AACT Herbal Dietary Supplement Section Abstracts November 2021

1. 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 Sep;27(9):796-802. doi: 10.1089/acm.2021.0016. Epub 2021 May 12.

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 [Indexed for MEDLINE]

2. Caffeine supplementation in the hospital: Potential role for the treatment of caffeine withdrawal. Agritelley MS, Goldberger JJ.

Food Chem Toxicol. 2021 Jul;153:112228. doi: 10.1016/j.fct.2021.112228. Epub 2021 Apr 28.

Caffeine use in the population is widespread. Caffeine withdrawal in the hospital setting is an underappreciated syndrome with symptoms including drowsiness, difficulty concentrating, mood disturbances, low motivation, flu-like symptoms, and headache. Withdrawal may occur upon abstinence from chronic daily exposure at doses as low as 100 mg/day and following only 3-7 days of consumption at higher doses. There are limited data investigating how caffeine withdrawal contributes to hospital morbidity. Some studies suggest caffeine withdrawal may contribute to intensive care delirium and that caffeine may promote wakefulness post-anesthesia. Caffeine supplementation has also shown promise in patients at risk of caffeine withdrawal, such as those placed on nil per os (NPO) status, in preventing caffeine withdrawal headache. These data on caffeine supplementation are not entirely consistent, and routine caffeine administration has not been implemented into clinical practice for patients at risk of withdrawal. Notably, caffeine serves a therapeutic role in the hospital for other conditions. Our review demonstrates that caffeine is largely safe in the general population and may be an appropriate therapeutic option for future studies, if administered properly. There is a need for a randomized controlled trial investigating in-hospital caffeine supplementation and the population that this would best serve.

DOI: 10.1016/j.fct.2021.112228
PMID: 33932520 [Indexed for MEDLINE]

3. Quantity of phenibut in dietary supplements before and after FDA warnings. Cohen PA, Ellison RR, Travis JC, Gaufberg SV, Gerona R.

Clin Toxicol (Phila). 2021 Sep 22:1-3. doi: 10.1080/15563650.2021.1973020. Online ahead of print.

INTRODUCTION: Phenibut is used to treat anxiety, insomnia, alcohol withdrawal and other conditions in Russia. The drug, however, has abuse potential and may cause lethargy, delirium, psychosis and coma. In the United States (US), the US Food and Drug Administration (FDA) has never approved the use of phenibut as a prescription medication, but the drug is available over-the-counter in dietary supplements. More than 80 cases of coma and death have been associated with phenibut consumption and withdrawal, and the FDA recently warned that the drug is not permitted in over-the-counter supplements. We designed our study to determine the presence and quantity of phenibut in over-the-counter supplements before and after the FDA warnings. METHODS: Phenibut products were included if they (a) listed phenibut or a synonym as an ingredient on the label, (b) were labeled as a dietary supplement, and (c) were available for sale both before and after the FDA warning. Supplements were analyzed by liquid chromatography time-of-flight mass spectrometry; quantification was performed by isotope dilution method. RESULTS: Four brands of dietary supplements labeled as containing phenibut met the inclusion criteria. Prior to the FDA warnings, two of the four brands contained phenibut, at dosages of 484 mg and 487 mg per serving. After the FDA warning, all four products contained phenibut, ranging in dosages from 21 mg to 1,164 mg per serving. Phenibut was first detected only after the FDA warnings in two brands, and the quantity of phenibut increased in three of four products after the FDA warnings. Quantities detected per dose were as much as 450% greater than a typical 250 mg pharmaceutical tablet manufactured in Russia. CONCLUSION: Following FDA issuing an advisory that phenibut is not permitted in dietary supplements, the quantity of phenibut increased in 3 of 4 brands of over-the-counter phenibut supplements.

DOI: 10.1080/15563650.2021.1973020
PMID: 34550038

4. Analysis of supplements available to UK consumers purporting to contain selective androgen receptor modulators. Leaney AE, Beck P, Biddle S, Brown P, Grace PB, Hudson SC, Mawson DH.

Drug Test Anal. 2021 Jan;13(1):122-127. doi: 10.1002/dta.2908. Epub 2020 Aug 16.

Selective androgen receptor modulators (SARMs) are compounds with specific androgenic properties investigated for the treatment of conditions such as muscle wasting diseases. The reported androgenic properties have resulted in their use by athletes, and consequently they have been on the World Anti-Doping Agency prohibited list for more than a decade. SARMs have been investigated by pharmaceutical companies as potential drug candidates, but to date no SARM has demonstrated sufficient safety and efficacy to gain clinical approval by either the European Medicines Agency or the U.S. Food and Drug Administration. Despite their lack of safety approval, SARMs are often illegally marketed as dietary supplements, available for consumers to buy online. In this study, a range of supplement products marketed as SARMs were purchased and analyzed using high resolution accurate mass - mass spectrometry to evaluate the accuracy of product claims and content labeling. This study found discrepancies ranging from a supplement in which no active ingredients were found, to supplements containing undeclared prohibited analytes. Where SARMs were detected, discrepancies were observed between the concentrations measured and those detailed on the product packaging. The outcome of this experiment highlights the high risk of such supplement products to consumers. The inaccurate product claims give rise to uncertainty over both the dose taken and the identity of any of these unapproved drugs. Even for supplements for which the product labeling is correct, the lack of complete toxicity data, especially for combinations of SARMs taken as stacks, means that the safety of these supplements is unknown.

