

AACT Herbal Dietary Supplements SIG Abstracts July 2017

1. A nationwide study of the incidence rate of herb-induced liver injury in Korea. Cho JH, Oh DS, Hong SH, Ko H, Lee NH, Park SE, Han CW, Kim SM, Kim YC, Kim KS, Choi CW, Shin SM, Kim KT, Choi HS, Lee JH, Kim JY, Kang JY, Lee DS, Ahn YC, Son CG.

Arch Toxicol. 2017 Jun 20. doi: 10.1007/s00204-017-2007-9. [Epub ahead of print]

Discrepant incidence has been reported regarding the incidence of herb-induced liver injury (HILI). To address the growing worldwide concern of HILI, we evaluated the risk of HILI in a nationwide prospective study. Between April 2013 and January 2016, 1001 inpatients (360 males and 641 females) from 10 tertiary hospitals throughout South Korea were treated with herbal drugs and had their liver enzymes periodically measured. A total of six patients met the criteria for HILI with RUCAM scores ranging from 4 to 7. All these participants were women and developed the hepatocellular type of HILI. One HILI participant met the criteria for Hy's law; however, none of six cases presented clinical symptoms related to liver injury. This is the first nationwide prospective study that estimated the extent of the incidence of HILI [total: 0.60%, 95% confidence interval (CI) 0.12-1.08; women: 0.95%, 95% CI 0.19-1.68] and described its features in hospitalized participants.

DOI: 10.1007/s00204-017-2007-9

PMID: 28634823

2. Hepatotoxicity associated with weight loss or sports dietary supplements, including OxyELITE Pro™ - United States, 2013. Chatham-Stephens K, Taylor E, Chang A, Peterson A, Daniel J, Martin C, Deuster P, Noe R, Kieszak S, Schier J, Klontz K, Lewis L.

Drug Test Anal. 2017 Jan;9(1):68-74. doi: 10.1002/dta.2036. Epub 2016 Aug 4.

In September 2013, the Hawaii Department of Health (HDOH) was notified of seven adults who developed acute hepatitis after taking OxyELITE Pro™, a weight loss and sports dietary supplement. CDC assisted HDOH with their investigation, then conducted case-finding outside of Hawaii with FDA and the Department of Defense (DoD). We defined cases as acute hepatitis of unknown etiology that occurred from April 1, 2013, through December 5, 2013, following exposure to a weight loss or muscle-building dietary supplement, such as OxyELITE Pro™. We conducted case-finding through multiple sources, including data from poison centers (National Poison Data System [NPDS]) and FDA MedWatch. We identified 40 case-patients in 23 states and two military bases with acute hepatitis of unknown etiology and exposure to a weight loss or muscle building dietary supplement. Of 35 case-patients who reported their race, 15 (42.9%) reported white and 9 (25.7%) reported Asian. Commonly reported symptoms included jaundice, fatigue, and dark urine. Twenty-five (62.5%) case-patients reported taking OxyELITE Pro™. Of these 25 patients, 17 of 22 (77.3%) with available data were hospitalized and 1 received a liver transplant. NPDS and FDA MedWatch each captured seven (17.5%) case-patients. Improving the ability to search surveillance systems like NPDS and FDA MedWatch for individual and grouped dietary supplements, as well as coordinating case-finding with DoD, may benefit ongoing surveillance efforts and future outbreak responses involving adverse health effects from dietary supplements. This investigation highlights opportunities and challenges in using multiple sources to identify cases of suspected supplement associated adverse events.

DOI: 10.1002/dta.2036

PMID: 27367536 [Indexed for MEDLINE]

3. Urgent Liver Transplantation for Dietary Supplements: An Under-Recognized Problem. Wong LL, Lacar L, Roytman M, Orloff SL.

Transplant Proc. 2017 Mar;49(2):322-325. doi: 10.1016/j.transproceed.2016.11.041.

BACKGROUND: The recent outbreak of acute liver failure caused by herbal/dietary supplements (HDS) in Hawaii prompted evaluation of those patients who underwent emergency liver transplantation (LT) for HDS in the United States. **METHODS:** We queried the Scientific Registry of Transplant Recipients (2003-2015) to identify patients who underwent urgent LT for acute hepatic necrosis (AHN) and identified those with HDS use. This group of patients was then characterized. **RESULTS:** Of 2408 adult cases, 625 were characterized as a drug-induced liver injury. The majority of cases (n = 300) were due to acetaminophen toxicity, but the fourth highest category was due to HDS (n = 21). Of these 21 cases caused by HDS, 13 did not list the specific agent responsible, mean age was 36 years, and all cases occurred after 2007. There probably are more cases because 25% of all LT cases in the study did not list a specific reason for liver failure and 20% of all drug-induced liver failure did not list a specific drug. **CONCLUSIONS:** Herbal/supplement use is the fourth most common cause of drug-induced AHN requiring LT, albeit an underestimation of the problem. Detailed questioning of patients and their support systems regarding herbal/supplement use and better reporting are imperative to further define this problem and identify products that have the potential to lead to liver failure.

DOI: 10.1016/j.transproceed.2016.11.041
PMID: 28219592 [Indexed for MEDLINE]

4. Dangerous dietary supplements: Garcinia cambogia-associated hepatic failure requiring transplantation. Lunsford KE, Bodzin AS, Reino DC, Wang HL, Busuttill RW.

World J Gastroenterol. 2016 Dec 7;22(45):10071-10076. doi: 10.3748/wjg.v22.i45.10071.

