AACT Herbal Dietary Supplements SIG Abstracts January 2019

1. **Unapproved Pharmaceutical Ingredients Included in Dietary Supplements Associated With US Food and Drug Administration Warnings.** Tucker J, Fischer T, Upjohn L, Mazzera D, Kumar M.

JAMA Netw Open.2018;1(6):e183337. doi:10.1001/jamanetworkopen.2018.3337

IMPORTANCE Over half of adults in the United States report consuming dietary supplements. The US Food and Drug Administration (FDA) has warned of numerous dietary supplements containing undeclared, unapproved pharmaceutical ingredients. These FDA warnings have not been comprehensively analyzed for recent years. OBJECTIVE To summarize trends across adulterated (containing unapproved ingredients) dietary supplements associated with a warning released by the FDA from 2007 through 2016. DESIGN, SETTING, AND PARTICIPANTS In this quality improvement study, data were extracted from the FDA's Center for Drug Evaluation and Research, Tainted Products Marketed as Dietary Supplements_CDER database from 2007 through 2016. Data from each warning were recorded unless multiple warnings were issued for the same product within a 6-month period. Date, product name, company, hidden ingredient(s), product category, source of sample, and warning document type were recorded for each included warning. Data analysis was conducted from February 2017 to June 2017. RESULTS From 2007 through 2016, 776 adulterated dietary supplements were identified by the FDA and 146 different dietary supplement companies were implicated. Most of these products were marketed for sexual enhancement (353 [45.5%]), weight loss (317 [40.9%]), or muscle building (92 [11.9%]), with 157 adulterated products (20.2%) containing more than 1 unapproved ingredient. The most common adulterants were sildenafil for sexual enhancement supplements (166 of 353 [47.0%]), sibutramine for weight loss supplements (269 of 317 [84.9%]), and synthetic steroids or steroid-like ingredients for muscle building supplements (82 of 92 [89.1%]). There were 28 products named in 2 or 3 warnings more than 6 months apart. Of these products, 19 (67.9%) were reported to contain new unapproved ingredients in the second or third warning, consistent with the assumption that the FDA found the product to be adulterated more than once. In recent years (2014-2016), 117 of 303 adulterated samples (38.6%) were identified through online sampling and 104 of 303 (34.3%) were identified through the examination of international mail shipments. CONCLUSIONS AND RELEVANCE Active pharmaceuticals continue to be identified in dietary supplements, especially those marketed for sexual enhancement or weight loss, even after FDA warnings. The drug ingredients in these dietary supplements have the potential to cause serious adverse health effects owing to accidental misuse, overuse, or interaction with other medications, underlying health conditions, or other pharmaceuticals within the supplement.

2. **Regulating the Dietary Supplement Industry: The Taming of the Slew.** Incze M, Katz MH.

JAMA Intern Med.2018;178(12):1723. doi:10.1001/jamainternmed.2018.5097

3. **Action by the US Food and Drug Administration. Prohibited Stimulants in Dietary Supplements After Enforcement.** Cohen PA, Wen A, Gerona R.

JAMA Intern Med. 2018;178(12):1721–1723. doi:10.1001/jamainternmed.2018.4846

The US Food and Drug Administration (FDA) is responsible for eliminating adulterated and potentially hazardous dietary supplements from the marketplace. TheFDA uses a variety of enforcement actions, including public notices, to remove potentially hazardous ingredients. However, it is not known whether public notices are effective. We explored the effectiveness of theFDA's public notices issued between 2013 and 2016 targeting prohibited sympathomimetic stimulants in supplements. We analyzed supplements purchased in 2014 and the same brands purchased again in 2017 to determine the presence of prohibited stimulants before and after the FDA issued public notices.

4.Probiotic Safety—No Guarantees. Cohen PA.

JAMA Intern Med. 2018;178(12):1577–1578. doi:10.1001/jamainternmed.2018.5403

For centuries, people have consumed live bacteria in many foods, such as yogurt, cheese, kimchi, and sauerkraut. The mass-marketing of isolated live bacteria for their purported beneficial or "probiotic"

properties, however, is a relatively recent phenomenon. The World Health Organization defines probiotics as “live microorganisms which when administered in adequate amounts confer a health benefit on the host.” Yet to be sold as a probiotic supplement in the United States, a live microorganism does not require evidence of efficacy or even safety.

5. **Finding the bad actor: Challenges in identifying toxic constituents in botanical dietary supplements.** Roberts GK, Gardner D, Foster PM, Howard PC, Lui E, Walker L, van Breemen RB, Auerbach SS, Rider C.

