AACT Herbal Dietary Supplements SIG Abstracts November 2017

1. Heart Toxicity Related to Herbs and Dietary Supplements: Online Table of Case Reports. Part 4 of 5. Brown AC.

J Diet Suppl. 2017 Oct 5:1-40. doi: 10.1080/19390211.2017.1356418. [Epub ahead of print]

BACKGROUND: The purpose of this review was to create an online research summary table of heart toxicity case reports related to dietary supplements (DS; includes herbs). METHODS: Documented PubMed case reports of DS appearing to contribute to heart-related problems were used to create a "Toxic Table" that summarized the research (1966 to April, 2016, and cross-referencing). Keywords included "herb," "dietary supplement," and cardiac terms. Case reports were excluded if they were herb combinations (some exceptions), Chinese herb mixtures, teas of mixed herb contents, mushrooms, poisonous plants, self-harm (e.g. suicide), excess dose (except vitamins/minerals), drugs or illegal drugs, drug-herbal interactions, and confounders of drugs or diseases. The spectrum of heart toxicities included hypertension, hypotension, hypokalemia, bradycardia, tachycardia, arrhythmia, ventricular fibrillation, heart attack, cardiac arrest, heart failure, and death. RESULTS: Heart related problems were associated with approximately seven herbs: Four traditional Chinese medicine herbs - Don quai (Angelica sinensis), Jin bu huan (Lycopodium serratum), Thundergod vine or lei gong teng (Tripterygiumwilfordii Hook F), and Ting kung teng (Erycibe henryi prain); one an Ayruvedic herb - Aswagandha, (Withania somnifera); and two North American herbs - blue cohosh (Caulophyllum thalictroides), and Yohimbe (Pausinystalia johimbe). Aconitum and Ephedra species are no longer sold in the United States. The DS included, but are not limited to five DS - bitter orange, caffeine, certain energy drinks, nitric oxide products, and a calming product. Six additional DS are no longer sold. Licorice was the food related to heart problems. CONCLUSION: The online "Toxic Table" forewarns clinicians, consumers and the DS industry by listing DS with case reports related to heart toxicity. It may also contribute to Phase IV post marketing surveillance to diminish adverse events that Government officials use to regulate DS.

DOI: 10.1080/19390211.2017.1356418
PMID: 28981338

2. Relationship between blood toxin level and clinical features in patients with grayanotoxin poisoning - six clinical cases. Choi HL, Park KH, Park JS, Choi HY, Kim H, Kim SM.

Clin Toxicol (Phila). 2017 Nov;55(9):991-995. doi: 10.1080/15563650.2017.1331448.
Epub 2017 Jun 8.

BACKGROUND: The purpose of this study was to investigate grayanotoxin (GTX) levels in the blood of patients with GTX intoxication and in the consumed Rhododendron liqueur, and to determine whether there was an association between blood GTX level and the patient's clinical status. METHODS: In September 2015, six patients were concurrently presented to the emergency department with various toxicity symptoms, which occurred after the consumption of Rhododendron liqueur at the same toxin concentration. Liquid chromatography-tandem mass spectrometry analysis was conducted on blood samples obtained from six cases of GTX intoxication treated in our emergency department. RESULTS: At the initial evaluation in the emergency department, the mean arterial pressure of the patients ranged from 36.7 to 76.7 mm Hg. The concentrations of GTX-I and GTX-III in Rhododendron liqueur were 1.436 and 16.907 ng/mL, respectively. The initial blood GTX-III and GTX-I levels ranged from 2.9 to 58.0 ng/mL and the lower limit of quantification (LLOQ) to 8.33 ng/mL, respectively. After 20 h, the mean arterial pressure ranged from 76.7 to 93.3 mm Hg, while the blood GTX-III and GTX-I levels ranged from the LLOQ to 17.8 and 2.52 ng/mL, respectively. DISCUSSION: We estimated that the minimum blood GTX-III and GTX-I levels that caused hypotension were between 17.83 and 27.3 ng/mL, and 2.52 and 4.55 ng/mL, respectively.

DOI: 10.1080/15563650.2017.1331448
PMID: 28594250 [Indexed for MEDLINE]

3. [Risk assessment of synephrine in dietary supplements]. [Article in German] Bakhyia N, Dusemund B, Richter K, Lindtner O, Hirsch-Ernst KI, Schäfer B, Lampen A.

Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz. 2017 Mar;60(3):323-331. doi: 10.1007/s00103-016-2506-5.

Synephrine is a sympathomimetic phenylethylamine derivative that occurs naturally in citrus fruits. It is often added to dietary supplements intended for weight loss and enhancement of sports performance, typically in the form of Citrus aurantium extracts and in many cases in combination with caffeine. The health risks of synephrine were evaluated on the basis of the available toxicological data and in accordance to the EFSA guidance on the safety assessment of botanicals and botanical preparations intended for use in food supplements. In animal studies, orally applied synephrine induced adrenergic effects on the cardiovascular system (increase of blood pressure, ventricular arrhythmias), which were enhanced by the concomitant application of caffeine as well as physical activity. Some human intervention studies investigating the acute effects of synephrine on blood pressure and heart rate of healthy, normotensive test persons indicate that synephrine can induce cardiovascular effects in humans. A series of published case reports of adverse cardiovascular effects (hypertension, cardiac arrhythmia, myocardial infarction) were associated with consumption of synephrine- and caffeine-containing dietary supplements. In conclusion, consumption of high amounts of synephrine, especially in combination with caffeine and physical exercise, is associated with an increased risk of adverse effects on the cardiovascular system. According to the assessment by the BfR (Bundesinstitut für Risikobewertung), daily intake of synephrine through dietary supplements should not exceed the median intake from conventional foods.

