detectable by standard urine drug screens. This case series describes five active duty patients who presented to the emergency department with altered mental status following the use of blue lotus products, four after vaping and one after making an infused beverage. Patients displayed similar symptoms, including sedation and perceptual disturbances. The patients in our series were successfully managed with supportive measures without the need for sedating agents. Recognizing and identifying new trends in substance use can help to provide directions in undifferentiated altered mental status.

DOI: 10.1093/milmed/usab328
PMID: 34345890

10. Case of cholestatic drug-induced liver injury (DILI) associated with black cohosh. Brar HS, Marathi R.

BMJ Case Rep. 2021 May 7;14(5):e240408. doi: 10.1136/bcr-2020-240408.

Drug-induced liver injury is an uncommon yet fatal cause of liver injury. Black cohosh is a herbal supplement that is derived from Actaea racemosa It has been used for vasomotor symptoms in postmenopausal women, but it can cause liver injury. A 50-year-old Afro-American woman presented with a 2-month history of malaise, itching and severe jaundice. The labs showed elevation of bilirubin and alkaline phosphatase. The patient had a history of black cohosh use for postmenopausal symptoms before she developed her current symptoms. The extensive workup for infective and autoimmune pathology was negative. Black cohosh was discontinued. The patient improved clinically, and her liver enzymes normalised 6 months after the discontinuation of black cohosh. This report emphasises the need to recognise black cohosh as a potential hepatotoxic agent and to monitor the liver enzymes for a patient on black cohosh.

DOI: 10.1136/bcr-2020-240408
PMCID: PMC8108679
PMID: 33962922 [Indexed for MEDLINE]

11. Coronary vasospasm and raspberry ketones weight-loss supplement: Is there a connection? Khattar A, Beeton I.

Anatol J Cardiol. 2020 Sep;24(3):205-208. doi: 10.14744/AnatolJCardiol.2020.53496.

DOI: 10.14744/AnatolJCardiol.2020.53496
PMCID: PMC7585971
PMID: 32870171 [Indexed for MEDLINE]

12. Case series and review of Ayurvedic medication induced liver injury. Karousatos CM, Lee JK, Braxton DR, Fong TL

BMC Complement Med Ther. 2021 Mar 13;21(1):91. doi: 10.1186/s12906-021-03251-z.

BACKGROUND: Complementary and alternative medicine use among Americans is prevalent. Originating in India, Ayurvedic medicine use in the United States has grown 57% since 2002. CAM accounts for a significant proportion of drug induced liver injury in India and China, but there have been only three reports of drug induced liver injury from Ayurvedic medications in the U.S. We report three cases of suspected Ayurvedic medication associated liver injury seen at a Southern California community hospital and review literature of Ayurvedic medication induced liver injury. CASE PRESENTATIONS: Three patients presented with acute hepatocellular injury and jaundice after taking Ayurvedic supplements for 90-120 days. First patient took Giloy Kwath consisting solely of Tinospora cordifolia. Second patient took Manjishthadi Kwatham and Aragwadhi Kwatham, which contained 52 and 10 individual plant extracts, respectively. Third patient took Kanchnar Guggulu, containing 10 individual plant extracts. Aminotransferase activities decreased 50% in < 30 days and all 3 patients made a full recovery. Roussel Uclaf Causality Assessment Method (RUCAM) scores were 7-8, indicating probable causality. These products all contained ingredients in other Ayurvedic and traditional Chinese medicines with previously reported associations with drug induced liver injury. CONCLUSIONS: These patients highlight the risk of drug induced liver injury from Ayurvedic medications and the complexity of determining causality. There is a need for a platform like LiverTox.gov to catalog Ayurvedic ingredients causing liver damage.

DOI: 10.1186/s12906-021-03251-z
PMCID: PMC7956115
PMID: 33714265 [Indexed for MEDLINE]

13. Unknown safety and efficacy of alcohol hangover treatments puts consumers at risk. Verster JC, van Rossum CJI, Scholey A.

Addict Behav. 2021 Nov;122:107029. doi: 10.1016/j.addbeh.2021.107029. Epub 2021 Jun 27.

