AACT Herbal Dietary Supplements SIG Abstracts May 2019

1. Kratom-Induced Cholestatic Liver Injury and Its Conservative Management. Fernandes CT, Iqbal U, Tighe SP, Ahmed A.

J Investig Med High Impact Case Rep. 2019 Jan-Dec;7:2324709619836138. doi 10.1177/2324709619836138.

Drug-induced liver injury (DILI) is a common cause of hepatotoxicity associated with prescription-based and over-the-counter exposure to medications and herbal supplements. Use of unapproved and inadequately tested herbal supplements can cause DILI. Therefore, thorough history-taking on exposure to herbal supplements must be an integral part of clinical evaluation of DILI. Kratom is an herbal supplement or remedy that has been known for its analgesic effects and has also been used for self-treatment of opiate withdrawals. A 52-year-old man was seen for evaluation of yellow discoloration of the eyes and skin. He reported taking kratom for right shoulder strain for at least a couple of months. On workup, his total bilirubin was noted to be 23.2 mg/dL, which peaked at 28.9 mg/dL. He was noted to have mild elevation of aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase. Extensive laboratory tests were ordered and known causes of chronic liver disease ruled out. Magnetic resonance imaging of the abdomen was unremarkable without stigmata of portal hypertension or signs of chronic liver disease. He demonstrated no evidence of coagulopathy or hepatic encephalopathy during his illness. He underwent liver biopsy, which demonstrated histologic evidence of acute cholestatic hepatitis highly suspicious of DILI. He was advised to avoid kratom or other herbal supplements in future and prescribed ursodeoxycholic acid with significant improvement in his liver chemistries. Kratom is associated with significant liver enzymes derangements leading to DILI. Kratom is not approved for use in the United States and should be avoided.

DOI: 10.1177/2324709619836138
PMCID: PMC6440031
PMID: 30920318

2. Notes from the Field: Unintentional Drug Overdose Deaths with Kratom Detected - 27 States, July 2016-December 2017. Olsen EO, O'Donnell J, Mattson CL, Schier JG, Wilson N.

MMWR Morb Mortal Wkly Rep. 2019 Apr 12;68(14):326-327. doi: 10.15585/mmwr.mm6814a2.

DOI: 10.15585/mmwr.mm6814a2
PMCID: PMC6459583
PMID: 30973850 [Indexed for MEDLINE]

3. The unexpected identification of the cannabimimetic, 5F-ADB, and dextromethorphan in commercially available cannabidiol e-liquids. Poklis JL, Mulder HA, Peace MR.

Forensic Sci Int. 2019 Jan;294:e25-e27. doi: 10.1016/j.forsciint.2018.10.019. Epub 2018 Nov 1.

Electronic cigarettes (e-cigarettes) were developed as an alternative method for nicotine delivery and had a significant surge in popularity. E-liquids are formulations used in e-cigarettes, and consist of a ratio of propylene glycol (PG) and vegetable glycerin (VG), a pharmaceutical and/or herbal remedy and, usually, a flavoring agent. Presented is the evaluation of nine cannabidiol (CBD) e-liquids from a single manufacturer for cannabinoids and other psychoactive compounds by Direct Analysis in Real Time Mass Spectrometry (DART-MS) and Gas Chromatography Mass Spectrometry (GC/MS). The analysis of these products resulted in the detection of CBD in all nine produces and the unexpected detections of 5-fluoro MDMB-PINACA (5F-ADB) in four of the products and dextromethorphan (DXM) in one of the products. The analysis of these products illustrates the potential quality control issues that can occur in an

unregulated industry. CBD products are believed by many users to offer heath benefits, but the detection of a dangerous cannabimimetic, 5F-ADB, and DXM in these products illustrates the need for oversight.

DOI: 10.1016/j.forsciint.2018.10.019
PMCID: PMC6321772 [Available on 2020-01-01]
PMID: 30442388 [Indexed for MEDLINE]

4. Fatal combination of mitragynine and quetiapine - a case report with discussion of a potential herb-drug interaction. Hughes RL.

Forensic Sci Med Pathol. 2019 Mar;15(1):110-113. doi: 10.1007/s12024-018-0049-9. Epub 2018 Nov 29.