Commercial dietary supplements are marketed as a panacea for the morbidly obese seeking sustainable weight-loss. Unfortunately, many claims cited by supplements are unsupported and inadequately regulated. Most concerning, however, are the associated harmful side effects, often unrecognized by consumers. Garcinia cambogia extract and Garcinia cambogia containing products are some of the most popular dietary supplements currently marketed for weight loss. Here, we report the first known case of fulminant hepatic failure associated with this dietary supplement. One active ingredient in this supplement is hydroxycitric acid, an active ingredient also found in weight-loss supplements banned by the Food and Drug Administration in 2009 for hepatotoxicity. Heightened awareness of the dangers of dietary supplements such as Garcinia cambogia is imperative to prevent hepatotoxicity and potential fulminant hepatic failure in additional patients.

DOI: 10.3748/wjg.v22.i45.10071
PMCID: PMC5143754
PMID: 28018115 [Indexed for MEDLINE]

5. Hepatotoxicity by herbs: a practical review of a neglected disease. Donet JA, Sornmayura K, Gulau M, Schiff E.

Rev Gastroenterol Peru. 2016 Oct-Dec;36(4):350-353.

Herbs are commonly used worldwide for the treatment of various diseases, constituting a multi-billion dollar market. Unfortunately, hepatotoxicity induced by herbs is also common. The true incidence and prevalence are not known. There is need for more strict regulations and experimental and pre-clinical studies regarding its efficacy and safety. There is no gold standard for the diagnosis of herbs-induced liver injury (HILI) and it constitutes a diagnostic challenge for the clinician, where establishing causality could be cumbersome. Clinical presentation varies from asymptomatic cases with mildly abnormal liver tests to fulminant liver failure requiring liver transplantation. In this review, we will discuss the epidemiology, clinical manifestations, challenges and diagnostic approach of HILI and will also present some exemplary cases from the University of Miami, Division of Hepatology.

PMID: 28062872 [Indexed for MEDLINE]

6. Hepatotoxicity evaluation of traditional Chinese medicines using a computational molecular model. Zhao P, Liu B, Wang C; Acute Liver Failure Study Team (ALFST).

Clin Toxicol (Phila). 2017 Jun 8;1. doi: 10.1080/15563650.2017.1333123. [Epub ahead of print]

BACKGROUND: Liver injury caused by traditional Chinese medicines (TCMs) is reported from many countries around the world. TCM hepatotoxicity has attracted worldwide concerns. **OBJECTIVE:** This study aims to develop a more applicable and optimal tool to evaluate TCM hepatotoxicity. **METHODS:** A quantitative structure-activity relationship (QSAR) analysis was performed based on published data and U.S. Food and Drug Administration's Liver Toxicity Knowledge Base (LTKB). **RESULTS:** Eleven herbal ingredients with proven liver toxicity in the literature were added into the dataset besides chemicals from LTKB. The finally generated QSAR model yielded a sensitivity of 83.8%, a specificity of 70.1%, and an accuracy of 80.2%. Among the externally tested 20 ingredients from TCMs, 14 hepatotoxic ingredients were all accurately identified by the QSAR model derived from the dataset containing natural hepatotoxins. **CONCLUSIONS:** Adding natural hepatotoxins into the dataset makes the QSAR model more applicable for TCM hepatotoxicity assessment, which provides a right direction in the methodology study for TCM safety evaluation. The generated QSAR model has the practical value to prioritize the hepatotoxicity risk of TCM compounds. Furthermore, an open-access international specialized database on TCM hepatotoxicity should be quickly established.

DOI: 10.1080/15563650.2017.1333123
PMID: 28594241

7. The Incidence of Drug- and Herbal and Dietary Supplement-Induced Liver Injury: Preliminary Findings from Gastroenterologist-Based Surveillance in the Population of the State of Delaware. Vega M, Verma M, Beswick D, Bey S, Hossack J, Merriman N, Shah A, Navarro V; Drug Induced Liver Injury Network (DILIN).

Drug Saf. 2017 May 29. doi: 10.1007/s40264-017-0547-9. [Epub ahead of print]

BACKGROUND AND AIM: The population-based incidence rate of drug-induced liver injury (DILI) in the USA is not known. The Drug-Induced Liver Injury Network (DILIN) accrues cases of hepatotoxicity due to medications and herbal and dietary supplements (HDS) from limited geographical areas. The current analysis was an ancillary study of DILIN aimed at determining the annual incidence of DILI in the USA on a population basis, through surveillance in the state of Delaware. **METHODS:** At the outset of the study, there were 41 gastroenterologists in the state of Delaware and all agreed to participate in surveillance for DILI, which comprised active reporting of suspected cases to the DILIN. The gastroenterologists underwent training in the diagnosis of DILI and were provided with DILIN inclusion criteria. Only cases that met the DILIN laboratory inclusion criteria in 2014 were included in the incidence calculation, and these patients were invited to participate in the DILIN Prospective Study. The number of suspected cases that met inclusion criteria served as the numerator and the 2014 Delaware adult population as the denominator. **RESULTS:** During 2014, 23 patients were identified by the surveillance network, 20 of whom met DILIN laboratory inclusion criteria, leading to an incidence of 2.7 cases of DILI per 100,000 adult residents [95% confidence interval (CI) 1.5-3.9 per 100,000]. Fourteen subjects agreed to participate in the DILIN; six declined. Among enrolled cases, the mean age was 51 years, 57% were women, and 71% were white. Eight cases were attributed to antibiotics (36%) and other drugs (21%) and six to HDS (43%). The pattern of injury was hepatocellular in all HDS cases, but only 50% of conventional drug cases ($p = 0.05$), which more commonly presented with eosinophilia ($p = 0.47$) and higher alkaline phosphatase levels ($p = 0.05$). Half of patients were jaundiced, none developed liver failure, and all recovered without the need for transplantation. **CONCLUSION:** Prospective, gastroenterologist-based surveillance for suspected DILI in Delaware yielded an incidence of 2.7 cases per 100,000 adults in 2014; this is the first prospective estimate of DILI for the USA. Because surveillance was limited to subspecialists, the actual incidence of DILI is likely to be higher. These findings provide a benchmark statistic for the epidemiology of DILI in the United States, to be refined with expansion of the surveillance period.