It is important that hangover products are both safe and effective. The aims of the current study were to evaluate (a) the ingredients of currently marketed hangover treatments, (b) whether companies make disease modification claims for these products, and (c) the extent and quality of any independent scientific evidence on their efficacy and safety. Of eighty-two hangover products identified, the most common ingredients were vitamin B, vitamin C, milk thistle extract (silymarin), dihydromyricetin (DHM), and N-acetyl L-cysteine (NAC), often in combination. Fifty-one products (62.2% of the 82 evaluated products) contained one or more vitamins of which the dose exceeded the corresponding daily recommended intake level. For 9 (28.1%) of 32 products that reported the dose of Vitamin B3 and 2 (8.0%) of 25 products that reported the dose of Vitamin B9 the corresponding tolerable upper intake level was exceeded. Further, in many other cases the dose of other ingredients was not reported (e.g., dosages of DHM and NAC were not reported by 59% and 73% of the products containing these ingredients), and corresponding tolerable upper limits are unknown. A review of scientific literature revealed no peer-reviewed human data demonstrating either safety or efficacy of any of the 82 evaluated hangover products. Further, the product name and/or package/insert included explicit disease modification claims in 64.6% of the products. Finally, 45.1% of the products contain NAC as an ingredient. As NAC is registered as a drug by the US Food and Drug Administration (FDA), it is prohibited as an ingredient in dietary supplements or foods. We conclude that, in the interest of consumers, independent research supporting the safety and efficacy of hangover treatments should be a minimum requirement for hangover treatment claims irrespective whether the products are registered as medicinal drugs or dietary supplements.

DOI: 10.1016/j.addbeh.2021.107029
PMID: 34225031 [Indexed for MEDLINE]

14. United States Pharmacopeia (USP) Safety Review of Gamma-Aminobutyric Acid (GABA). Oketch-Rabah HA, Madden EF, Roe AL, Betz JM.

Nutrients. 2021 Aug 10;13(8):2742. doi: 10.3390/nu13082742.

Gamma-amino butyric acid (GABA) is marketed in the U.S. as a dietary supplement. USP conducted a comprehensive safety evaluation of GABA by assessing clinical studies, adverse event information, and toxicology data. Clinical studies investigated the effect of pure GABA as a dietary supplement or as a natural

constituent of fermented milk or soy matrices. Data showed no serious adverse events associated with GABA at intakes up to 18 g/d for 4 days and in longer studies at intakes of 120 mg/d for 12 weeks. Some studies showed that GABA was associated with a transient and moderate drop in blood pressure (<10% change). No studies were available on effects of GABA during pregnancy and lactation, and no case reports or spontaneous adverse events associated with GABA were found. Chronic administration of GABA to rats and dogs at doses up to 1 g/kg/day showed no signs of toxicity. Because some studies showed that GABA was associated with decreases in blood pressure, it is conceivable that concurrent use of GABA with anti-hypertensive medications could increase risk of hypotension. Caution is advised for pregnant and lactating women since GABA can affect neurotransmitters and the endocrine system, i.e., increases in growth hormone and prolactin levels.

DOI: 10.3390/nu13082742
PMCID: PMC8399837
PMID: 34444905

15. Detection of 94 compounds related to sexual enhancement including sildenafil, tadalafil, vardenafil and their analogues in various formulations of dietary supplements and food samples using HPLC and LC-MS/MS. Lee JH, Min AY, Park OR, Han JH, Yang YJ, Kim H, Baek SY.

Food Addit Contam Part A Chem Anal Control Expo Risk Assess. 2021 May;38(5):769-781. doi: 10.1080/19440049.2021.1881623. Epub 2021 Apr 5.

