AACT Herbal Dietary Supplement SIG Abstracts May 2015

1. Determination of anabolic-androgenic steroid adulterants in counterfeit drugs by UHPLC-MS/MS. Cho SH, Park HJ, Lee JH, Do JA, Heo S, Jo JH, Cho S.

J Pharm Biomed Anal. 2015 Mar 28;111:138-146. doi: 10.1016/j.jpba.2015.03.018. [Epub ahead of print]

Abstract:
Anabolic-androgenic steroids (AASs) have been illegally used in counterfeit drugs to improve the performance of athletes. In addition, AASs have been used for cosmetic purpose by non-athletes. To determine the presence of 26 AASs, an analysis method using ultra-liquid chromatography-tandem mass spectrometry (UHPLC-MS/MS) was developed and validated. The validated method was applied to 19 counterfeit drugs collected from the Internet and off-line markets during 2014. Nearly 50% (9/19) of the samples contained one of these 26 AASs. In addition, the concentration ranges of the AASs ranged from 0.09 to 119,228.57mg/kg in the suspected samples. The determined AASs primarily consisted of testosterone and testosterone 17-propionate (26%) followed by boldenone (21%). These results indicate the adulteration of over-the-counter counterfeit drugs, and the continuous monitoring of counterfeit drugs or dubious dietary supplements containing anabolic steroids is warranted.

PMID: 25880245 [PubMed - as supplied by publisher]

2. Anabolic steroids detected in bodybuilding dietary supplements - a significant risk to public health. Abbate V, Kicman AT, Evans-Brown M, McVeigh J, Cowan DA, Wilson C, Coles SJ, Walker CJ.

Drug Test Anal. 2014 Oct 6. doi: 10.1002/dta.1728. [Epub ahead of print]

Abstract:
Twenty-four products suspected of containing anabolic steroids and sold in fitness equipment shops in the United Kingdom (UK) were analyzed for their qualitative and semi-quantitative content using full scan gas chromatography-mass spectrometry (GC-MS), accurate mass liquid chromatography-mass spectrometry (LC-MS), high pressure liquid chromatography with diode array detection (HPLC-DAD), UV-Vis, and nuclear magnetic resonance (NMR) spectroscopy. In addition, X-ray crystallography enabled the identification of one of the compounds, where reference standard was not available. Of the 24 products tested, 23 contained steroids including known anabolic agents; 16 of these contained steroids that were different to those indicated on the packaging and one product contained no steroid at all. Overall, 13 different steroids were identified; 12 of these are controlled in the UK under the Misuse of Drugs Act 1971. Several of the products contained steroids that may be considered to have considerable pharmacological activity, based on their chemical structures and the amounts present. This could unwittingly expose users to a significant risk to their health, which is of particular concern for naïve users.

PMID: 25284752 [PubMed - as supplied by publisher]

3. Designer steroids - over-the-counter supplements and their androgenic component: review of an increasing problem. Rahnema CD, Crosnoe LE, Kim ED.

Andrology. 2015 Mar;3(2):150-5. doi: 10.1111/andr.307. Epub 2015 Feb 13.

Abstract:
Colloquially referred to by various misleading monikers ('pro-hormones', ‘natural steroids', 'testosterone boosters', etc.) designer anabolic steroids have been popular now for over a decade as a way to achieve classic anabolic steroid-like results from products sold in the legal marketplace. Recent evidence suggests that anabolic steroid use may be the most common cause of hypogonadism in men of reproductive age. Despite recent regulatory efforts that have banned specific compounds, many anabolic-androgenic steroids (AAS) remain available in over-the-counter dietary supplements that are legally sold in the United States. Severe side effects including hepatotoxicity, cholestasis, renal failure, hypogonadism, gynecomastia, and infertility have been reported secondary to the use of these products. While some of these side effects may be reversible, more aggressive use may result in more permanent end-organ damage as has been previously described for the case of aggressive AAS users (Rahnema et al., Fertil Steril, 2014). Designer AAS remain easily available for purchase in over-the-counter bodybuilding supplements and these products appear to be increasingly popular, despite the known health risks associated with

their use. We conducted a systematic search to identify the designer steroids that are most commonly sold in dietary supplements as of April 2014 and review what is known regarding their potency and toxicity. We propose that the impact of AAS use on the reproductive and hormonal health of men is underestimated in the literature owing to previous studies' failure to account for designer steroid use. Lastly, we make clinical recommendations to help physicians steer patients away from potentially harmful supplements, and summarize key regulatory obstacles that have allowed potent androgens to remain unregulated in the legal marketplace.

PMID: 25684733 [PubMed - in process]

4. Determination of anabolic agents in dietary supplements by liquid chromatography-high-resolution mass spectrometry. Odoardi S, Castrignanò E, Martello S, Chiarotti M, Strano-Rossi S.

Food Addit Contam Part A Chem Anal Control Expo Risk Assess. 2015 May;32(5):635-47. doi: 10.1080/19440049.2015.1014868. Epub 2015 Mar 4.