Food Chem Toxicol. 2018 Dec 21. pii: S0278-6915(18)30899-8. doi:10.1016/j.fct.2018.12.026. [Epub ahead of print]

Botanical-derived dietary supplements have widespread use in the general population. The complex and variable nature of botanical ingredients and reports of adverse responses have led to concern for negative human health impacts following consumption of these products. Toxicity testing of the vast number of available products, formulations, and combinations is not feasible due to the time and resource intensive nature of comprehensive testing. Methods are needed to assess the safety of a large number of products via more efficient frameworks. Identification of toxicologically-active constituents is one approach being used, with many advantages toward product regulation. Bioassay-guided fractionation (BGF) is the leading approach used to identify biologically-active constituents. Most BGF studies with botanicals focus on identifying pharmacologically-active constituents for drug discovery or botanical efficacy research. Here, we explore BGF in a toxicological context, drawing from both efficacy and poisonous plant research. Limitations of BGF, including loss of mixture activity and bias toward abundant constituents, and recent advancements in the field (e.g., biochemometrics) are discussed from a toxicological perspective. Identification of active constituents will allow better monitoring of market products for known toxicologically-active constituents, as well as surveying human exposure, two important steps to ensuring the safety of botanical dietary supplements.

DOI: 10.1016/j.fct.2018.12.026
PMID: 30582954

6. **Herbal assault: liver toxicity of herbal and dietary supplements.**

Lancet Gastroenterol Hepatol. 2018 Mar;3(3):141. doi: 10.1016/S2468-1253(18)30011-6.

DOI: 10.1016/S2468-1253(18)30011-6
PMID: 29870727 [Indexed for MEDLINE]

7. Battle Over Herb-Induced Liver Injury: Low Prevalence Confirmed through Secondary Evaluation and Research Team's Clarifying Rebuttal to Unwarranted Public Claims. Lee J, Shin JS, Lee YJ, Kim MR, Shin BC, Lee JH, Lee MS, Ha IH.

J Altern Complement Med. 2018 Nov 8. doi: 10.1089/acm.2018.0253. [Epub ahead of print]

DOI: 10.1089/acm.2018.0253
PMID: 30407070

8. **Chemical Analysis of Weight Loss Herbal Supplement Safe Lean™ Associated With Acute Liver Injury - A Concern for Spurious Drug, Misbranding and Adulteration.** Philips CA, Augustine P.

J Clin Exp Hepatol. 2018 Dec;8(4):471-473. doi: 10.1016/j.jceh.2018.05.001. Epub 2018 May 17.

Liver injury due to herbal and dietary supplements are well described in literature and its incidence has been on the rise in the past decade. Labelling an herbal product as non-medicinal and as a supplement precludes protocols needed for testing, trials and marketing criteria. This has led to rampant use of clinically unproven multi-herb-based drugs use for a myriad of lifestyle diseases. In this report, we discuss a new dietary weight loss supplement, SafeLean™ that was found to be the cause of liver injury in a young obese woman, that resolved after discontinuation, and discuss current literature on component, toxicology and chemical analysis of the offending drug.

DOI: 10.1016/j.jceh.2018.05.001

PMCID: PMC6286438 [Available on 2019-12-01]
PMID: 30564005

9. The Case | Life-threatening lactic acidosis in a patient with jaundice and liver masses. Abdalla H, Bernardo JF.

Kidney Int. 2018 Mar;93(3):763-764. doi: 10.1016/j.kint.2017.08.021.

DOI: 10.1016/j.kint.2017.08.021
PMID: 29475549 [Indexed for MEDLINE]

10. Regressive pyridoxine-induced sensory neuronopathy in a patient with homocystinuria. Echaniz-Laguna A, Mourot-Cottet R, Noel E, Chanson JB.

BMJ Case Rep. 2018 Jun 28;2018. pii: bcr-2018-225059. doi: 10.1136/bcr-2018-225059.

Pyridoxine (vitamin B6) is an essential vitamin playing a crucial role in amino acid metabolism. Pyridoxine is used for isoniazid side-effects prevention, pyridoxine-dependent epilepsy treatment and cystathionine beta-synthase deficiency (homocystinuria) treatment. However, vitamin B6 hypervitaminosis is neurotoxic and may provoke a progressive sensory neuronopathy (sensory ganglionopathy), usually when daily uptake is above 50 mg. We describe the case of a 30-year-old patient with homocystinuria who was treated with pyridoxine 1250-1750 mg/day for 20 years and developed progressive sensory neuropathy with ataxia and impaired sensation in the extremities. Electrodiagnostic testing demonstrated non-length-dependent abnormalities of sensory nerve potentials, and sensory ganglionopathy was diagnosed. Pyridoxine dosage was reduced to 500 mg/day, resulting in the disappearance of sensory symptoms and ataxia, and the normalisation of sensory nerve potentials. Our case indicates that pyridoxine-induced sensory ganglionopathy may be reversible, even after prolonged ingestion of high doses of vitamin B6 for more than 20 years.