DOI: 10.1007/s00103-016-2506-5
PMID: 28058460 [Indexed for MEDLINE]

4. Yellow Oleander Seed, or "Codo de Fraile" (Thevetia spp.): A Review of Its Potential Toxicity as a Purported Weight-Loss Supplement. González-Stuart A, Rivera JO.

J Diet Suppl. 2017 Sep 28:1-13. doi: 10.1080/19390211.2017.1353565. [Epub ahead of print]

The Dietary Supplements and Health Education Act (DSHEA), passed by the United States Congress in October of 1994, defines herbal products as nutritional supplements, not medications. This opened the market for diverse products made from plants, including teas, extracts, essential oils, and syrups. Mexico and the United States share an extensive border, where diverse herbal products are available to the public without a medical prescription. Research undertaken in the neighboring cities of Ciudad Juarez, Mexico, and El Paso, Texas, USA, shows the use of herbs is higher in this border area compared to the rest of the United States. A portion of the population is still under the erroneous impression that "natural" products are completely safe to use and therefore lack side effects. We review the dangers of ingesting the toxic seed of Thevetia spp. (family Apocynaceae), commonly known as "yellow oleander" or "codo de fraile," misleadingly advertised on the Internet as an effective and safe dietary supplement for weight loss. Lack of proper quality control regarding herbs generates a great variability in the quantity and quality of the products' content. Herb-drug interactions occur between some herbal products and certain prescription pharmaceuticals. Certain herbs recently introduced into the U.S. market may not have been previously tested adequately for purity, safety, and efficacy. Due to the lack of reliable clinical data regarding the safe use of various herbal products currently available, the public should be made aware regarding the possible health hazards of using certain herbs for therapeutic purposes. The potentially fatal toxicity of yellow oleander seed is confirmed by cases reported from various countries, while the purported benefits of using it for weight loss have not been evaluated by any known clinical trials. For this reason, the use of yellow oleander seed as a dietary supplement should be avoided.

DOI: 10.1080/19390211.2017.1353565
PMID: 28956681

5. Ephedrine-induced mitophagy via oxidative stress in human hepatic stellate cells. Lee AY, Jang Y, Hong SH, Chang SH, Park S, Kim S, Kang KS, Kim JE, Cho MH.

J Toxicol Sci. 2017;42(4):461-473. doi: 10.2131/jts.42.461.

The herb Ephedra sinica (also known as Chinese ephedra or Ma Huang), used in traditional Chinese medicine, contains alkaloids identical to ephedrine and pseudoephedrine as its principal active constituents. Recent studies have reported that ephedrine has various side effects in the cardiovascular and nervous systems. In addition, herbal Ephedra, a plant containing many pharmacologically active alkaloids, principally

ephedrine, has been reported to cause acute hepatitis. Many studies reported clinical cases, however, the cellular mechanism of liver toxicity by ephedrine remains unknown. In this study, we investigated hepatotoxicity and key regulation of mitophagy in ephedrine-treated LX-2 cells. Ephedrine triggered mitochondrial oxidative stress and depolarization. Mitochondrial swelling and autolysosome were observed in ephedrine-treated cells. Ephedrine also inhibited mitochondrial biogenesis, and the mitochondrial copy number was decreased. Parkin siRNA recovered the ephedrine-induced mitochondrial damage. Excessive mitophagy lead to cell death through imbalance of autophagic flux. Moreover, antioxidants and reducing Parkin level could serve as therapeutic targets for ephedrine-induced hepatotoxicity.

DOI: 10.2131/jts.42.461
PMID: 28717105 [Indexed for MEDLINE]

6. Cancer Related to Herbs and Dietary Supplements: Online Table of Case Reports. Part 5 of 5. Brown AC.

J Diet Suppl. 2017 Oct 5:1-26. doi: 10.1080/19390211.2017.1355865. [Epub ahead of print]

A current listing of potentially life-threatening, cancer-related dietary supplements (DSs; includes herbs) based on PubMed case reports was summarized in online tables that can now be updated continually to forewarn United States consumers, clinicians, and DS companies. Documented PubMed case reports were used to create a "Toxic Table" related to cancer (1966 to April 2016, and cross-referencing). Keywords included "herb" or "dietary supplement" combined with "cancer" as well as the specific herb "name" combined with "cancer" and sometimes "toxicity." Excluded were herb combinations (some exceptions), Chinese herb mixtures, teas of mixed herb contents, fungi (mycotoxins from molds and mushrooms), poisonous plants, self-harm, excessive doses (except vitamins/minerals), legal or illegal drugs, drug-herb interactions, and confounders of drugs or diseases related to cancer. Also included were a few foods related to cancer. Over the past 50+ years, PubMed case reports revealed an increased risk of cancer related to approximately one herb (guang fang ji), no dietary supplements (except those containing guang fang ji or aristolochic acid), and two foods (bracken fern, which is sometimes sold as an herbal supplement, and hot maté). This online "Toxic Table" can now be continually updated to assist researchers and clinicians in preventing serious adverse events from DSs related to cancer.

DOI: 10.1080/19390211.2017.1355865
PMID: 28981366

7. Aristolochic acids and their derivatives are widely implicated in liver cancers in Taiwan and throughout Asia. Ng AWT, Poon SL, Huang MN, Lim JQ, Boot A, Yu W, Suzuki Y, Thangaraju S, Ng CCY, Tan P, Pang ST, Huang HY, Yu MC, Lee PH, Hsieh SY, Chang AY, Teh BT, Rozen SG.

Sci Transl Med. 2017 Oct 18;9(412). pii: eaan6446. doi: 10.1126/scitranslmed.aan6446.

