AACT Herbal Dietary Supplement Section Abstracts July 2021

1.Preoperative Management of Surgical Patients Using Dietary Supplements: Society for Perioperative Assessment and Quality Improvement (SPAQI) Consensus Statement. Cummings KC 3rd, Keshock M, Ganesh R, Sigmund A, Kashiwagi D, Devarajan J, Grant PJ, Urman RD, Mauck KF.

Mayo Clin Proc. 2021 May;96(5):1342-1355. doi: 10.1016/j.mayocp.2020.08.016. Epub 2021 Mar 16.

The widespread use of complementary products poses a challenge to clinicians in the perioperative period and may increase perioperative risk. Because dietary supplements are regulated differently from traditional pharmaceuticals and guidance is often lacking, the Society for Perioperative Assessment and Quality Improvement convened a group of experts to review available literature and create a set of consensus recommendations for the perioperative management of these supplements. Using a modified Delphi method, the authors developed recommendations for perioperative management of 83 dietary supplements. We have made our recommendations to discontinue or continue a dietary supplement based on the principle that without a demonstrated benefit, or with a demonstrated lack of harm, there is little downside in temporarily discontinuing an herbal supplement before surgery. Discussion with patients in the preoperative visit is a crucial time to educate patients as well as gather vital information. Patients should be specifically asked about use of dietary supplements and cannabinoids, as many will not volunteer this information. The preoperative clinic visit provides the best opportunity to educate patients about the perioperative management of various supplements as this visit is typically scheduled at least 2 weeks before the planned procedure.

DOI: 10.1016/j.mayocp.2020.08.016
PMID: 33741131 [Indexed for MEDLINE]

2. Commentary: Unintended Perils of Herbal Supplements: Anticoagulation. Mullaj K, Bulsara KK, Bulsara KR, Guha A.

Oper Neurosurg (Hagerstown). 2021 Jan 13;20(2):E156-E158. doi: 10.1093/ons/opaa317.

DOI: 10.1093/ons/opaa317
PMID: 33027817 [Indexed for MEDLINE]

3. Risk of Birth Defects From Vitamin A "Acne Supplements" Sold Online. Zamil DH, Burns EK, Perez-Sanchez A, Parke MA, Katta R.

Dermatol Pract Concept. 2021 May 20;11(3):e2021075. doi: 10.5826/dpc.1103a75. eCollection 2021 May.

BACKGROUND: Dietary supplements are popular among US consumers and claim to address a variety of conditions, including acne. Acne supplements containing vitamin A are of particular interest, due to the potentially teratogenic effects of vitamin A doses over 10,000 IU. OBJECTIVE: This study examined dosage, pregnancy risks, and labeling of vitamin A-containing acne supplements available online. METHODS: An Internet search of acne supplements sold online was conducted between March and May 2020. Supplement labels and websites were analyzed for vitamin A content and pregnancy warnings, and then divided into categories based on dosage and teratogenic risk. RESULTS: A total of 49 acne supplements was found, and of these 26 (53%) contain vitamin A. Three supplements are likely teratogenic, 4 contain vitamin A doses exceeding the daily level of intake that meets the nutritional needs of most people, and 15 have an unknown teratogenic risk. Among the 6 supplements with over 10,000 IU vitamin A, 2 have no pregnancy warning at all, including the supplement with the highest vitamin A dose found in this study. CONCLUSIONS: Dietary supplements are not subject to the same stringent regulations as drugs, and as such, consumers may be unaware of pregnancy risks. Furthermore, FDA requirements on labeling of vitamin A supplements may lead to consumer confusion regarding dosage. As such, we encourage stricter labeling requirements for vitamin A-containing supplements, including pregnancy warnings for high-dose supplements and clearer dosage labeling.

DOI: 10.5826/dpc.1103a75

PMCID: PMC8172008
PMID: 34123566

4. Markedly Delayed Night Blindness Due to Vitamin A Insufficiency Secondary to Bowel Resection. Chatzistergiou V, Ambresin A, Borruat FX.

Klin Monbl Augenheilkd. 2021 Apr;238(4):428-430. doi: 10.1055/a-1354-5816. Epub 2021 Feb 22.

DOI: 10.1055/a-1354-5816
PMID: 33618384 [Indexed for MEDLINE]

5. Online Marketing of Ephedra Weight Loss Supplements: Labeling and Marketing Compliance with the U.S. Food and Drug Administration Ban on Ephedra. Lai S, Yu C, Dennehy CE, Tsourounis C, Lee KP.

J Altern Complement Med. 2021 May 12. doi: 10.1089/acm.2021.0016. Online ahead of print.