With an increase in the detection of structural and functional analogues of phosphodiesterase type 5 inhibitors (PDE-5i) in dietary supplements (DS) and foods, public health is threatened. Some products advertise natural ingredients despite containing PDE-5i that can cause serious adverse effects on human health. To avoid detection during routine screening, novel PDE-5i have been synthesised and added to DS and foods. The purpose of this study was to detect, identify, and quantify 94 PDE-5i and related compounds in DS and foods. Furthermore, the study investigated the detection cases and compared them by sample type, formulation, and compounds. The HPLC and LC-MS/MS methods were validated for limit of detection (LOD), limit of quantification (LOQ), linearity, and recovery in solid and liquid type samples. Both HPLC and LC-MS/MS showed satisfactory results, which were in conformance with the ICH guidelines. A total of 404 samples, including DS (99), and foods (305) were purchased from online and offline markets. Samples divided into 5 types of formulation were analysed; tablet, capsule, pilula (herbal medicine pill), powder and liquid type. Of these 130 samples (47 of 99 DS, and 83 of 305 foods) contained one or more PDE-5i or related compounds. Among the five types of formulation, the tablet type showed the highest detection rate (61.1%) in DS, whereas the capsule type showed the highest detection rate (53.8%) in food samples. This study will be helpful for monitoring illegal ED-related products, providing information to consumers, and ultimately contributing to protecting public health.

DOI: 10.1080/19440049.2021.1881623
PMID: 33818311 [Indexed for MEDLINE]

16. Warfarin and food, herbal or dietary supplement interactions: A systematic review. Tan CSS, Lee SWH.

Br J Clin Pharmacol. 2021 Feb;87(2):352-374. doi: 10.1111/bcp.14404. Epub 2020 Jul 1.

AIMS: To present an updated overview on the safety of concurrent use of food, herbal or dietary supplement and warfarin. METHODS: A systematic literature review was performed on 5 databases from inception up to 31 December 2019. These interactions were classified depending on the likelihood of interaction and supporting evidences. RESULTS: A total of 149 articles describing 78 herbs, food or dietary supplements were reported to interact with warfarin. These reports described potentiation with 45 (57.7%) herbs, food or dietary supplements while 23 (29.5%) reported inhibition and 10 (12.8%) reported limited impact on warfarin pharmacokinetics and pharmacodynamics. Twenty unique herb and dietary supplements also reported to result in minor bleeding events, such as purpura and gum bleeding as well as major events such as intracranial bleeding that led to death. CONCLUSION: While most food, herbs and supplements can be safely taken in moderation, healthcare professionals should be aware of the increased risk of bleeding when taking several food and herbs. These include Chinese wolfberry, chamomile tea, cannabis, cranberry, chitosan, green tea, Ginkgo biloba, ginger, spinach, St. John's Wort, sushi and smoking tobacco. Patients

should be counselled to continue to seek advice from their healthcare professionals when starting any new herbs, food or supplement.

DOI: 10.1111/bcp.14404
PMID: 32478963 [Indexed for MEDLINE]

17. DNA damage by Withanone as a potential cause of liver toxicity observed for herbal products of Withania somnifera (Ashwagandha). Siddiqui S, Ahmed N, Goswami M, Chakrabarty A, Chowdhury G.

Curr Res Toxicol. 2021 Feb 16;2:72-81. doi: 10.1016/j.crtox.2021.02.002. eCollection 2021.

Withania somnifera, commonly known as Ashwagandha, is a medicinal plant used for thousands of years for various remedies. Extracts of Ashwagandha contain more than 200 metabolites, with withanone (win) being one of the major ones responsible for many of its medicinal properties. Recently, several cases of liver toxicity resulting from commercially available Ashwagandha products have been reported. The first report of Ashwagandha-related liver damage was from Japan, which was quickly resolved after drug-withdrawal. Later, similar cases of liver toxicity due to Ashwagandha consumption were reported from the USA and Iceland. Towards understanding the liver toxicity of Ashwagandha extracts, we studied win, a representative withanolide having toxicophores or structural alerts that are commonly associated with adverse drug reactions. We found that win can form non-labile adducts with the nucleosides dG, dA, and dC. Using various biochemical assays, we showed that win forms adducts in DNA and interfere with its biological property. Win also forms adducts with amines and this process is reversible. Based on the data presented here we concluded that win is detoxified by GSH but under limiting GSH levels it can cause DNA damage. The work presented here provides a potential mechanism for the reported Ashwagandha-mediated liver damage.