DOI: 10.1002/dta.2908
PMID: 32748554 [Indexed for MEDLINE]

5. Androstenedione (a Natural Steroid and a Drug Supplement): A Comprehensive Review of Its Consumption, Metabolism, Health Effects, and Toxicity with Sex Differences. Badawy MT, Sobeh M, Xiao J, Farag MA.

Molecules. 2021 Oct 14;26(20):6210. doi: 10.3390/molecules26206210.

Androstenedione is a steroidal hormone produced in male and female gonads, as well as in the adrenal glands, and it is known for its key role in the production of estrogen and testosterone. Androstenedione is also sold as an oral supplement, that is being utilized to increase testosterone levels. Simply known as "andro" by athletes, it is commonly touted as a natural alternative to anabolic steroids. By boosting

testosterone levels, it is thought to be an enhancer for athletic performance, build body muscles, reduce fats, increase energy, maintain healthy RBCs, and increase sexual performance. Nevertheless, several of these effects are not yet scientifically proven. Though commonly used as a supplement for body building, it is listed among performance-enhancing drugs (PEDs) which is banned by the World Anti-Doping Agency, as well as the International Olympic Committee. This review focuses on the action mechanism behind androstenedione's health effects, and further side effects including clinical features, populations at risk, pharmacokinetics, metabolism, and toxicokinetics. A review of androstenedione regulation in drug doping is also presented.

DOI: 10.3390/molecules26206210
PMCID: PMC8539210
PMID: 34684800 [Indexed for MEDLINE]

6. United States Pharmacopeia (USP) Safety Review of Gamma-Aminobutyric Acid (GABA). Oketch-Rabah HA, Madden EF, Roe AL, Betz JM.

Nutrients. 2021 Aug 10;13(8):2742. doi: 10.3390/nu13082742.

Gamma-amino butyric acid (GABA) is marketed in the U.S. as a dietary supplement. USP conducted a comprehensive safety evaluation of GABA by assessing clinical studies, adverse event information, and toxicology data. Clinical studies investigated the effect of pure GABA as a dietary supplement or as a natural constituent of fermented milk or soy matrices. Data showed no serious adverse events associated with GABA at intakes up to 18 g/d for 4 days and in longer studies at intakes of 120 mg/d for 12 weeks. Some studies showed that GABA was associated with a transient and moderate drop in blood pressure (<10% change). No studies were available on effects of GABA during pregnancy and lactation, and no case reports or spontaneous adverse events associated with GABA were found. Chronic administration of GABA to rats and dogs at doses up to 1 g/kg/day showed no signs of toxicity. Because some studies showed that GABA was associated with decreases in blood pressure, it is conceivable that concurrent use of GABA with anti-hypertensive medications could increase risk of hypotension. Caution is advised for pregnant and lactating women since GABA can affect neurotransmitters and the endocrine system, i.e., increases in growth hormone and prolactin levels.

DOI: 10.3390/nu13082742
PMCID: PMC8399837
PMID: 34444905 [Indexed for MEDLINE]

7. The Safety and Efficacy of Botanicals with Nootropic Effects. Roe AL, Venkataraman A.

Curr Neuropharmacol. 2021;19(9):1442-1467. doi: 10.2174/1570159X19666210726150432.

Recent estimates for the global brain health supplement category, i.e. nootropic market size, will grow to nearly $5.8 billion by 2023. Overall, nearly one-quarter (23%) of adults currently take a supplement to maintain or improve brain health or delay and reverse dementia. Not surprisingly, the use of such supplements increases with age - more than one-third of the oldest generation (ages 74 and older) takes a supplement for brain health. This widespread use is being driven by a strong desire both in the younger and older generations to enhance cognitive performance and achieve healthy aging. The most prevalent botanicals currently dominating the nootropic marketplace include Gingko biloba, American ginseng, and Bacopa monnieri. However, other botanicals that affect stress, focus, attention, and sleep have also been procured by dietary supplement companies developing products for improving both, short and long-term brain health. This review focuses on efficacy data for neuroactive botanicals targeted at improving cognitive function, stress reduction, memory, mood, attention, concentration, focus, and alertness, including Bacopa monnieri, Ginkgo biloba, Holy basil, American ginseng, Gotu kola, Lemon balm, Common and Spanish sages and spearmint. Botanicals are discussed in terms of available clinical efficacy data and current safety profiles. Data gaps are highlighted for both efficacy and safety to bring attention to unmet needs and future research.