Many traditional pharmacopeias include Aristolochia and related plants, which contain nephrotoxins and mutagens in the form of aristolochic acids and similar compounds (collectively, AA). AA is implicated in multiple cancer types, sometimes with very high mutational burdens, especially in upper tract urothelial cancers (UTUCs). AA-associated kidney failure and UTUCs are prevalent in Taiwan, but AA's role in hepatocellular carcinomas (HCCs) there remains unexplored. Therefore, we sequenced the whole exomes of 98 HCCs from two hospitals in Taiwan and found that 78% showed the distinctive mutational signature of AA exposure, accounting for most of the nonsilent mutations in known cancer driver genes. We then searched for the AA signature in 1400 HCCs from diverse geographic regions. Consistent with exposure through known herbal medicines, 47% of Chinese HCCs showed the signature, albeit with lower mutation loads than in Taiwan. In addition, 29% of HCCs from Southeast Asia showed the signature. The AA signature was also detected in 13 and 2.7% of HCCs from Korea and Japan as well as in 4.8 and 1.7% of HCCs from North America and Europe, respectively, excluding one U.S. hospital where 22% of 87 "Asian" HCCs had the signature. Thus, AA exposure is geographically widespread. Asia, especially Taiwan, appears to be much more extensively affected, which is consistent with other evidence of patterns of AA exposure. We propose that additional measures aimed at primary prevention through avoidance of AA exposure and investigation of possible approaches to secondary prevention are warranted.

DOI: 10.1126/scitranslmed.aan6446
PMID: 29046434

8. Marked decrease in urgent listing for liver transplantation over time: evolution of characteristics and outcomes of Status-1 liver transplantation. Wong LL, Truong HP, Seto T, Lacar L, Naugler WE.

Transplantation. 2017 Sep 29. doi: 10.1097/TP.0000000000001967. [Epub ahead of print]

BACKGROUND: Approximately 5% of liver transplants annually are performed urgently with "status-1" designation. This study aims to determine if the demand, characteristics and outcome for status-1 liver transplantation has changed over time. METHODS: We utilized the Scientific Registry of Transplant Patients (2003-2015) to characterize 2352 adult patients who underwent 2408 status-1 liver transplants and compared them between Era1 (2003-6/2009) and Era2 (7/2009 -2015). RESULTS: Overall, there were fewer liver transplants performed with the Status-1 designation in Era2 than Era1 (1099 vs 1309). Although the number of urgent liver transplants was relatively constant with successive years, the proportion transplanted with Status-1 designation decreased markedly over time. Era2 patients were older (43.2 vs 41.7 years, p=0.01) and less likely be ABO-incompatible (1.1% vs 2.4%, p=0.01) or re-transplant (77 vs 124, p=0.03). In terms of disease etiology, the largest group was "ALF, nonspecified" (43.4%). There was no difference in proportion with drug-induced liver injury (DILI), but the subset of herbal/dietary supplements increased in Era2 (1.3% vs 0.46 %, p=0.04). Survival was increased in Era2 in the overall cohort and for patients with autoimmune disease (p <0.05), despite longer waiting-times for this etiology (186 vs 149 days). DILI or nonspecified ALF had shorter waiting-times and 90% were transplanted within 7 days. CONCLUSIONS: LT for the most urgent indications (Status-1) is decreasing, while survival remains excellent. Fewer incidences of acute liver failure are classified as indeterminate, mostly as a result of increasing awareness of Autoimmune Hepatitis and DILI as causes of the syndrome.

DOI: 10.1097/TP.0000000000001967
PMID: 28968354

9. Hepatotoxicity of monoterpenes and sesquiterpenes. Zárybnický T, Boušová I, Ambrož M, Skálová L.

Arch Toxicol. 2017 Sep 13. doi: 10.1007/s00204-017-2062-2. [Epub ahead of print]

Public interest in natural therapies has increased significantly over past decades. Herbs and herbal products are extensively consumed worldwide and they are generally considered as safe. However, this may not always be true as many cases of herb-induced liver injury are reported every year. The liver is a frequent target tissue of toxicity from all classes of toxicants as liver structure and function predispose it to high sensitivity to xenobiotics. The present review is focused on the hepatotoxic properties of monoterpenes and sesquiterpenes, plant secondary metabolites that represent the major components of essential oils wildly used in folk medicines, pharmaceutical industry and cosmetics. Most of these terpenes easily enter the human body by oral absorption, penetration through the skin, or inhalation leading to measurable blood concentrations. Several studies showed that some monoterpenes (e.g., pulegone, menthofuran, camphor, and limonene) and sesquiterpenes (e.g., zederone, germacrone) exhibited liver toxicity, which is mainly based on reactive metabolites formation, increased concentration of reactive oxygen species and impaired antioxidant defense. There is a high probability that many other terpenes, without sufficiently known metabolism and effects in human liver, could also exert hepatotoxicity. Especially terpenes, that are important components of essential oils with proved hepatotoxicity, should deserve more attention. Intensive research in terpenes metabolism and toxicity represent the only way to reduce the risk of liver injury induced by essential oils and other terpenes-containing products.

DOI: 10.1007/s00204-017-2062-2
PMID: 28905185

10. Frequency and Pathological Characteristics of Drug-Induced Liver Injury in a Tertiary Medical Center. Ettel M, Gonzalez GA, Gera S, Eze O, Sigal S, Park JS, Xu R.