Objective: To characterize dietary supplements marketed online as "ephedra-containing or ephedra-like products" for weight management and to assess labeling/marketing compliance with the ban on the sale of ephedrine alkaloids. Materials and Methods: This cross-sectional study assessed websites selling ephedra-like supplements using the search term "buy ephedra." For each website, the first three featured products were characterized by evaluating the label for (1) Ephedra sp. or its alkaloid content, (2) serving size, (3) other ingredients, (4) directions, (5) side effects, (6) reported interactions, (7) recommendation to consult a health care provider, (8) recommendation to use with diet and exercise, and (9) Food and Drug Administration (FDA) disclaimer. Results: Thirty-six (71%) of the first 51 websites evaluated sold at least one weight loss product. A total of 105 products were assessed, 93 had labeling with 10 (11%) in possible violation of the ephedra ban. Five were labeled as containing ephedrine or ephedrine hydrochloride, two reported containing ephedrine alkaloids, and two reported containing unidentified Ephedra sp. not formulated as an extract; one reported containing Ma Huang. Sixty-seven (72%) products listed caffeine with a daily serving size averaging 400 mg. Other ingredients with stimulant properties include green tea, yohimbe, and phenylethylamine. Conclusions: Nearly 20% of websites sold weight loss products that potentially violated the 2004 ban of ephedra alkaloids. Ephedrine, unidentified Ephedra sp. not formulated as an extract, and Ma Huang were labeled as present in 11% of products evaluated. Incomplete reporting of adverse effects and drug interactions was common.

DOI: 10.1089/acm.2021.0016
PMID: 33979529

6. Hypercalcemia, nephrolithiasis, and hypervitaminosis D precipitated by supplementation in a susceptible individual. Haridas K, Holick MF, Burmeister LA.

Nutrition. 2020 Jun;74:110754. doi: 10.1016/j.nut.2020.110754. Epub 2020 Jan 29.

Vitamin D supplementation is common among the general public. Although generally considered safe, vitamin D supplement-induced toxicity has been reported, often in association with manufacturing or labeling errors. Additionally, selected patient populations may have a hypersensitivity to vitamin D supplementation, leading to consequences due to supraphysiologic serum 25-hydroxyvitamin D levels. A 58-y-old woman developed hypercalcemia and its sequelae while on vitamin D supplementation. Despite being vitamin D replete, a functional medicine practitioner prescribed vitamin D starting at 8000 IU/d, tapering to 2000 IU/d over 3 mo. Nephrolithiasis was diagnosed after 3 mo of vitamin D treatment. Laboratory testing revealed a high serum calcium, low parathyroid hormone (PTH), high 25-hydroxyvitamin D [25(OH)D] and high 1,25 dihydroxyvitamin D [1,25(OH)2D]. Further investigation demonstrated low serum 24,25 dihydroxyvitamin D [24,25(OH)2D] and a very high ratio of 25(OH)D to 24,25(OH)2D, leading to the consideration of loss of function mutation in cytochrome P450 (CYP)24A1, a key enzyme involved in the degradation of 25(OH)D and 1,25(OH)2D into inactive metabolites. This leads to the persistence of high levels of bioactive vitamin D metabolites, increasing the risk for development of intoxication with vitamin D supplementation. Vitamin D supplementation can precipitate hypercalcemia and nephrolithiasis in individuals with altered vitamin D catabolism. This highlights the importance of monitoring serum calcium levels in patients who are being supplemented with vitamin D.

DOI: 10.1016/j.nut.2020.110754
PMID: 32222584 [Indexed for MEDLINE]

7. Vitamin D Toxicity. Lim K, Thadhani R.

J Bras Nefrol. 2020 Apr 3;42(2):238-244. doi: 10.1590/2175-8239-JBN-2019-0192.

Fortification of food products with vitamin D was central to the eradication of rickets in the early parts of the 20th century in the United States. In the subsequent almost 100 years since, accumulating evidence has linked vitamin D deficiency to a variety of outcomes, and this has paralleled greater public interest and awareness of the health benefits of vitamin D. Supplements containing vitamin D are now widely available in both industrialized and developing countries, and many are in the form of unregulated formulations sold to the public with little guidance for safe administration. Together, this has contributed to a transition whereby a dramatic global increase in cases of vitamin D toxicity has been reported. Clinicians are now faced with the challenge of managing this condition that can present on a spectrum from asymptomatic to acute life-threatening complications. This article considers contemporary data on vitamin D toxicity, and diagnostic and management strategies relevant to clinical practice.

DOI: 10.1590/2175-8239-JBN-2019-0192
PMCID: PMC7427646
PMID: 32255467 [Indexed for MEDLINE]

8. Vitamin D toxicity in a pediatric toxicological referral center; a cross-sectional study from Iran. Farnaghi F, Hassanian-Moghaddam H, Zamani N, Gholami N, Gachkar L, Hosseini Yazdi M.

BMC Pediatr. 2020 Jul 20;20(1):350. doi: 10.1186/s12887-020-02240-4.

