AACT Herbal Dietary Supplement Section Abstracts July 2020

1. Outbreak of Severe Hypoglycemia After Ingestion of a Male Enhancement Supplement - Virginia, August-November 2019. Ross JA, Downs JW, Bazydlo LA, Bordwine PH, Gineste CE, Kopatic MC, Rege SV, Saady DM, Utah OF, Wyatt SA, Wills BK, Rose SR, Holstege C.

MMWR Morb Mortal Wkly Rep. 2020 Jun 19;69(24):740-743. doi: 10.15585/mmwr.mm6924a3.

In August 2019, the Virginia Poison Center (VPC) and the Blue Ridge Poison Center (BRPC) were contacted concerning patients experiencing repeated episodes of marked hypoglycemia following ingestion of a male enhancement supplement tablet marketed as "V8" in convenience stores in central Virginia. Over the following 3 months, the Virginia Department of Agriculture and Consumer Services (VDACS) and the Virginia Department of Health (VDH) conducted an investigation and identified 17 patients meeting the case definition (severe hypoglycemia within 48 hours of consuming an over-the-counter male enhancement supplement in a man with no history of use of insulin or other medication used to control blood glucose). Analysis of the V8 tablets revealed that most contained glyburide, a sulfonylurea oral hypoglycemic used in the treatment of diabetes and associated with prolonged hypoglycemia following overdose (1). To stem this outbreak, V8 was removed from stores when found, and public service announcements were released. The public health implications of V8 use include the potential for substantial morbidity from hypoglycemic episodes and the potential for mortality if health care services are not accessed in a timely manner when hypoglycemia occurs. The presence of V8 in the market poses a serious threat to public health because of its potentially life-threatening adverse effects.

DOI: 10.15585/mmwr.mm6924a3
PMCID: PMC7302474
PMID: 32555139 [Indexed for MEDLINE]

2. Are There Adverse Events after the Use of Sexual Enhancement Nutrition Supplements? A Nationwide Online Survey from Japan. Nishijima C, Kobayashi E, Sato Y, Chiba T.

Nutrients. 2019 Nov 18;11(11):2814. doi: 10.3390/nu11112814.

Dozens of safety alerts for sexual enhancement and weight loss dietary supplements have been launched from the government not only in Japan but also overseas. However, adverse events have been reported only for the use of weight loss supplements, and the prevalence of use and adverse events in sexual enhancement supplements is not known in Japan. To address this issue, we assessed the situation of sexual enhancement supplement use through a nationwide online survey. The prevalence of sexual enhancement supplement use among males was 23.0%. Use of these supplements was higher among younger people than among older people ($p < 0.001$). In total, 17.6% of users had experienced adverse events, but 58.3% of them did not consult about the events with anybody because of the temporality of their symptoms and their sense of shame. In addition, eight supplement products were found to be possible adulterated supplements in this survey. It is necessary to inform the public about the risk of sexual enhancement supplement use and also prepare a place for consultation on media channels that younger people are more familiar with, in order to monitor adverse events while also preserving their privacy.

DOI: 10.3390/nu11112814
PMCID: PMC6893827
PMID: 31752104 [Indexed for MEDLINE]

3. Simultaneous analysis of 31 anti-impotence compounds potentially illegally added to herbal-based dietary supplements by ultra-high-performance liquid chromatography coupled with quadrupole time-of-flight mass spectrometry. Shi S, Wu Y, Zhou M, Cheng Q.

J Chromatogr B Analyt Technol Biomed Life Sci. 2020 May 1;1144:122077. doi: 10.1016/j.jchromb.2020.122077. Epub 2020 Mar 22.