Hum Pathol. 2017 Sep 2. pii: S0046-8177(17)30314-3. doi: 10.1016/j.humpath.2017.08.029. [Epub ahead of print]

Drug-induced liver injury (DILI) accounts for approximately 10% of acute hepatitis cases. DILI can arise as idiosyncratic or intrinsic injury from hundreds of drugs, herbals, and nutritional supplements and is essential to recognize as one of the differential diagnoses of hepatitis in a liver biopsy. The purpose of this study is to

investigate the frequency and pathological characteristics of DILI related to the variety of hepatotoxic agents. We searched our pathology database for all patients with hepatitis diagnosed on liver biopsy from January 2012 to May 2016, and selected patients with a diagnosis of DILI. Electronic medical records were reviewed for patient medication list, history of herbal medicine or supplement use, and pre-biopsy liver function test (LFT) results. Clinical and pathologic correlation was used to determine the causative or related agents for DILI. We then assessed histopathologic features of liver injury and categorized biopsy findings as primarily bile duct injury, lobular/portal hepatitis, or mixed changes. 604 total liver biopsies for hepatitis or liver injury were identified, of which 70 cases (11.6%) carried the diagnosis of DILI confirmed by clinical correlation. The most common etiologies associated with DILI were supplements and herbal products (31.4%), antimicrobials (14.3%), chemotherapeutics (11.4%), antilipidemics (7.1%) and immunomodulatory agents (7.1%). LFT results positively correlated with histological findings. Nutritional/herbal supplements have emerged as one of the major hepatotoxicity agents. DILI can manifest as predominantly hepatitis, bile duct injury or combination. Histological pattern recognition in the liver biopsy may help identify specific hepatotoxic agents causing DILI.

DOI: 10.1016/j.humpath.2017.08.029
PMID: 28873351

11. Dietary Supplements, Isotretinoin, and Liver Toxicity in Adolescents: A Retrospective Case Series. DeKlotz CMC, Roby KD, Friedlander SF.

Pediatrics. 2017 Oct;140(4). pii: e20152940. doi: 10.1542/peds.2015-2940. Epub 2017 Sep 1.

Isotretinoin is the most effective acne therapy available, but has the potential for a number of adverse side effects, including transaminitis. The iPLEDGE isotretinoin program recommends avoiding some herbals and supplements due to potential side effects. However, little is known about the effects of protein supplements on the liver, particularly in patients taking isotretinoin. We designed a retrospective chart review to evaluate the symptoms, diagnosis, treatment, and outcome of patients on or preparing to take isotretinoin therapy who were concurrently ingesting protein or herbal supplementation and who developed transaminitis. In 100% (8/8) of cases, dietary supplementation was determined to be at least a possible cause of elevated liver transaminases. In 75% (6/8) of cases, dietary supplement appears to be the most likely cause at some point in their evaluation. Most of our patients' elevations in aspartate aminotransferase and/or alanine aminotransferase were likely caused by supplementation with protein, creatine, or herbal extracts, rather than prescribed isotretinoin or tetracycline antibiotics for acne. Hence, dietary supplementation may cause liver function abnormalities. As supplement usage appears common in teenagers, clinicians should consider counseling their patients to avoid these products, particularly when prescribing known hepatotoxic drugs.

DOI: 10.1542/peds.2015-2940
PMID: 28864554 [Indexed for MEDLINE]

12. Hepatic veno-occlusive disease induced by Chinese medicinal herbs. Mejías Manzano MLÁ, Giráldez Gallego Á, Serrano Jiménez M.

Rev Esp Enferm Dig. 2017 Oct 16;109. doi: 10.17235/reed.2017.4969/2017. [Epub ahead of print]

The potential hepatotoxic effects of products containing medicinal herbs, which are increasingly used without adequate control by health authorities, is well known. We report a case of toxic hepatic veno-occlusive disease (HVOD) presumably associated with the use of such herbal remedies.

DOI: 10.17235/reed.2017.4969/2017
PMID: 29032695

13. Incidence of Pyrrolizidine Alkaloids in Herbal Medicines from German Retail Markets: Risk Assessments and Implications to Consumers. Letsyo E, Jerz G, Winterhalter P, Lindigkeit R, Beuerle T.

Phytother Res. 2017 Sep 28. doi: 10.1002/ptr.5935. [Epub ahead of print]

The occurrence of potentially toxic pyrrolizidine alkaloids (PAs) in herbal medicines (HMs) is currently intensely being discussed in Europe. Pyrrolizidine alkaloids, particularly the 1,2-unsaturated PAs, are undesired compounds in HMs due to their potential hepatotoxic and carcinogenic properties. In this study, 98

widely patronized HMs from six popular German retail supermarkets/drugstores, as well as from pharmacies, were analyzed by high-performance liquid chromatography-electrospray ionization-tandem mass spectrometry for the presence of PAs. The results showed that about 63% of the HMs were PA positive, whereas the average PA concentration of the samples was 201 μg/kg, the highest concentration of PAs (3270 μg/kg) was attributed to a product that was purchased from the pharmacy and contained Hypericum perforatum L. (St. John's Wort) as an active ingredient. In addition, H. perforatum-containing products were frequently contaminated with PAs from Echium spp., while both Cynara cardunculus L. products and fixed-combination products of Gentiana lutea L., Rumex acetosa L., Verbena officinalis L., Sambucus nigra L., and Primula veris L. products were commonly contaminated with PAs of Senecio spp. The study showed that H. perforatum, C. cardunculus, Urtica dioica L., and fixed-combination products were frequently contaminated with PA levels above the recommended values of both the German and European Medicines Agencies.

DOI: 10.1002/ptr.5935
PMID: 28960556

14. Dietary Supplement Use Was Very High among Older Adults in the United States in 2011-2014. Gahche JJ, Bailey RL, Potischman N, Dwyer JT.

J Nutr. 2017 Oct;147(10):1968-1976. doi: 10.3945/jn.117.255984. Epub 2017 Aug 30.

