AACT Herbal Dietary Supplement Section Abstracts November 2020

1. Are side effects of cannabidiol (CBD) products caused by tetrahydrocannabinol (THC) contamination? Lachenmeier DW, Habel S, Fischer B, Herbi F, Zerbe Y, Bock V, Rajcic de Rezende T, Walch SG, Sproll C.

F1000Res. 2019 Aug 8;8:1394. doi: 10.12688/f1000research.19931.3. eCollection 2019.

Cannabidiol (CBD)-containing products are widely marketed as over the counter products, mostly as food supplements, to avoid the strict rules of medicinal products. Side-effects reported in anecdotal consumer reports or during clinical studies were first assumed to be due to hydrolytic conversion of CBD to psychotropic Δ 9-tetrahydrocannabinol (Δ 9-THC) in the stomach after oral consumption. However, research of pure CBD solutions stored in simulated gastric juice or subjected to various storage conditions such as heat and light with specific liquid chromatographic/tandem mass spectrometric (LC/MS/MS) and ultra-high pressure liquid chromatographic/quadrupole time-of-flight mass spectrometric (UPLC-QTOF) analyses was unable to confirm THC formation. Another hypothesis for the side-effects of CBD products may be residual Δ 9-THC concentrations in the products as contamination, because most of them are based on crude hemp extracts containing the full spectrum of cannabinoids besides CBD. Analyses of 67 food products of the German market (mostly CBD oils) confirmed this hypothesis: 17 products (25%) contained Δ 9-THC above the lowest observed adverse effects level (2.5 mg/day). Inversely, CBD was present in the products below the no observed adverse effect level. Hence, it may be assumed that the adverse effects of some commercial CBD products are based on a low-dose effect of Δ 9-THC and not due to effects of CBD itself. The safety, efficacy and purity of commercial CBD products is highly questionable, and all of the products in our sample collection showed various non-conformities to European food law such as unsafe Δ 9-THC levels, full-spectrum hemp extracts as non-approved novel food ingredients, non-approved health claims, and deficits in mandatory food labelling requirements. In view of the growing market for such lifestyle products, the effectiveness of the instrument of food business operators' own responsibility for product safety must obviously be challenged.

DOI: 10.12688/f1000research.19931.3
PMCID: PMC7029751
PMID: 32117565 [Indexed for MEDLINE]

2. Dietary Supplement Use in Children and Adolescents Aged ≤19 Years - United States, 2017-2018. Stierman B, Mishra S, Gahche JJ, Potischman N, Hales CM.

MMWR Morb Mortal Wkly Rep. 2020 Oct 30;69(43):1557-1562. doi: 10.15585/mmwr.mm6943a1.

Dietary supplement use is common among children and adolescents. During 2013-2014, approximately one third of children and adolescents (persons aged ≤19 years) in the United States were reported to use a dietary supplement in the past 30 days, and use varied by demographic characteristics (1,2). Dietary supplements can contribute substantially to overall

nutrient intake, having the potential to both mitigate nutrient shortfalls as well as to lead to nutrient intake above recommended upper limits (3). However, because nutritional needs should generally be met through food consumption according to the 2015-2020 Dietary Guidelines for Americans, only a few dietary supplements are specifically recommended for use among children and adolescents and only under particular conditions (4). The most recently released data from the National Health and Nutrition Examination Survey (NHANES) during 2017-2018 were used to estimate the prevalence of use among U.S. children and adolescents of any dietary supplement, two or more dietary supplements, and specific dietary supplement product types. Trends were calculated for dietary supplement use from 2009-2010 to 2017-2018. During 2017-2018, 34.0% of children and adolescents used any dietary supplement in the past 30 days, with no significant change since 2009-2010. Use of two or more dietary supplements increased from 4.3% during 2009-2010 to 7.1% during 2017-2018. Multivitamin-mineral products were used by 23.8% of children and adolescents, making these the products most commonly used. Because dietary supplement use is common, surveillance of dietary supplement use, combined with nutrient intake from diet, will remain an important component of monitoring nutritional intake in children and adolescents to inform clinical practice and dietary recommendations.