BACKGROUND: Vitamin D is an essential element for body health with its supplements generally administered to prevent vitamin D deficiency. Since these supplements are available in domestic settings, vitamin D toxicity may happen in children. METHODS: All children younger than 12 years who presented to the pediatric emergency department of Loghman Hakim Hospital, Tehran, Iran with history of ingestion of more than 1500 IU/day of vitamin D supplements were enrolled. Patients' demographic data, on-presentation signs and symptoms, laboratory findings, treatments given, and outcome were evaluated. RESULT: Fifteen patients presented during the study period. Their mean age was 46.53 ± 10.14 months and 12 (80%) were girls. All of them had unintentionally ingested vitamin D. Mean ingested dose was 406700.7 ± 227400.1 IU. In eight patients (53.3%), 25 hydroxy vitamin D level was more than 100 ng/mL. One patient experienced hypercalcemia while all of them were asymptomatic and discharged without complications. There was no significant difference between patients with and without high levels of 25 OH vitamin D regarding lab tests, toxicity course, and outcome. CONCLUSIONS: It seems that acute vitamin D toxicity is a benign condition in our pediatric population which may be due to high prevalence of vitamin D deficiency in Iran.

DOI: 10.1186/s12887-020-02240-4
PMCID: PMC7370494
PMID: 32684163 [Indexed for MEDLINE]

9. Case of cholestatic drug-induced liver injury (DILI) associated with black cohosh. Brar HS, Marathi R.

BMJ Case Rep. 2021 May 7;14(5):e240408. doi: 10.1136/bcr-2020-240408.

Drug-induced liver injury is an uncommon yet fatal cause of liver injury. Black cohosh is a herbal supplement that is derived from Actaea racemosa It has been used for vasomotor symptoms in postmenopausal women, but it can cause liver injury. A 50-year-old Afro-American woman presented with a 2-month history of malaise, itching and severe jaundice. The labs showed elevation of bilirubin and alkaline phosphatase. The patient had a history of black cohosh use for postmenopausal symptoms before she developed her current symptoms. The extensive workup for infective and autoimmune pathology was negative. Black cohosh was discontinued. The patient improved clinically, and her liver enzymes normalised

6 months after the discontinuation of black cohosh. This report emphasises the need to recognise black cohosh as a potential hepatotoxic agent and to monitor the liver enzymes for a patient on black cohosh.

DOI: 10.1136/bcr-2020-240408
PMCID: PMC8108679
PMID: 33962922 [Indexed for MEDLINE]

10. Yellow Oleander (Thevetia peruviana), a source of toxic cardiac glycosides, may be substituted for candlenuts (Aleurities moluccana) when taken as a weight-loss supplement. Cole JB, Corcoran JN.

Cardiol Young. 2020 Nov;30(11):1755-1756. doi: 10.1017/S1047951120003480. Epub 2020 Nov 10.

DOI: 10.1017/S1047951120003480
PMID: 33168127 [Indexed for MEDLINE]

11. Life-Threatening Cyanide Intoxication after Ingestion of Amygdalin in Prehospital Care. Cmorej P, Bruthans P, Halamka J, Voriskova I, Peran D.

Prehosp Emerg Care. 2021 May 25:1-10. doi: 10.1080/10903127.2021.1924903. Online ahead of print.

Amygdalin is originally a natural cyanogenic glycoside available as a dietary supplement used in the alternative treatment of cancer patients. Amygdalin hydroxylates to toxic cyanide in the body, which can cause life-threatening intoxication. The case report presents a 72-year-old patient with life-threatening cyanide poisoning after ingesting a dietary supplement containing amygdalin identified in prehospital care, which was successfully treated with hydroxocobalamin.

DOI: 10.1080/10903127.2021.1924903
PMID: 33955827

12 Serum ceruloplasmin monitoring in a case of silver intoxication due to intravenous silver infusion. Law CY, Leung SC, Loong F, Ling TK, Wong KC, Lau NK, Tsui SH, Lai CL, Lam CW.

Clin Toxicol (Phila). 2021 May 28:1-4. doi: 10.1080/15563650.2021.1919692. Online ahead of print.

INTRODUCTION: Colloidal silver packaged as a dietary supplement is readily available online and is thought to be safe. Literature describing its toxicity in humans is scarce. CASE REPORT: A 47-year-old man presented to us for sensory and gait problems. He had unremarkable past health except dystrophic nails. He further volunteered a history of receiving chronic oral and intravenous administration of colloidal silver. We confirmed his plasma silver was 1200-fold elevated, measuring 11990 nmol/L (normal < 10 nmol/L). He had deranged liver function tests, and liver biopsy showed distorted acinar architecture, bridging fibrosis and lymphocytic infiltrate with silver particles clustering along the vascular endothelium and portal venules. Brain magnetic resonance imagining showed features of mineralization over bilateral globus pallidi. There was biochemical evidence of central adrenal insufficiency, intracellular iron overload and hypoceruloplasminemia (<0.05 g/L). Gradual clinical and biochemical improvement was noted after silver cessation: his plasma silver dropped to 4800 nmol/L (3 months) and 1650 nmol/L (12 months), and serum ceruloplasmin reverted to 0.13 g/L (10 months) and 0.29 g/L (20 months). CONCLUSIONS: The potential effects of silver to liver and copper metabolism were shown in this case. Serum ceruloplasmin also serves as a surrogate marker in monitoring silver intoxication.