Kratom is a plant with dose-dependent mixed stimulant and opioid properties whose pharmacologic characteristics and social impact continue to be described. The main active isolate of kratom is mitragynine, an indole-containing alkaloid with opioid-like effects. Kratom toxicity and kratom-associated fatalities have been described, including those in association with additional drugs. In this paper we describe the case of a 27-year-old man who was found deceased with a toxic blood concentration of quetiapine in conjunction with the qualitative presence of mitragynine. Investigative and autopsy findings suggested perimortem hyperthermia and seizure-like activity. Kratom toxicity and kratom-associated fatalities are being increasingly reported. Experiments with kratom extracts have shown inhibitory effects upon hepatic CYP enzymes, leading to previous speculation of the potential for clinically significant interactions between kratom and a wide array of medications. Herein is described a fatal case of quetiapine toxicity complicated by mitragynine use. The potential ability of mitragynine to alter the pharmacokinetics of a prescription medication via inhibition of its hepatic metabolism is discussed.

DOI: 10.1007/s12024-018-0049-9
PMID: 30498933 [Indexed for MEDLINE]

5. Possible Garcinia cambogia-Induced Mania With Psychosis: A Case Report. Nguyen DC, Timmer TK, Davison BC, McGrane IR.

J Pharm Pract. 2019 Feb;32(1):99-102. doi: 10.1177/0897190017734728. Epub 2017 Oct 5.

Garcinia cambogia is a Southeast Asian fruit becoming increasingly popular as a weight management supplement. Hydroxycitric acid (HCA) is the primary active ingredient which demonstrates serotonergic- and muscarinic-enhancing properties via inhibition of selective serotonin reuptake and acetylcholinesterase. We report a young adult female with no history of bipolar disorder who developed mania and psychosis approximately 1 week following initiation of G cambogia and the Cleanse and Detox™ dietary supplement manufactured by Apex Vitality Health. She presented with a predominantly expansive mood, psychomotor agitation, disorganized and pressured speech, flight of ideas, grandiosity, delusions, and auditory hallucinations. Following discontinuation of G cambogia and the initiation of lithium and quetiapine, the patient experienced rapid and progressive mood stabilization and was discharged after 8 days. Seven previous case reports associating (hypo)mania and/or psychosis with G cambogia consumption have been published. The chronology of mania and/or psychosis onset may appear between 1 and 8 weeks following initiation of G cambogia. Psychiatric symptoms have resolved with G cambogia discontinuation in some instances and may not require chronic pharmacotherapy. Our report should encourage further research and case reports regarding this adverse event and the reconciliation of complete herbal supplement use at clinic visits and hospital admissions.

DOI: 10.1177/0897190017734728
PMID: 28982303 [Indexed for MEDLINE]

6. Acute liver injury following Garcinia cambogia weight-loss supplementation: case series and literature review. Crescioli G, Lombardi N, Bettiol A, Marconi E, Risaliti F, Bertoni M, Menniti Ippolito F, Maggini V, Gallo E, Firenzuoli F, Vannacci A.

Intern Emerg Med. 2018 Sep;13(6):857-872. doi: 10.1007/s11739-018-1880-4. Epub 2018 May 25.

Comment in
Intern Emerg Med. 2018 Sep;13(6):833-835.

Herbal weight-loss supplements are sold as self-medication products, and are often used under the misconception that their natural origin guarantees their safety. Food supplements are not required to provide any benefit/risk profile evaluation before marketing; however, possible risks associated with use of herbal extracts in food supplements are becoming more and more documented in the literature. Some herbs are listed as the leading cause of herb-induced liver injury, with a severe or potentially lethal clinical course, and unpredictable herb-drug interactions. Garcinia cambogia (GC) extract and GC-containing products are some of the most popular dietary supplements currently marketed for weight loss. Here, we present four cases of acute liver failure in women taking GC extract for weight loss, and a literature review of clinical evidences about hepatic toxicity in patients taking dietary supplements containing GC extract.

DOI: 10.1007/s11739-018-1880-4
PMID: 29802521 [Indexed for MEDLINE]

7. Syrian rue seeds interacted with acacia tree bark in an herbal stew resulted in N,N-dimethyltryptamine poisoning. Liu CH, Chu WL, Liao SC, Yang CC, Lin CC.