DOI: 10.1007/s40264-017-0547-9
PMID: 28555362

8. Prediction models for drug-induced hepatotoxicity by using weighted molecular fingerprints. Kim E, Nam H.

BMC Bioinformatics. 2017 May 31;18(Suppl 7):227. doi: 10.1186/s12859-017-1638-4.

BACKGROUND: Drug-induced liver injury (DILI) is a critical issue in drug development because DILI causes failures in clinical trials and the withdrawal of approved drugs from the market. There have been many attempts to predict the risk of DILI based on in vivo and in silico identification of hepatotoxic compounds. In the current study, we propose the in silico prediction model predicting DILI using weighted molecular fingerprints. **RESULTS:** In this study, we used 881 bits of molecular fingerprint and used as features describing presence or absence of each substructure of compounds. Then, the Bayesian probability of each substructure was calculated and labeled (positive or negative for DILI), and a weighted fingerprint was determined from the ratio of DILI-positive to DILI-negative probability values. Using weighted fingerprint features, the prediction models were trained and evaluated with the Random Forest (RF) and Support Vector Machine (SVM) algorithms. The constructed models yielded accuracies of 73.8% and 72.6%, AUCs of 0.791 and 0.768 in cross-validation. In independent tests, models achieved accuracies of 60.1% and 61.1% for RF and SVM, respectively. The results validated that weighted features helped increase overall performance of prediction models. The constructed models were further applied to the prediction of natural compounds in herbs to identify DILI potential, and 13,996 unique herbal compounds were predicted as DILI-positive with the SVM model. **CONCLUSIONS:** The prediction models with weighted features increased the performance compared to non-weighted models. Moreover, we predicted the DILI potential of herbs with the best performed model, and the prediction results suggest that many herbal compounds could have potential to be DILI. We can thus infer that taking natural products without detailed references about the relevant pathways may be dangerous. Considering the frequency of use of compounds in natural herbs and their increased application in drug development, DILI labeling would be very important.

DOI: 10.1186/s12859-017-1638-4
PMID: 28617228

9. Moderate doses of commercial preparations of Ginkgo biloba do not alter markers of liver function but moderate alcohol intake does: A new approach to identify and quantify biomarkers of 'adverse effects' of dietary supplements. Lieberman HR, Kellogg MD, Fulgoni VL 3rd, Agarwal S.

Regul Toxicol Pharmacol. 2017 Mar;84:45-53. doi: 10.1016/j.yrtph.2016.12.010. Epub 2016 Dec 24.

It is difficult to determine if certain dietary supplements are safe for human consumption. Extracts of leaves of Ginkgo biloba trees are dietary supplements used for various purported therapeutic benefits. However, recent studies reported they increased risk of liver cancer in rodents. Therefore, this study assessed the association between ginkgo consumption and liver function using NHANES 2001-2012 data (N = 29,684). Since alcohol is known to adversely affect liver function, association of its consumption with liver function was also assessed. Alcohol and ginkgo extract intake of adult consumers and clinical markers of liver function (alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, gamma glutamyl transferase, lactate dehydrogenase, bilirubin) were examined. Moderate

consumers of alcohol (0.80 ± 0.02 drinks/day) had higher levels of aspartate aminotransferase and gamma glutamyl transferase than non-consumers ($P < 0.001$). There was no difference ($P > 0.01$) in levels of markers of liver function in 616 ginkgo consumers (65.1 ± 4.4 mg/day intake) compared to non-consumers. While moderate alcohol consumption was associated with changes in markers of liver function, ginkgo intake as typically consumed by U.S. adults was not associated with these markers. Biomarkers measured by NHANES may be useful to examine potential adverse effects of dietary supplements for which insufficient human adverse event and toxicity data are available.

DOI: 10.1016/j.yrtph.2016.12.010

PMID: 28025058 [Indexed for MEDLINE]

10. The increasing problem of subclinical and overt hypervitaminosis D in India: An institutional experience and review. Sharma LK, Dutta D, Sharma N, Gadpayle AK

Nutrition 2017 Feb;34:76–81

<http://dx.doi.org/10.1016/j.nut.2016.09.014>

Objective: The aim of this study was to determine the changes in serum vitamin D distribution at an institute in India over the past 6 y and compare it with global trends. **Methods:** We conducted an audit of 25-hydroxyvitamin D (25-OHD), calcium, and plasma intact parathyroid hormone (iPTH) reporting from January 2011 to February 2016. **References for review** were identified through searches of PubMed, Medline, and Embase for articles published until February 2016 using keywords “hypervitaminosis D” (MeSH Terms) OR “vitamin D toxicity” (All Fields) OR “vitamin-D intoxication” (All Fields). **Results:** Reports of 25-OHD from 5527 patients were analyzed. Calcium and iPTH were available for 5501 (99.5%) and 1787 (32.3%) patients, respectively. Vitamin D deficiency and insufficiency were observed in 59.4 and 77.3%. Hypervitaminosis D (25-OHD >250 nmol/L) was noted in 225 (4.1%) patients, of whom 151 (2.7%) had vitamin D intoxication (25-OHD >375 nmol/L). We found that 46.22% (104 of 225) patients with hypervitaminosis D and 62.25% (94 of 151) with vitamin D intoxication had elevated calcium or suppressed iPTH. Orthopedic, pediatric, and surgery patients had the highest rates of hypervitaminosis D (7.9, 7.2, and 7% respectively; $P < 0.001$). An increasing trend for hypervitaminosis D was observed (1.48, 3.62, 3.90, 4.78, 6.21, and 7.82% in 2011, 2012, 2013, 2014, 2015, and 2016, respectively). A similar steady upward trend in 25-OHD has been reported in Ireland, England, Canada, and Australia. However, hypervitaminosis D reports are scant and have not increased over the years in the developed world. **Conclusion:** There is a global secular trend of increases in 25-OHD over years. There is a disturbing trend of increased hypervitaminosis D at an Indian institute. Empiric, unmonitored, prolonged vitamin D supplementation, using non-recommended supraphysiological doses, especially when administered intramuscularly, should be discouraged.