Background: Dietary supplements (DSs) have the potential to be both beneficial and harmful to health, especially in adults aged ≥60 y, and therefore it is important to monitor the patterns of their use.Objective: This study evaluated DS use by adults aged ≥60 y to characterize the use of DSs, determine the motivations for use, and examine the associations between the use of DSs and selected demographic, lifestyle, and health characteristics.Methods: Data from 3469 older adults aged ≥60 from the 2011-2014 NHANES were analyzed. DSs used in the past 30 d were ascertained via an interviewer-administered questionnaire in participants' homes. The prevalence of overall DS use and specific types of DSs were estimated. The number of DSs reported and the frequency, duration, and motivation(s) for use were assessed. Logistic regression models were constructed to examine the association between DS use and selected characteristics.Results: Seventy percent of older adults in the United States reported using ≥1 DS in the past 30 d; 54% of users took 1 or 2 products, and 29% reported taking ≥4 products. The most frequently reported products were multivitamin or mineral (MVM) (39%), vitamin D only (26%), and omega-3 fatty acids (22%). Women used DSs almost twice as often as men [adjusted OR (aOR), 1.8; 95% CI: 1.5, 2.3). Those not reporting prescription medications were less likely to take a DS than those reporting ≥3 prescription medications (aOR, 0.4; 95% CI: 0.3, 0.6). The most frequently reported motivation for DS use was to improve overall health (41%).Conclusions: Use of DSs among older adults continues to be high in the United States, with 29% of users regularly taking ≥4 DSs, and there is a high concurrent usage of them with prescription medications.

DOI: 10.3945/jn.117.255984
PMCID: PMC5610553 [Available on 2018-10-01]
PMID: 28855421 [Indexed for MEDLINE]

15. Behaviors of consumers, physicians and pharmacists in response to adverse events associated with dietary supplement use. Chiba T, Sato Y, Kobayashi E, Ide K, Yamada H, Umegaki K.

Nutr J. 2017 Mar 18;16(1):18. doi: 10.1186/s12937-017-0239-4.

BACKGROUND: The prevalence of dietary supplements has increased in Japan, and, as a consequence, the adverse events associated with dietary supplement use have become more prominent. Severe adverse events must be reported to the Japanese government via public health centers. However, the number of cases reported to the Japanese government is limited. To clarify this discrepancy, we conducted an internet questionnaire, and surveyed how consumers, physicians and pharmacists acted when they or their patients developed adverse events due to dietary supplement use. METHODS: This study was completed by 2732 consumers, 515 physicians, and 515 pharmacist via internet surveillance on November 2015. RESULTS: Although 8.8% of consumers developed adverse events including diarrhea, constipation, stomachache, headache, and nausea and vomiting, most of them did not report their adverse events to public health centers. However, some consumers went to hospitals because of adverse events. We also surveyed how physicians and pharmacists acted when their patients developed adverse events due to dietary supplement use. Most physicians and pharmacists did not report these cases to public health centers because they were unable to

definitively prove the cause-and-effect relationship of these adverse events. Furthermore, some physicians and pharmacists did not know how or where to report these adverse events. CONCLUSIONS: We clarified the reasons for the limited number of reports of adverse events to the Japanese government in this survey. It is important to encourage not only consumers, but also physicians and pharmacists to report adverse events to public health centers. In addition, an analyzing tool of cause-and-effect relationships might be helpful for physicians and pharmacists.

DOI: 10.1186/s12937-017-0239-4
PMCID: PMC5357328
PMID: 28315635 [Indexed for MEDLINE]

16. We Need Studies of the Mortality Effect of Vitamin A Supplementation, Not Surveys of Vitamin A Deficiency. Benn CS.

Nutrients. 2017 Mar 15;9(3). pii: E280. doi: 10.3390/nu9030280.

It is usually acknowledged that high-dose vitamin A supplementation (VAS) provides no sustained improvement in vitamin A status, and that the effect of VAS on mortality is more likely linked to its immunomodulating effects. Nonetheless, it is widely assumed that we can deduce something about the need for continuing or stopping VAS programs based on studies of the biochemical prevalence of vitamin A deficiency (VAD). This is no longer a tenable assumption. The justification for using VAS is to reduce child mortality, but there is now doubt that VAS has any effect on overall child mortality. What we need now are not surveys of VAD, but proper randomized trials to evaluate whether VAS has beneficial effects on overall child survival.

DOI: 10.3390/nu9030280
PMCID: PMC5372943
PMID: 28294986 [Indexed for MEDLINE]

17. Case Report of Calciphylaxis Secondary to Calcium and Vitamin D3 Supplementation. Storan ER, O'Gorman SM, Murphy A, Laing M.

J Cutan Med Surg. 2017 Mar/Apr;21(2):162-163. doi: 10.1177/1203475416668162. Epub 2016 Sep 21.

BACKGROUND: Calciphylaxis is a rare disorder that is very unusual outside the setting of end-stage kidney disease. CASE SUMMARY: A 64-year-old woman with normal renal function presented with painful leg ulcers. She had previously received 300 000 IU of vitamin D3 followed by daily calcium and vitamin D3 supplementation. A skin biopsy was consistent with calciphylaxis, and she was treated with sodium thiosulphate infusions and wound debridement. CONCLUSION: Calcium and vitamin D3 supplements are widely prescribed. We report a case of calciphylaxis triggered by calcium and vitamin D3 supplementation in a patient with none of the typical risk factors. Our patient had an excellent response to treatment with sodium thiosulphate.

DOI: 10.1177/1203475416668162
PMID: 27566435 [Indexed for MEDLINE]

18. Potential drug interactions with dietary and herbal supplements during hospitalization. Levy I, Attias S, Ben-Arye E, Goldstein L, Schiff E.

Intern Emerg Med. 2017 Apr;12(3):301-310. doi: 10.1007/s11739-016-1548-x. Epub 2016 Oct 5.