In this paper, an ultra-high-performance liquid chromatography coupled with quadrupole time-of-flight mass spectrometry (UHPLC-Q-TOF HRMS) method was developed and validated for screening, confirmation and quantitation of 31 anti-impotence compounds potentially illegally added to herbal-based dietary supplements. The analytes were well separated by the mobile phase consisted of 0.1% formic acid solution and acetonitrile with gradient elution at a flow rate of 0.3 mL/min. The MS analysis was operated in positive mode and the mass error of the 31 compounds were below 2.9 ppm. The method validation showed good linearity with coefficients of determination (r2) higher than 0.9973 for all analytes. LODs and LLOQs ranged from 0.005 to 0.50 μg/g or μg /mL and from 0.02 to 1.24 μg /g or μg/mL, respectively. The accuracy was in the range of 86.6% to 113.7%, while the intra-and inter-day precision were in the ranges of 0.9-7.6% and 0.9-11.4%, respectively. The absolute and relative matrix effect were in the range of 65.8-115.6% and 0.6-13.3%. The mean recoveries were in the range of 80.5-116.9%. The stability ranged from 0.4% to 8.5%. Among 200 batches of herbal-based dietary supplements, sildenafil and/or tadalafil were found to be added illegally in two samples, while not very high concentration of icariin was detected in one sample. The Q-TOF mass spectrometry has been proved to be a very powerful and efficient tool for rapid screening of 31 anti-impotence compounds potentially illegally added to herbal-based dietary supplements, ensuring food safety and public health.

DOI: 10.1016/j.jchromb.2020.122077
PMID: 32251992 [Indexed for MEDLINE]

4. Hypertensive Urgency: An Undesirable Complication of a "Male Performance" Herbal Product. Prescott A, Smereck J.

J Emerg Med. 2019 Jul;57(1):43-46. doi: 10.1016/j.jemermed.2019.03.008. Epub 2019 Apr 25.

BACKGROUND: Hypertensive urgency is a clinical scenario that may be associated with herbal supplement use and that requires special consideration with regard to emergency department management. CASE REPORT: A 49-year-old man presented to the emergency department with palpitations and severely elevated blood pressure without evidence of end organ dysfunction. Hypertension failed to be controlled with multiple doses of oral clonidine and intravenous labetalol. The patient later admitted to using an herbal supplement containing yohimbine, a selective α2-adrenoreceptor antagonist specifically linked to cases of refractory hypertension. WHY SHOULD AN EMERGENCY PHYSICIAN BE AWARE OF THIS?: Between 17-35% of the U.S. adult population may use herbal supplements on a sporadic or regular basis; pharmacologically active agents in herbal supplements may affect both a patient's presentation and response to treatment. Most patients do not mention over-the-counter and herbal products in their medication profile unless specifically asked, and therefore it is important for emergency physicians to be aware of the pharmacologic effects of herbal supplements in the evaluation and treatment of refractory severe hypertension.

DOI: 10.1016/j.jemermed.2019.03.008
PMID: 31031073 [Indexed for MEDLINE]

5. Common anticholinergic solanaceaous plants of temperate Europe - A review of intoxications from the literature (1966-2018). Fatur K, Kreft S.

Toxicon. 2020 Apr 15;177:52-88. doi: 10.1016/j.toxicon.2020.02.005. Epub 2020 Feb 13.

Datura stramonium, Atropa belladonna, Hyoscyamus niger, and Scopolia carniolica are all temperate plants from the family Solanaceae, which as a result of their anticholinergic tropane alkaloids, hyoscyamine/atropine and scopolamine, have caused many cases of poisoning around the world. Despite the danger these nightshade plants represent, the literature often presents incomplete cases lacking in details and filled with ambiguity, and reviews on the topic tend to be limited in scope. Many also point to a gap in knowledge of these plants among physicians. To address this, the following review focuses on intoxications involving these plants as reported in the literature between 1966 and 2018, with brief mention to pertinent related plants to contextualise and provide a fuller picture of the situation surrounding the presently discussed temperate plants. Analysis of the literature displays that D. stramonium is largely associated with drug use among teens while A. belladonna is primarily ingested as a result of the berries being mistaken for edible fruits. H. niger was found to be largely ingested when mistaken for other plants, and S. carniolica was the cause of incredibly few intoxications.