DOI: 10.1080/15563650.2021.1919692
PMID: 34047646

13. [A CASE OF REPEATED DRUG-INDUCED LUNG DISEASES DUE TO MULTIPLE HERBAL MEDICINES CONTAINING COMMON INGREDIENTS]. [Article in Japanese] Mori R, Oyama Y, Morita M, Nakamura S, Takuma S, Ikeda M, Kusagaya H.

Arerugi. 2021;70(3):204-209. doi: 10.15036/arerugi.70.204.

We present a rare case of repetitive lung disease caused by various herbal medicines containing common ingredients. In June 201X-2, an 81-year-old man with chronic sinusitis was treated with Shini-seihai-to. One month later, the patient experienced liver dysfunction, and pulmonary opacity was observed on a chest radiograph; this condition improved following the discontinuation of Shini-seihai-to. In October 201X-2, the patient developed fever and dyspnea after treatment with Saiko-keishi-to, which was administered to treat irritable bowel syndrome, and was diagnosed with pneumonia. His condition did not improve with antimicrobial treatment but did improve with systemic corticosteroids. Following discharge from the hospital, the patient took both Shini-seihai-to and Hochu-ekki-to. He developed a fever two days later, which improved after discontinuing the medicines. The patient developed a cough after taking Sairei-to in February 201X and was subsequently admitted to our hospital with respiratory failure; pulmonary opacity was observed on a chest computed tomography scan. On the basis of clinical course, lymphocytosis in bronchoalveolar lavage fluid, and drug-induced lymphocyte stimulation tests, we diagnosed the patient with Sairei-to-induced lung disease. The patient's condition improved after discontinuing Sairei-to. We conclude that common ingredients in different herbal medicines may cause drug-induced lung injury. Therefore, we recommend that scrupulous attention should be paid to Chinese herbal medicine use in patients with a history of lung injury induced by herbal medicines.

DOI: 10.15036/arerugi.70.204
PMID: 34011775 [Indexed for MEDLINE]

14.Elevated serum creatinine in the context of HIV - who is the culprit? Over-the-counter supplements vs. antiretrovirals. Gill A, Fernando KA.

Int J STD AIDS. 2020 Dec;31(14):1411-1413. doi: 10.1177/0956462420958343. Epub 2020 Oct 22.

We present a case of a 53-year-old male living with well-controlled HIV who, as part of routine monitoring, was noted to have an unexpected decline in renal function. His antiretrovirals were switched accordingly. It subsequently transpired that he had recently started taking creatine supplements in order to build muscle mass. He underwent specialist renal review and further investigation with a chromium-labelled scan which revealed his renal function was, in fact, stable. He continues under renal and HIV follow-up. It is now more widely recognised that creatine can affect renal function, and result in difficulty in interpretation of traditional renal blood tests. However, the further investigations that may be undertaken in such settings and HIV treatment considerations are not as widely reported. This case serves as a reminder to ensure over-the-counter and herbal supplements are part of routine questioning in HIV clinics, and outlines the specialist investigations that may be undertaken in cases of apparent renal decline.

DOI: 10.1177/0956462420958343
PMID: 33086938 [Indexed for MEDLINE]

15. Garlic burn injuries- a systematic review of reported cases. Hitl M, Kladar N, Gavarić N, Srđenović Čonić B, Božin B.

Am J Emerg Med. 2021 Jun;44:5-10. doi: 10.1016/j.ajem.2021.01.039. Epub 2021 Jan 31.

Medicinal plants have many beneficial effects on human health. Garlic (Allium sativum, Alliaceae) is one of the most famous herbal species, used for various diseases and conditions. Unfortunately, garlic is also associated with adverse effects, including cutaneous manifestations. In this review, burn injuries caused by application of raw garlic are reported. Searching through PubMed, Google Scholar and ResearchGate, a total of 32 articles with 39 patients were found. Demographics of patients, reasons for garlic use, details on garlic application, as well as description of burns and its treatment are thoroughly described and discussed. In most of the cases, garlic caused second-degree burns, although some circumstances can cause formation of necrotic tissue. Various body parts were affected, legs being most common. The chemistry of garlic is also presented, with focus on volatile organic sulfur compounds, which also seem to be responsible for burns formation. Treatment of garlic burns was mainly symptomatic, and various types of drugs were used. Although not commonly expected, garlic should be taken into consideration as causative agents of burns by treating doctors, and patients should be advised against application of fresh garlic onto skin and mucosa.

DOI: 10.1016/j.ajem.2021.01.039
PMID: 33571752 [Indexed for MEDLINE]

16. Assessing the therapeutic potential and toxicity of Mitragyna speciosa in opioid use disorder. Sharma A, McCurdy CR.

Expert Opin Drug Metab Toxicol. 2021 Mar;17(3):255-257. doi: 10.1080/17425255.2021.1853706. Epub 2020 Dec 11.