Dietary and herbal supplements (DHS) are widely used in the general population, including during hospitalization. Yet, their potential interactions with prescription drugs have seldom been delineated among inpatients. We aimed to evaluate potentially dangerous interactions of DHS with prescribed medications among inpatients. This was a cross-sectional prospective study involving a cohort of patients hospitalized in 12 departments of a public academic medical center (Bnai Zion Medical Center, Haifa, Israel) from 2009 to 2014. DHS users were determined via a questionnaire. The Natural Medicine database was used to search for potential DHS-drug interactions for identified DHS, and the clinical significance was evaluated using Lexi-interact online interaction analysis. Medical files were assessed for documentation of DHS use. Univariate and multivariate logistic regression analyses were used to characterize potential risk factors for DHS-drug

interactions. Of 927 patients consenting to answer the questionnaire, 458 (49 %) reported DHS use. Of these, 215 (47 %) had at least one potential interaction during hospitalization (759 interactions). Of these interactions, 116 (15 %) were potentially clinically significant. Older age [OR = 1.02 (1.01-1.04), p = 0.002], males [OR = 2.11 (1.35-3.29), p = 0.001] and increased number of used DHS [OR = 4.28 (2.28-8.03), p < 0.001] or drugs [OR = 1.95 (1.17-3.26), p = 0.011] were associated with potential interactions in DHS users. Physicians documented only 16.5 % of DHS involved in these interactions in patients' medical files. In conclusion, a substantial number of inpatients use DHS with potential interactions with concomitant medications. Medical staff should be aware of this, question patients on DHS usage and check for such interactions.

DOI: 10.1007/s11739-016-1548-x
PMID: 27709322 [Indexed for MEDLINE]

19. Co-administration of St. John's wort and hormonal contraceptives: a systematic review. Berry-Bibee EN, Kim MJ, Tepper NK, Riley HE, Curtis KM.

Contraception. 2016 Dec;94(6):668-677. doi: 10.1016/j.contraception.2016.07.010. Epub 2016 Jul 18.

OBJECTIVES: St. John's wort (SJW) is a known strong inducer of the cytochrome P450 (CYP) 3 A4 enzyme, and both the ethinyl estradiol and progestin components of hormonal contraceptives are substrates of CYP3A4. This systematic review examined whether the co-administration of SJW and hormonal contraceptives leads to significant safety or efficacy concerns. STUDY DESIGN: Systematic review. METHODS: PubMed and Cochrane Library databases were searched for articles of any comparative study design (clinical or pharmacokinetic) that examined potential interactions between SJW and hormonal contraceptives in women of reproductive age. RESULTS: Of the 48 identified articles, four studies met inclusion criteria and compared use of combined oral contraceptives (COCs) alone to the use of COCs co-administered with SJW. Two studies demonstrated no change in markers of ovulation, but one study demonstrated increased follicular growth and probable ovulation when COCs were co-administered with SJW. Three studies demonstrated an increased risk of breakthrough bleeding with COCs and SJW. Three studies showed changes in at least one pharmacokinetic parameter that suggested a significantly decreased exposure to hormone concentrations when COCs were co-administered with SJW. The only study that did not demonstrate any significant pharmacokinetic differences examined a SJW product containing a low amount of hypericin. CONCLUSION: Limited evidence showing increased risk of ovulation and breakthrough bleeding raises concern for decreased contraceptive efficacy when COCs are co-administered with SJW. The pharmacokinetic evidence is mixed but suggests that SJW administration may be associated with weak to moderate induction of the
metabolism of COCs.

DOI: 10.1016/j.contraception.2016.07.010
PMID: 27444983 [Indexed for MEDLINE]

20. A review of drug-drug interactions in older HIV-infected patients. Chary A, Nguyen NN, Maiton K, Holodniy M.

Expert Rev Clin Pharmacol. 2017 Sep 19:1-24. doi: 10.1080/17512433.2017.1377610. [Epub ahead of print]

INTRODUCTION: The number of older HIV-infected people is growing due to increasing life expectancies resulting from the use of antiretroviral therapy (ART). Both HIV and aging increase the risk of other comorbidities, such as cardiovascular disease, osteoporosis, and some malignancies, leading to greater challenges in managing HIV with other conditions. This results in complex medication regimens with the potential for significant drug-drug interactions and increased morbidity and mortality. Area covered: We review the metabolic pathways of ART and other medications used to treat medical co-morbidities, highlight potential areas of concern for drug-drug interactions, and where feasible, suggest alternative approaches for treating these conditions as suggested from national guidelines or articles published in the English language. Expert commentary: There is limited evidence-based data on ART drug interactions, pharmacokinetics and pharmacodynamics in the older HIV-infected population. Choosing and maintaining effective ART regimens for older adults requires consideration of side effect profile, individual comorbidities, interactions with concurrent prescriptions and non-prescription medications and supplements, dietary patterns with respect to dosing, pill burden and ease of dosing, cost and affordability, patient preferences, social situation, and ART resistance history.

Practitioners must remain vigilant for potential drug interactions and intervene when there is a potential for harm.

DOI: 10.1080/17512433.2017.1377610
PMID: 28922979

21. Omega-3 Fatty Acid Supplementation and Warfarin: A Lethal Combination in Traumatic Brain Injury. Gross BW, Gillio M, Rinehart CD, Lynch CA, Rogers FB.

J Trauma Nurs. 2017 Jan/Feb;24(1):15-18. doi: 10.1097/JTN.0000000000000256.

Polyunsaturated fatty acids such as omega-3 eicosapentaenoic acid and omega-6 docosahexaenoic acid, found in over-the-counter fish oil supplements, are often consumed for their beneficial, prophylactic, anti-inflammatory effects. Although the mechanisms of action are not fully known, a diet rich in polyunsaturated fats may reduce the risk of hyperlipidemia, atherosclerosis, high low-density lipoprotein cholesterol levels, hypertension, and inflammatory diseases. Masked by its many benefits, the risks of omega-3 fatty acid supplementation are often underappreciated, particularly its ability to inhibit platelet aggregation and promote bleeding in patients taking anticoagulant medications. The following details the clinical case of an elderly patient taking warfarin and fish oil supplementation whose warfarin-induced coagulopathy could not be reversed after suffering blunt head trauma.

DOI: 10.1097/JTN.0000000000000256
PMID: 28033135 [Indexed for MEDLINE]

22. N-acetylcysteine in Cleistanthus collinus Poisoning: A Report of Two Cases in Children. Sharma S, Rameshkumar R, Mahadevan S.