Abstract:
A sensitive method for the identification and quantification of anabolic steroids and clenbuterol at trace levels in dietary supplements by liquid chromatography-high-resolution mass spectrometry (LC-HRMS) in atmospheric pressure ionisation (APCI) mode using a single-stage Orbitrap analyser operating at a resolution power of 100 000 full width at half maximum (FWHM) was developed and validated. A total of 1 g of dietary supplement was added with testosterone-d3 as internal standard, dissolved in methanol, evaporated to dryness, diluted in sodium hydroxide solution and extracted with a mixture of pentane/ethyl ether 9:1. The extract was directly injected into the LC-HRMS system. The method was fully validated. Limits of detection (LODs) obtained for anabolic androgenic steroids (AASs) varied from 1 to 25 ng g(-1) and the limit of quantitation (LOQ) was 50 ng g(-1) for all analytes. The calibration was linear for all compounds in the range from the LOQ to 2000 ng g(-1), with correlation coefficients always higher than 0.99. Accuracy (intended as %E) and repeatability (%CV) were always lower than 15%. Good values of matrix effect and recovery were achieved. The ease of the sample preparation together with a fast run time of only 16 min permitted rapid identification of the analytes. The method was applied to the analysis of 30 dietary supplements in order to check for the presence of anabolic agents not labelled as being present in these supplements. Many AASs were often detected in the same sample: indeed, androstenedione was detected in nine supplements, 5-androsten-3β-ol-17-one (DHEA) in 12, methandienone in three, stanozolol in one, testosterone in seven and testosterone esters in four of them. A retrospective analysis of suspected compounds not included at the beginning of the method development was also possible by means of the full acquisition spectra obtained with the HRMS technique.

PMID: 25719897 [PubMed - in process]

5. Monitoring of 35 illegally added steroid compounds in foods and dietary supplements.
Cho SH, Park HJ, Lee JH, Kim HJ, Cho S, Yoon CY, Kim WS.

Food Addit Contam Part A Chem Anal Control Expo Risk Assess. 2014;31(9):1470-5. doi: 10.1080/19440049.2014.946100. Epub 2014 Aug 4.

Abstract:
The adulteration of foods and dietary supplements with steroids has been well attested and has the potential to be dangerous owing to various possible side-effects. Therefore, detecting the presence of steroids in various health food products has become increasingly important. The purpose of this study was to monitor illegally adulterated health food products by applying multiple reaction monitoring techniques to tandem liquid chromatography-mass spectrometry (LC-MS/MS). Various food and supplement samples advertised for the treatment of arthritis, bone ache and joint pain were collected over a 4-year period (2010-13) from local and online Korean sources. The method was validated based on limits of quantification of 0.5-15.0 ng g(-1) and recoveries in spiked solid samples of 81-119%. Approximately 30% of the tested samples were identified as having been illicitly adulterated. Six compounds were observed overall, including dexamethasone (45.1%), cotrisone-21-aceteate and prednisone-21-acetate (16.2%), and betamethasone (14.4%), and found in some samples in high concentrations.

PMID: 25036882 [PubMed - indexed for MEDLINE]

6. Determination of non-opioid analgesics in adulterated food and dietary supplements by LC-MS/MS. Kim HJ, Lee JH, Park HJ, Kim JY, Cho S, Kim WS.

Food Addit Contam Part A Chem Anal Control Expo Risk Assess. 2014;31(6):973-8. doi: 10.1080/19440049.2014.908262. Epub 2014 May 9.

Abstract:
Commercially available non-opioid analgesics such as acetaminophen and non-steroidal anti-inflammatory drugs (NSAIDs) have been used to adulterate some foods and dietary supplements. Considering the rapid growth of the dietary supplement market, it is essential to analyse various analgesics used for adulteration over a time period. Acetaminophen and 16 NSAIDs used to adulterate food and dietary supplements were simultaneously determined by LC-MS/MS. The method was validated by determining the coefficient of determinations, limit of quantification and recovery, and samples were analysed for the determination of analgesics. Consequently, acetaminophen, diclofenac, ibuprofen, indomethacin, naproxen and piroxicam were detected in 53 samples (n = 214). Ibuprofen was the most commonly used adulterant, which was detected in a wide concentration range (1.06-233.40 mg g(-1)) and was present in about one-third of the adulterated samples. Various types of samples, in particular pills and capsules (73.6% of the total positive samples), were found to be adulterated with non-opioid analgesics. Samples containing high concentrations of analgesics can have a deleterious effect on human health, and thus the continued monitoring of adulterated food and dietary supplements is essential to maintain a healthy life.

PMID: 24679138 [PubMed - in process]

7. A comprehensive scientific overview of Garcinia cambogia. Semwal RB, Semwal DK, Vermaak I, Viljoen A.

Fitoterapia. 2015 Apr;102:134-148. doi: 10.1016/j.fitote.2015.02.012. Epub 2015 Feb 27.