DOI: 10.15585/mmwr.mm6943a1
PMCID: PMC7641005
PMID: 33119556 [Indexed for MEDLINE]

3. Taking Stock of Dietary Supplements' Harmful Effects on Children, Adolescents, and Young Adults. Or F, Kim Y, Simms J, Austin SB.

J Adolesc Health. 2019 Oct;65(4):455-461. doi: 10.1016/j.jadohealth.2019.03.005. Epub 2019 Jun 5.

PURPOSE: The aim of the study was to evaluate the relationship between supplement categories and adverse events in children, adolescents, and young adults. METHODS: This is a retrospective observational study using adverse event reports between January 2004 and April 2015 in the U.S. Food and Drug Administration Adverse Event Reporting System on food and dietary supplements database. We quantified the relative risks for severe medical events of dietary supplements sold for various functions relative to vitamins among individuals aged between 0 and 25 years. Severe medical events include death, disability, life-threatening events, hospitalization, emergency room visit, and/or required intervention to prevent permanent disability. RESULTS: There were 977 single-supplement-related adverse event reports affecting individuals aged between 0 and 25 years over 11 years (50.6% female; age: mean = 16.5 years, standard deviation = 7.5 years). Supplements sold for muscle building (risk ratio [RR] = 2.7; 95% confidence interval [CI] = 1.9-4.0), energy (RR = 2.6; 95% CI = 1.9-3.6), and weight loss (RR = 2.6; 95% CI = 1.9-3.4) were associated with almost three times the risk for severe medical events compared with vitamins. CONCLUSIONS: Consumption of dietary supplements sold for weight loss, muscle building, and energy involved increased risks for severe medical events compared with vitamins. Proactive enforcement of regulations is needed to reduce access and consumption among children, adolescents, and young adults.

DOI: 10.1016/j.jadohealth.2019.03.005
PMID: 31176525 [Indexed for MEDLINE]

4. Serious Adverse Events Reported with Dietary Supplement Use in the United States: A 2.5 Year Experience. Schmitz SM MD, MPH, Lopez HL MD, MS, Mackay D ND, Nguyen H BS, Miller PE BS.

J Diet Suppl. 2020;17(2):227-248. doi: 10.1080/19390211.2018.1513109. Epub 2018 Dec 4.

Dietary supplement marketers assure the safety of their products by complying with current good manufacturing practices and a host of federal regulations, including those enforced by the Food and Drug Administration (FDA). Post-market surveillance is a key part of identifying safety problems associated with dietary supplement products. FDA requires dietary supplement marketers to provide a domestic address or phone number on product labels for consumers, family members, or health care professionals to report adverse events (AEs) associated with product use and to report all serious adverse events (SAEs) to the agency within 15 business days of receipt. We aimed to evaluate the characteristics of AEs reported with dietary supplement use, including dietary supplement type and Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) that occur with reported SAEs. A total of 41,121 unique adverse event cases reported to two large, U.S.-based dietary supplement marketers in a 2.5-year period (March 1, 2014-August 31, 2016) were assessed for seriousness using established criteria. Each SAE was assigned one or more MedDRA preferred terms and system organ classes (SOC). The types of supplements most responsible for SAEs were assessed. Of the 41,121 AE cases reported, 203 (0.48%) were SAEs. SAEs tended to occur with products marketed for weight loss (69.0%) and glycemic control (19.2%). SAEs occurred most commonly in the cardiovascular, gastrointestinal, and nervous system disorder SOCs. The percentage of SAEs reported to dietary supplement marketers is low, predominantly among consumers of two types of supplements. Further study is needed among a larger cohort of supplement users to determine causal associations between types of supplement products and serious adverse events.