DOI: 10.1080/17425255.2021.1853706
PMID: 33213215 [Indexed for MEDLINE]

17. Kratom exposures among older adults reported to U.S. poison centers, 2014-2019. Graves JM, Dilley JA, Terpak L, Brooks-Russell A, Whitehill JM, Klein TA, Liebelt E.

J Am Geriatr Soc. 2021 Jun 18. doi: 10.1111/jgs.17326. Online ahead of print.

BACKGROUND: In recent years, use of the herbal supplement kratom has increased in the United States. The reasons for use include pain relief, particularly as a substitute for opioids. OBJECTIVES: To describe epidemiologic trends in kratom-related exposures among older adults reported to U.S. poison centers. DESIGN: Retrospective analysis of American Association of Poison Control Center's National Poison Data System (NPDS). SETTING: Data from all U.S. poison centers from 2014 to 2019 were examined. PARTICIPANTS: Kratom exposure cases involving adults aged 18 and older. Kratom cases were identified by product and NPDS generic codes. Non-human and information-only calls were excluded. Data were examined for all calls for exposures among adults, with a focus on older adults aged 60-69 years and above 70 years. MEASUREMENTS: Descriptive analyses were used to characterize individual demographic, exposure information, clinical effects, and medical outcomes associated with kratom exposures among older adults. Comparisons across age groups (18-59, 60-69, and 70+ years) were made using Fisher's exact tests. RESULTS: Among 3484 kratom-related exposures reported between 2014 and 2019, 4.6% (n = 162) were among adults over 60 years. The number of kratom-related exposures increased over time. Most cases originated with calls from healthcare facilities (81.1%) and involved kratom as a single ingestant (63.0%). The reason for most ingestions was intentional (74.5%). One in five exposures among adults aged 70 and older involved an adverse reaction (e.g., drug interaction; 21.9%), compared with 12.3% among ages 60-69 and 9.6% among ages 18-59 years. Neurological and cardiovascular clinical effects were observed. Twenty-three deaths were observed among older adults. CONCLUSION: Healthcare providers and older adult patients should be aware of the potential risks of kratom use, including medication interactions and falls. When reviewing medication lists, providers should query this population for all medications and substances being used, especially in people being treated for pain.

DOI: 10.1111/jgs.17326
PMID: 34143890

18. Risks Associated with the Use of Garcinia as a Nutritional Complement to Lose Weight. Andueza N, Giner RM, Portillo MP.

Nutrients. 2021 Jan 29;13(2):450. doi: 10.3390/nu13020450.

Nowadays, obesity is one of the great nutritional problems facing public health. The prevalence of this pathology has increased in a worrying way over recent years, currently reaching epidemic proportions. In this context, nutritional supplements are presented as a therapeutic alternative to which more and more people are turning to. Nutritional supplements to lose weight based on the Garcinia plant, specifically on Garcinia cambogia, are commonly used. The active principle of this plant to which these properties have been attributed, is hydroxycitric acid (HCA). The aim of the present review is to gather reported data concerning the effectiveness of nutritional supplements based on Garcinia extracts on weight loss and their possible negative effects. Contradictory results have been observed regarding the effectiveness of the supplements. While statistically significant weight loss was observed in some studies, no changes were found in others. Regarding safety, although Garcinia supplements have been revealed as safe in the vast majority of the studies carried out in animal models and humans, some cases of hepatotoxicity, serotonin toxicity and mania have been reported. In conclusion, the results suggest that Garcinia-based supplements could be effective in short-term weight loss, although the data are not conclusive. In addition, the safety of the complement should be further studied.

DOI: 10.3390/nu13020450
PMCID: PMC7911601
PMID: 33572973 [Indexed for MEDLINE]

19. Epidemiology of Drug- and Herb-Induced Liver Injury Assessed for Causality Using the Updated RUCAM in Two Hospitals from China. Chen Y, Wang C, Yang H, Huang P, Shi J, Tong Y, Jiang J, Zhang X, Chen W, Xuan Z.

Biomed Res Int. 2021 Feb 24;2021:8894498. doi: 10.1155/2021/8894498. eCollection 2021.

Drug- and herb-induced liver injury (DILI and HILI) is an increasingly common and serious condition. Here, data for DILI and HILI patients from two large tertiary hospitals were retrospectively analyzed. Patient characteristics, causes and severity of DILI and HILI, the correlation between expression of p62 and the severity of DILI and HILI, treatment of DILI and HILI, and the prognostic factors of DILI and HILI were studied. A total of 82 patients with DILI and HILI were recruited for the study. Most patients presented with hepatocellular injury, followed by cholestatic injury and mixed injury. Our results indicate that traditional Chinese medicine or herbal and dietary supplements were the prevalent causal agents of HILI, which was characterized by higher frequencies of hepatocellular injury. Expression of p62 in the liver correlated with the severity of DILI and HILI. Improvements in the results of the liver enzymatic tests correlated with alanine transaminase (ALT) levels upon the first diagnosis of DILI and HILI and with the hepatocellular type of DILI and HILI. In conclusion, we provide an epidemiological assessment of DILI and HILI based on causality using the updated RUCAM on patients from two hospitals in China. ALT levels at first diagnosis and the hepatocellular type of injury may be prognostic factors of DILI and HILI.