Abstract:
The fruit rind of Garcinia gummi-gutta, commonly known as Garcinia cambogia (syn.), is extensively used traditionally as a flavourant in fish curries due to its sharp sour taste. Additional ethnobotanical uses include its use as a digestive and a traditional remedy to treat bowel complaints, intestinal parasites and rheumatism. This small fruit, reminiscent of a pumpkin in appearance, is currently most popularly used and widely advertised as a weight-loss supplement. Studies have shown that the extracts as well as (-)-hydroxycitric acid (HCA), a main organic acid component of the fruit rind, exhibited anti-obesity activity including reduced food intake and body fat gain by regulating the serotonin levels related to satiety, increased fat oxidation and decreased de novo lipogenesis. HCA is a potent inhibitor of adenosine triphosphate-citrate lyase, a catalyst for the conversion process of citrate to acetyl-coenzyme A, which plays a key role in fatty acid, cholesterol and triglycerides syntheses. The crude extract or constituents from the plant also exerted hypolipidaemic, antidiabetic, anti-inflammatory, anticancer, anthelmintic, anticholinesterase and hepatoprotective activities in in vitro and in vivo models. Phytochemical studies of various plant parts revealed the presence of mainly xanthones (e.g. carbogiol) and benzophenones (e.g. garcinol) together with organic acids (e.g. HCA) and amino acids (e.g. gamma aminobutyric acid). Currently, a large number of G. cambogia/HCA dietary supplements for weight management are being sold although the possible toxicity associated with the regular use of these supplements has raised concerns. In most cases, complaints have been related to multicomponent formulations and at this stage G. cambogia has not been confirmed as the potentially toxic culprit. This review presents a scientific overview of G. cambogia with reference to relevant botanical aspects, ethnobotanical uses, phytochemistry and biological activity as well as toxicity.

PMID: 25732350 [PubMed - as supplied by publisher]

8. Inhibition of monoamine oxidase (MAO) by α-ethylphenethylamine and N,α-diethylphenethylamine, two compounds related to dietary supplements. Santillo MF.

Food Chem Toxicol. 2014 Dec;74:265-9.

Abstract:
Phenethylamines can interact with the metabolic enzyme monoamine oxidase (MAO), which can cause neurochemical dysfunction or changes in drug potency. A methamphetamine analog, N,α-diethylphenethylamine (N,α-DEPEA), was recently discovered in athletic performance-enhancing supplements, along with discovery of its metabolite, α-ethylphenethylamine (AEPEA). In vitro inhibition of human recombinant MAO by AEPEA and N,α-

DEPEA was evaluated by measuring the fluorescence of 4-hydroxyquinoline produced from MAO substrate, kynuramine. AEPEA competitively inhibited human recombinant MAO A (Ki = 14.0 μM), which was 17-fold stronger compared to MAO B (Ki = 234 μM). Furthermore, N,α-DEPEA was a weak inhibitor of both MAO A (Ki = 251 μM) and MAO B (Ki = 159 μM). Trends regarding MAO A inhibition were explored among structural analogs, yielding the following ranking: amphetamine (Ki = 5.3 μM), AEPEA (Ki = 14.0 μM), methamphetamine (Ki = 17.2 μM), phentermine (Ki = 196 μM), and N,α-DEPEA (Ki = 251 μM). This study provides important data relating chemical structures and biochemical effects for two emerging compounds associated with dietary supplements.

PMID: 25455893 [PubMed - in process]

9. Population-Representative Incidence of Drug-Induced Acute Liver Failure Based on an Analysis of an Integrated Health Care System. Goldberg DS, Forde KA, Carbonari DM, Lewis JD, Leidl KB, Reddy KR, Haynes K, Roy J, Sha D, Marks AR, Schneider JL, Strom BL, Corley DA, Lo Re V 3rd.

Gastroenterology. 2015 Feb 28. pii: S0016-5085(15)00299-1. doi:10.1053/j.gastro.2015.02.050. [Epub ahead of print]