DOI: 10.1016/j.crtox.2021.02.002
PMCID: PMC8320610
PMID: 34345852

18. Fatal pyrrolizidine alkaloid poisoning of infants caused by adulterated Senecio coronatus. Van Schalkwyk FJ, Stander MA, Nsizwane M, Mathee A, Van Wyk BE.

Forensic Sci Int. 2021 Mar;320:110680. doi: 10.1016/j.forsciint.2020.110680. Epub 2020 Dec 31.

Senecio coronatus (known as izonkozonko and ubulibazi in Zulu) is commonly used in traditional medicine in South Africa as purification purgative and enemas for infants during weaning. We show for the first time that this species does not contain pyrrolizidine alkaloids and that reported cases of fatal hepatic sinusoidal obstruction syndrome in infants were caused by wrongly identified Senecio species containing large amounts of retrorsine-N-oxide. A validated ultra performance liquid chromatography tandem mass spectrometry (UPLC-MS/MS) method for the detection and quantitation of pyrrolizidine alkaloids is described.

DOI: 10.1016/j.forsciint.2020.110680
PMID: 33461004 [Indexed for MEDLINE]

19. Herb-induced autoimmune-like hepatitis associated with Xiang-tian-guo (Swietenia macrophylla seeds): A case report and literature review. Shao YM, Zhang Y, Yin X, Qin TT, Jin QL, Wen XY.

Medicine (Baltimore). 2021 Jan 15;100(2):e24045. doi: 10.1097/MD.0000000000024045.

RATIONALE: Drug-induced liver injury (DILI) has a relatively low incidence, whereas the incidence of herb-induced liver injury (HILI) is still under investigation. As a special type of DILI, the diagnosis of drug-induced autoimmune-like hepatitis presents a persistent challenge, because this condition has partial characteristics of both DILI and autoimmune hepatitis (AIH), such as a certain history of medication use and histology that similar is to AIH. Thus, the differential diagnosis between DILI and AIH can be confusing. PATIENT CONCERNS: A 67-year-old woman taking xiang-tian-guo for 6 months was admitted to our hospital with a complaint of experiencing jaundice for 2 weeks. DIAGNOSIS: A liver biopsy exhibited interface inflammation, foam cells, and "rosette" -like hepatocytes. She was diagnosed with herb-induced liver injury (hepatocellular and acute), a RUCAM score of 7 (probable), a severity for grade 4 liver injury, and accompanied autoimmune-like changes. INTERVENTIONS: The patient was instructed to cease the administration of suspicious drugs. The patient also received liver protection and albumin transfusion.

OUTCOMES: After 25 days of hospitalization, the patients aminotransferase levels returned to normal. No recurrence was observed after the administration of the treatments and a close follow-up. LESSONS: We must to be vigilant about the safety of xiang-tian-guo as a herbal medicine. When faced with the difficulty of distinguishing between AIH and DILI, long-term follow-up observations for recurrence can aid clinicians in making a judgment.

DOI: 10.1097/MD.0000000000024045
PMCID: PMC7808451
PMID: 33466156 [Indexed for MEDLINE]

20. Acute liver injury following turmeric use in Tuscany: An analysis of the Italian Phytovigilance database and systematic review of case reports. Lombardi N, Crescioli G, Maggini V, Ippoliti I, Menniti-Ippolito F, Gallo E, Brilli V, Lanzi C, Mannaioni G, Firenzuoli F, Vannacci A.

Br J Clin Pharmacol. 2021 Mar;87(3):741-753. doi: 10.1111/bcp.14460. Epub 2020 Jul 20.