DOI: 10.2174/1570159X19666210726150432
PMID: 34315377 [Indexed for MEDLINE]

8. Nine prohibited stimulants found in sports and weight loss supplements: deterenol, phenpromethamine (Vonedrine), oxilofrine, octodrine, beta-methylphenylethylamine (BMPEA), 1,3-dimethylamylamine (1,3-DMAA), 1,4-dimethylamylamine (1,4-DMAA), 1,3-dimethylbutylamine (1,3-DMBA) and higenamine. Cohen PA, Travis JC, Vanhee C, Ohana D, Venhuis BJ.

Clin Toxicol (Phila). 2021 Nov;59(11):975-981. doi: 10.1080/15563650.2021.1894333. Epub 2021 Mar 23.

BACKGROUND: Weight loss and sports supplements containing deterenol have been associated with serious adverse events including cardiac arrest. OBJECTIVE: To determine the presence and quantity of experimental stimulants in dietary supplements labeled as containing deterenol sold in the United States. METHODS: Dietary supplements available for sale in the US and labeled as containing deterenol or one of its synonyms (e.g., isopropylnorsynephrine and isopropyloctopamine) were purchased online. For each brand, one container or subsample was analyzed by NSF International (Ann Arbor, MI) and one container or subsample by the Netherland's National Institute for Public Health and the Environment (RIVM, Bilthoven, The Netherlands). When differences existed between the two containers or subsamples of the same brand, both products were reanalyzed by Sciensano (Brussels, Belgium). NSF International carried out qualitative and quantitative analyses using ultra-high-performance liquid chromatography (UHPLC) quadrupole-Orbitrap mass spectrometry. RIVM performed qualitative and quantitative analysis using UHPLC quadrupole time-of-flight mass spectrometry. Sciensano carried out qualitative analysis using UHPLC quadrupole-Orbitrap mass spectrometry. RESULTS: Seventeen brands of supplements were analyzed. Many brands included more than one prohibited stimulant in the same product: 4 brands (24%, 4/17) included 2 stimulants, 2 (12%, 2/17) combined 3 stimulants, and 2 (12%, 2/17) combined 4 stimulants. The range of quantities per recommended serving size of the 9 stimulants detected were 2.7 mg to 17 mg of deterenol; 1.3 mg to 20 mg of phenpromethamine (Vonedrine); 5.7 mg to 92 mg of beta-methylphenylethylamine (BMPEA); 18 mg to 73 mg of octodrine; 18 mg to 55 mg of oxilofrine; 48 mg of higenamine; 17 mg of 1,3-dimethylamylamine (1,3-DMAA); 1.8 mg to 6.6 mg of 1,3-dimethylbutylamine (1,3-DMBA); and 5.3 mg of 1,4-dimethylamylamine (1,4-DMAA). CONCLUSION: Weight loss and sports supplements listing deterenol as an ingredient contained 9 prohibited stimulants and 8 different mixtures of stimulants, with as many as 4 experimental stimulants per product. These cocktails of stimulants have never been tested in humans and their safety is unknown.

DOI: 10.1080/15563650.2021.1894333
PMID: 33755516 [Indexed for MEDLINE]

9. Adulteration of Weight Loss Supplements by the Illegal Addition of Synthetic Pharmaceuticals. Jairoun AA, Al-Hemyari SS, Shahwan M, Zyoud SH.

Molecules. 2021 Nov 16;26(22):6903. doi: 10.3390/molecules26226903

Weight loss supplements that have illegal additives of pharmaceutical drugs or analogues have additional health risks, and customers may not be aware of what they are taking. This research is an essential investigation and quantification of illegally added pharmaceuticals or prescription medications, specifically fluoxetine, phenolphthalein, and sibutramine, in herbal weight loss supplements offered for sale in the United Arab Emirates (UAE). In this case, 137 weight loss supplements were collected and analyzed in this study. Reversed-phase high-performance liquid chromatography with UV absorption detection coupled to tandem mass spectrometry (RP-HPLC-MS/MS) analyses were used to determine the presence of the pharmaceutical chemicals. Among the weight loss supplements, 15.3% (95% CI: 9.2-21.4) contained undeclared sibutramine, 13.9% (95% CI: 8.01-19.7) contained undeclared phenolphthalein, and 5.1% (95% CI: 1.4-8.8) contained undeclared fluoxetine. Amongst all weight loss supplements, 17.5% (95% CI: 11.07-24) contained significant concentrations of either sibutramine, phenolphthalein, or fluoxetine. Whilst weight loss herbal supplements offered for sale in the UAE have relatively low percentages of undeclared pharmaceuticals, many people take several different supplements daily and may encounter quite high levels of combined exposure to toxic compounds.

DOI: 10.3390/molecules26226903
PMCID: PMC8621677
PMID: 34833995

10. Adulteration of the Herbal Weight Loss Products by the Illegal Addition of Synthetic Antiobesity Medications: A Pilot Study. Firozian F, Nili-Ahmadabadi A, Moradkhani S, Moulaei M, Fasihi Z, Ahmadimoghaddam D.