DOI: 10.1155/2021/8894498
PMCID: PMC8067772
PMID: 33954202 [Indexed for MEDLINE]

20 The successful treatment of multiple organ dysfunction syndrome and severe hypernatremia, secondary to joint supplement toxicity in a dog. Weatherson HO, Bellis T, Tse Y.

J Vet Emerg Crit Care (San Antonio). 2021 May;31(3):432-438. doi: 10.1111/vec.13033. Epub 2021 Mar 10.

OBJECTIVE: To describe a case of the successful management of hypernatremia and multiple organ dysfunction syndrome secondary to joint supplement toxicity in a dog. CASE SUMMARY: A 6-year-old neutered male Dachshund was presented for severe hypernatremia and neurological abnormalities after ingestion of a large quantity of joint supplements. The patient developed evidence of multiple organ dysfunction in the form of increased hepatocellular enzymes, prolongation of prothrombin and partial thromboplastin times, azotemia, and thrombocytopenia. Treatment was successful at correcting the hypernatremia and restoring neurological function, and organ dysfunction was successfully managed. Following multiple days of hospitalization and aggressive supportive care, the patient survived to discharge. NEW OR UNIQUE INFORMATION PROVIDED: This case report describes the successful management and survival of multiple organ dysfunction associated with joint supplement toxicity. It also serves to highlight the potential for joint supplement overdose in veterinary patients, which is currently believed to be underrecognized.

DOI: 10.1111/vec.13033
PMID: 33751791 [Indexed for MEDLINE]

21. Suspected adverse reactions to performance enhancing dietary supplements: Spontaneous reports from the Italian phytovigilance system. Ippoliti I, Menniti-Ippolito F, Mazzanti G, Di Giacomo S.

Phytother Res. 2021 Jun;35(6):3246-3261. doi: 10.1002/ptr.7040. Epub 2021 Feb 10.

Herbal tonic and adaptogens are often used to improve overall well-being. However, few clinical evidence supports their use and their safety is not known before marketing. In this context, the aim of our study was to analyze the spontaneous reports of suspected adverse reactions (ARs) to performance enhancing herbal dietary supplements collected by the Italian Phytovigilance System. Between March 2002 and September 2020, 110 spontaneous reports were collected, 58 of which related to products containing botanicals, alone or in association. Twenty-three serious reactions were reported, 21 of which required hospitalization, one was

life-threatening and another caused disability. Dermatological and cardiovascular reactions were the most frequent. Hepatic ARs were the most serious (9 out of 10). A positive dechallenge was indicated in 69% of cases, while a positive rechallenge occurred in 15%. Concomitant use of other products was present in 18 reports (31%), while predisposing conditions were indicated in 17 (29%). Present data highlight safety concerns on herbal dietary supplements used as cognitive and physical performance enhancers, mainly due to their quality and use without expert supervision. Considering that postmarketing surveillance is not required for these products, spontaneous reports represent the only tool to point out risks related to food supplements.

DOI: 10.1002/ptr.7040
PMID: 33569860 [Indexed for MEDLINE]

22. An overview on performance and image enhancing drugs (PIEDs) confiscated in Italy in the period 2017-2019. Odoardi S, Mestria S, Biosa G, Valentini V, Federici S, Strano Rossi S.

Clin Toxicol (Phila). 2021 Jan;59(1):47-52. doi: 10.1080/15563650.2020.1770277. Epub 2020 Jun 1.

CONTEXT: The illegal market of counterfeit and falsified medicines and supplements containing unlabeled pharmaceuticals is expanding worldwide. They are usually referred to by the term "performance and image enhancing drugs" (PIEDs) and are mainly steroids, stimulants, hormones, and drugs for erectile dysfunction. PIEDs are easily accessible through the online or black markets. We analyzed over 400 such medicines confiscated in Italy in the period 2017-2019, to determine their composition. METHODS: Confiscated products were analyzed by gas chromatography/mass spectrometry and liquid chromatography/high-resolution mass spectrometry, in order to ascertain their composition and to evaluate the correspondence between what was declared on the label and the actual content, or to identify unknown products. RESULTS: The most commonly found substance was anabolic steroids, found in 64% of products, with 11% containing hormone modulators, 6% stimulants, 6% sexual enhancers (mainly sildenafil) and other drugs, including thyroid hormones, melanin stimulators, and vitamins. These substances were often in mixtures. The products were often mislabeled, containing contaminants in addition to the drug declared, or consisted of a drug completely different from the one reported on the label. Fifteen percent of products had a qualitative composition completely different from that declared, while 10% of products showed cross-contamination with other drugs, mainly testosterone esters, probably due to the presence of residues of other drugs in the production line. In addition, 11% of products were not labeled, so their purported composition was unknown. DISCUSSION: PIEDs pose a threat to public health. The main risks are related to the intrinsic toxicity of the substances found, especially when taken without a therapeutic indication. Another issue is related to the mislabeling of the fake medicines, and the poor-quality standard of counterfeit product preparation, with additional risks of the presence of other toxic ingredients or microbial contamination. CONCLUSIONS: The use of counterfeit products is a public health concern, as it constitutes a high risk for consumer health. It is mainly caused by the uncontrolled use of steroids, stimulants, sexual enhancers, and other medicaments, without medical indication or supervision, with variable and unknown compositions and doses, as well as other contaminants as a result of the absence of good manufacturing practices.