Clin Toxicol (Phila). 2019 Mar 4:1-3. doi: 10.1080/15563650.2019.1576877. [Epub ahead of print]

INTRODUCTION: Illicit substance use is an increasing problem all over the world, especially in adolescents and young adults. It is a challenge to make a definitive diagnosis of a specific substance in a poisoning case without toxicology laboratory confirmation. We confirmed the presence of N,N-dimethyltryptamine (DMT) by liquid chromatograph tandem mass spectrometer (LC/MS/MS) in biologic samples from two patients who presented with signs and symptoms consistent with sympathomimetic toxicity following the consumption of an herbal stew. CASE: Two patients consumed an herbal stew together developed DMT poisoning from the interaction between Syrian rue seeds containing alkaloids with monoamine oxidase inhibitor (MAOI) activity and Acacia tree bark containing DMT. Patients' blood and spot urine was analyzed by LC/MS/MS which revealed the presence of DMT (case 1 urine: 1206 ng/mL, serum: 25 ng/mL; case 2 urine: 478 ng/mL, serum: undetectable) and harmaline (case 1 urine: 1564 ng/mL, serum: 3.3 ng/mL; case 2 urine: 1230 ng/mL, serum: undetectable). DISCUSSION: The diagnosis of DMT poisoning is confirmed by the presence of DMT and harmaline in patients' serum and urine. Case 1 exhibited more severe signs and symptoms (e.g., altered consciousness, rhabdomyolysis, and elevated liver enzyme) than case 2. This may be explained by the presence of psychoactive DMT levels in the blood of case 1 whereas DMT was undetected in the blood of case 2. CONCLUSIONS: Consumption of an herbal stew composed of Syrian rue seeds and Acacia tree bark may be equivalent to taking a combination of DMT and MAOI, which may precipitate a sympathomimetic syndrome. Physicians should be aware that unusual clinical presentations may be the result of drug-drug interactions from a mixed herbal preparation.

DOI: 10.1080/15563650.2019.1576877
PMID: 30831037

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

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

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

DOI: 10.1136/bcr-2018-227531
PMID: 30573541 [Indexed for MEDLINE]

9. Thyroxine-induced periodic paralysis: a rare complication of nutritional supplements. Cheema MA, Zain MA, Cheema K, Ullah W

BMJ Case Rep. 2018 Dec 13;11(1). pii: e227946. doi: 10.1136/bcr-2018-227946.

The consumption of daily nutritional supplements has risen dramatically all over the world. Many people believe that dietary supplements, if not useful, are at least safe to fulfil small dietary gaps. Many nutritional supplements have not been approved by Federal Drug Administration due to their unregulated active ingredients, but they are available as over the counter. One of the active ingredients, exogenous triiodothyronine (T3), has been reported in dietary supplements. We present a case of sudden onset of tetraparesis. Laboratory workup showed hypokalaemia, low thyroid-stimulating hormone and thyroxine (T4) but normal T3 and thyroglobulin levels. The radioiodine uptake scan also showed reduced uptake. After aggressive serum potassium correction and stopping supplements, his condition got improved. So the suspicion of exogenous T3-induced thyrotoxic periodic paralysis was confirmed.

DOI: 10.1136/bcr-2018-227946
PMID: 30567254 [Indexed for MEDLINE]

10. Fatal acute arsenic poisoning by external use of realgar: Case report and 30 years literature retrospective study in China. Zheng J, Zhang K, Liu Y, Wang Y.

Forensic Sci Int. 2019 Apr 5. pii: S0379-0738(18)31009-0. doi: 10.1016/j.forsciint.2019.03.012. [Epub ahead of print]

Realgar (arsenic sulfide) is widely used in combination with other herbs as Chinese patent medicine to treat a variety of diseases in China. As a mineral arsenic, its mild toxicity was also well known. Longtime over-dose usage or wrongly oral intake of realgar can cause chronic arsenic poisoning and/or death, but acute fatal arsenic poisoning resulted from short-term dermal use of realgar-containing medicine was very rare. Here, we present the case of a 35-year-old Chinese man, who was diagnosed with severe psoriasis and died of fatal acute arsenic poisoning after he applied a local folk prescription ointment containing mainly the realgar to the affected skin for about 4 days. The autopsy showed multiple punctate hemorrhages over the limbs, pleural effusion, edematous lungs with consolidation, mild myocardial hypertrophy and normal-looking kidneys. The histopathological examination of renal tissue showed severe degeneration, necrosis and desquamation of renal tubular epithelial cells, presence of protein cast and a widened edematous interstitium with interstitial fibrosis. The presence of arsenic in large amount in the ointment (about 6%), in blood (1.76 μg/mL), and in skin (4.71 μg/g), were confirmed analytically. We

also provide the clinical records of the deceased and briefly reviewed 7 similar cases in literature (6 in Chinese and 1 in English) in the past 30 years in China.