DOI: 10.1016/j.toxicon.2020.02.005
PMID: 32217234 [Indexed for MEDLINE]

6. Isolated Orotic Aciduria in an 11-Year-Old Boy. Vakili H, Umaña LA, Patel K.

Clin Chem. 2020 Feb 1;66(2):396-397. doi: 10.1093/clinchem/hvz012.

DOI: 10.1093/clinchem/hvz012
PMID: 32040582 [Indexed for MEDLINE]

7. Crataegus mexicana (Tejocote) Exposure Associated with Cardiotoxicity and a Falsely Elevated Digoxin Level. Palmer KG, Lebin JA, Cronin MT, Mazor SS, Burns RA.

J Med Toxicol. 2019 Oct;15(4):295-298. doi: 10.1007/s13181-019-00727-w. Epub 2019 Aug 12.

INTRODUCTION: A species of hawthorn, Crataegus mexicana (tejocote), has been marketed as a weight-loss supplement that is readily available for purchase online. While several hawthorn species have shown clinical benefit in the treatment of heart failure owing to their positive inotropic effects, little is known about hawthorn, and tejocote in particular, when consumed in excess. We describe a case of tejocote exposure from a weight-loss supplement resulting in severe cardiotoxicity. CASE REPORT: A healthy 16-year-old girl presented to an emergency department after ingesting eight pieces of her mother's tejocote root weight-loss supplement. At arrival, she was drowsy, had active vomiting and diarrhea, and had a heart rate of 57 with normal respirations. Her initial blood chemistries were unremarkable, except for an elevated digoxin assay of 0.7 ng/mL (therapeutic range 0.5-2.0 ng/mL). All other drug screens were negative. She later developed severe bradycardia and multiple episodes of hypopnea that prompted a transfer to our institution, a tertiary pediatric hospital. Her ECG demonstrated a heart rate of 38 and

Mobitz type 1 second-degree heart block. She was subsequently given two vials of Digoxin Immune Fab due to severe bradycardia in the setting of suspected digoxin-like cardiotoxicity after discussion with the regional poison control center. No clinical improvement was observed. Approximately 29 hours after ingestion, subsequent ECGs demonstrated a return to normal sinus rhythm, and her symptoms resolved. DISCUSSION: Tejocote root toxicity may cause dysrhythmias and respiratory depression. Similar to other species of hawthorn, tejocote root may cross-react with some commercial digoxin assays, resulting in a falsely elevated level.

DOI: 10.1007/s13181-019-00727-w
PMCID: PMC6825057
PMID: 31407210 [Indexed for MEDLINE]

8. Pre-workout supplement induced cardiac ischaemia in a young female. Wang SSY.

J Sports Sci. 2020 Jan;38(2):187-191. doi: 10.1080/02640414.2019.1689598. Epub 2019 Nov 29.

The popularity of pre-workout supplements is rising amongst professional athletes and fitness enthusiasts. Despite increased usage, the safety profile of pre-workout supplements is likely to be not well understood. Additionally, many different brands use various undisclosed proprietary blends of active ingredients creating safety regulation difficulties. This lack of oversight could prove unsafe for certain patients. This patient MK is a 33-year-old healthy housewife who presented with central chest tightness, pre-syncope and mild dyspnoea to the emergency department via ambulance. The presentation was in the context of recent strenuous exercise and ingestion of a pre-workout supplement (Alpha Lean-7). Most striking in her presentation was a troponin rise of 50 ng/L, while not very high it is unusual given her lack of cardiac risk factors. She had a 3-day uneventful admission with a downtrending troponin prior to discharge. This case highlights the possible dangers of pharmacologically active ingredients in pre-workout supplements.

DOI: 10.1080/02640414.2019.1689598
PMID: 31783721 [Indexed for MEDLINE]

9. Alternative Medicine and Oncology: Erroneous Biochemical Failure Following Herbal Supplementation in Early-Stage Prostate Cancer. Abel S, Renz P, Hasan S, White R, Dawodu D, Wegner RE, Fuhrer R.

J Am Osteopath Assoc. 2019 Nov 1;119(11):763-767. doi: 10.7556/jaoa.2019.126.