DOI: 10.1136/bcr-2018-225059
PMID: 29954767 [Indexed for MEDLINE]

11.Vitamin B6 in Health Supplements and Neuropathy: Case Series Assessment of Spontaneously Reported Cases. van Hunsel F, van de Koppel S, van Puijenbroek E, Kant A.

Drug Saf. 2018 Sep;41(9):859-869. doi: 10.1007/s40264-018-0664-0.

INTRODUCTION: In the literature, vitamin B6 has been linked to the development of polyneuropathy. Most often, these complaints were seen when taking high doses of vitamin B6 for a long time. Evidence as to whether a lower dosage range of vitamin B6 (< 50 mg/day) can also induce neuropathy is scarce. OBJECTIVE: We aim to comprehensively describe the cases of neuropathy associated with vitamin B6 received by the Netherlands Pharmacovigilance Centre Lareb and to assess the case series concerning the use of vitamin B6 and neuropathic complaints. METHODS: We describe the number and nature of the reported cases, including suspect product, dosage, duration of use, and vitamin B6 serum levels. In addition, we describe the causality for the individual cases (Naranjo Probability Scale) and for the entire case series (Bradford Hill criteria). RESULTS: In total, 90 reports on products containing vitamin B6 included at least one adverse drug reaction in the standardized Medical Dictionary for Regulatory Activities (MedDRA®) query (SMQ; broad) 'peripheral neuropathy'. The amount of vitamin B6 in the products varied between 1.4 and 100 mg per tablet. The serum vitamin B6 level was known in 36 cases (88-4338 nmol/l), and the mean serum vitamin B6 level was 907 nmol/l. However, no statistical correlation between dosage and vitamin B6 blood levels was found. DISCUSSION AND CONCLUSION: Causality assessment of the case series of 90 reports to Lareb shows it is plausible for the vitamin B6 supplements to have caused complaints such as neuropathies. This is especially the case with higher dosages and prolonged use, but dosages < 50 mg/day also cannot be excluded.

DOI: 10.1007/s40264-018-0664-0
PMID: 29737502 [Indexed for MEDLINE]

12. Multiple renal calculi due to hypercalcaemia induced by over-the-counter vitamin D intoxication. Manappallil RG, Shylendran S, Kakkattil A, Thomas AD.

BMJ Case Rep. 2018 Aug 20;2018. pii: bcr-2018-225849. doi: 10.1136/bcr-2018-225849.

Renal stone disease is a common and painful condition. Even though it is rarely fatal, patients describe it as the worst pain in their life. While dietary calcium may decrease the risk of stone formation, patients on supplemental calcium are at higher risk. Moreover, patients with diabetes are more prone to develop renal calculi. Hypervitaminosis D is a rare cause of hypercalcaemia. This is a case of an elderly diabetic man who developed multiple calcium oxalate renal stones due to hypercalcaemia following calcium-vitamin D supplementation.

DOI: 10.1136/bcr-2018-225849
PMID: 30131404 [Indexed for MEDLINE]

13. Dangerous mistake: an accidental caffeine overdose. Andrade A, Sousa C, Pedro M, Fernandes M.

BMJ Case Rep. 2018 Jun 8;2018. pii: bcr-2018-224185. doi:10.1136/bcr-2018-224185.

Caffeine (1,3,7-trimethylxanthine) is a natural product commonly presented in food's composition, beverages and medicinal products. Generally, it is thought to be safe under normal dosage, yet it can be fatal in case of severe intoxication. We report a case of a healthy 32-year-old woman who went to the local emergency department (ED) 30 min after ingesting, accidentally, 5000 mg of anhydrous caffeine for a preworkout supplement. At the ED, she presented an episode of presyncope followed by agitation. ECG showed polymorphic broad complex QRS tachycardia and arterial blood gas revealed metabolic acidaemia with severe hypokalemia. The dysrhythmia was successfully treated with intravenous propranolol. Acid-base and hydroelectrolytic disorders were also corrected. A persistent sinus tachycardia was observed in the first 2 days in the ward and 5 days later she was discharged asymptomatic with internal medicine follow-up.