DOI: 10.1016/j.forsciint.2019.03.012
PMID: 31023496

11. Chronic arsenic poisoning from traditional Chinese medicine. Spilchuk V, Thompson A.

CMAJ. 2019 Apr 15;191(15):E424. doi: 10.1503/cmaj.181176.

DOI: 10.1503/cmaj.181176
PMCID: PMC6464887 [Available on 2020-04-15]
PMID: 30988044

12. Membranous nephropathy due to chronic mercury poisoning from traditional Indian medicines: report of five cases. Doshi M, Annigeri RA, Kowdle PC, Subba Rao B, Varman M.

Clin Kidney J. 2018 Jun 3;12(2):239-244. doi: 10.1093/ckj/sfy031. eCollection 2019 Apr.

Mercury contained in traditional medicines can cause chronic poisoning, which can cause membranous nephropathy (MN). We report five cases of nephrotic syndrome caused by MN with evidence of chronic mercury poisoning due to consumption of traditional Indian medicines such as Siddha and Ayurveda, which to our knowledge are the first such reports. All patients were seronegative for antibodies against phospholipase A2 receptor (PLA2R). Two patients, who had severe nephrotic syndrome, had received Siddha medicine for prolonged period and oral chelation with dimercaptopropane-1-sulfonic acid was successful in eliminating mercury, resulting in an improvement in nephrotic state in these patients. We suggest that mercury poisoning should be entertained in patients with anti-PLA2R antibody-negative MN, with history of consumption of traditional Indian medicines.

DOI: 10.1093/ckj/sfy031
PMCID: PMC6452196
PMID: 30976402

13. Slimming to the Death: Herbalife®-Associated Fatal Acute Liver Failure-Heavy Metals, Toxic Compounds, Bacterial Contaminants and Psychotropic Agents in Products Sold in India. Philips CA, Augustine P, Rajesh S, John SK, Valiathan GC, Mathew J, Phalke S, Antony KL

J Clin Exp Hepatol. 2019 Mar-Apr;9(2):268-272. doi: 10.1016/j.jceh.2018.08.002. Epub 2018 Aug 28.

Herbalife® is a global nutrition and weight management company selling and marketing nutritional and weight loss supplements. The United States Federal Trade Commission described Herbalife® in 2016 as a scam disguised as healthy living. Herbalife®-associated liver injury was reported from multiple countries in the West. India is fast becoming the largest growing market for Herbalife® products, expected to surpass the United States in sales revenue. We report the first case of a fatal acute liver failure from the Asia-Pacific region, in a young woman who consumed Herbalife® products over 2 months. We also present unsettling data that showcase heavy metal contamination, toxic compounds, psychotropic substances, and pathogenic bacterial contamination in similar Herbalife® products in India. The growth of Herbalife® in India and expansion of its nutrition clubs in major cities that promise fake health benefits portend a serious public health concern.

DOI: 10.1016/j.jceh.2018.08.002
PMCID: PMC6477126 [Available on 2020-03-01]
PMID: 31024209

14. Acute onset/flares of dermatomyositis following ingestion of IsaLean herbal supplement: Clinical and immunostimulatory findings. Zeidi M, Chansky PB, Werth VP.

J Am Acad Dermatol. 2019 Mar;80(3):801-804. doi: 10.1016/j.jaad.2018.08.019. Epub 2018 Aug 27.

DOI: 10.1016/j.jaad.2018.08.019
PMID: 30165168 [Indexed for MEDLINE]

15. Development of Pulmonary Arterial Hypertension in a Patient Treated with Qing-Dai (Chinese Herbal Medicine). Misumi K, Ogo T, Ueda J, Tsuji A, Fukui S, Konagai N, Asano R, Yasuda S.

Intern Med. 2019 Feb 1;58(3):395-399. doi: 10.2169/internalmedicine.1523-18. Epub 2018 Sep 12.

Pulmonary arterial hypertension (PAH) is a rare, devastating disease, characterized by elevated pulmonary arterial pressure due to pulmonary microvascular obstruction, which can result in heart failure and death. PAH can be associated with exposure to certain drugs or toxins. We herein report a case in which PAH developed in a patient with refractory ulcerative colitis during treatment with "Qing-Dai," a Chinese herbal medicine. The patient's PAH improved after the discontinuation of Qing-Dai.