DOI: 10.1080/15563650.2020.1770277
PMID: 32475176 [Indexed for MEDLINE]

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

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

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

DOI: 10.1002/dta.2806
PMID: 32307880 [Indexed for MEDLINE]

24. Liquid chromatography-high-resolution mass spectrometry analysis of erectile dysfunction drugs and their analogues in food products. Mohd Yusop AY, Xiao L, Fu S.

Forensic Sci Int. 2021 May;322:110748. doi: 10.1016/j.forsciint.2021.110748. Epub 2021 Mar 4.

The presence of erectile dysfunction (ED) drugs in adulterated dietary supplements, mainly in pharmaceutical dosage forms, is frequently addressed in the literature. Little attention is given to food products despite their increasing adulteration trend. To address this knowledge gap targeted, suspected-target, and non-targeted strategies were utilised to analyse ED drugs and their analogues in powdered drink mix (PDM), honey, jelly, hard candy, and sugar-coated chewing gum using liquid chromatography-high-resolution mass spectrometry (LC-HRMS). The method was optimised and validated using 23 target analytes, representing different ED drugs with structural similarities. The modified quick, easy, cheap, effective, rugged, and safe (QuEChERS) extraction exhibited insignificant matrix effect (ME) within -9.2-8.8% and provided complete coverage of target analytes with acceptable extraction recovery (RE) within 75.5-123.9%, except for carbodenafil in the PDM matrix. Based on the ME and RE performance, the analytical method was validated to analyse 25 food samples that claimed to enhance male sexual performance. The method exhibited good specificity and linearity with a limit of detection within 10-70 ng/mL and limit of quantification of 80 ng/mL. Similarly, the accuracy and precision were satisfactory within 77.4-122.0% and< 16.7%RSD, respectively. The LC-HRMS targeted analysis, together with suspected-target and non-targeted screenings, identified and detected ten ED drugs from 24 food samples. The modified QuEChERS extraction with LC-HRMS-based method was demonstrated to be universally applicable to various food products, covering an extensive range of known and potentially novel ED drugs, which is valuable for routine casework.

DOI: 10.1016/j.forsciint.2021.110748
PMID: 33711768 [Indexed for MEDLINE]

25. Structure elucidation of a PDE5 inhibitor detected as an illegal adulteration in a libido-boosting dietary supplement. Tachikawa H, Nishiyama R, Ichikawa-Kaji Y, Uemura N, Takaku Y, Kishimoto K, Ono Y, Tayama K, Suzuki T, Suzuki J, Moriyasu T.

Food Addit Contam Part A Chem Anal Control Expo Risk Assess. 2020 Dec;37(12):2023-2032. doi: 10.1080/19440049.2020.1826582. Epub 2020 Nov 2.

A compound with potent inhibitory activity for phosphodiesterase type 5 (PDE5) was identified as an illegal adulteration in a libido-boosting dietary supplement being sold at a store in Tokyo. This compound was identified as 5,6-diethyl-2-{5-[(4-methylpiperazin-1-yl)sulphonyl]-2-propoxyphenyl}pyrimidin-4(3H)-one using liquid chromatography-diode array detector (LC-DAD), liquid chromatography-tandem mass spectrometer (LC-MS), LC-HRMS, nuclear magnetic resonance (NMR), and X-ray crystallography. The IC50 value of the inhibitory activity for PDE5A1 (one of the PDE5 isoforms) was 2.0 nM (sildenafil IC50 value was 4.5 nM). This compound was previously synthesised as a PDE5 inhibitor by Shanghai Institute of Materia Medica. The dietary supplement contained 85 mg of this compound in a capsule, which was about 26% of the capsule content (320 mg).

DOI: 10.1080/19440049.2020.1826582
PMID: 33136535 [Indexed for MEDLINE]

26. Isolation and characterisation of N-benzyl tadalafil as a novel adulterant in a coffee-based dietary supplement. Dong PZ, Liu XP, Zhang L, Shen GH, Wang ZL, Yang GW, Li W, Xiang XH.