11. Trends in Use of High-Dose Vitamin D Supplements Exceeding 1000 or 4000 International Units Daily, 1999-2014. Rooney MR, Harnack L, Michos ED, Ogilvie RP, Sempos CT, Lutsey PL.

JAMA. 2017 Jun 20;317(23):2448-2450. doi: 10.1001/jama.2017.4392.

DOI: 10.1001/jama.2017.4392

PMID: 28632857

12. Prevalence, Adverse Events, and Factors Associated with Dietary Supplement and Nutritional Supplement Use by US Navy and Marine Corps Personnel. Knapik JJ, Trone DW, Austin KG, Steelman RA, Farina EK, Lieberman HR.

J Acad Nutr Diet. 2016 Sep;116(9):1423-42. doi: 10.1016/j.jand.2016.02.015. Epub 2016 Apr 12.

BACKGROUND: About 50% of Americans and 60% to 70% of US military personnel use dietary supplements, some of which have been associated with adverse events (AEs). Nutritional supplements like sport drinks and sport bars/gels are also commonly used by athletes and service members. Previous dietary supplement and nutritional supplement surveys were conducted on Army, Air Force, and Coast Guard personnel. **OBJECTIVE:** The aim of this cross-sectional study was to investigate dietary and nutritional supplement use in Navy and Marine Corps personnel, including the prevalence, types, factors associated with use, and AEs. **DESIGN:** A random sample of 10,000 Navy and Marine Corps personnel were contacted. Service members were asked to complete a detailed questionnaire describing their personal characteristics, supplement use, and AEs experienced. **RESULTS:** In total, 1,708 service members completed the questionnaire during August through December 2014, with 1,683 used for analysis. Overall, 73% reported using dietary supplements one or more times per week. The most commonly used dietary supplements (used one or more times per week) were multivitamins/multiminerals (48%), protein/amino acids (34%), combination products (33%), and individual vitamins and minerals (29%). About 31% of service members reported using five or more dietary supplements. Sport drinks and sport bars/gels were used by 45% and 23% of service members, respectively. Monthly expenditures on dietary supplements averaged \$39; 31% of service members spent \geq \$50/mo. Multivariate logistic regression modeling indicated that female sex (women/men; odds ratio [OR]=1.76, 95% CI 1.32 to 2.36), higher educational level (college degree/no college degree; OR=2.23, 95% CI 1.62 to 3.30), higher body mass index (calculated as kg/m^2) (≥ 30 / <25 ; OR=1.67, 95% CI 1.06 to 2.63), and a greater amount of resistance

training ($\geq 271/0$ to 45 min/week; OR=2.85, 95% CI 1.94 to 4.17) were associated with dietary supplement use. Twenty-two percent of dietary supplement users and 6% of nutritional supplement users reported one or more AEs. For combination products alone, 29% of users reported one or more AEs. CONCLUSIONS: The prevalence of dietary supplement use in Navy and Marine Corps personnel was considerably higher than reported in civilian investigations for almost all types of dietary supplements, although similar to most other military services. Factors associated with dietary supplement use were similar to those reported in previous military and civilian investigations. Prevalence of self-reported AEs was very high, especially for combination products.

13. Changes in the Supplementation Practices of Elite Australian Swimmers Over 11 Years. Shaw G, Slater G, Burke LM.

Int J Sport Nutr Exerc Metab. 2016 Dec;26(6):565-571. doi: 10.1123/ijsnem.2016-0060. Epub 2016 Aug 24.

Thirty nine elite Australian swimmers (13 AIS, 26 OTHER) completed a standardized questionnaire regarding their supplement use during a pre competition camp. The data were compared with a similar study conducted 11 years earlier (11 AIS, 23 OTHER) and framed around the classification system of the Sport Supplement Program of the Australian Institute of Sport. The prevalence of supplement use remained constant over time (2009: 97%, 1998: 100%). However, the current swimmers used a greater number of dietary supplements (9.2 ± 3.7 and 5.9 ± 2.9 ; $p = .001$), accounted for by an increase in the reported use of supplements with a greater evidence base (Sports Foods, Ergogenics, and Group B supplements). In contrast, fewer supplements considered less reputable (Group C and D) were reported by the 2009 cohort (0.7 ± 1.0 and 1.6 ± 1.3 ; $p = .003$). AIS swimmers reported a greater use of Ergogenics (4.3 ± 1.8 and 3.1 ± 1.7 ; $p = .002$), and less use of Group C and D supplements overall (0.8 ± 1.2 and 1.3 ± 1.2 ; $p = .012$), which was explained primarily by a smaller number of these supplements reported by the 2009 group (1998 AIS: 1.5 ± 1.4 , 2009 AIS: 0.2 ± 0.6 ; $p = .004$). Although the prevalence of supplement use has not changed over time, there has been a significant increase in the number and type of products they are using. The potential that these changes can be attributed to a Sports Supplement Program merit investigation.