DOI: 10.2169/internalmedicine.1523-18
PMCID: PMC6395113
PMID: 30210129 [Indexed for MEDLINE]

16. Acquired short QT syndrome in a cancer patient treated with Bufonis Venenum. Huang Y, Xu Y, Barajas-Martinez H, Hu D.

Pacing Clin Electrophysiol. 2019 Apr 29. doi: 10.1111/pace.13708. [Epub ahead of print]

Although drug-induced short QT syndrome (SQTS) has been recognized, we currently report the first acquired SQTS case induced by Bufotalinin (toad, an antineoplastic drug), which is a traditional Chinese folk prescription. It has cross reaction with digoxin and affects the Na+ -K+ -ATPase, the SR Ca2+ release from RyR2, the ROS production from the mitochondria. The case presented with bradycardia, extreme QT shortening and sino-atrial block that were resolved after gastric lavage, rehydration, electrolyte (hyperkalemia, hyponatremia, hypocalcemia) correction and atropine injection. Clinicians should recognize a potential association between toad poisoning and SQTS from this case.

DOI: 10.1111/pace.13708
PMID: 31037741

17. Dietary supplement regulation: FDA's bitter pill. Anon.

Lancet. 2019 Feb 23;393(10173):718. doi: 10.1016/S0140-6736(19)30406-4.

DOI: 10.1016/S0140-6736(19)30406-4
PMID: 30799001 [Indexed for MEDLINE]

18. Herb induced liver injury after using herbal medicine: A systemic review and case-control study. Lin NH, Yang HW, Su YJ, Chang CW.

Medicine (Baltimore). 2019 Mar;98(13):e14992. doi: 10.1097/MD.0000000000014992.

In Taiwan, traditional herbal medication was included in Taiwan's National Health Insurance (NHI) system since 1996 and in 9 out of 10 hospitals have developed their own departments of traditional

medicine. This study aims to address the herb-induced liver injury (HILI) after using herbal medicine on the relationship between age, gender, epidemiology, laboratory data, pathogenesis, mobility, and mortality.We searched the PubMed database with "hepatitis after herbal medicine" and "in human" till 2018 April and returned 163 articles in a systemic review manner. Two cases reports describing in-vitro liver injury were excluded. Reviews and articles without the detailed report, laboratory data and history were excluded from this study. In the end, there were 53 articles enrolled in this study. These enrolled literatures are from France (n=13), Germany (n=12), Switzerland (n=5) United States of America (n=4), Korea (n=4), Hong Kong (n=4), Greece (n=3), China (n=2), Canada (n=1), Italy (n=1), Thailand (n=1), Finland (n=1), Taiwan (n=1), and Japan (n=1). The data were analyzed with a commercial statistical software Stata/SE 12.0 program Stata Corporation, College Station, TX, USA. Statistical χ tests were performed and the significance was set at a P value of less than .05 (2-tailed).The ages are ranged from 15 to 78 years with the mean±SD (standard deviation) of 48.3±16.2 years old. The majority of cases are female (n=37). In elderly, man is more commonly seen than female in HILI (37.5% vs 10.5%, P =.02). Female is vulnerable to cholestatic type of HILI than male (21.1% vs 0.0%, P=.04). Of all the cases in HILI, using pure substance are more commonly seen than mixed substance (P=.02). In gender, male patients have higher alanine aminotransferase (GPT) (IU/L) level in HILI than female ones (1560± 819 vs 1047±706, P=.03).In HILI, the female is more commonly seen than male, but less than male in the elderly. The pure substance more often happens to HILI than mixture substance. Female is predominant in the cholestatic type of HILI. The major prevalence of HILI is in Europe rather than Asia. HILI cases in Europe is 2.75-fold than in Asia. This could be due to fewer reports of the herb induced liver injury in Asia compared to Europe. Prevention of HILI is the best policy, because it needs to take 78 ±59 days to recover.

DOI: 10.1097/MD.0000000000014992
PMID: 30921214 [Indexed for MEDLINE]

19. Potential Influence of Centrally Acting Herbal Drugs on Transporters at the Blood-Cerebrospinal Fluid Barrier and Blood-Brain Barrier. Kibathi LW, Bae S, Penzak SR, Kumar P.

Eur J Drug Metab Pharmacokinet. 2018 Dec;43(6):619-635. doi:10.1007/s13318-018-0486-6.