AIMS: Several cases of acute non-infectious cholestatic hepatitis recently appeared in Italy following consumption of Curcuma longa-containing dietary supplements. The aim of this research was to describe the Tuscan (Italy) cases of acute hepatitis and to compare them with similar cases of hepatotoxicity published in the literature by performing a systematic review. METHODS: Records of Tuscan cases of acute hepatitis were obtained from the Italian Phytovigilance system. Each spontaneous report was analysed in order to collect all relevant clinical information of patients and information concerning the Curcuma longa-containing dietary supplement. Moreover, both the RUCAM and WHO-UMC systems were used to evaluate the causal relationship between the use of dietary supplement and acute hepatitis. A systematic literature review was performed in MEDLINE and Embase and all case-reports and case-series published in English were included. RESULTS: Seven cases of acute hepatitis occurring in Tuscany up to September 2019 are described. In all cases, hepatotoxicity was associated with Curcuma longa formulations with high bioavailability and high dosage of curcumin/curcuminoids. The causal relationship was also supported by the positive dechallenge observed in most cases. In the 23 cases identified through the systematic review, the majority of patients were concomitantly exposed to at least one other medication and 16 of them experienced a positive dechallenge. CONCLUSIONS: Within the frame of poorly controlled and regulated products, such as dietary supplements, the evaluation of Italian cases of Curcuma longa-induced acute hepatitis and the systematic review of literature confirmed the association between Curcuma longa and liver injury.

DOI: 10.1111/bcp.14460
PMID: 32656820 [Indexed for MEDLINE]

21. Fatal poisoning by accidental ingestion of the "heartbreak grass" (Gelsemium elegans) verified by toxicological and medico-legal analyses. Qu D, Qiao DF, Chen XC, Feng CQ, Luo QZ, Tan XH.

Forensic Sci Int. 2021 Apr;321:110745. doi: 10.1016/j.forsciint.2021.110745. Epub 2021 Feb 27.

We present a case of fatal poisoning from accidental ingestion of Gelsemium elegans (G. elegans), a rarely toxic plant. A 41-year-old man was found dead, at his home, 6 h after drinking homemade herbal liqueur during lunch. Autopsy and routine toxicological analyses identified neither significant pathological findings nor routine poisons. However, a local botanist revealed that the homemade herbal liqueur contained G. elegans, a poisonous plant specific to Asia. To ascertain whether the decedent had ingested G. elegans, we performed liquid chromatography-mass spectrometry (LC-MS) and found two alkaloids (gelsemine and koumine) in his blood, gastric contents, as well as the suspected herbal liqueur. The cause of death was therefore confirmed to be G. elegans poisoning. Case reports of fatal poisoning due to ingestion of G. elegans are quite rare in English. Therefore, the present case broadens the scope on the possibility of death due to ingestion of G. elegans for forensic pathologists and toxicologists.

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22. Prevalence, factors associated with use, and adverse effects of sport-related nutritional supplements (sport drinks, sport bars, sport gels): the US military dietary supplement use study. Knapik JJ, Trone DW, Steelman RA, Farina EK, Lieberman HR.

J Int Soc Sports Nutr. 2021 Aug 25;18(1):59. doi: 10.1186/s12970-021-00457-x.

BACKGROUND: Sport-related nutritional supplements (SRNSs) include sport drinks, sport bars, and sport gels. Previous studies indicate that 25-35 % of athletes and 25-50 % of military personnel report using these supplements. This study SRNSs among United States military service members (SMs). METHODS: A stratified random sample of 200,000 SMs was obtained from military workforce records, and asked to complete a survey on demographics, SRNS use, and AEs experienced. About 18 % (n = 26,681) of contacted SMs (n = 146,365) completed the survey between December 2018 and August 2019. RESULTS: Overall, 45 % of SMs used ≥ 1 SRNS at least once per week in the past 6 months. Prevalence of use (± standard error) for sport drinks, bars, and gels were 32 ± 0.3, 27 ± 0.3, and 3 ± 0.1 %, respectively. Use of 1, 2, or 3 SRNSs was 28.9 ± 0.5, 13.6 ± 0.6, and 2.2 ± 0.6 %, respectively. Multivariable logistic regression indicated greater use of any SRNS was independently associated with male gender, younger age, single marital status, more weekly aerobic or resistance training, tobacco use, higher alcohol intake, officer status, combat arms occupations, and service in the Marine Corps or Navy (compared to the Air Force). Overall, the proportion of users reporting ≥ 1 AE was 2.0 ± 0.1 %, with 1.3 ± 0.1 % for sport drinks, 1.6 ± 0.2 % for sport bars, and 2.8 ± 0.6 % for sport gels. CONCLUSIONS: This large study of a stratified random sample of SMs found that nearly half of SMs consumed SRNSs weekly, and self-reported AEs were comparatively low. The AE incidence for SRNSs was much lower than typically found for dietary supplements, possibly because of more rigorous regulatory oversight for SRNSs.