DOI: 10.1136/bcr-2018-224185
PMCID: PMC6011436
PMID: 29884665 [Indexed for MEDLINE]

14. The risky side of weight-loss dietary supplements: disrupting arrhythmias causing sudden cardiac arrest. Inayat F, Majeed CN, Ali NS, Hayat M, Vasim I.

BMJ Case Rep. 2018 Dec 19;11(1). pii: e227531. doi: 10.1136/bcr-2018-227531.

The worldwide increasing prevalence of obesity has led to a corresponding increase in consumption of weight-loss dietary supplements. The limited de novo regulatory oversight and under-reported toxicity profile of these products reflect as a constellation of newer adverse events. We chronicle here the case of an otherwise healthy woman who developed ventricular fibrillation-related cardiac arrest secondary to the use of Hydroxycut and Metaboost preparations. Published medical literature has a handful of case reports associating these products with potentially life-threatening cardiac arrhythmias. The proposed hypothesis implicates ingredients of these diet aids to have proarrhythmogenic effects. Physicians should remain vigilant for possible cardiotoxicity associated with the use of dietary supplements. Individuals who are at risk of developing cardiac arrhythmias should avoid herbal weight-loss formulas, given the serious clinical implications. Additionally, this paper highlights the need for a proper framework to delineate the magnitude and scope of this association.

DOI: 10.1136/bcr-2018-227531
PMID: 30573541

15. Accelerated idioventricular rhythm degenerating into bidirectional ventricular tachycardia following acute myocardial infarction. Zhao YT, Zhou H, Cui Y.

Am J Emerg Med. 2018 Apr;36(4):735.e1-735.e3. doi: 10.1016/j.ajem.2018.01.030.
Epub 2018 Jan 8.

Bidirectional ventricular tachycardia (BVT) is a rare ventricular tachyarrhythmia. It is usually regular, demonstrating a beat-to-beat alternation in the QRS frontal axis that varies between -20° to -30° and +110°. The tachycardia rate is typically between 140 and 180 beats/min and the QRS is relatively narrow, with a

duration of 120 to 150 ms. The etiology of published BVT cases is most commonly digitalis toxicity and, rarely, herbal aconitine poisoning, hypokalemic periodic paralysis, catecholaminergic polymorphic ventricular tachycardia (CPVT), myocarditis, and Andersen-Tawil syndrome. We report a case of accelerated idioventricular rhythm (AIVR) degenerating into BVT following acute myocardial infarction, and briefly discuss the proposed mechanisms underlying BVT.

DOI: 10.1016/j.ajem.2018.01.030
PMID: 29429799 [Indexed for MEDLINE]

16. High-Throughput Electrophysiology Screen Revealed Cardiotoxicity of Strychnine by Selectively Targeting hERG Channel. Wang T, Chen X, Yu J, Du Q, Zhu J, Yang M, Wu H, Wang M, Zhu Y.

Am J Chin Med. 2018 Dec 14:1-16. doi: 10.1142/S0192415X1850091X. [Epub ahead of print]

Although the efficacy and the health care advantages of Chinese herbal medicine (CHM) have become increasingly recognized worldwide, the potential side effects and toxicity still restrict its broader application. This study established and applied an integrated platform anchored on automatic patch clamp system to screen and evaluate a collection of CHM extracts, compositions and monomeric compounds for in vitro cardiac toxicity. Of 1036 CHM samples screened, 2.79% significantly inhibited hERG channel activity. Among them, Strychnine was identified for the first time as a potent hERG inhibitor with an IC 50 of 6.65±1.04μ M in comparison to that of Dofetilide at 1.80±0.24μ M and Quinidine at 7.42±0.54μ M. Langendorff-perfusion experiments confirmed that strychnine increased QT interphase from 71.69±5.34 ms to 98.61±5.54 ms and decreased heart rates from 227.65±5.40 bmp to 162.91±14.70 bmp in isolated rat hearts. The cardiac toxicity effect of strychnine appears to be specific to hERG channel since an in vitro multiplex imaging analysis showed that it did not affect cellular phenotypes such as cell vitality, nucleus area, mitochondria mass and function, nor intracellular calcium in rat primary myocytes. This integrated high-throughput hERG patch clamp and high-content multi-parameter imaging cardiac toxicity screen approach should be useful for large-scale preclinical evaluation of complex Chinese herbal medicine.

DOI: 10.1142/S0192415X1850091X
PMID: 30545237

17. Risk factors for hepatic veno-occlusive disease caused by Gynura segetum: a retrospective study. Wang Y, Qiao D, Li Y, Xu F.

BMC Gastroenterol. 2018 Oct 26;18(1):156. doi: 10.1186/s12876-018-0879-7.