Complementary and alternative medications (CAM) with known or suspected pharmacologic activity in the central nervous system (CNS) are common. These herbal preparations may cause clinically significant drug-drug interactions (DDIs) when coadministered with medications that act in the CNS. This can result in negative outcomes such as toxicity or loss of efficacy. Most drug interaction reports with CAM focus on cytochrome P450 (CYP) modulation. However, drug interactions between CAM and conventional medications may occur via mechanisms other than CYP inhibition or induction; in particular, modulation of drug transport proteins represents an important mechanism by which such interactions may occur. This article provides an updated review of transporter-mediated mechanisms by which herbal products may theoretically interact with centrally acting medications at the blood-brain barrier and blood-cerebrospinal fluid (CSF) barrier. Further research is required before the true clinical impact of interactions involving modulation of centrally located membrane transporters can be fully understood.

DOI: 10.1007/s13318-018-0486-6
PMID: 29858835 [Indexed for MEDLINE]

20. Predictors of poor outcomes in 488 patients with herb-induced liver injury. Zhu Y, Niu M, Wang JB, Wang RL, Li JY, Ma YQ, Zhao YL, Zhang YF, He TT, Yu SM, Guo YM, Zhang F, Xiao XH, Schulze J.

Turk J Gastroenterol. 2019 Jan;30(1):47-58. doi: 10.5152/tjg.2018.17847.

BACKGROUND/AIMS: Herb-induced liver injury (HILI) can lead to chronic liver injury, liver transplantation, or even death. This study aimed to identify the predictors of poor HILI outcomes,

especially chronic HILI. MATERIALS AND METHODS: Clinical data of 488 patients with HILI were retrospectively analyzed from a Chinese center between January 2010 and January 2014. Logistic regression and C-statistic were used to identify risk factors and prognostic models for HILI outcomes. RESULTS: In all patients, 69 (14.1%) developed chronic HILI, and 20 (4.1%) died due to liver injury or underwent liver transplantation. To predict the fatal HILI prognosis, the model for end-stage liver disease (MELD) with a C-statistic of 0.981 (95%CI 0.968-0.995) was better than Hy's law (C-statistic 0.569; 95%CI 0.449-0.689). The latency, course of peak alanine aminotransferase decreasing >50% after discontinuation of herb application, peak triglyceride value, and platelet count at liver injury onset were identified as independent risk factors for chronicity with the adjusted odds ratios of 1.268 (95% confidence interval [CI] 1.034-1.554), 2.303 (95%CI 1.588-3.340), 0.580 (95%CI 0.343-0.978), and 0.183 (95%CI 0.091-0.368), respectively. A prognostic model for chronic HILI based on these four factors yielded the best prediction with a C-statistic of 0.812 (95%CI 0.755-0.868), compared with MELD (C-statistic 0.506; 95%CI 0.431-0.581) and Hy's law (C-statistic 0.418; 95%CI 0.343-0.492). CONCLUSION: Model for end-stage liver disease can be used to predict the fatal prognosis of HILI. A long latency, slow recovery, and low triglyceride value and platelet counts are important determinants for chronic HILI.

DOI: 10.5152/tjg.2018.17847
PMCID: PMC6389292
PMID: 30289391 [Indexed for MEDLINE]

21. Can adverse effects of excessive vitamin D supplementation occur without developing hypervitaminosis D? Razzaque MS.

J Steroid Biochem Mol Biol. 2018 Jun;180:81-86. doi: 10.1016/j.jsbmb.2017.07.006. Epub 2017 Jul 19.

Vitamin D is a fat-soluble hormone that has endocrine, paracrine and autocrine functions. Consumption of vitamin D-supplemented food & drugs have increased significantly in the last couple of decades due to campaign and awareness programs. Despite such wide use of artificial vitamin D supplements, serum level of 25 hydroxyvitamin D does not always reflect the amount of uptake. In contrast to the safe sunlight exposure, prolonged and disproportionate consumption of vitamin D supplements may lead to vitamin D intoxication, even without developing hypervitaminosis D. One of the reasons why vitamin D supplementation is believed to be safe is, it rarely raises serum vitamin D levels to the toxic range even after repeated intravenous ingestion of extremely high doses of synthetic vitamin D analogs. However, prolonged consumption of vitamin D supplementation may induce hypercalcemia, hypercalciuria and hyperphosphatemia, which are considered to be the initial signs of vitamin D intoxication. It is likely that calcium and phosphorus dysregulation, induced by exogenous vitamin D supplementation, may lead to tissue and organ damages, even without developing hypervitaminosis D. It is needed to be emphasized that, because of tight homeostatic control of calcium and phosphorus, when hypercalcemia and/or hyperphosphatemia is apparent following vitamin D supplementation, the process of tissue and/or organ damage might already have been started.