DOI: 10.1080/19390211.2018.1513109
PMID: 30513022 [Indexed for MEDLINE]

5. Adverse Events Reported to the United States Food and Drug Administration Related to Caffeine-Containing Products. Jagim AR, Harty PS, Fischer KM, Kerksick CM, Erickson JL.

Mayo Clin Proc. 2020 Aug;95(8):1594-1603. doi: 10.1016/j.mayocp.2020.02.033.
Comment in Mayo Clin Proc. 2020 Aug;95(8):1562-1564.

OBJECTIVE: To examine differences in the frequency and severity of federally reported adverse events between caffeine-containing and non-caffeine-containing products while also identifying the category of caffeine-containing products associated with the highest frequency and severity of adverse events. PATIENTS AND METHODS: All adverse event reports that met specified eligibility criteria and were submitted to the Center for Food Safety and Applied Nutrition Adverse Event Reporting System between January 1, 2014, and June 29, 2018, were extracted. In this retrospective observational study, the most severe adverse event experienced, an ordinal

variable, was categorized into death, life-threatening, hospitalization/disability, and emergency department visit. A nonproportional odds model was used to compare the odds of caffeine-containing products being associated with more severe adverse events relative to a noncaffeine group. The analysis is of data only from those reporting adverse events and may or may not be representative of the entire population exposed to these products, which is not known from the examined data. RESULTS: Energy and preworkout products saw a significant increase in the odds of the adverse event experienced being death rather than the other less severe outcomes relative to the noncaffeinated group. Those products, along with weight loss products, had greater odds of the adverse event being death or life-threatening vs the less severe outcomes relative to the noncaffeinated group. CONCLUSION: Caffeine-containing products have a greater association with severe adverse events compared with non-caffeine-containing products. Exposure to preworkout and weight loss products had greater odds of being associated with a more serious adverse event relative to noncaffeinated products. Health care practitioners should use these outcomes to better inform and educate patients about the many factors related to caffeine intake and adverse outcomes.

DOI: 10.1016/j.mayocp.2020.02.033
PMID: 32753134 [Indexed for MEDLINE]

6. Pharmacology of Herbal Sexual Enhancers: A Review of Psychiatric and Neurological Adverse Effects. Brunetti P, Lo Faro AF, Tini A, Busardò FP, Carlier J.

Pharmaceuticals (Basel). 2020 Oct 14;13(10):309. doi: 10.3390/ph13100309.

Sexual enhancers increase sexual potency, sexual pleasure, or libido. Substances increasing libido alter the concentrations of specific neurotransmitters or sex hormones in the central nervous system. Interestingly, the same pathways are involved in the mechanisms underlying many psychiatric and neurological disorders, and adverse reactions associated with the use of aphrodisiacs are strongly expected. However, sexual enhancers of plant origin have gained popularity over recent years, as natural substances are often regarded as a safer alternative to modern medications and are easily acquired without prescription. We reviewed the psychiatric and neurological adverse effects associated with the consumption of herbal aphrodisiacs Areca catechu L., Argemone Mexicana L., Citrus aurantium L., Eurycoma longifolia Jack., Lepidium meyenii Walp., Mitragyna speciosa Korth., Panax ginseng C. A. Mey, Panax quinquefolius L., Pausinystalia johimbe (K. Schum.) Pierre ex Beille, Piper methysticum G. Forst., Ptychopetalum olacoides Benth., Sceletium tortuosum (L.) N. E. Brown, Turnera diffusa Willd. ex. Schult., Voacanga africana Stapf ex Scott-Elliot, and Withania somnifera (L.) Dunal. A literature search was conducted on the PubMed, Scopus, and Web of Science databases with the aim of identifying all the relevant articles published on the issue up to June 2020. Most of the selected sexual enhancers appeared to be safe at therapeutic doses, although mild to severe adverse effects may occur in cases of overdosing or self-medication with unstandardized products. Drug interactions are more concerning, considering that herbal aphrodisiacs are likely used together with other plant extracts and/or pharmaceuticals. However, few data are available on the side effects of several plants included in this review, and more clinical studies with controlled administrations should be conducted to address this issue.