Food Addit Contam Part A Chem Anal Control Expo Risk Assess. 2020 Dec;37(12):2033-2039. doi: 10.1080/19440049.2020.1825829. Epub 2020 Nov 2.

Erratum in: Food Addit Contam Part A Chem Anal Control Expo Risk Assess. 2020 Dec;37(12):2204.

A new tadalafil analogue was detected via high-performance liquid chromatography (HPLC)-diode array detection (DAD) during routine screening of health foods suspected of adulteration with erectile dysfunction

drugs. The UV absorption spectrum of the unknown was almost identical to that of tadalafil. The analogue was purified by preparative HPLC and structural elucidation carried out by mass spectrometric and NMR spectroscopic experiments. The spectral data revealed that this tadalafil analogue bears a benzyl group instead of the methyl group. The isolated compound was identified as N-benzyl tadalafil. Considering the risk it poses to public health, this new PDE-5 analogues for ED should be included on the inspection list for illegal products.

DOI: 10.1080/19440049.2020.1825829
PMID: 33136528 [Indexed for MEDLINE]

27. F-phenibut (β-(4-Fluorophenyl)-GABA), a potent GABA(B) receptor agonist, activates an outward-rectifying K(+) current and suppresses the generation of action potentials in mouse cerebellar Purkinje cells. Irie T, Yamazaki D, Kikura-Hanajiri R.

Eur J Pharmacol. 2020 Oct 5;884:173437. doi: 10.1016/j.ejphar.2020.173437. Epub 2020 Jul 28.

The GABA analog phenibut (β-Phenyl-GABA) is a GABAB receptor agonist that has been licensed for various uses in Russia. Phenibut is also available as a dietary supplement from online vendors worldwide, and previous studies have indicated that phenibut overdose results in intoxication, withdrawal symptoms, and addiction. F-phenibut (β-(4-Fluorophenyl)-GABA), a derivative of phenibut, has not been approved for clinical use. However, it is also available as a nootropic supplement from online suppliers. F-phenibut binds to GABAB with a higher affinity than phenibut; therefore, F-phenibut may lead to more serious intoxication than phenibut. However, the mechanisms by which F-phenibut acts on GABAB receptors and influences neuronal function remain unknown. In the present study, we compared the potency of F-phenibut, phenibut, and the GABAB agonist (±)-baclofen (baclofen) using in vitro patch-clamp recordings obtained from mouse cerebellar Purkinje cells slice preparations. Our findings indicate that F-phenibut acted as a potent GABAB agonist. EC50 of outward current density evoked by the three GABAB agonists decreased in the following order: phenibut (1362 μM) > F-phenibut (23.3 μM) > baclofen (6.0 μM). The outward current induced by GABAB agonists was an outward-rectifying K+ current, in contrast to the previous finding that GABAB agonists activates an inward-rectifying K+ current. The K+ current recorded in the present study was insensitive to extracellular Ba2+, intra- or extracellular Cs+, and intra- or extracellular tetraethylammonium-Cl. Moreover, F-phenibut suppressed action potential generation in Purkinje cells. Thus, abuse of F-phenibut may lead to severe damage by inhibiting the excitability of GABAB-expressing neurons.

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PMID: 32735986 [Indexed for MEDLINE]

28. Investigation of toxic heavy metals content and estimation of potential health risks in Chinese herbal medicine. Yang CM, Chien MY, Chao PC, Huang CM, Chen CH.

J Hazard Mater. 2021 Jun 15;412:125142. doi: 10.1016/j.jhazmat.2021.125142. Epub 2021 Jan 23.

The content of toxic heavy metals (THMs), including lead (Pb), arsenic (As), cadmium (Cd), and mercury (Hg), was determined in a total of 10,245 samples for 279 types of Chinese herbal medicine (CHM) using a validated inductively coupled plasma mass spectrometry method. The exceeding rate (ER) for the four THMs were calculated based on diverse permissible limits (PLs) established by different organizations and national pharmacopeias. Cluster analysis was used to classify the degree risk of THMs contamination according to the calculated ER. Results revealed that Cibotii rhizome, Selaginellae herba, Morindae officinalis radix, Asprellae ilicis radix, and Toxicodendri resina exhibited high-degree risk of Pb contamination. Eckloniae/Laminariae thallus, Spirodelae herba, and Naturalis indigo possessed high-degree risk of As contamination. Tetrapanacis medulla, Centipedae herba, Cyathulae radix, Linderae radix, Meretricis/Cyclinae concha, and Tabanus displayed high-degree risk of Cd contamination. Toxicodendri resina has high-degree risk of Hg contamination. In addition, six types of CHM, including Asprellae ilicis radix, Toxicodendri resina, Eckloniae/Laminariae thallus, Fossilia Ossis Mastodi, Haematitum, and Hedyotidis diffusae herba, may have non-carcinogenic health risk after consumption of raw materials because the calculated hazard quotient and hazard index were over 1.0. In summary, these data provide useful information about THMs contamination in CHM.

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