DOI: 10.1123/ijsnem.2016-0060

PMID: 27206222 [Indexed for MEDLINE]

14. Natural products modulating the hERG channel: heartaches and hope. Kratz JM, Grienke U, Scheel O, Mann SA, Rollinger JM.

Nat Prod Rep. 2017 May 12. doi: 10.1039/c7np00014f. [Epub ahead of print]

The human Ether-à-go-go Related Gene (hERG) channel is a voltage-gated potassium channel playing an essential role in the normal electrical activity in the heart. It is involved in the repolarization and termination of action potentials in excitable cardiac cells. Mutations in the hERG gene and hERG channel blockage by small molecules are associated with increased risk of fatal arrhythmias. Several drugs have been withdrawn from the market due to hERG channel-related cardiotoxicity. Moreover, as a result of its notorious ligand promiscuity, this ion channel has emerged as an important antitarget in early drug discovery and development. Surprisingly, the hERG channel blocking profile of natural compounds present in frequently consumed botanicals (i.e. dietary supplements, spices, and herbal medicinal products) is not routinely assessed. This comprehensive review will address these issues and provide a critical compilation of hERG channel data for isolated natural products and extracts over the past two decades (1996-2016). In addition, the review will provide (i) a solid basis for the molecular understanding of the physiological functions of the hERG channel, (ii) the translational potential of in vitro/in vivo results to cardiotoxicity in humans, (iii) approaches for the identification of hERG channel blockers from natural sources, (iv) future perspectives for cardiac safety guidelines and their applications within phytopharmaceuticals and dietary supplements, and (v) novel applications of hERG channel modulation (e.g. as a drug target).

DOI: 10.1039/c7np00014f

PMID: 28497823

15. Herbal Supplements Association with Reversible Cerebral Vasoconstriction Syndrome: A Case Report. Costa I, Mendonça MD, Cruz E Silva V, Calado S, Viana-Baptista M.

J Stroke Cerebrovasc Dis. 2017 Mar;26(3):673-676. doi: 10.1016/j.jstrokecerebrovasdis.2016.11.125. Epub 2016 Dec 27.

BACKGROUND: Reversible cerebral vasoconstriction syndrome (RCVS) is a clinico-radiologic syndrome characterized by thunderclap headache and reversible multifocal arterial constrictions that resolves within 3 months. RCVS can be either spontaneous or related to a trigger; vasoactive drugs including over-the-counter medicine are common culprits. Nevertheless, there are sparse data on the association of herbal supplements in the genesis of unexplained RCVS. METHODS: We describe a case of RCVS with a temporal association with the consumption of a diet pill composed of green tea, L-carnitine, and conjugated linoleic acid. We reviewed the literature describing RCVS cases associated with consumption of herbal supplements or plants. RESULTS: A 50-year-old black woman presented at

the emergency room with a thunderclap headache less than 1 week after beginning a new herbal supplement with weight loss purpose. Angiographic study revealed multiple arterial constriction of virtually all intracranial territories that were reversed 28 days later. The patient was discharged with minimal symptoms. From our review, we identified 5 previous reports of herbal product-related triggers. **CONCLUSIONS:** Different factors can trigger RCVS. Besides our case, at least 5 other nutraceutical products were described to be associated with the disorders, 3 of them in patients without any other clear cause. Clinicians should be aware of the possible role of herbal supplements in RCVS, and their use should be systematically assessed in large RCVS cohorts to clarify this association.

DOI: 10.1016/j.jstrokecerebrovasdis.2016.11.125

PMID: 28038897 [Indexed for MEDLINE]

16. Cardiomyopathy Related to a Weight Loss Supplement: A Case Report and Review of Literature. Murtaza G, Adhikari S, Siddiqui I, Lu H, Kuruvilla A.

J Investig Med High Impact Case Rep. 2017 Jun 2;5(2):2324709617711462. doi: 10.1177/2324709617711462. eCollection 2017 Apr-Jun.

There are various etiologies of dilated cardiomyopathy. However, in young patients without a strong family history of cardiovascular disease, alcohol or drug abuse, viral infections, and absence of endocrine and metabolic abnormalities, ischemia is an unlikely cause. We present an interesting case of a young female without traditional risk factors who developed dilated cardiomyopathy following administration of a weight loss supplement xenadrine and had resolution of symptoms after discontinuation of the supplement.

DOI: 10.1177/2324709617711462

PMCID: PMC5459224

PMID: 28616440

17. [Anticholinergic syndrome caused by contaminated herbal tea; acting swiftly to identify the source]. [Article in Dutch]. Oerlemans C, de Vries I, van Riel AJHP.

Ned Tijdschr Geneeskd. 2017;161(0):D1261.

BACKGROUND: Despite good manufacturing practice and quality control, consumer products can become contaminated. In some cases, this can result in severe and life-threatening intoxication with potentially fatal consequences. **CASE DESCRIPTION:** A 27-year-old man and a 28-year-old pregnant woman presented to the Emergency Department with severe anticholinergic syndrome after using a marshmallow root (*Althaea officinalis*) herbal remedy, mixed into hot chocolate drink, to reduce symptoms of common cold. After a short stay in Intensive Care, the symptoms diminished and the patients could be released from hospital. The herbs were found to be contaminated with atropine, most probably derived from deadly nightshade (*Atropa belladonna*). Analyses of the contaminated product indicated that the patients were exposed to 20-200 mg atropine, while a dose of 2 mg is already considered mildly toxic. **CONCLUSION:** Consultation of the Dutch National Poisons Information Center resulted in rapid detection of the contamination; close collaboration with the Netherlands Food and Consumer Product Safety Authority and the manufacturer of the product allowed rapid identification of the source of contamination and facilitated the prevention of an epidemic.