DOI: 10.1016/j.jsbmb.2017.07.006
PMID: 28734988 [Indexed for MEDLINE]

22. Liver Cirrhosis From Chronic Hypervitaminosis A Resulting in Liver Transplantation: A Case Report. García-Muñoz P, Bernal-Bellido C, Marchal-Santiago A, Cepeda-Franco C, Álamo-Martínez JM, Marín-Gómez LM, Suárez-Artacho G, Castillo-Tuñón JM, Navarro-Morales L, Padillo-Ruíz FJ, Gómez-Bravo MA.

Transplant Proc. 2019 Jan - Feb;51(1):90-91. doi: 10.1016/j.transproceed.2018.03.141. Epub 2019 Jan 14.

Herein we report a case of liver dysfunction caused by consumption of vitamin A supplements leading to liver transplantation. The patient was a 48-year-old male with a medical history of congenital

ichthyosiform erythroderma in treatment with vitamin A until 12 years of age, at which point he discontinued the supplements because he had developed ascites. Liver cirrhosis was diagnosed as secondary to hypervitaminosis A on the basis of histologic examination of liver biopsy and the absence of other potential causes of chronic liver disease. Despite interruption of administration of vitamin A, the patient continued to deteriorate over the years, with development of portal hypertension signs. His medical conditions were aggravated with the development of hepatic insufficiency manifested by refractory ascites, renal insufficiency, and severe encephalopathy and he underwent orthotopic liver transplantation, followed by disappearance of all signs of portal hypertension. This case highlights the need to take a careful history of consumption of vitamin A when evaluating a patient with liver failure.

DOI: 10.1016/j.transproceed.2018.03.141
PMID: 30655144 [Indexed for MEDLINE]

23. Impact of obesity on the toxicity of a multi-ingredient dietary supplement, OxyELITE Pro™ (New Formula), using the novel NZO/HILtJ obese mouse model:Physiological and mechanistic assessments. Skinner CM, Miousse IR, Ewing LE, Sridharan V, Cao M, Lin H, Williams DK, Avula B, Haider S, Chittiboyina AG, Khan IA, ElSohly MA, Boerma M, Gurley BJ, Koturbash I.

Food Chem Toxicol. 2018 Dec;122:21-32. doi: 10.1016/j.fct.2018.09.067. Epub 2018 Sep 30.

Herbal dietary supplement (HDS)-induced hepato- and cardiotoxicity is an emerging clinical problem. In this study, we investigated the liver and heart toxicity of HDS OxyELITE-PRO™ New Formula (OEP-NF), a dietary supplement marketed for weight loss and performance enhancement that was recently withdrawn from the market. Using a novel NZO/HlLtJ obese mouse model, we demonstrated that administration of clinically relevant mouse equivalent doses (MED) of OEP-NF produced cardio- and hepatotoxic risks following both short- and long-term administration schedules. Specifically, gavaging female NZO/HlLtJ with up to 2X MED of OEP-NF resulted in 40% mortality within two weeks. Feeding mice with either 1X or 3X MED of OEP-NF for eight weeks, while not exhibiting significant effects on body weights, significantly altered hepatic gene expression, increased the number of apoptotic and mast cells in the heart and affected cardiac function. The degree of toxicity in NZO/HlLtJ mice was higher than that observed previously in non-obese CD-1 and B6C3F1 strains, suggesting that an overweight/obese condition can sensitize mice to OEP-NF. Adverse health effects linked to OEP-NF, together with a number of other hepato- and cardiotoxicity cases associated with HDS ingestion, argue strongly for introduction of quality standards and pre-marketing safety assessments for multi-ingredient HDS.

DOI: 10.1016/j.fct.2018.09.067
PMCID: PMC6219625 [Available on 2019-12-01]
PMID: 30282009 [Indexed for MEDLINE]

24. Poisoning by toxic plants in Hong Kong: a 15-year review. Ng WY, Hung LY, Lam YH, Chan SS, Pang KS, Chong YK, Ching CK, Mak TWL.

Hong Kong Med J. 2019 Apr;25(2):102-112. doi: 10.12809/hkmj187745. Epub 2019 Apr 10.