J Obes. 2021 Jul 14;2021:9968730. doi: 10.1155/2021/9968730. eCollection 2021

BACKGROUND: Some anorexic agents are used to fraudulent augmentation herbal weight loss formulations. This study was designed to evaluate the potential existence of illicit substances in 63 herbal weight loss formulations collected from local apothecaries in Hamadan, Iran. METHODS: The thin-layer chromatography method was applied for the primary screening of potential illicit substances in the samples. The positive samples were analyzed using an isocratic high-performance liquid chromatography method. RESULTS: The results showed that 26.98% of the samples contained 17.76 ± 6.02 mg/cap of sibutramine. Daily therapeutic dose intake of sibutramine is in the range of 5 to 15 mg daily. CONCLUSION: Since apothecaries have advised consumers to take at least two capsules a day, it seems that the blood concentration of sibutramine will likely rise beyond the therapeutic concentration and become toxic. Therefore, the usage of such products could pose serious risks to consumers' health.

DOI: 10.1155/2021/9968730
PMCID: PMC8294965
PMID: 34336274 [Indexed for MEDLINE]

11. Hypoglycemic Effect of Two Mexican Medicinal Plants. Andrade-Cetto A, Espinoza-Hernández F, Mata-Torres G, Escandón-Rivera S.

Plants (Basel). 2021 Sep 29;10(10):2060. doi: 10.3390/plants10102060.

Type 2 diabetes is a worldwide prevalent disease that is due to a progressive loss of adequate β-cell insulin secretion, frequently against a background of insulin resistance. In Mexican traditional medicine, the therapeutic use of hypoglycemic plants to control the disease is a common practice among type 2 diabetic patients. In the present work, we examined the traditional use of the aerial parts of Eryngium longifolium and the rhizome of Alsophila firma, consumed by people use over the day (in fasting state) to control their blood glucose levels, therefore, we aimed to assess the acute hypoglycemic effect of both plants. First, basic phytochemical profiles of both plants were determined and, subsequently, acute toxicity tests were carried out. Then, in vivo hypoglycemic tests were performed in streptozotocin-nicotinamide (STZ-NA) induced hyperglycemic Wistar rats and finally the effect of the plants on three enzymes involved in glucose metabolism was assayed in vitro. Through HPLC-DAD chromatography, caffeic acid, chlorogenic acid, rosmarinic acid, isoflavones, and glycosylated flavonoids were identified in E. longifolium, while the possible presence of flavanones or dihydroflavonols was reported in A. firma. Both plants exhibited a statistically significant hypoglycemic effect, without a dose-dependent effect. Furthermore, they inhibited glucose 6-phosphatase and fructose 1,6-bisphosphatase in in vitro assays, which could be associated with the hypoglycemic effect in vivo. Thus, this study confirmed for the first time the traditional use of the aerial part of E. longifolium and the rhizome of A. firma as hypoglycemic agents in a hyperglycemic animal model. In addition, it was concluded that their ability to regulate hyperglycemia could involve the inhibition of hepatic glucose output, which mainly controls glucose levels in the fasting state.

DOI: 10.3390/plants10102060
PMCID: PMC8539009
PMID: 34685869

12. Poppies as a sleep aid for infants: The "Hypnos" remedy of Cretan folk medicine. Mathianaki K, Tzatzarakis M, Karamanou M.

Toxicol Rep. 2021 Oct 4;8:1729-1733. doi: 10.1016/j.toxrep.2021.10.002. eCollection 2021.

Opium Poppy (Papaver somniferum L.) is considered as one of the earliest medicinal plants known to mankind. Derived from the Greek name "opos" meaning juice, referring to its psychotropic latex, the plant was known and extensively used since Antiquity during religious rituals and for Medical purposes, mainly as hypnotic and pain reliever agent. In Cretan folk medicine it was recommended along with other poppies until the early 20th century to induce children sedation, by the name: "Hypnos" meaning sleep.

DOI: 10.1016/j.toxrep.2021.10.002
PMCID: PMC8511716
PMID: 34692423

13. Speaking of the (Barely legal) elephant in the room: Herbal or dietary supplement related acute liver failure. Aithal GP.

Liver Transpl. 2021 Nov 26. doi: 10.1002/lt.26377. Online ahead of print.

Titled 'Barely legal', Banksy's first United States (USA) exhibition showcased Tai, an Indian elephant, painted with pink and gold pattern to blend in with the wallpaper of the living room, intended to mock the art world's claim for the true portrayal of the state of the world where over 650 million people live below the poverty line, yet, never actually doing anything about it [1]. Irony befitting the title of the exhibition was that Los Angeles's Animal Services Department which had permitted the elephant's appearance at the exhibition, later stated that the 'paint that was used although non-toxic, was unsafe according to government regulations'. Tai appeared unpainted in the living room the following day!

DOI: 10.1002/lt.26377
PMID: 34825768

14. Herbal and dietary supplement induced liver injury: Highlights from the recent literature. Woo SM, Davis WD, Aggarwal S, Clinton JW, Kiparizoska S, Lewis JH.

World J Hepatol. 2021 Sep 27;13(9):1019-1041. doi: 10.4254/wjh.v13.i9.1019.