PMID: 28612694

18. The effects of kratom on restraint-stress-induced analgesia and its mechanisms of action. Vázquez López JL, Schild L, Günther T, Schulz S, Neurath H, Becker A.

J Ethnopharmacol. 2017 Jun 9;205:178-185. doi: 10.1016/j.jep.2017.05.008. Epub 2017 May 10.

ETHNOPHARMACOLOGICAL RELEVANCE: *Mitragyna speciosa* and its extracts are called kratom (dried leaves, extract). They contain several alkaloids with an affinity for different opioid receptors. They are used in traditional medicine for the treatment of different diseases, as a substitute by opiate addicts, and to mitigate opioid withdrawal symptoms. Apart from their medical properties, they are used to enhance physical endurance and as a means of overcoming stress. **PURPOSE:** The aim of this study was to determine the mechanisms underlying the effects of kratom on restraint-stress-induced analgesia which occurs during or following exposure to a stressful or fearful stimulus. **METHODS:** To gain further insights into the action of kratom on stress, we conducted experiments using restraint stress as a test system and stress-induced analgesia as a test parameter. Using transgenic mu opioid-receptor (MOR) deficient mice, we studied the involvement of this receptor type. We used nor-binaltorphimine (BNT), an antagonist at kappa opioid receptors (KOR), to study functions of this type of receptor. Membrane potential assay was also employed to measure the intrinsic activity of kratom in comparison to U50,488, a highly selective kappa agonist. **RESULTS:** Treatment with kratom diminished stress-induced analgesia in wildtype and MOR knockout animals. Pretreatment of MOR deficient mice with BNT resulted in similar effects. In comparison to U50,488, kratom exhibited negligible

intrinsic activity at KOR alone. CONCLUSIONS: The results suggest that the use of kratom as a pharmacological tool to mitigate withdrawal symptoms is related to its action on KOR.

DOI: 10.1016/j.jep.2017.05.008
PMID: 28501425

19. Herbal Highs: Review on Psychoactive Effects and Neuropharmacology. Graziano S, Orsolini L, Rotolo MC, Tittarelli R, Schifano F, Pichini S.

Curr Neuropharmacol. 2017;15(5):750-761. doi: 10.2174/1570159X14666161031144427.

BACKGROUND: A new trend among users of new psychoactive substances' the consumption of "herbal highs": plant parts containing psychoactive substances. Most of the substances extracted from herbs, in old centuries were at the centre of religious ceremonies of ancient civilizations. Currently, these herbal products are mainly sold by internet web sites and easily obtained since some of them have no legal restriction. OBJECTIVE: We reviewed psychoactive effects and neuropharmacology of the most used "herbal highs" with characterized active principles, with studies reporting mechanisms of action, pharmacological and subjective effects, eventual secondary effects including intoxications and/or fatalities Method: The PubMed database was searched using the following key words: herbal highs, *Argyrea nervosa*, *Ipomoea violacea* and *Rivea corymbosa*; *Catha edulis*; *Datura stramonium*; *Piper methysticum*; *Mitragyna speciosa*. RESULTS: Psychoactive plants here reviewed have been known and used from ancient times, even if for some of them limited information still exist regarding subjective and neuropharmacological effects and consequent eventual toxicity when plants are used alone or in combination with "classical" drugs of abuse. CONCLUSION: Some "herbal highs" should be classified as harmful drugs since chronic administration has been linked with addiction and cognitive impairment; for some others taking into consideration only the recent trends of abuse, studies investigating these aspects are lacking.

DOI: 10.2174/1570159X14666161031144427
PMID: 27799032

20. Thujone inhibits the function of $\alpha 7$ -nicotinic acetylcholine receptors and impairs nicotine-induced memory enhancement in one-trial passive avoidance paradigm. Sultan A, Yang KS, Isaev D, Nebrisi EE, Syed N, Khan N, Howarth CF, Sadek B, Oz M.

Toxicology. 2017 Jun 1;384:23-32. doi: 10.1016/j.tox.2017.04.005. Epub 2017 Apr 7.

Effects of thujone, a major ingredient of absinthe, wormwood oil and some herbal medicines, were tested on the function of $\alpha 7$ subunit of the human nicotinic acetylcholine ($\alpha 7$ nACh) receptor expressed in *Xenopus* oocytes using the two-electrode voltage-clamp technique. Thujone reversibly inhibited ACh (100 μ M)-induced currents with an IC50 value of 24.7 μ M. The effect of thujone was not dependent on the membrane potential and did not involve Ca(2+)-dependent Cl(-) channels expressed endogenously in oocytes. Inhibition by thujone was not reversed by increasing ACh concentrations. Moreover, specific binding of [(125)I] α -bungarotoxin was not altered by thujone. Further experiments in SH-EP1 cells expressing human $\alpha 7$ nACh receptor indicated that thujone suppressed choline induced Ca(2+) transients in a concentration-dependent manner. In rat hippocampal CA3-dentate gyrus synapses, nicotine-induced enhancement of long-term potentiation was also inhibited by thujone. Furthermore, the results observed in in-vivo one-trial passive avoidance paradigm show that thujone (1.25mg/kg, i.p.) significantly impaired nicotine-induced enhancement of learning and memory in Wistar rats. Collectively, our results indicate that thujone inhibits the function of the $\alpha 7$ -nACh receptor and impairs cellular and behavioral correlates of cholinergic modulation of learning and memory.

DOI: 10.1016/j.tox.2017.04.005
PMID: 28395994 [Indexed for MEDLINE]

21. Woman With Yellow Palms and Soles. Wang ZS, Liu XK, Li J.

JAMA. 2017 Apr 18;317(15):1574-1575. doi: 10.1001/jama.2017.1229.