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23. Prevalence of and Factors Associated with Dietary Supplement Use in a Stratified, Random Sample of US Military Personnel: The US Military Dietary Supplement Use Study. Knapik JJ, Trone DW, Steelman RA, Farina EK, Lieberman HR.

J Nutr. 2021 Jul 22:nxab239. doi: 10.1093/jn/nxab239. Online ahead of print.

BACKGROUND: About 50% of Americans and 70% of US military service members use dietary supplements (DSs). OBJECTIVES: This cross-sectional survey examined current prevalence of and factors associated with DS use in service members. METHODS: A stratified random sample of 200,000 service members from the Air Force, Army, Marine Corps, and Navy was obtained from military manpower records, and these service members were asked to complete a questionnaire on their DS use and personal characteristics. Chi-square statistics and multivariable logistic regression examined differences across various strata of demographic, lifestyle, and military characteristics. RESULTS: About 18% of successfully contacted service members (n = 26,681) completed the questionnaire between December 2018 and August 2019 (mean ± SD age: 33 ± 8 y, 86% male). Overall, 74% reported using ≥1 DS/wk. Multivitamins/multiminerals were the most commonly used DSs (45%), followed by combination products (44%), proteins/amino acids (42%), individual vitamins/minerals (31%), herbals (20%), joint health products (9%), and purported prohormones (5%). In multivariable analysis, factors independently associated with DS use included female gender [OR (female/male): 1.91; 95% CI: 1.73, 2.11], older age [OR (≥40/18-24 y): 1.25; 95% CI: 1.08, 1.44], higher education level [OR (college degree/high school or less): 1.35; 95% CI: 1.19, 1.53], higher BMI [OR (≥30/<25 kg/m2): 1.37; 95% CI: 1.25, 1.52], more weekly resistance training [OR (>300/≤45 min/wk): 5.05; 95% CI: 4.55, 5.61], smokeless tobacco use [OR (user/nonuser): 1.30; 95% CI: 1.17, 1.44], higher alcohol intake [OR (≥72/0 mL/wk): 1.41; 95% CI: 1.29, 1.54], and higher military rank [OR (senior officer/junior enlisted): 1.26; 95% CI: 1.06, 1.51]. CONCLUSIONS: Compared with civilian data from the NHANES, service members were much more likely to use DSs and used different types of DSs, especially combination products and proteins/amino acids often used to purportedly enhance physical performance. Comparisons with previous military data suggest DS use has increased over time.

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24. A Comparison of Current Regulatory Frameworks for Nutraceuticals in Australia, Canada, Japan, and the United States. Blaze J.

Innov Pharm. 2021 Apr 21;12(2):10.24926/iip.v12i2.3694. doi: 10.24926/iip.v12i2.3694. eCollection 2021.

The nutraceutical market is growing and the demand for products is increasing. Consumers are looking for cheaper alternatives to prescription medications as well as health products to supplement their dietary intake on a regular basis. Many countries classify these products into different categories based on their health claims. The purpose of this review is to compare and contrast the differences of regulatory frameworks in countries of similar status in regard to nutraceutical products: vitamins, minerals, herbal supplements, and probiotics. This review also takes into consideration the aspects of nutraceutical safety in relation to government regulations. It is evident that further discussion is indicated with regard to the harmonization of nutraceutical product regulation in a global context in order to promote and protect public health. This literature review selected 27 documents for a review using a systematic search of internet databases and search engines including PUBMED and Google Scholar. These documents were reviewed and synthesized for data relating to nutraceutical regulation within the four different countries of focus. Outcomes included information on safety and toxicity, drug interactions, classification of products, and regulatory processes for nutraceutical product approval in each country.

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