DOI: 10.3390/ph13100309
PMCID: PMC7602496
PMID: 33066617

7. EBCOG position statement about the use of herbal medication during pregnancy. Savona-Ventura C, Mahmood T.

Eur J Obstet Gynecol Reprod Biol. 2020 Jan;244:38-39. doi: 10.1016/j.ejogrb.2019.10.008. Epub 2019 Nov 1.

Pregnant women often resort to herbal medication to ameliorate the disturbing symptoms associated with pregnancy in the mistaken belief that these are safe and carry no potential harmful effects to the developing fetus. Healthcare personnel must be cognizant of the potential adverse side effects of these substances to be able to better advise their patients.

DOI: 10.1016/j.ejogrb.2019.10.008
PMID: 31734622 [Indexed for MEDLINE]

8. Presence of Piracetam in Cognitive Enhancement Dietary Supplements. Cohen PA, Zakharevich I, Gerona R.

JAMA Intern Med. 2020 Mar 1;180(3):458-459. doi: 10.1001/jamainternmed.2019.5507.

This study analyzes 5 brands of dietary supplements to determine the prevalence of the nootropic drug piracetam in supplements advertised as cognitive enhancers.

DOI: 10.1001/jamainternmed.2019.5507
PMCID: PMC6902196
PMID: 31764936 [Indexed for MEDLINE]

9. Amphetamine-Like Neurochemical and Cardiovascular Effects of a -Ethylphenethylamine Analogs Found in Dietary Supplements. Schindler CW, Thorndike EB, Partilla JS, Rice KC, Baumann MH.

J Pharmacol Exp Ther. 2020 Oct 20:JPET-AR-2020-000129. doi: 10.1124/jpet.120.000129. Online ahead of print.

Dietary supplements often contain additives not listed on the label, including a-ethyl homologs of amphetamine such as N, a-diethylphenethylamine (DEPEA). Here we examined the neurochemical and cardiovascular effects of a-ethylphenethylamine (AEPEA), N-methyl-a-ethylphenethylamine (MEPEA), and DEPEA as compared to the effects of amphetamine. All drugs were tested in vitro using uptake inhibition and release assays for monoamine transporters. As expected, amphetamine acted as a potent and efficacious releasing agent at dopamine transporters (DAT) and norepinephrine transporters (NET) in vitro AEPEA and MEPEA were also releasers at catecholamine transporters, with greater potency at NET than DAT. DEPEA displayed fully efficacious release at NET but weak partial release at DAT (i.e., 40% of maximal

effect). In freely moving, conscious male rats fitted with biotelemetry transmitters for physiological monitoring, amphetamine (0.1-3.0 mg/kg, sc) produced robust dose-related increases in blood pressure (BP), heart rate (HR), and motor activity. AEPEA (1-10 mg/kg, sc) produced significant increases in BP but not HR or activity, whereas DEPEA and MEPEA (1-10 mg/kg, sc) increased BP, HR, and activity. In general, the phenethylamine analogs were approximately 10-fold less potent than amphetamine. Our results show that a-ethylphenethylamine analogs are biologically active. While less potent than amphetamine, they produce cardiovascular effects that could pose risks to humans. Given that MEPEA and DEPEA increased locomotor activity, these substances may also have significant abuse potential. Significance Statement The a-ethyl homologs of amphetamine have significant cardiovascular, behavioral and neurochemical effects in rats. Given that these compounds are often not listed on the ingredient label of dietary supplements, these compounds could pose a risk to humans using these products.

DOI: 10.1124/jpet.120.000129
PMID: 33082158

10. Death from Poppy Tea Consumption. Bishop-Freeman SC, Fox L, Winecker RE, Hudson JS.

J Anal Toxicol. 2020 Oct 12;44(7):734-740. doi: 10.1093/jat/bkaa093.