Abstract:
BACKGROUND & AIMS: Medications are a major cause of acute liver failure (ALF) in the United States, but no population-based studies have evaluated the incidence of ALF from drug-induced liver injury. We aimed to determine the incidence and outcomes of drug-induced ALF in an integrated health care system that approximates a population-based cohort. METHODS: We performed a retrospective cohort study using data from the Kaiser Permanente Northern California (KPNC) health care system between January 1, 2004, and December 31, 2010. We included all KPNC members age 18 years and older with 6 months or more of membership and hospitalization for potential ALF. The primary outcome was drug-induced ALF (defined as coagulopathy and hepatic encephalopathy without underlying chronic liver disease), determined by hepatologists who reviewed medical records of all KPNC members with inpatient diagnostic and laboratory criteria suggesting potential ALF. RESULTS: Among 5,484,224 KPNC members between 2004 and 2010, 669 had inpatient diagnostic and laboratory criteria indicating potential ALF. After medical record review, 62 (9.3%) were categorized as having definite or possible ALF, and 32 (51.6%) had a drug-induced etiology (27 definite, 5 possible). Acetaminophen was implicated in 18 events (56.3%), dietary/herbal supplements in 6 events (18.8%), antimicrobials in 2 events (6.3%), and miscellaneous medications in 6 events (18.8%). One patient with acetaminophen-induced ALF died (5.6%; 0.06 events/1,000,000 person-years) compared with 3 patients with non-acetaminophen-induced ALF (21.4%; 0.18/1,000,000 person-years). Overall, 6 patients (18.8%) underwent liver transplantation, and 22 patients (68.8%) were discharged without transplantation. The incidence rates of any definite drug-induced ALF and acetaminophen-induced ALF were 1.61 events/1,000,000 person-years (95% confidence interval, 1.06-2.35) and 1.02 events/1,000,000 person-years (95% confidence interval 0.59-1.63), respectively. CONCLUSIONS: Drug-induced ALF is uncommon, but over-the-counter products and dietary/herbal supplements are its most common causes.

PMID: 25733099 [PubMed - as supplied by publisher]

10. Hepatotoxicity of herbal and dietary supplements: an update. Stickel F, Shouval D.

Arch Toxicol. 2015 Feb 14. [Epub ahead of print]

Abstract:
Herbal and dietary supplements (HDS) have been used for health-related purposes since more than 5000 years, and their application is firmly anchored in all societies worldwide. Over last decades, a remarkable renaissance in the use of HDS can be noticed in affluent societies for manifold reasons. HDS are forms of complementary and alternative medicines commonly used to prevent or treat diseases, or simply as a health tonic. Another growing indication for HDS is their alleged benefit for weight loss or to increase physical fitness. Access is easy via internet and mail-order pharmacies, and their turnover reaches billions of dollars in the USA and Europe alone. However, HDS are generally not categorized as drugs and thus less strictly regulated in most countries. As a result, scientific evidence proving their beneficial effects is mostly lacking, although some HDS may have purported benefits. However, the majority lacks such proof of value, and their use is predominantly based on belief and hope. In addition to missing scientific evidence supporting their use, HDS are typically prone to batch-to-batch variability in composition and concentration,contamination, and purposeful adulteration. Moreover, numerous examples of preparations emerged which have been linked to significant liver injury. These include single ingredients, such as kava, germander, and

several Chinese herbals. Other HDS products associated with liver toxicity consist of multiple, often ill-defined ingredients, such as Hydroxycut and Herbalife. Affirmative diagnostic tests are not available, and the assessment of liver injury ascribed to HDS depends on a thorough and proactive medical history, careful exclusion of other causes, and a search for available reports on similar events linked to the intake of the suspected preparation or ingredients contained therein.

PMID: 25680499 [PubMed - as supplied by publisher]

11.. Drug-induced liver injury: an overview over the most critical compounds. Björnsson ES.

Arch Toxicol. 2015 Mar;89(3):327-34. doi: 10.1007/s00204-015-1456-2. Epub 2015 Jan 25.

Abstract:
There has been a substantial interest in drug-induced liver injury (DILI) recently. National Institutes of Health has sponsored a multicenter study in the USA for the last 10 years, which has collected valuable information in this context. Idiosyncratic DILI is like other adverse effects of drugs underestimated and underreported in most epidemiological studies. A recent prospective population-based study from Iceland found a crude incidence of approximately 19 cases per 100,000 and year. Antibiotic is the class of drugs most commonly implicated in patients with DILI. Amoxicillin-clavulanate continues to be the most commonly implicated agent occurring in approximately 1 out of 2,300 users. Drugs with the highest risk of DILI in the Icelandic study were azathioprine and infliximab. Although rare, statin-induced hepatotoxicity has been well documented. Liver injury associated with the use of herbal medicines and dietary supplements seems to be increasing. Information on the documented hepatotoxicity of drugs has recently been made easier by a website available in the public domain: LiverTox (http://livertox.nlm.nih.gov). Unfortunately, at the current time, pre-therapy risk assessment for DILI in the individual patient is difficult but previous well-documented hepatotoxicity is usually a contraindication for a subsequent treatment with the same drug.

PMID: 25618544 [PubMed - in process]

12. Three cases of liver toxicity with a dietary supplement intended to stop hair loss. Fernández J, Navascués C, Albines G, Franco L, Pipa M, Rodríguez M.

Rev Esp Enferm Dig. 2014 Dec;106(8):552-5.

Abstract:
Liver toxicity associated with herbal remedies and dietary supplements is an increasing concern. Several toxic hepatitis cases have been reported in the literature in association with products intended for weight loss where green tea extracts are an ingredient.Three hepatotoxicity cases are reported below in association with the use of Inneov masa capilar®, a dietary supplement intended to stop hair loss whose primary component is green tea catechins. In all of them, other potential causes of acute hepatitis were ruled out.We highlight the importance of awareness regarding these substances at history taking in order to identify and report hepatic adverse reactions secondary to apparently safe herbs as described in the present manuscript.