Herbal-induced liver injury (HILI) is an important and increasingly concerning cause of liver toxicity, and this study presents recent updates to the literature. An extensive literature review was conducted encompassing September 2019 through March 2021. Studies with clinically significant findings were analyzed and included in this review. We emphasized those studies that provided a causality assessment methodology, such as Roussel Uclaf Causality Assessment Method scores. Our review includes reports of individual herbals, including Garcinia cambogia, green tea extract, kratom as well as classes such as performance enhancing supplements, Traditional Chinese medicine, Ayurvedic medicine and herbal contamination. Newly described herbals include ashwagandha, boldo, skyfruit, and 'Thermo gun'. Several studies discussing data from national registries, including the United States Drug-Induced Liver Injury (DILI) Network, Spanish DILI Registry, and Latin American DILI Network were incorporated. There has also been a continued interest in hepatoprotection, with promising use of herbals to counter hepatotoxicity from anti-tubercular medications. We also elucidated the current legal conversation surrounding use of herbals by presenting updates from the Federal Drug Administration. The highlights of the literature over the past year indicate interest in HILI that will continue as the supplement industry in the United States grows.

DOI: 10.4254/wjh.v13.i9.1019
PMCID: PMC8473494
PMID: 34630872

15. Revisiting supplement safety: a near fatal overdose with novel supplement tejocote. Mudan A, Livshits Z, Lebin J.

Clin Toxicol (Phila). 2021 Jun;59(6):531-532. doi: 10.1080/15563650.2020.1832235. Epub 2020 Oct 20.

DOI: 10.1080/15563650.2020.1832235
PMID: 33078966 [Indexed for MEDLINE]

16. Clinical Pharmacology of the Dietary Supplement, Kratom (Mitragyna speciosa). Hartley C, Bulloch M, Penzak SR.

J Clin Pharmacol. 2021 Nov 13. doi: 10.1002/jcph.2001. Online ahead of print.

Kratom (Mitragyna speciosa) consists of over 40 alkaloids with two of them, mitragynine (MG) and 7-OH-mitragynine (7-OH-MG) being the main psychoactive compounds. MG and 7-OH-MG each target opioid receptors and have been referred to as atypical opioids. They exert their pharmacologic effects on the μ, δ,

and κ opioid receptors. In addition, they affect adrenergic, serotonergic, and dopaminergic pathways. Kratom has been touted as an inexpensive, legal alternative to standard opioid replacement therapy such as methadone and buprenorphine. Other uses for kratom include chronic pain, attaining a "legal high," and numerous CNS disorders including anxiety depression and post-traumatic stress disorder (PTSD). Kratom induces analgesia and mild euphoria with a lower risk of respiratory depression or adverse central nervous system effects compared to traditional opioid medications. Nonetheless, kratom has been associated with both physical and psychological dependence with some individuals experiencing classic opioid withdrawal symptoms upon abrupt cessation. Kratom use has been linked to serious adverse effects including liver toxicity, seizures, and death. These risks are often compounded by poly-substance abuse. Further, kratom may potentiate the toxicity of coadministered medications through modulation of cytochrome P450, P-glycoprotein, and uridine diphosphate glucuronosyltransferase enzymes (UGDT). In 2016 the U.S. Drug Enforcement Administration (DEA) took steps to classify kratom as a federal schedule 1 medication; however, due to public resistance, this plan was set aside. Until studies are conducted that define kratom's role in treating opioid withdrawal and/or other CNS conditions, kratom will likely remain available as a dietary supplement for the foreseeable future.

DOI: 10.1002/jcph.2001
PMID: 34775626

17. Is kratom (Mitragyna speciosa Korth.) use associated with ECG abnormalities? Electrocardiogram comparisons between regular kratom users and controls. Leong Abdullah MFI, Tan KL, Narayanan S, Yuvashnee N, Chear NJY, Singh D, Grundmann O, Henningfield JE.

Clin Toxicol (Phila). 2021 May;59(5):400-408. doi: 10.1080/15563650.2020.1812627. Epub 2020 Sep 1.

Erratum in Clin Toxicol (Phila). 2020 Sep 9;:1.

OBJECTIVES: Little is known about the cardiotoxic effects of kratom (Mitragyna speciosa Korth.), a medicinal plant. This analytical cross-sectional study investigated the prevalence of electrocardiogram (ECG) abnormalities and QTc intervals in regular kratom users compared with non-kratom-using control subjects. METHODS: We enrolled regular kratom users and non-kratom-using control subjects from three communities. Demographic data, clinical data, kratom use characteristics, and ECG findings were recorded. The mitragynine content of kratom juice was quantified using a validated gas chromatography-mass spectrometry (GC-MS) method. RESULTS: A total of 200 participants (100 kratom users and 100 control subjects) participated in this study. The prevalence of ECG abnormalities in kratom users (28%) did not differ from that of control subjects (32%). Kratom use was not associated with ECG abnormalities, except for significantly higher odds of sinus tachycardia (OR = 8.61, 95% CI = 1.06-70.17, p = 0.035) among kratom users compared with control subjects. The odds of observing borderline QTc intervals were significantly higher for kratom users compared with control subjects, regardless of the age of first use, the duration of use, the daily quantity consumed, and the length of time that had elapsed between last kratom use and ECG assessment. Nevertheless, there were no differences in the odds of having prolonged QTc intervals between kratom users and controls. The estimated average daily intake of mitragynine consumed by kratom users was 434.28 mg. CONCLUSION: We found no link between regular kratom use and electrocardiographic abnormalities with an estimated average daily intake of 434.28 mg of mitragynine.