DOI: 10.1001/jama.2017.1229
PMID: 28418462 [Indexed for MEDLINE]

22. Possible Parkinson's Disease Induced by Chronic Manganese Supplement Ingestion. Schuh MJ.

Consult Pharm. 2016 Dec 1;31(12):698-703. doi: 10.4140/TCP.n.2016.698.

OBJECTIVE: The objective is to report a case of possible neurotoxicity resulting from an incorrect dietary supplement for osteoporosis taken at a toxic dose. SUMMARY: The case study examined here is a 37-year-old African-American female who consumed excessive manganese over a period of years, resulting in Parkinson's disease (PD). This patient

was referred to the pharmacist pharmacotherapy service by a neurology physician. PD has been shown in the medical literature to be caused by chronic exposure to high levels of manganese. It may be concluded that daily doses of manganese well above the upper limit of 9 mg per day were taken by this patient for an extended period of time, possibly causing PD via manganism. **CONCLUSION:** This case illustrates the unknown risks taken by patients who use excessive amounts of over-the-counter herbals and supplements and how pharmacists can assist patients and physicians in the proper use of these popular products.

DOI: 10.4140/TCP.n.2016.698

PMID: 28074748 [Indexed for MEDLINE]

23. Lead Poisoning Can Be Easily Misdiagnosed as Acute Porphyria and Nonspecific Abdominal Pain. Tsai MT, Huang SY, Cheng SY.

Case Rep Emerg Med. 2017;2017:9050713. doi: 10.1155/2017/9050713. Epub 2017 May 29.

Lead poisoning (LP) is less commonly encountered in emergency departments (ED). However, lead exposure still occurs, and new sources of poisoning have emerged. LP often goes unrecognized due to a low index of suspicion and nonspecific symptoms. We present a case of a 48-year-old man who had recurring abdominal pain with anemia that was misdiagnosed. His condition was initially diagnosed as nonspecific abdominal pain and acute porphyria. Acute porphyria-like symptoms with a positive urine porphyrin test result led to the misdiagnosis; testing for heme precursors in urine is the key to the differential diagnosis between LP and acute porphyria. The final definitive diagnosis of lead toxicity was confirmed based on high blood lead levels after detailed medical history taking. The lead poisoning was caused by traditional Chinese herbal pills. The abdominal pain disappeared after a course of chelating treatment. The triad for the diagnosis of lead poisoning should be a history of medicine intake, anemia with basophilic stippling, and recurrent abdominal pain.

DOI: 10.1155/2017/9050713

PMCID: PMC5467293

PMID: 28630774

24. Liver abscess and bacteremia caused by lactobacillus: role of probiotics? Case report and review of the literature. Sherid M, Samo S, Sulaiman S, Husein H, Sifuentes H, Sridhar S.

BMC Gastroenterol. 2016 Nov 18;16(1):138.

BACKGROUND: Lactobacilli are non-spore forming, lactic acid producing, gram-positive rods. They are a part of the normal gastrointestinal and genitourinary microbiota and have rarely been reported to be the cause of infections. Lactobacilli species are considered non-pathogenic organisms and have been used as probiotics to prevent antibiotic associated diarrhea. There are sporadic reported cases of infections related to lactobacilli containing probiotics. **CASE PRESENTATION:** In this paper we discuss a case of an 82 year old female with liver abscess and bacteremia from lactobacillus after using probiotics containing lactobacilli in the course of her treatment of Clostridium difficile colitis. The Lactobacillus strain identification was not performed and therefore, both commensal microbiota and the probiotic product should be considered as possible sources of the strain. **CONCLUSION:** Lactobacilli can lead to bacteremia and liver abscesses in some susceptible persons and greater awareness of this potential side effect is warranted with the increasing use of probiotics containing lactobacilli.

DOI: 10.1186/s12876-016-0552-y

PMCID: PMC5116133

PMID: 27863462 [Indexed for MEDLINE]

25. Which potential harms and benefits of using ginger in the management of nausea and vomiting of pregnancy should be addressed? a consensual study among pregnant women and gynecologists. Shawahna R, Taha A.

BMC Complement Altern Med. 2017 Apr 8;17(1):204. doi: 10.1186/s12906-017-1717-0.

BACKGROUND: Nausea and vomiting of pregnancy (NVP) affect approximately 80-90% of the pregnant women. Ginger (*Zingiber officinale* Roscoe) is the most widely used herbal therapy in the management of NVP. Like conventional therapies, herbal therapies have potential harms and benefits that patients need to be informed about in order to develop their therapy preferences. The aim of this study was to achieve consensus among women who suffered NVP and physicians often consulted by pregnant women on a core list of potential harms and benefits of using ginger to manage NVP to be addressed during clinical consultations. **METHODS:** In this study, the Delphi technique was used to achieve consensus on a core list of important harms and benefits of using ginger in the management of NVP to be addressed during the clinical consultation. A Delphi process was followed in two panels in parallel sessions. One panel was composed of 50 gynecologists and other physicians who are often consulted by pregnant women suffering NVP and the other panel was composed of 50 women who suffered NVP. **RESULTS:** Consensus was achieved on 21 (75%) of the

28 potential harms presented to the panelists. Panelists agreed that potential harms of the anticoagulant effects of ginger, risk with other co-morbidities, and risk of potential allergic reactions are important to address during the clinical consultation. Of the 14 potential benefits presented to the panelists in both panels, consensus was achieved on 13 (92.9%). Partial consensus on 7 potential harms and 1 potential benefit was achieved in both panels. **CONCLUSIONS:** Addressing important potential harms and benefits of using ginger for the management of NVP during the clinical consultations is important in promoting congruence and reducing patient dissatisfaction in clinical practice. Consensus was achieved on a core list of important harms and benefits of using ginger for the management of NVP to be addressed during the clinical consultations by a panel of women and a panel of physicians. Further studies are still needed to investigate what is being addressed during clinical consultations.