PMID: 25544415 [PubMed - in process]

13. A decades-long investigation of acute metabolism-based hepatotoxicity by herbal constituents: a case study of pennyroyal oil. Gordon P, Khojasteh SC.

Drug Metab Rev. 2014 Dec 16:1-9. [Epub ahead of print]

Abstract:
Herbal supplements are often regarded as "natural", and are, therefore, considered by many to be safer than pharmaceuticals; however, the adverse effects of these supplements are under-reported in many cases. Many herbal supplements, such as pyrrolizidine alkaloids, kava, chaparral and germander, are known to induce liver injury, which, in general, is one of the main toxicity liabilities observed in the clinic and accounts for about half of total liver failures. One example is the hepatotoxicity of pennyroyal oil, which is ingested as an abortifacient, among other uses. For three decades, the late Professor Sidney Nelson contributed to our understanding of the mechanism of toxicity of pennyroyal and broadened our understanding of chemical toxicology. Here we present the studies and

review the findings on acute hepatotoxicity of pennyroyal oil. These studies involved the isolation and characterization of pennyroyal components, determination of the appropriate animal models, identification of the structural requirement for toxicity and determination of the target enzymes and the enzymes involved in the process of bioactivation. Studies with stable isotope labeled pennyroyal metabolites, pulegone and menthofuran, furthered our understanding of the role of cytochrome P450 in the oxidation of these compounds. This review presents the investigational tools used in the study of pennyroyal oil, allowing the reader to not only appreciate these methods but also utilize them to tackle and better understand metabolism-based toxicity in their own projects.

PMID: 25512112 [PubMed - as supplied by publisher]

14. Concentrated green tea extract induces severe acute hepatitis in a 63-year-old woman--a case report with pharmaceutical analysis. Pillukat MH, Bester C, Hensel A, Lechtenberg M, Petereit F, Beckebaum S, Müller KM, Schmidt HH.

J Ethnopharmacol. 2014 Aug 8;155(1):165-70. doi: 10.1016/j.jep.2014.05.015. Epub 2014 May 24.

Abstract:
ETNOPHARMACOLOGICAL RELEVANCE: The popularity of concentrated green tea extracts as dietary supplements for a wide range of applications is increasing due to their health-promoting effects attributed to the high amounts of catechins they contain. The most important of the green tea catechins is (-)-epigallocatechin-3-O-gallate (EGCG). While their beneficiary effects have been studied extensively, a small number of adverse events have been reported in the medical literature. Here we present a typical reversible course of severe hepatitis after green tea consumption.MATERIALS AND METHODS: The case study describes in a 63-year old woman during treatment with green tea-capsules upon recommendation of a cancer support group. RESULTS: The histological finding was consistent with drug induced hepatitis, and other possible causes of hepatitis were excluded. According to the CIOMS/RUCAM score the causality was assessed as "probable". After discontinuation of medication, followed by extracorporal albumin dialysis, rapid and sustained recovery occurred. Pharmaceutically analysis (HPLC) of the green tea capsules did not give evidence for contaminants but revealed the two typical compounds of green tea, namely (-)-epigallocatechin-3-O-gallate (EGCG, 93.2%) and epicatechin (EC, 6.8%) at a very high dose level. CONCLUSION: The present case highlights the fact that such concentrated herbal extracts from green tea may not be free of adverse effects under certain circumstances. There is still a lack of a uniform European Union-wide surveillance system for adverse drug reactions of herbal products. Therefore this case underlines the importance of public awareness in the potential risks in use of herbal products.

PMID: 24862489 [PubMed - indexed for MEDLINE]

15. Dietary supplement use among patients with hepatocellular carcinoma. Lee V, Goyal A, Hsu CC, Jacobson JS, Rodriguez RD, Siegel AB.

Integr Cancer Ther. 2015 Jan;14(1):35-41. doi: 10.1177/1534735414550038. Epub 2014 Sep 15.

Abstract:
BACKGROUND: More than 50% of US adults, and an even larger proportion of cancer patients, use dietary supplements. Since many supplements require hepatic metabolism, they may be particularly likely to cause toxicities in patients with hepatocellular carcinoma (HCC). However, little is known about supplement use in patients with HCC. METHODS: From 2008 to 2012, we gave newly diagnosed HCC patients at our institution a standardized questionnaire about dietary supplement use, demographic factors, and clinical characteristics. We then followed patients for four years or until time to death to examine the relationship with supplement use. RESULTS: Of 146 patients, 71% had used vitamins and 45% herbal supplements. Most commonly used supplements were antioxidants (51%), multivitamins (46%), vitamin D (25%), and milk thistle (23%). People in mid-higher income brackets were more likely to use herbal supplements (19% of those earning <$30 000, 50% of those earning $30 000-60 000, and 34% of those earning >$60 000 used supplements). Hepatitis C (HCV) patients were more likely to use milk thistle than those without HCV (30% vs 13%, P = .03), and patients with hepatitis B (HBV) were more likely than non-HBV patients to use vitamin C (32% vs 14%, P = .01). Supplement use was not associated with overall survival. CONCLUSIONS: Like cancer patients in other studies, the majority of our HCC patients used dietary supplements. Supplement use was not associated with overall survival but should be studied in larger patient samples.