Prostate-specific antigen (PSA) levels are routinely surveilled after oncologic intervention in patients with prostate cancer. Occasionally, PSA levels are elevated because of factors unrelated to disease recurrence, such as herbal supplement use. False-positive PSA elevations may confound the clinical picture and subsequent decision-making processes, potentially leading to unnecessary diagnostic and therapeutic interventions. In this case report, a patient with low-risk prostate cancer who was treated with low-dose-rate interstitial brachytherapy presented several years after treatment with an erroneously elevated PSA level after taking an herbal supplement. This case highlights the importance of a holistic approach to patient care, whereby tactful assessment of the psychosocial and spiritual aspects of health led to the identification of an uncommon but potentially morbid entity.

DOI: 10.7556/jaoa.2019.126
PMID: 31657830 [Indexed for MEDLINE]

10. Adulterants in selected dietary supplements and their detection methods. Muschietti L, Redko F, Ulloa J.

Drug Test Anal. 2020 Jul;12(7):861-886. doi: 10.1002/dta.2806. Epub 2020 May 29.

At present, there is a growing trend toward the intentional adulteration of dietary supplements (DS) with synthetic pharmaceuticals, which represents an alarming emerging risk to consumers and a serious problem for regulatory agencies. An amazing array of synthetic drugs and their analogues have been reported as adulterants in DS. Mainly, the presence of analogues represents a serious health risk as their efficacy and toxic effects have not been clinically assessed yet and may result in unpredictable adverse effects. The purpose of this review is to provide an overview, over the period 2009-2019, of the most frequently reported adulterants in DS for the treatment of erectile dysfunction, obesity/overweight, diabetes mellitus, and hypertension and the analytical methods used for their detection.

DOI: 10.1002/dta.2806
PMID: 32307880

11. Research Progress on the Molecular Mechanisms of Toxicology of Ethanol-Aconitine Induced Arrhythmia. Pan MC, Liu Y, Wang YN, Qiu XG, Wu SF, Liu Q.

Fa Yi Xue Za Zhi. 2020 Feb;36(1):115-119. doi: 10.12116/j.issn.1004-5619.2020.01.022.
[Article in Chinese, English; Abstract available in Chinese from the publisher]

Aconitum is one of the most widely used Chinese herbal medicines, and aconitine is the major toxic component in it. Aconitine can induce a variety of arrhythmias, resulting in death. Acute ethanol consumption causes arrhythmia as well. Poisoning cases caused by aconitum medicinal liquor are frequently encountered in the practice of forensic medicine. The molecular mechanisms of myocardial toxicity of these two drugs have much in common, and both of them affect the sodium channel, calcium channel and potassium channel of myocardial cell membrane and so on. This paper analyzes and discusses the possible co-effects of ethanol-aconitine on cardiomyocyte channel proteins, by reviewing researches on the mechanism of cardiotoxicity of ethanol and aconitine in recent years, in order to provide ideas and references for the research on the molecular mechanism of arrhythmia caused by combined poisoning.

DOI: 10.12116/j.issn.1004-5619.2020.01.022
PMID: 32250090 [Indexed for MEDLINE]

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

Br J Clin Pharmacol. 2020 Jun 1. doi: 10.1111/bcp.14404. Online ahead of print.

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

13. Prevalence and Knowledge of Potential Interactions Between Over-the-Counter Products and Apixaban. Tarn DM, Barrientos M, Wang AY, Ramaprasad A, Fang MC, Schwartz JB.

J Am Geriatr Soc. 2020 Jan;68(1):155-162. doi: 10.1111/jgs.16193. Epub 2019 Oct 28.