J Trop Pediatr. 2016 Dec;62(6):487-489. Epub 2016 May 29.

Cleistanthus collinus, also known as Oduvanthalai in Tamil, is the most commonly encountered plant poison in southern India. The leaves are used for poisoning humans (suicide or homicide) and animals (cattle and fish) and as an abortifacient, especially in rural south India. Although this poisoning is commonly reported in adults, data regarding the use of N-acetylcysteine in pediatric poisoning is lacking. We report two previously healthy male siblings of pediatric age group who ingested the liquid extracted from crushed leaves of this plant given to them by their mother as a means of deliberate harm. Both patients developed distal renal tubular acidosis, with hypokalemia. The younger sibling also developed myocardial toxicity. Other significant findings noted include hypocalcemia, hypomagnesemia and elevated liver enzymes. Both patients received supportive care along with N-acetylcysteine infusion, and showed complete recovery within 10 days.

DOI: 10.1093/tropej/fmw030
PMID: 27240665 [Indexed for MEDLINE]

23. Falsely low values of oxygen saturation measured by pulse oximetry in a boy treated with Chinese herb tea. Meidert AS, Lang A, Hennig G, Bernasconi P, Peraud A, Briegel J, Hüttl TK.

J Clin Monit Comput. 2017 Apr;31(2):481-484. doi: 10.1007/s10877-016-9865-1. Epub 2016 Mar 25.

An 8-year-old boy suffering from progressive glioblastoma was scheduled for neurosurgery. Prior to induction of anaesthesia pulse oximetry measured 64 % saturation of oxygen (SpO2). Arterial blood gas analysis revealed normal oxygen saturation and normal oxygen partial pressure. After having ruled out technical problems of pulse oximetry the neurosurgical procedure was halted. Meticulous examination of the child's history and medication did not explain a possible interaction of drugs with pulse oximetry. A Chinese herb tea had been given to the child, but was then stopped on the day of admission. The surgical procedure took place the next day without any complications. During the subsequent inpatient stay, repeated blood gas analyses showed normal oxygenation, but pulse oximetry measured initially SpO2 values of 64 %, gradually increasing over 7 days up to 91 % by the time of discharge from hospital. Blood samples were taken and analysed. Absorption spectroscopy from the patient's blood showed an uncommon absorption maximum at 684 nm besides the normal maxima. The normalisation of SpO2 values after stopping Chinese herb tea

administration leads to the conclusion that one of its ingredients caused the distorted pulse oximetry measurement.

DOI: 10.1007/s10877-016-9865-1
PMID: 27013078 [Indexed for MEDLINE]

24. Involvement of herbal medicine as a cause of mesenteric phlebosclerosis: results from a large-scale nationwide survey. Shimizu S, Kobayashi T, Tomioka H, Ohtsu K, Matsui T, Hibi T.

J Gastroenterol. 2017 Mar;52(3):308-314. doi: 10.1007/s00535-016-1218-9. Epub 2016 May 24.

BACKGROUND: Mesenteric phlebosclerosis (MP) is a rare disease characterized by venous calcification extending from the colonic wall to the mesentery, with chronic ischemic changes from venous return impairment in the intestine. It is an idiopathic disease, but increasing attention has been paid to the potential involvement of herbal medicine, or Kampo, in its etiology. Until now, there were scattered case reports, but no large-scale studies have been conducted to unravel the clinical characteristics and etiology of the disease. METHODS: A nationwide survey was conducted using questionnaires to assess possible etiology (particularly the involvement of herbal medicine), clinical manifestations, disease course, and treatment of MP. RESULTS: Data from 222 patients were collected. Among the 169 patients (76.1 %), whose history of herbal medicine was obtained, 147 (87.0 %) used herbal medicines. The use of herbal medicines containing sanshishi (gardenia fruit, Gardenia jasminoides Ellis) was reported in 119 out of 147 patients (81.0 %). Therefore, the use of herbal medicine containing sanshishi was confirmed in 70.4 % of 169 patients whose history of herbal medicine was obtained. The duration of sanshishi use ranged from 3 to 51 years (mean 13.6 years). Patients who discontinued sanshishi showed a better outcome compared with those who continued it. CONCLUSIONS: The use of herbal medicine containing sanshishi is associated with the etiology of MP. Although it may not be the causative factor, it is necessary for gastroenterologists to be aware of the potential risk of herbal medicine containing sanshishi for the development of MP.

DOI: 10.1007/s00535-016-1218-9
PMID: 27220772 [Indexed for MEDLINE]

25. Worldwide Occurrence and Investigations of Contamination of Herbal Medicines by Tropane Alkaloids. Chan TYK.

Toxins (Basel). 2017 Sep 15;9(9). pii: E284. doi: 10.3390/toxins9090284.

Tropane alkaloids occur mainly in Solanaceae plants. In the present review, the main objective is to describe the worldwide occurrence and investigations of anticholinergic poisoning due to the contamination of herbal teas and herbs by tropane alkaloids. Tropane alkaloid poisoning can occur after consumption of any medicinal plant if Solanaceae plants or plant parts are present as contaminants. Globally, almost all reports in 1978-2014 involve herbal teas and one of the prescribed herbs in composite formulae. Contamination most likely occurs during harvest or processing. As for prescribed herbs, on-site inspection is necessary to exclude cross-contamination and accidental mix-up at the retail level. The diagnosis is confirmed by screening for the presence of Solanaceae species and tropane alkaloids. Herbal teas and herbs contaminated by tropane alkaloids can pose a serious health hazard because these relatively heat-stable alkaloids may exist in large quantities. The WHO repeatedly emphasises the importance of good agricultural and collection practices for medicinal plants. DNA barcoding is increasingly used to exclude the presence of contaminants (particularly toxic species) and product substitution. All suspected cases should be reported to health authorities so that investigations along the supply chain and early intervention measures to protect the public can be initiated.