PMID: 25228537 [PubMed - in process]

16. Detection of a tadalafil analogue as an adulterant in a dietary supplement for erectile dysfunction. Ulloa J, Sambrotta L, Redko F, Mazza ON, Garrido G, Becher EF, Muschietti L.

J Sex Med. 2015 Jan;12(1):152-7. doi: 10.1111/jsm.12759. Epub 2014 Nov 17.

INTRODUCTION: Several cases of adulteration of dietary supplements with tadalafil, sildenafil, and vardenafil, or their unapproved analogues have been reported worldwide. Mainly, the presence of the latter represents a serious health risk to consumers as their efficacy and toxic effects have not been assessed and may result in unpredictable adverse effects. AIM: To investigate the suspected adulteration with synthetic phosphodiesterase type 5 (PDE-5) inhibitors in a dietary supplement marketed in Argentina for the treatment of erectile dysfunction (ED). METHODS: The content of the capsules of the dietary supplement (sample A) was analyzed by thin layer chromatography (TLC) and high-performance liquid chromatography (HPLC) diode-array detection. From the organic extract of sample A, a major compound was purified by column chromatography (CC). The isolated compound was identified by proton nuclear magnetic resonance (1H NMR) and carbon NMR (13C NMR), heteronuclear single quantum coherence, distortionless enhancement by polarization transfer (DEPT 135), electrospray ionization mass spectrometry, and ultraviolet, and infrared (Fourier transform infrared spectroscopy) spectroscopy. MAIN OUTCOME MEASURE: Proof of adulteration of herbal products with synthetic PDE-5 inhibitors. RESULTS: By TLC and HPLC analysis, a major compound was detected in sample A organic extract. The purification of this extract by CC led to the isolation of a pure compound which was identified according to its spectral data as (6R 12aR)-2-amino-6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydropyrazino [1',2':1,6] pyrido [3,4-b] indole-1,4-dione or aminotadalafil. CONCLUSIONS: An unapproved PDE-5 inhibitor analogue, which was identified as aminotadalafil, has been detected in a dietary supplement. This study represents the first report in Latin America and one of the few independent studies of an adulteration with an unapproved PDE-5 inhibitor of an herbal product for ED treatment.

PMID: 25402198 [PubMed - in process]

17. Multi-ingredient, caffeine-containing dietary supplements: history, safety, and efficacy. Gurley BJ, Steelman SC, Thomas SL.

Clin Ther. 2015 Feb 1;37(2):275-301. doi: 10.1016/j.clinthera.2014.08.012. Epub 2014 Sep 26.

Abstract:
PURPOSE: Our objective was to review the history, safety, and efficacy of caffeine-containing dietary supplements in the United States and Canada. METHODS: PubMed and Web of Science databases (1980-2014) were searched for articles related to the pharmacology, toxicology, and efficacy of caffeine-containing dietary supplements with an emphasis on Ephedra-containing supplements, Ephedra-free supplements, and energy drinks or shots. FINDINGS: Among the first and most successful dietary supplements to be marketed in the United States were those containing Ephedra—combinations of ephedrine alkaloids, caffeine, and other phytochemicals. A decade after their inception, serious tolerability concerns prompted removal of Ephedra supplements from the US and Canadian markets. Ephedra-free products, however, quickly filled this void. Ephedra-free supplements typically contain multiple caffeine sources in conjunction with other botanical extracts whose purposes can often be puzzling and their pharmacologic properties difficult to predict. Ingestion of these products in the form of tablets, capsules, or other solid dosage forms as weight loss aids, exercise performance enhancers, or energy boosters have once again brought their tolerability and efficacy into question. In addition to Ephedra-free solid dosage forms, caffeine-containing energy drinks have gained a foothold in the world market along with concerns about their tolerability. IMPLICATIONS: This review addresses some of the pharmacologic and pharmaceutical issues that distinguish caffeine-containing dietary supplement formulations from traditional caffeine-containing beverages. Such distinctions may account for the increasing tolerability concerns affiliated with these products.

PMID: 25262198 [PubMed - in process]

18. Vitamin D toxicity in an infant: case files of the University of California, San Francisco medical toxicology fellowship. Smollin C, Srisansanee W.

J Med Toxicol. 2014 Jun;10(2):190-3. doi: 10.1007/s13181-013-0365-0.

Vitamin D toxicity in an infant: case files of the University of California, San Francisco medical toxicology fellowship.