BACKGROUND: Direct-acting oral anticoagulants (DOACs), such as apixaban, are the most commonly prescribed anticoagulants, with advantages in that they do not require routine monitoring. However, less frequent contact with healthcare professionals may contribute to poor patient knowledge about potential interactions between over-the-counter (OTC) products and DOACs. OBJECTIVE: Determine the prevalence of use of OTC products (OTC medications and dietary supplements) with potentially serious apixaban interactions and assess patient knowledge of potential interactions. DESIGN: Cross-sectional survey. SETTING: Academic-affiliated outpatient medical practices in northern and southern California. PARTICIPANTS: A total of 791 English- or Spanish-speaking patients prescribed apixaban. MEASUREMENTS: Use and knowledge of OTC medications and dietary supplements with potentially serious apixaban interactions. RESULTS: Almost all respondents (n = 771; 97.5%) reported OTC product use. Of respondents, 33% (n = 266) took at least one OTC product with potentially serious apixaban interactions daily/most days and 53 (6.7%) took multiple products (mean = 2.6 [SD = 2.6]). Aspirin was taken daily by 116 (14.7%; of which 75 [64.7%] also consumed other potentially interacting OTC products), and some days/as needed by an additional 82 (10.4%). Ibuprofen and naproxen were taken daily/most days by 14 (1.8%) and occasionally by 225 (28.5%). Dietary supplements with potentially serious interactions were taken daily/most days by 160 (20.2%). Approximately 66% of respondents were either uncertain or incorrect about the potential for increased bleeding from combining nonsteroidal anti-inflammatory drugs and apixaban. Less knowledge about OTC products with potentially serious interactions was associated with greater OTC product use (odds ratio = 0.54; 95% confidence interval = 0.35-0.85). CONCLUSION: Significant numbers of patients take OTC products (particularly dietary supplements) with potentially serious interactions with the DOAC apixaban and appear to lack knowledge about potentially harmful interactions. Interventions are needed to educate patients and healthcare providers about potential dangers of taking interacting OTC products in combination with apixaban, and data are needed on outcomes associated with concomitant apixaban-OTC product use. J Am Geriatr Soc 68:155-162, 2019.

DOI: 10.1111/jgs.16193
PMCID: PMC7141171
PMID: 31658372

14. Vitamin and herbal supplements' use among patients with advanced gastrointestinal cancers included in eight clinical trials. Abdel-Rahman O, Spratlin J, Koski S.

J Cancer Res Clin Oncol. 2020 Aug;146(8):2089-2097. doi: 10.1007/s00432-020-03201-1. Epub 2020 Mar 29.

OBJECTIVE: To evaluate the patterns of vitamin and herbal supplement use among patients with advanced gastrointestinal (GI) cancers and the association of such behavior with the efficacy and toxicity of systemic anticancer treatment. METHODS: Project data sphere (PDS) was used to access de-identified datasets of eight clinical trials of advanced GI cancers. Multivariable logistic regression analysis was used to identify factors predicting the use of supplements. Kaplan-Meier survival estimates were used to evaluate the association of supplement use with overall and progression-free survival. Results were stratified according to the site of the primary tumor [pancreatic, gastric, colorectal or hepatocellular carcinoma (HCC)] The association between supplement use and selected chemotherapy side effects was evaluated through Chi-squared testing and subsequent logistic regression. RESULTS: A total of 3441 patients were included in the analysis. Of these, 775 patients reported use of supplements and 2666 patients reported no use of supplements. Higher ECOG performance score (Odds ratio: OR for ECOG 1 versus 0: 1.629; 95% CI 1.363-1.947; $P < 0.001$) and pancreatic primary site (OR for gastric cancer versus pancreatic cancer: 0.538; 95% CI 0.408-0.709; $P < 0.001$) was associated with greater use of these supplements. Supplement use was associated with a better overall survival among patients with pancreatic cancer ($P = 0.002$) but not other GI malignancies. Supplement use was associated with a higher probability of anemia and diarrhea among patients with pancreatic cancer ($P < 0.001$ for both), gastric cancer ($P = 0.016$; $P = 0.036$, respectively) and colorectal cancer ($P < 0.001$ for both). CONCLUSIONS: There is an association between the use of vitamin and herbal supplements and a higher probability of hematologic and gastrointestinal toxicities. There is a need for more studies to confirm the association between such behavior and better overall survival among patients with pancreatic cancer.

DOI: 10.1007/s00432-020-03201-1
PMID: 32227265 [Indexed for MEDLINE]