DOI: 10.1080/15563650.2020.1812627
PMID: 32870119 [Indexed for MEDLINE]

18. Unusual Presentation of Kratom Overdose With Rhabdomyolysis, Transient Hearing Loss, and Heart Failure. Sangani V, Sunnoqrot N, Gargis K, Ranabhotu A, Mubasher A, Pokal M.

J Investig Med High Impact Case Rep. 2021 Jan-Dec;9:23247096211005069. doi: 10.1177/23247096211005069.

Kratom mainly grows in Southeast Asia. It is widely used for pain management and opioid withdrawal, which is available online for cheaper prices. Alkaloids extracted from kratom such as mitragynine and 7-hydroxy mitragynine exhibit analgesic properties by acting through μ receptors. Commonly reported side effects of kratom include hypertension, tachycardia, agitation, dry mouth, hallucinations, cognitive and behavioral impairment, cardiotoxicity, renal failure, cholestasis, seizures, respiratory depression, coma, and sudden cardiac death from cardiac arrest. Rhabdomyolysis is a less commonly reported lethal effect of

kratom. Limited information is available in the literature. In this article, we present a case of a 45-year-old female who is overdosed with kratom and presented with lethargy, confusion, transient hearing loss, and right lower extremity swelling and pain associated with weakness who was found to have elevated creatinine phosphokinase. She was diagnosed with rhabdomyolysis, compartment syndrome, multiorgan dysfunction including acute kidney injury, liver dysfunction, and cardiomyopathy. She underwent emergent fasciotomy and required hemodialysis. Her renal and liver function subsequently improved. We described the case and discussed pharmacology and adverse effects of kratom toxicity with a proposed mechanism and management. We conclude that it is essential for emergency physicians, internists, intensivists, cardiologists, and nephrologists to be aware of these rare manifestations of kratom and consider a multidisciplinary approach.

DOI: 10.1177/23247096211005069
PMID: 33764201 [Indexed for MEDLINE]

19. Repetitive drug-induced liver injury with kedaling tablets. Wang J.

Clin Toxicol (Phila). 2021 Sep;59(9):853-854. doi: 10.1080/15563650.2021.1881536. Epub 2021 Feb 12.

DOI: 10.1080/15563650.2021.1881536
PMID: 33576258 [Indexed for MEDLINE]

20. Excessive Prenatal Supplementation of Iodine and Fetal Goiter: Report of Two Cases Using Three-dimensional Ultrasound and Magnetic Resonance Imaging. Castro P, Werner H, Marinho PRS, Matos AP, Pires P, Araujo Júnior E.

Rev Bras Ginecol Obstet. 2021 Apr;43(4):317-322. doi: 10.1055/s-0041-1729143. Epub 2021 May 12.

Fetal thyroid complications in pregnancy are uncommon, and are commonly related to the passage of substances through the placenta. The excessive iodine intake during the pregnancy is a well-known mechanism of fetal thyroid enlargement or goiter, and invasive procedures have been proposed for the treatment of fetal thyroid pathologies. In the present report, we demonstrate two cases from different centers of prenatal diagnosis of fetal thyroid enlargement and/or goiter in three fetuses (one pair of twins, wherein both fetuses were affected, and one singleton pregnancy). The anamnesis revealed the ingestion of iodine by the patients, prescribed from inadequate vitamin supplementation. In both cases, the cessation of iodine supplement intake resulted in a marked reduction of the volume of the fetal thyroid glands, demonstrating that conservative treatment may be an option in those cases. Also, clinicians must be aware that patients may be exposed to harmful dosages or substances during pregnancy.

DOI: 10.1055/s-0041-1729143
PMID: 33979892 [Indexed for MEDLINE]

21. Vitamin D intoxication due to misuse: 5-year experience. Çağlar A, Tuğçe Çağlar H.

Arch Pediatr. 2021 Apr;28(3):222-225. doi: 10.1016/j.arcped.2020.12.009. Epub 2021 Jan 19.