PMID: 24558014 [PubMed - indexed for MEDLINE]

19. Ginkgo biloba: reduced efficacy of efavirenz. [No authors listed]

Prescrire Int. 2015 Jan;24(156):21.

Ginkgo biloba: reduced efficacy of efavirenz.

PMID: 25729835 [PubMed - indexed for MEDLINE]

20. Cross matching observations on toxicological and clinical data for the assessment of tolerability and safety of Ginkgo biloba leaf extract. Heinonen T, Gaus W.

Toxicology. 2015 Jan 2;327:95-115. doi: 10.1016/j.tox.2014.10.013. Epub 2014 Nov 11.

Abstract:
Ginkgo biloba is one of the most widely used herbal remedies in Europe and the US. It may be purchased in different types of formulations, but most of the clinical studies have been performed with the controlled G. biloba extract EGb761(®). Indications include Alzheimers disease, cardiovascular disease, dementia, memory loss, and cerebral ischemia. The pharmacological modes of action cover antioxidant effects, radical scavenging, inhibition of platelet activating factor, alterations in membrane fluidity (signal transduction), and inhibition of glucocorticoid synthesis. Due to the widespread and long-term use of G. biloba - about a million doses of EGb761(®) are sold per day - tolerability and safety are a crucial issue. Based on broad and long-term clinical use of G. biloba extracts, it is regarded as well tolerated in man. Cross matching, a tool we introduced, combines different fields of knowledge and types of data to a consolidated result. In this article, we combine toxicological and clinical data and utilize other sources of information to assess tolerability and safety of G. biloba. It is well known that because of biological differences between animals and man or even between animal species, animal experiments do not necessarily mimic the effects in humans. Therefore, for adequate risk assessment, the relevance of non-clinical toxicological findings should be correlated with human data. The cross matching of toxicological data and results from clinical studies is possible because many toxicological and clinical studies are available on G. biloba. We give an in depth analysis of the modes of action in animals and describe toxicological studies with regard to metabolism, pharmacokinetics, genotoxicity, as well as carcinogenicity (e.g., the Technical Report TR 578 of the US National Toxicology Program). In addition, 75 clinical trials with high methodological quality are summarized. They included a total of 7115 patients treated with G. biloba. Based on this extensive amount of information, the broad variety of investigations, and their accordance we conclude that G. biloba extract is well tolerated and safe for humans.

PMID: 25446328 [PubMed - indexed for MEDLINE]

21. Use of St. John's Wort in potentially dangerous combinations. Davis SA, Feldman SR, Taylor SL.

J Altern Complement Med. 2014 Jul;20(7):578-9. doi: 10.1089/acm.2013.0216. Epub 2014 Jun 23.

Abstract:
OBJECTIVES: The objective of this study was to assess how often St. John's wort (SJW) is prescribed with medications that may interact dangerously with it. DESIGN: The study design was a retrospective analysis of nationally representative data from the National Ambulatory Medical Care Survey. SETTINGS: The study setting was U.S. nonfederal outpatient physician offices. SUBJECTS: Those prescribed SJW between 1993 and 2010 were the subjects. OUTCOME MEASURES: The outcome measures were medications co-prescribed with SJW. RESULTS: Twenty-eight percent (28%) of SJW visits involved a drug that has potentially dangerous interaction with SJW. These included selective serotonin reuptake inhibitors, benzodiazepines, warfarin, statins, verapamil, digoxin, and oral contraceptives. CONCLUSIONS: SJW is frequently used in potentially dangerous combinations. Physicians should be aware of these common interactions and warn patients appropriately.

PMID: 24956073 [PubMed - indexed for MEDLINE]

22. Acute interstitial nephritis induced by Dioscorea quinqueloba. Kim HY, Kim SS, Bae SH, Bae EH, Ma SK, Kim SW.

BMC Nephrol. 2014 Sep 3;15:143. doi: 10.1186/1471-2369-15-143.

Abstract:
BACKGROUND: The use of herbal medicine may be a risk factor for the development of kidney injury, as it has been reported to cause various renal syndromes. Dioscorea quinqueloba is a medicinal herb that is used as an alternative therapy for cardiovascular disease and various medical conditions. CASE PRESENTATION: A 52-year-old man was admitted with complaints of skin rash and burning sensation. He had ingested a raw extract of D. quinqueloba as a traditional remedy. Laboratory tests revealed the following values: absolute eosinophil count, 900/mm(3); serum creatinine level, 2.7 mg/dL; and blood urea nitrogen, 33.0 mg/dL. The immunoglobulin E level was markedly increased at 1320.0 IU/mL. Urinalysis revealed a fractional excretion of sodium of 3.77%, protein 1+, and blood 3+. Histological examination of the renal biopsy specimen showed a diffusely edematous interstitium with infiltrates composed of eosinophils, lymphocytes, and neutrophils. CONCLUSION: Here, we present the first reported case of biopsy-proven acute interstitial nephritis following ingestion of D. quinqueloba associated with skin rash, eosinophilia, and increased plasma immunoglobulin E level.