BACKGROUND: Hepatic veno-occlusive disease (HVOD) caused by Gynura segetum has been increasingly reported in China in recent years. The aim of this retrospective study was to identify independent prognostic markers for survival in patients with Gynura segetum-induced HVOD and to evaluate the effect of anticoagulants and transjugular intrahepatic portosystemic shunt (TIPS) on survival rate. METHODS: Clinical data including symptoms, signs, imaging characteristics, laboratory test results, results of liver tissue biopsies, type of treatment during follow-up and clinical outcomes were collected. Univariate, multivariate and time-dependent Cox regression analyses were performed. RESULTS: Survival rates were 91% (95% confidence interval [CI], 82-95%), 64% (95% CI, 53-69%) and 57% (95% CI, 51-65%) at 1, 3 and 60 months, respectively. Total bilirubin, albumin and hepatic encephalopathy were independent prognostic markers of survival. Anticoagulants were administered to 76% of the patients. Among 75 patients treated with anticoagulants, 49 patients (65.3%) were cured, whereas 26 patients (34.7%) died; the cure rate in anticoagulant-treated patients was higher than that of those not treated with anticoagulants ($\chi2 = 9.129$, $P = 0.004$). Cure rate of the anticoagulation + TIPS treatment group was 64.3%, which was also higher than that of the non-anticoagulation group; however, this was not significantly different ($\chi2 = 3.938$, $P = 0.096$). CONCLUSIONS: The presence of hepatic encephalopathy, serum bilirubin and albumin levels were major prognostic factors for Gynura segetum-induced HVOD. Anticoagulation therapy significantly increased the cure rate; however, TIPS treatment did not have a beneficial effect on the cure rate.

DOI: 10.1186/s12876-018-0879-7
PMCID: PMC6204041
PMID: 30367628 [Indexed for MEDLINE]

18. Adverse event reporting patterns of concomitant botanical dietary supplements with CYP3A4 interactive & CYP3A4 non-interactive anticancer drugs in the U.S. Food and Drug Administration Adverse Event Reporting System (FAERS). Fahim SM, Mishuk AU, Cheng N, Hansen R, Calderón AI, Qian J.

Expert Opin Drug Saf. 2018 Dec 21. doi: 10.1080/14740338.2019.1562546. [Epub ahead of print]

BACKGROUND: To examine adverse event (AE) reporting patterns for concomitant Botanical Dietary Supplements (BDS) and anticancer drugs. RESEARCH DESIGN AND METHODS: Using the 2004-2015 U.S. Food and Drug Administration Adverse Event Reporting System (FAERS) database, AEs involving commonly used BDS and anticancer drugs (categorized into CYP3A4 interactive and CYP3A4 non-interactive) were focused on. Disproportionality analyses using reporting odds ratios (RORs) assessed the relative reporting rates of 1) serious AEs (i.e., mortality and morbidity) with concomitant use of BDS (overall and by type) and anticancer drugs compared to anticancer drugs only; and 2) AEs by specific System Organ Classes (SOCs). RESULTS: A total of 3,264 AEs were reported involving concomitant BDS and CYP3A4 interactives, and 3,885 involving concomitant BDS and non-interactive anticancer drugs. ROR of serious AEs with concomitant all BDS and anticancer drugs compared to anticancer drugs alone showed a potential protective signal (ROR=0.65, 95% CI=0.62,0.68), but ROR for açaí and non-interactive anticancer drugs indicated potential risk (ROR=1.70, 95% CI=1.01,2.86). Heterogeneity of reporting patterns of AEs related to certain SOCs was observed for use of BDS along with anticancer drugs. CONCLUSION: This study identified potential protective and risk signals for AEs with concomitant use of BDS and anticancer drugs.

DOI: 10.1080/14740338.2019.1562546
PMID: 30576263

19. Suspected Driving Under the Influence Case Involving Mitragynine. Wright TH.

J Anal Toxicol. 2018 Sep 1;42(7):e65-e68. doi: 10.1093/jat/bky028.