INTRODUCTION: Vitamin D intoxication (VDI) is a well-known cause of hypercalcemia in children and leads to serious kidney, heart, and neurological problems. In the treatment of VDI, the goal is to correct hypercalcemia. Our aim was to evaluate the clinical features of patients with VDI, identify the causes of VDI in our region, and help guide precautions and treatment of VDI. MATERIALS AND METHODS: The medical records of patients with VDI presenting between January 2015 and December 2019 were retrospectively analyzed. RESULTS: In total, 38 patients aged 0.3-4 years including 20 males (52.6%) were included in the study. Vomiting (65.8%), loss of appetite (47.4%), and constipation (31.6%) were the most common symptoms. The cause of intoxication was prescribed D3 vials in 23 patients, non prescribed D3 vials in nine patients, and incorrectly produced fish oil supplement in six patients. Admission serum calcium and 25 (OH) D levels were 3.75±0.5mmol/L and 396±110ng/mL, respectively. A statistically significant correlation was found between the serum calcium levels at the time of diagnosis and the dose of vitamin D received, serum 25 (OH) D, phosphorus, and parathyroid (PTH) levels. Nephrocalcinosis was present in 15 (39.5%) patients. The mean time to achieve normocalcemia was 6.18±2 days. The mean time to achieve normocalcemia in patients treated with pamidronate was 5.94±0.7 days. CONCLUSION: Stoss therapy should not be administered for children of families with problems of adherence to treatment. It should be

noted that VDI may develop as a result of improperly produced nutritional supplements. General practitioners and pediatricians must be aware of VDI risks and explain them to parents. Pamidronate is effective for treating VDI in children.

DOI: 10.1016/j.arcped.2020.12.009
PMID: 33483193 [Indexed for MEDLINE]

22. Acute kidney injury in a man taking vitamin supplements for COVID-19 prophylaxis. Koratala A, Gallan AJ.

Clin Nephrol. 2021 Oct;96(4):251-252. doi: 10.5414/CN110632.

DOI: 10.5414/CN110632
PMID: 34402787 [Indexed for MEDLINE]

23. St. John's Wort (Hypericum perforatum)-Related Acute Kidney Injury. Adibelli Z, Karacay I, Demir M, Duran C.

Blood Purif. 2021 Aug 24:1-3. doi: 10.1159/000518349. Online ahead of print.

Some herbal products were reported to cause nephrotoxicity through different mechanisms. This case report defines an acute kidney injury (AKI) in a patient who used Hypericum perforatum tea as a sleep disorder remedy. The patient developed AKI after ingestion of tea prepared from Hypericum perforatum and underwent hemodialysis because of acute kidney failure. After 1 week, the kidney recovered, and she was discharged with normal kidney function. This is the first case reported having acute kidney failure caused by ingestion of Hypericum perforatum.

DOI: 10.1159/000518349
PMID: 34515077

24. Cutaneous mercury granulomas, hyperpigmentation and systemic involvement: A case of mercury toxicity following herbal medication for psoriasis. Jagadeesan S, Duraisamy P, Panicker VV, Anjaneyan G, Sajini L, Velayudhan S, Thomas J.

Indian J Dermatol Venereol Leprol. 2021 Nov-Dec;87(6):892. doi: 10.25259/IJDVL_888_20.

DOI: 10.25259/IJDVL_888_20
PMID: 34623046

25. Multi-Criteria Decision Analysis Model for Assessing the Risk from Multi-Ingredient Dietary Supplements (MIDS). Oketch-Rabah HA, Hardy ML, Patton AP, Chung M, Sarma ND, Yoe C, Ayyadurai VAS, Fox MA, Jordan SA, Mwamburi M, Mould DR, Osterberg RE, Hilmas C, Tiwari R, Valerio L Jr, Jones D, Deuster PA, Giancaspro GI.

J Diet Suppl. 2021;18(3):293-315. doi: 10.1080/19390211.2020.1741485. Epub 2020 Apr 22.

Military personnel use dietary supplements (DS) for performance enhancement, bodybuilding, weight loss, and to maintain health. Adverse events, including cardiovascular (CV) effects, have been reported in military personnel taking supplements. Previous research determined that ingestion of multi-ingredient dietary supplements (MIDS), can lead to signals of safety concerns. Therefore, to assess the safety of MIDS, the Department of Defense via a contractor explored the development of a model-based risk assessment tool. We present a strategy and preliminary novel multi-criteria decision analysis (MCDA)-based tool for assessing the risk of adverse CV effects from MIDS. The tool integrates toxicology and other relevant data available on MIDS; likelihood of exposure, and biologic plausibility that could contribute to specific aspects of risk.Inputs for the model are values of four measures assigned based on the available evidence supplemented with the opinion of experts in toxicology, modeling, risk assessment etc. Measures were weighted based on the experts' assessment of measures' relative importance. Finally, all data for the four measures were integrated to provide a risk potential of 0 (low risk) to 100 (high risk) that defines the relative risk of a MIDS to cause adverse reactions.We conclude that the best available evidence must be supplemented with the opinion of experts in medicine, toxicology and pharmacology. Model-based approaches are useful to inform

risk assessment in the absence of data. This MCDA model provides a foundation for refinement and validation of accuracy of the model predictions as new evidence becomes available.

DOI: 10.1080/19390211.2020.1741485
PMID: 32319852 [Indexed for MEDLINE]

26. Dietary Supplement Use Among Adults: United States, 2017-2018. Mishra S, Stierman B, Gahche JJ, Potischman N.

NCHS Data Brief. 2021 Feb;(399):1-8.