DOI: 10.1186/s12906-017-1717-0

PMCID: PMC5385053

PMID: 28390419 [Indexed for MEDLINE]

26. Use of herbal product among pregnant women in Turkey. Kıssal A, Çevik Güner Ü, Batkın Ertürk D.

Complement Ther Med. 2017 Feb;30:54-60. doi: 10.1016/j.ctim.2016.11.001. Epub 2016 Nov 11.

OBJECTIVE: This study was conducted to determine the herbal product use of pregnant women as there is not adequate information relating to the rate of herbal product use during pregnancy in Turkey and what is thought about effects and side effects thereof. **METHODS:** It is a descriptive study consisted of 366 pregnant women admitted to hospital for childbirth in gynaecology and obstetrics clinics of a public hospital or a university hospital. Data were collected with individual information form and question form of herbal product use in pregnancy. We conducted number, percentage, chi-square analyses. **RESULTS:** It was determined that 47.3% of the women had used at least one herbal product during pregnancy; the relationship between education level, working status, family structure, and status of herbal product use is statistically significant ($p < 0.05$). Linden, peppermint-lemon, ginger are the first three herbs used due to common cold-influenza frequently in pregnancy during 1st and 2nd trimesters. More than half of the pregnant women stated that they had started herbal product use without any suggestions from anyone, and profoundly low healthcare professional suggestion was detected. **CONCLUSION:** Our study has showed that almost half of women use at least one herbal product during pregnancy. So few healthcare professionals give information to pregnant women thereabout. Thus, providing information in general health education to pregnant women about benefits and damages of herbal product use, planning researchers on effectiveness of herbal products, assessment of healthcare professionals relating to the matter and provision of available guidelines and in-service education relating to herbal products that can be used during pregnancy may be suggested.

DOI: 10.1016/j.ctim.2016.11.001

PMID: 28137527 [Indexed for MEDLINE]

27. Herbal medicinal products in pregnancy - which data are available? Wiesner J, Knöss W.

Reprod Toxicol. 2017 Jun 17. pii: S0890-6238(17)30137-5. doi: 10.1016/j.reprotox.2017.06.046. [Epub ahead of print]

This review aims to highlight recent approaches concerning usage of (traditional) herbal medicinal products in pregnancy and to discuss appropriate strategies to handle limited information. Therefore, published monographs of the Committee on Herbal Medicinal products (HMPC) and selected publicly funded webpages, medicinal handbooks, publications and industry and health care organisations webpages were evaluated. While within the monographs of the HMPC a rather conservative approach could be found (mainly because of lacking nonclinical and/or clinical studies), all other sources display a wide variety of information or assessments, thereby often giving contradictory recommendations. However, some experience with the usage of herbal substances/preparations exists in daily clinical practise without clinical trials or observational studies and some herbal substances/preparations are also used as food/food supplements/cosmetics/medical devices. Discussions should be started how to use that knowledge and experience to adjust regulatory decisions on a case-by-case basis, if possible.

DOI: 10.1016/j.reprotox.2017.06.046

PMID: 28633984

28. Review of Ginkgo biloba-induced toxicity, from experimental studies to human case reports. Mei N, Guo X, Ren Z, Kobayashi D, Wada K, Guo L.

J Environ Sci Health C Environ Carcinog Ecotoxicol Rev. 2017 Jan 2;35(1):1-28. doi: 10.1080/10590501.2016.1278298.

Ginkgo biloba seeds and leaves have been used as a traditional herbal remedy for thousands of years, and its leaf extract has been consumed as a botanical dietary supplement for decades. Ginkgo biloba extract is a complex mixture with numerous components, including flavonol glycosides and terpene lactones, and is one of the most widely sold botanical dietary supplements worldwide. Concerns about potential health risks for the general population have been raised because of the widespread human exposure to Ginkgo biloba and its potential toxic and carcinogenic activities in rodents. The National Toxicology Program conducted 2-year gavage studies on one Ginkgo biloba leaf extract and

concluded that there was clear evidence of carcinogenic activity of this extract in mice based on an increased incidence of hepatocellular carcinoma and hepatoblastoma. Recently, Ginkgo biloba leaf extract has been classified as a possible human carcinogen (Group 2B) by the International Agency for Research on Cancer. This review presents updated information on the toxicological effects from experimental studies both in vitro and in vivo to human case reports (caused by ginkgo seeds or leaves), and also summarizes the negative results from relatively large clinical trials.

DOI: 10.1080/10590501.2016.1278298

PMID: 28055331 [Indexed for MEDLINE]

29. Mycotoxins in spices and herbs-An update. Kabak B, Dobson AD.

Crit Rev Food Sci Nutr. 2017 Jan 2;57(1):18-34.

Spices and herbs have been used since ancient times as flavor and aroma enhancers, colorants, preservatives, and traditional medicines. There are more than 30 spices and herbs of global economic and culinary importance. Among the spices, black pepper, capsicums, cumin, cinnamon, nutmeg, ginger, turmeric, saffron, coriander, cloves, dill, mint, thyme, sesame seed, mustard seed, and curry powder are the most popular spices worldwide. In addition to their culinary uses, a number of functional properties of aromatic herbs and spices are also well described in the scientific literature. However, spices and herbs cultivated mainly in tropic and subtropic areas can be exposed to contamination with toxigenic fungi and subsequently mycotoxins. This review provides an overview on the mycotoxin risk in widely consumed spices and aromatic herbs.

DOI: 10.1080/10408398.2013.772891

PMID: 26528824 [Indexed for MEDLINE]