INTRODUCTION: Hong Kong has a great diversity of plants, many of which are toxic to humans. The aim of this study was to identify the plant species most commonly involved in cases of plant poisoning in Hong Kong and to provide clinicians with a reference tool for the diagnosis and management of plant poisoning. METHODS: We retrospectively reviewed all plant poisoning cases referred to the Hospital Authority Toxicology Reference Laboratory from 1 January 2003 to 31 December 2017. Demographics, clinical presentation, laboratory findings, treatment and outcomes of patients, as well as morphological identification and analytical testing of the plant specimens, were investigated. RESULTS: A total of 62 cases involving 26 poisonous plant species were identified, among which Alocasia macrorrhizos (Giant Alocasia), Gelsemium elegans (Graceful Jessamine), and Rhododendron (Azalea) species were the three most commonly encountered. Gastrointestinal toxicity (n=30, 48%), neurological toxicity (n=22, 35%),

and hepatotoxicity (n=6, 10%) were the three most common clinical problems. Forty-nine (79%) and eight (13%) patients had mild and moderate toxicity, respectively; they all recovered shortly with supportive treatment. The remaining five (8%) patients experienced severe toxicity requiring intensive care support. Most patients (n=61, 98%) used the plants intentionally: as a medicinal herb (n=31), as food (n=29), and for attempting suicide (n=1). Reasons for using the poisonous plants included misidentification (n=34, 55%), unawareness of the toxicity (n=20, 32%), and contamination (n=6, 10%). CONCLUSIONS: Although most plant exposure resulted in a self-limiting disease, severe poisonings were encountered. Epidemiology of plant poisonings is geographically specific. Clinicians should be aware of local poisonous plants and their toxicities.

DOI: 10.12809/hkmj187745
PMID: 30967518

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

Expert Opin Drug Saf. 2019 Feb;18(2):145-152. doi: 10.1080/14740338.2019.1562546. Epub 2018 Dec 27.

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

DOI: 10.1080/14740338.2019.1562546
PMID: 30576263 [Indexed for MEDLINE]

26. Determination of synthetic pharmaceutical adulterants in herbal weight gain supplements sold in herb shops, Tehran, Iran. Saberi N, Akhgari M, Bahmanabadi L, Bazmi E, Mousavi Z.

Daru. 2018 Dec;26(2):117-127. doi: 10.1007/s40199-018-0216-2. Epub 2018 Sep 21.

BACKGROUND: Nowadays with the growing popularity of herbal remedies across the world, large sections of population rely on herbal drug practitioners for their primary care. Therefore there is a need to ensure about the safety of herbal drugs and to detect adulteration with undeclared active pharmaceutical ingredients. Herbal drugs are used as first-line drug therapy in some instances. Unfortunately even if there are claims as to be natural, undeclared active pharmaceutical ingredients have been detected in these supplements. OBJECTIVES: The purpose of the present study was to analyse herbal weight gain drugs collected from herb shops located in Tehran, Iran to detect hidden pharmaceutical ingredients using UHPLC and GC/MS instrumentations. METHODS: Sixty herbal drugs advertised as weight gain

supplements were gathered from herb shops Tehran province, Iran. All samples were analysed from analytical toxicology point of view to detect undeclared active pharmaceutical ingredients. Method was validated for quantitative analysis of cyproheptadine and dexamethasone. RESULTS: Method validity parameters showed good results for quantitative analysis of pharmaceutical ingredients. Cyproheptadine, dexamethasone, sildenafil, tramadol, caffeine and acetaminophen were detected in herbal weight gain drugs. Analysed dosage forms contained cyproheptadine and dexamethasone in concentrations higher than therapeutic doses. Quantitative analysis of contaminated drugs showed that the content of pharmacologic ingredients were 0.2-67 and 5.5-10.1 mg/tablet or capsule for cyproheptadine and dexamethasone respectively. CONCLUSIONS: Despite natural supplements producers' claim, herbal weight gain drugs were not natural at all. Undeclared active pharmaceutical ingredients can predispose patients to health problems and even life-threatening situations.

DOI: 10.1007/s40199-018-0216-2
PMCID: PMC6279663 [Available on 2019-09-21]
PMID: 30242673 [Indexed for MEDLINE]

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

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

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

DOI: 10.1016/j.jpba.2018.11.007
PMID: 30472590 [Indexed for MEDLINE]