Dietary supplement use is common in the United States (1). The additional nutrients provided by dietary supplements can help meet recommended nutrient targets but can also potentially lead to excess intakes (2,3). This report describes recent prevalence estimates for dietary supplement use among U.S. adults, the distribution of the number of dietary supplements used, and the most common types of dietary supplements used. Trends in dietary supplement use from 2007-2008 through 2017-2018 are also reported.

PMID: 33663653 [Indexed for MEDLINE]

27. Dietary Supplement Use in US Army Personnel: A Mixed-Methods, Survey and Focus-Group Study Examining Decision Making and Factors Associated With Use. Bukhari AS, DiChiara AJ, Merrill EP, Wright AO, Cole RE, Hatch-McChesney A, McGraw SM, Caldwell JA, Montain SJ, Thompson LA, Lieberman HR.

J Acad Nutr Diet. 2021 Jun;121(6):1049-1063. doi: 10.1016/j.jand.2021.01.011. Epub 2021 Feb 27.

BACKGROUND: Dietary supplement (DS) use by Army personnel is high and is a safety and readiness issue. OBJECTIVE: Our aim was to examine factors motivating use of DSs among US Army personnel and preferred safety education strategies. DESIGN: This mixed-method study used a validated DS questionnaire and subsequent focus groups that were formed based on questionnaire-identified demographic characteristics. An embedded qualitative dominant design was used. PARTICIPANTS/SETTING: Data were collected from April to July 2015 from active duty soldiers at 3 military installations in the United States. MAIN OUTCOME MEASURES: A self-report questionnaire (n = 289) provided data on demographic characteristics, health, exercise, detailed use, and attitudes regarding DS safety and efficacy. Fourteen focus-group sessions (n = 129) examined factors motivating DS use, education strategies, and identified themes and DS-related behaviors. STATISTICAL ANALYSIS PERFORMED: Descriptive statistics and $\chi 2$ analyses were conducted. RESULTS: Of the soldiers who completed questionnaires, 83% were male, 60% were enlisted, and 40% were officers; mean age ± standard deviation was 27.6 ± 0.36 years and 75% used at least 1 type of DS per week: 52% used protein/amino acids, 47% used multivitamins/minerals, and 35% used a combination of products. Focus groups indicated reasons for use included physical appearance, fitness, peer endorsement, ease of access, limited availability of healthy food, occupational demands, and health. Participants requested education from an expert on safe use that was not focused on dangerous products. CONCLUSIONS: Soldiers are high DS users, especially products marked for purported performance enhancement. Motivating factors for DS use are fitness/appearance and occupational demands, but soldiers lack knowledge of DS regulatory requirements and safety/efficacy. Soldiers wished to receive education on DSs from trusted health care professionals, such as registered dietitian nutritionists, that was not focused on dangerous products. Study findings suggest guidance and education should occur before periods of high DS use, such as deployment.

DOI: 10.1016/j.jand.2021.01.011
PMID: 33653678 [Indexed for MEDLINE]

28. Dietary Supplements Use among Adults with Cancer in the United States: A Population-Based Study. Abdel-Rahman O.

Nutr Cancer. 2021;73(10):1856-1863. doi: 10.1080/01635581.2020.1820050. Epub 2020 Sep 15.

To assess the patterns of use of dietary supplements among cancer survivors in the United States in a population-based setting. National Health and Nutrition Examination Survey (NHANES) datasets (1999-2016) were accessed, and adult respondents (≥ 20 years old) with a known status of cancer diagnosis

and a known status of dietary supplements intake were included. Multivariable logistic regression analysis was then used to assess factors associated with dietary supplements intake. Moreover, and to evaluate the impact of dietary supplements on overall survival among respondents with cancer, multivariable Cox regression analysis was conducted. A total of 49,387 respondents were included in the current analysis, including a total of 4,575 respondents with cancer. Among respondents with cancer, 3,024 (66.1%) respondents have reported the use of dietary supplements; while 1,551 (33.9%) did not report the use of dietary supplements. Using multivariable logistic regression analysis, factors associated with the use of dietary supplements included older age (OR: 1.028; 95% CI: 1.027-1.030); white race (OR for black race vs. white race: 0.67; 95% CI: 0.63-0.72); female gender (OR for males vs. females: 0.56; 95% CI: 0.53-0.59), higher income (OR: 1.13; 95% CI: 1.11-1.14), higher educational level (0.59; 95% CI: 0.56-0.63), better self-reported health (OR: 1.36; 95% CI: 1.17-1.58), health insurance (OR: 1.35; 95% CI: 1.27-1.44), and history of cancer (OR: 1.20; 95% CI: 1.10-1.31). Using multivariable Cox regression analysis and within the subgroup of respondents with a history of cancer, the use of dietary supplements was not found to be associated with a difference in overall survival (HR: 1.13; 95% CI: 0.98-1.30). Dietary supplement use has increased in the past two decades among individuals with cancer in the United States, and this increase seems to be driven mainly by an increase in the use of vitamins. The use of dietary supplements was not associated with any improvement in overall survival for respondents with cancer in the current study cohort.

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