PMID: 25186588 [PubMed - indexed for MEDLINE]

23. Unexplained hypoxia in an in-flight emergency. Coffey DD.

Aviat Space Environ Med. 2014 Jun;85(6):662-7.

Abstract:
BACKGROUND: The use of over-the-counter medications and nutritional supplements is prohibited while flying without approval from an aeromedical professional. Despite prohibition, the use of nutritional supplements is common in aircrew due to the perception that these supplements are harmless; in reality, the use of nutritional supplements may be more dangerous than the use of traditional medications. Multiple case reports of adverse neurologic and cardiovascular events associated with the use of specific supplements led the FDA to ban ephedra in 2004 and DMAA in 2012, both marketed as "natural stimulants." These incidents are sobering reminders of the lack of safety data on commonly marketed nutritional supplements. There are few, if any, case reports or clinical trials addressing the safety of common nutritional supplements in flight. CASE REPORT: This is a case of an aircrew member who experienced hypoxia during an in-flight emergency. He underwent thorough medical evaluation to determine the cause of his hypoxic event and ultimately admitted to the use of a pre-workout supplement: C4 Extreme. He was exposed to simulated altitude both on and off of the supplement and was found to have an improved tolerance to a hypoxic environment after discontinuation. DISCUSSION: While not conclusive, the data suggests that the use of C4 Extreme may be implicated in this aircrewman's increased susceptibility to hypoxia. A randomized controlled trial would be required to determine if this is a patient-specific response or if this is a normal physiologic response to the use of this and similar supplements.

PMID: 24919389 [PubMed - indexed for MEDLINE]

24. A beating heart cell model to predict cardiotoxicity: Effects of the dietary supplement ingredients higenamine, phenylethylamine, ephedrine and caffeine. Calvert R, Vohra S, Ferguson M, Wiesenfeld P.

Food Chem Toxicol. 2015 Apr;78:207-13. doi: 10.1016/j.fct.2015.01.022. Epub 2015 Feb 12.

Abstract:
Some dietary supplements may contain cardiac stimulants and potential cardiotoxins. In vitro studies may identify ingredients of concern. A beating human cardiomyocyte cell line was used to evaluate cellular effects following phenylethylamine (PEA), higenamine, ephedrine or caffeine treatment. PEA and higenamine exposure levels simulated published blood levels in humans or animals after intravenous administration. Ephedrine and caffeine levels approximated published blood levels following human oral intake. At low or midrange levels, each chemical was examined plus or minus 50 μM caffeine, simulating human blood levels reported after consumption of caffeine-enriched dietary supplements. To measure beats per minute (BPM), peak width, etc., rhythmic rise and fall in intracellular calcium levels following 30 min of treatment was examined. Higenamine 31.3 ng/ml or 313 ng/ml significantly increased BPM in an escalating manner. PEA increased BPM at 0.8 and 8 μg/ml, while 80 μg/ml PEA

reduced BPM and widened peaks. Ephedrine produced a significant BPM dose response from 0.5 to 5.0 μM. Caffeine increased BPM only at a toxic level of 250 μM. Adding caffeine to PEA or higenamine but not ephedrine further increased BPM. These in vitro results suggest that additional testing may be warranted in vivo to further evaluate these effects.

PMID: 25684415 [PubMed - in process]

25. Detection and Characterization of SiO2 and TiO2 Nanostructures in Dietary Supplements. Lim JH, Sisco P, Mudalige TK, Sánchez-Pomales G, Howard PC, Linder SW.

J Agric Food Chem. 2015 Apr 1;63(12):3144-52. doi: 10.1021/acs.jafc.5b00392. Epub 2015 Mar 18.

Abstract:
Nanomaterials are beginning to enter our daily lives through various consumer products as the result of technology commercialization. The development of methodologies to detect the presence of nanomaterials in consumer products is an essential element in understanding our exposure. In this study, we have developed methods for the separation and characterization of silicon dioxide (SiO2) and titanium dioxide (TiO2) nanostructures in dietary supplements marketed in products specifically targeted for women. A total of 12 commercial products claiming the inclusion of SiO2 and TiO2, but not making any claims regarding the particle size, were randomly selected for purchase through various retailers. To isolate nanostructures from these products, a simple methodology that combines acid digestion and centrifugation was utilized. Once isolated, the chemical composition, size, morphology, and crystal structure were characterized using mass spectroscopy, light scattering, electron microscopy, and X-ray diffraction techniques. SiO2 and TiO2 nanostructures were detected in 11 of 12 products using these methods. Many of the isolated nanoscale materials showed a high degree of aggregation; however, identified individual structures had at least one dimension below 100 nm. These robust methods can be used for routine monitoring of commercial products for nanoscale oxides of silica and titanium.

PMID: 25738207 [PubMed - in process]