Mitragynine is a novel psychoactive substance (NPS) that has emerged as a designer opioid being distributed on the street. Mitragynine, also known as kratom, has dose-dependent pharmacological effects and possesses both stimulant-like and sedative effects due to dual-binding of α-adrenergic and μ-opioid receptors. This herbal remedy readily available online has caused adverse effects including tachycardia, agitation, tremors, hallucination and death; however, this is the first reported suspected driving under the influence case involving mitragynine. Additional testing outside of the normal routine protocol for suspected impaired driving cases was performed based on the admission of kratom use from the suspect to the drug recognition expert (DRE) officer. Based on the evaluation, the DRE officer concluded that the driver was under the influence of a central nervous system stimulant and cannabis. An alkaline drug screen identified mitragynine in a 37-year-old female driver who was suspected of driving under the influence after nearly striking an oncoming vehicle. A blood amphetamine concentration was quantified at 0.052 mg/L and mitragynine and citalopram were reported qualitatively. The goal of this case study is to provide demographic history, adverse effects and a DRE evaluation in a driver known to have abused mitragynine.

DOI: 10.1093/jat/bky028
PMID: 29718282 [Indexed for MEDLINE]

20. A Rare Cause of Acute Anisocoria in a Child: The Angel's Trumpet Plant. Serin HM, Ozen B, Yilmaz S.

J Pediatr Ophthalmol Strabismus. 2018 Nov 2;55:e33-e35. doi 10.3928/01913913-20181009-01.

Anisocoria is a significant finding in several ocular and potentially life-threatening neurological disorders. The angel's trumpet (Datura suaveolens), widely used as a garden plant, is a natural alkaloid with anticholinergic effects containing high levels of scopolamine. The authors present a pediatric case of acute anisocoria secondary to contact with the angel's trumpet plant. This case report emphasizes the importance of considering herbal mydriatics in patients with acute, isolated, unilateral mydriasis. It is also important to raise public awareness about the potential risks of the angel's trumpet plant, particularly in areas close to schools and playgrounds.

DOI: 10.3928/01913913-20181009-01
PMID: 30388279 [Indexed for MEDLINE]

21. Datura and Brugmansia plants related antimuscarinic toxicity: an analysis of poisoning cases reported to the Taiwan poison control center. Doan UV, Wu ML, Phua DH, Mendez Rojas B, Yang CC.

Clin Toxicol (Phila). 2018 Dec 6:1-8. doi: 10.1080/15563650.2018.1513527. [Epub ahead of print]

INTRODUCTION: Datura and Brugmansia plants, especially Datura species, have been used for their hallucinogenic effects in the United States and Europe; whereas Datura plants have been used as a traditional medicine in many Asian countries. This study was conducted to better understand the pattern and outcome of Datura/Brugmansia plant related poisoning in Taiwan. METHODS: This is a retrospective case series study of all cases with Datura/Brugmansia exposure reported to the Taiwan Poison Control Center between 1986 and 2015. Data for patients with relevant poisoning were reviewed and abstracted. Logistic regression analysis was used to identify potential predictors of the severity of poisoning; bivariate analysis was employed to assess the effectiveness of physostigmine in the treatment of Datura/Brugmansia poisoning. RESULTS: A total of 203 cases involving 114 Datura exposures and 89 Brugmansia suaveolens exposures were eligible for analysis. Using Datura/Brugmansia for a medicinal purpose by the patients without consulting Chinese medicine practitioners was the most common reason of poisoning (81.2%); whereas only 2% of the patients were poisoned after medicinal use associated with the prescription from Chinese medicine practitioners. None of the 203 patients had used Datura/Brugmansia plant for recreational purpose. Most frequently observed clinical effect was mydriasis (53.2%), followed by confusion (40%), tachycardia (35.5%), dry mouth (35.5%), dizziness (34%), dry skin (32.5%), and delirium (31%). Seventy-three cases (36%) had severe effects; none of them died. Misidentification of the plants and ingestion of plant parts other than flowers were positively associated with the severity of poisoning. Forty patients (19.7%) received physostigmine therapy and patients receiving physostigmine had an earlier resolution of central nervous system toxicity than those who did not. CONCLUSIONS: Medicinal use without consulting Chinese medicine practitioners is the main reason for Datura/Brugmansia poisoning in Taiwan. Consumption of parts other than flowers and misidentification of the plants predicted the severity of poisoning in this study. Patients who received physostigmine appear to have earlier improvement in the central nervous system effects. No adverse events were reported from physostigmine administration.

DOI: 10.1080/15563650.2018.1513527
PMID: 30522351

22. Spontaneous spinal epidural hematoma of the thoracic spine after herbal medicine: a case report. Kim EJ, Ahn J, Kim SJ.

BMC Complement Altern Med. 2018 Oct 29;18(1):291. doi: 10.1186/s12906-018-2354-y.