DOI: 10.3390/toxins9090284
PMCID: PMC5618217
PMID: 28914776

26. Steroids in traditional Chinese medicine: what is the evidence? Fung FY, Linn YC.

Singapore Med J. 2017 Mar;58(3):115-120. doi: 10.11622/smedj.2017016.

Local healthcare providers often question the possible steroidal activity of traditional Chinese medicine (TCM) herbs or herbal products and implicate them as a cause for adrenal insufficiency or Cushing's

syndrome in patients with a history of TCM intake. We conducted a comprehensive database search for evidence of potential glucocorticoid, mineralocorticoid, androgenic or oestrogenic activity of herbs or herbal products. Overall, there are not many herbs whose steroidal activity is well established; among these, most cases were based on preclinical studies. Liquorice root may cause pseudoaldosteronism through interference with the steroidogenesis pathway. Although ginseng and cordyceps have some in vitro glucocorticoid activities, the corroborating clinical data is lacking. Deer musk and deer antler contain androgenic steroids, while epimedium has oestrogenic activity. On the other hand, adulteration of herbal products with exogenous glucocorticoids is a recurrent problem encountered locally in illegal products masquerading as TCM. Healthcare providers should stay vigilant and report any suspicion to the relevant authorities for further investigations.

DOI: 10.11622/smedj.2017016
PMCID: PMC5360864
PMID: 28361161 [Indexed for MEDLINE]

27. Identification of natural products as inhibitors of human organic anion transporters (OAT1 and OAT3) and their protective effect on mercury-induced toxicity. Wang X, Han L, Li G, Peng W, Gao X, Klaassen CD, Fan G, Zhang Y.

Toxicol Sci. 2017 Oct 13. doi: 10.1093/toxsci/kfx216. [Epub ahead of print]

Mercury accumulates in kidneys and produces acute kidney injury. Semen cassiae (SC), a widely consumed tea and herbal medicine in Eastern Asia, has been reported to have protective effects on kidneys. In this study, SC extract was shown to almost abolish the histological alterations induced by mercuric chloride ($HgCl_2$) in rat kidneys. A total of 22 compounds were isolated from SC, and 1,7,8-methoxyl-2-hydroxyl-3-methyl-anthraquinone was detected in SC for the first time. Among the 8 compounds identified in the blood of rats after SC treatment, 6 were strong inhibitors of human organic anion transporter 1 and 3 (OAT1 and OAT3). Inhibitory studies revealed that OAT1 and OAT3 were inhibited by SC constituents, in both a competitive and non-competitive manner. Both OAT1- and OAT3-overexpressing cells were susceptible to the cytotoxicity of the cysteine-mercury conjugate (Cys-Hg), but only OAT1-overexpressing cells could be protected by 200 μM probenecid or 10 μM of the 8 inhibitors in SC, suggesting that OAT1 is the major determinant in the cellular uptake of mercury. To facilitate the identification of inhibitors of OAT1 and OAT3, models of OAT1 and OAT3 were constructed using recently determined protein templates. By combining in silico and in vitro methods, inhibitors of OAT1 and OAT3 were predicted and validated from SC constituents. Collectively, the present study suggests that additional inhibitors of OAT1 and OAT3 can be predicted and validated from natural products by combining docking and in vitro screening, and could be a source of pharmaceutical compounds for developing treatments for mercury-induced kidney injury.

DOI: 10.1093/toxsci/kfx216
PMID: 29045746

28. A review of cinnabar (HgS) and/or realgar (As_4S_4)-containing traditional medicines. Liu J, Wei LX, Wang Q, Lu YF, Zhang F, Shi JZ, Li C, Cherian MG.

J Ethnopharmacol. 2017 Aug 31;210:340-350. doi: 10.1016/j.jep.2017.08.037. [Epub ahead of print]

ETHNOPHARMOCOLOGICAL RELEVANCE: Herbo-metallic preparations have a long history in the treatment of diseases, and are still used today for refractory diseases, as adjuncts to standard therapy, or for economic reasons in developing countries. AIM OF THE REVIEW: This review uses cinnabar (HgS) and realgar (As_4S_4) as mineral examples to discuss their occurrence, therapeutic use, pharmacology, toxicity in traditional medicine mixtures, and research perspectives. MATERIALS AND METHODS: A literature search on cinnabar and realgar from PubMed, Chinese pharmacopeia, Google and other sources was carried out. Traditional medicines containing both cinnabar and realgar (An-Gong-Niu-Huang Wan, Hua-Feng-Dan); mainly cinnabar (Zhu-Sha-An-Shen Wan; Zuotai and Dangzuo), and mainly realgar (Huang-Dai Pian; Liu-Shen Wan; Niu-Huang-Jie-Du) are discussed. RESULTS: Both cinnabar and realgar used in traditional medicines are subjected to special preparation procedures to remove impurities. Metals in these traditional medicines are in the sulfide forms which are different from environmental mercurials ($HgCl_2$, MeHg) or arsenicals ($NaAsO_2$, NaH_2AsO_4). Cinnabar and/or realgar are seldom used alone, but rather as mixtures with herbs and/or animal products in traditional medicines. Advanced technologies are now used to characterize these preparations. The bioaccessibility, absorption, distribution, metabolism and elimination of

these herbo-metallic preparations are different from environmental metals. The rationale of including metals in traditional remedies and their interactions with drugs need to be justified. At higher therapeutic doses, balance of the benefits and risks is critical. Surveillance of patients using these herbo-metallic preparations is desired. CONCLUSION: Chemical forms of mercury and arsenic are a major determinant of their disposition, efficacy and toxicity, and the use of total Hg and As alone for risk assessment of metals in traditional medicines is insufficient.

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