BACKGROUND: Spontaneous spinal epidural hematoma (SSEH) is an uncommon disease, but it can lead to acute cord compression with disabling consequences. Identifiable reasons for spontaneous hemorrhage are vascular malformations and bleeding disorders. However, SSEH after taking herbal medicines has not been described yet. CASE PRESENTATION: A 60-year-old female experienced sudden back pain combined with numbness and weakness in the lower limbs for several hours with no trauma, drug use, family history or any disease history. Her deep tendon reflexes were normoactive, and Babinski was negative. An emergent MRI showed a spinal epidural hematoma extending from T3 to T5. She was taken to surgery after immediate clinical and laboratory evaluations had been completed. Emergency decompression with laminectomy was performed and the patient recovered immediately after the surgery. Additional history taken from the patient at outpatient clinic after discharge revealed that she had been continuously taking herbal medicine containing black garlic for 8 weeks. CONCLUSION: To our knowledge, no report has been previously issued on SSEH after taking herbal medicines. Although contradictory evidence is present on bleeding risks with herbal uses, we believe that it's reasonable to ascertain if patients with SSEP are taking herbal medication before or during spinal surgery.

DOI: 10.1186/s12906-018-2354-y
PMCID: PMC6206678
PMID: 30373581 [Indexed for MEDLINE]

23. Possible Drug-nutraceutical Interaction leading to Unexpected Sequelae after Inguinal Hernia Repair. Smith MR, Faingold C, Mellinger JD.

Am J Case Rep. 2018 Jul 17;19:836-838. doi: 10.12659/AJCR.908117.

BACKGROUND Nutraceutical formulations are an area in which physicians should be increasingly aware of their side effects. This case study shows the adverse effects that ginkgo biloba can have when combined with tadalafil following an inguinal hernia repair. CASE REPORT A 74-year-old male presented for repair of a recurrent inguinal hernia and for which the procedure was performed without complication. Upon follow-up, it was noted that he had significant ecchymosis not only in the inguinal region but in the ventral aspect of his penis. Upon further questioning, he reported that he had been taking ginkgo biloba that was stopped 5 days prior to the operation and restarted postoperative day 1. This, combined with tadalafil, was thought to be the reason for the unexpected induration and ecchymosis at the shaft of the penis. After discontinuing both medications, the ecchymosis and induration did resolve. CONCLUSIONS While ecchymosis and induration are expected in the inguinal region, the appearance of significant ecchymosis and induration down the shaft of the penis was unexpected in this case, and therefore we thought it could be due to nutraceutical use of ginkgo biloba combined with tadalafil, which were started postoperatively.

DOI: 10.12659/AJCR.908117
PMCID: PMC6066968
PMID: 30013020 [Indexed for MEDLINE]

24. Analysis of phosphodiesterase type 5 inhibitors as possible adulterants of botanical-based dietary supplements: extensive survey of preparations available at the Czech market. Jiru M, Stranska-Zachariasova M, Dzuman Z, Hurkova K, Tomaniova M, Stepan R, Cuhra P, Hajslova J.

J Pharm Biomed Anal. 2019 Feb 5;164:713-724. doi: 10.1016/j.jpba.2018.11.007. Epub 2018 Nov 3.

Popularity of natural-based preparations supporting the sexual potency significantly increased in recent years, which also led to the increase of illegal use of phosphodiesterase type 5 inhibitor (PDE-5) in sexual performance enhancement products. In this study, a rapid U-HPLC–HRMS/MS method has been developed to simultaneously determine 59 PDE-5 inhibitors and their analogues. Within the development of sensitive method for analysis of 59 PDE-5 inhibitors and their analogues, both sample preparation procedure, as well as separation /detection conditions have been optimized. Extraction efficiency of particular extraction solvents, influence of different mobile phase additives on target analytes separation, as well as impact of various settings of mass analyzer on sensitivity of detection were examined. Data were collected in the 'full MS/data dependent MS/MS' acquisition mode (full MS-dd-MS/MS). Before the U-HPLC–HRMS/MS method was used for analysis of real samples, proper validation had been conducted. The precision of the method expressed as the relative standard deviation (RSD) was ≤4.2% and ≤5.2% at spiking concentrations 5 μg/g and 0.25 μg/g, respectively. The limits of quantification were in the range 0.25 -0.05 μg/g and the recovery ranged between 71 and 90%. The optimized method was successfully applied for analysis of 64 real samples, and 10 of them were proved to contain both registered or unregistered synthetic PDE-5 inhibitors. Additionally, the acquired U-HPLC–HRMS/MS fingerprints were demonstrated to serve as an efficient tool for revealing of other type of possible fraud in products labeling. Retrospective mining of markers of herbs declared on dietary supplements packaging allowed to assess the trueness / untruth in the declaration of medical herbs composition.

DOI: 10.1016/j.jpba.2018.11.007
PMID: 30472590

25. Morphine Concentrations in Human Urine Following Poppy Seed Paste Consumption. Özbunar E, Aydoğdu M, Döğer R, Bostancı Hİ, Koruyucu M, Akgür SA.

Forensic Sci Int. 2018 Dec 5;295:121-127. doi: 10.1016/j.forsciint.2018.11.026. [Epub ahead of print]

Papaver somniferum (opium poppy) is one of the world's oldest medicinal plants which are widely used for medicinal, nutritive and scientific purposes. Turkey is one of the major legal opium poppy producer countries in the world and the seed paste of the poppies is consumed in great deal, even more than 100g per meal. The main objective of this study is to investigate the influence of poppy seed paste ingestion on urine tests for opiates whether or not could lead to opiate positive urine test results. For this purpose, a variety of poppies

were used and the morphine content of white, yellow and blue-black poppies were determined as 1.9, 4.0 and 2.6mg/kg, respectively. 100g of these seed pastes were consumed in the breakfast by ten healthy adults enrolled in the study over three days and urine samples were collected before and after the breakfast. Opiate screening analysis was carried out by enzyme immunoassay method and the results were evaluated by two different cut-off values (300 and 2000ng/mL). Morphine confirmation analysis was made by GC-MS system and the chromatographic method was validated in terms of selectivity, extraction efficiency, linearity (25-2000ng/ml), intra-assay precision, accuracy, limit of detection (LOD) and limit of quantitation (LOQ) (3 and 10ng/ml), carryover, matrix effect, dilution integrity and stability. According to cut-off value 300ng/ml, opiate concentrations were found positive up to 48h. For cut-off value 2000ng/mL; this time was up to 12h in collected urine samples after consumption of three different colored poppy seed pastes. In all urine samples, thebaine was detected while the heroin abuse metabolite 6-acetyl morphine (6-AM) was not. Urine drug testing legislation was revised on 2016 in Turkey and opiate screening cut-off values increased from 300 to 2000ng/mL. Overall results have shown that poppy seed paste as food consumption could lead to opiate positive urine test result even if increased cut off levels are used. It can also be deduced that thebaine can be taken as supportive biomarker for poppy seed paste consumption. Awareness of interpretation of urine test results and defining the procedures especially for forensic drug testing must be done in legal aspect to ensure justice for each individual (workplace, traffic, court etc.).

DOI: 10.1016/j.forsciint.2018.11.026
PMID: 30579243

26. Traditional Chinese medicine and drug-induced anaphylaxis: data from the Beijing pharmacovigilance database. Li X, Thai S, Lu W, Sun S, Tang H, Zhai S, Wang T.

Int J Clin Pharm. 2018 Aug;40(4):921-927. doi: 10.1007/s11096-018-0699-4. Epub 2018 Jul 26.

Background Traditional Chinese medicine (TCM) is one of the major triggers for drug-induced anaphylaxis (DIA). Objective We aimed to use the Beijing pharmacovigilance database (BPD) to analyze TCM-induced DIAs in Beijing, China. Setting Drug allergy case reports from the BPD provided by the Beijing Center for Adverse Drug Reaction Monitoring. Method Drug allergy cases from January 2004 to December 2014 were adjudicated. DIA triggered by TCMs were analyzed and compared with those triggered by non-TCM drugs by calculating the reported risk ratio (RRR). We also calculated the RRRs based on severe DIA and death outcomes. Main outcome measure TCMs implicated in DIAs were identified and compared with non-TCM drugs. Results TCMs accounted for 1651 (18.2%) of the total 9074 allergic cases, in which 84.4% (1393/1651) were triggered by injections. Of the TCM allergic cases, 8.5% (141) were DIAs and 7.3% (120) were severe DIAs, and three patients died from injections. The RRR between TCMs and non-TCM-induced DIAs was 0.63. When anaphylactic cases were compared between TCMs to the top four non-TCM drug triggers, RRRs were 0.73 (95% CI 0.61-0.87) for antibiotics, 0.36 (95% CI 0.29-0.44) for radiocontrast agents, 0.55 (95% CI 0.43-0.68) for chemotherapeutics, and 0.29 (95% CI 0.23-0.37) for biologics. Compared to TCM oral or topic formulations, TCM injections had higher RRRs in each of the above comparisons. Conclusion TCM was associated with a decreased risk of DIA compared to non-TCM drugs in drug allergy cases, and the risk was higher for TCM injections.

DOI: 10.1007/s11096-018-0699-4
PMID: 30051226 [Indexed for MEDLINE]