The historical practice of brewing poppy tea for its opioid-like effects is reoccurring with modern-day substance users. We present four postmortem cases with toxicology results that serve as case studies for the potential hazards of poppy tea ingestion. There is limited information regarding the risks of this practice due to the variability of the morphine content of the opium exuded from the plant. While internet tea recipes offer guidance, differences in poppy cultivation, washing, and infusing time are some of the reasons why the beverage may contain inconsistent and clinically significant alkaloid concentrations for each preparation. Variability in opioid tolerance along with additional drugs taken will impact the overall degree of toxicity experienced from the opiates in the tea. Advancements in the genetic modification of the poppy plant could greatly alter the ratio of alkaloids seen in biological fluids and will be highly dependent on the source of the poppy product. The blood concentrations of free morphine and free codeine in cases 1-3 where the toxicity from the tea was considered the primary cause of death were 0.94 and 0.11 mg/L, 0.62 and 0.034 mg/L, and 0.16 and 0.010 mg/L, respectively. The urine concentrations of morphine and codeine were 13 and 0.94 mg/L in case 1 and 16 and 1.6 mg/L in case 2, respectively. The opium alkaloids thebaine and laudanosine were identified qualitatively by our routine organic base/neutral drug detection procedure.

DOI: 10.1093/jat/bkaa093
PMID: 33043985 [Indexed for MEDLINE]

11. Calotropis poisoning with severe cardiac toxicity A case report. Iyadurai R, Gunasekaran K, Jose A, Pitchaimuthu K.

J Family Med Prim Care. 2020 Aug 25;9(8):4444-4447. doi: 10.4103/jfmpc.jfmpc_783_20. eCollection 2020 Aug.

Calotropis is a widely prevalent plant in the Indian Subcontinent. The extract and various parts of the plant are used by traditional healers for treating miscellaneous diseases. All parts of the plants are toxic; there are many case reports of gastrointestinal, cutaneous and ocular toxicity with Calotropis. The plant contains Cardenolide glycosides which have Digoxin like effects and can cause severe cardiotoxicity. We report a patient who developed cardiovascular collapse after oral ingestion and cutaneous application of Calotropis following snake bite by a traditional healer, this case thus highlights the potential cardiotoxicity of Calotropis.

DOI: 10.4103/jfmpc.jfmpc_783_20
PMCID: PMC7586564
PMID: 33110881

12. Death in Children After Atractylis gummifera L. Poisoning in Morocco-Report of Three Cases and Review of Literature. Nya S, Abouzahir H, Dami A, Saif Z, Najdi A, Belhouss A, Benyaich H.

Am J Forensic Med Pathol. 2020 Oct 29. doi: 10.1097/PAF.0000000000000633. Online ahead of print.

BACKGROUND: Atractylis gummifera L. is a poisonous thistle plant that grows in the Mediterranean regions especially in northern Africa like Morocco and southern Europe. It has been used frequently to treat some diseases in traditional medicine, and its ingestion is a common cause of fatal poisoning. Here, we report 3 death cases in children after accidental ingestion of the Atractylis gummifer L. CASES REPORTS: We report 3 cases of death in children after accidental ingestion of the poisonous plant Atractylis gummifer L. The poisoned children were admitted to hospital in deteriorated general state with clinical symptoms, such as nausea, vomiting, epigastric, and abdominal pain, diarrhea, followed by coma. However, they died a few hours later. The postmortem investigations were performed, and the diagnosis of Atractylis gummifer L. poisoning was confirmed by toxicological examination (chromatography), the latter showed the presence of atractyloside (potassium atractylate), a toxic compound of the plant Atractylis gummifera L.Atractylis gummifer L. poisoning was discussed with review through the literature. CONCLUSIONS: Through the presented cases, we show that Atractylis gummifera L. poisoning remains a health problem that involves children in Morocco, where the plant grows spontaneously. Thus, teaching children to recognize dangerous plants will be helpful to prevent accidental ingestion.

DOI: 10.1097/PAF.0000000000000633
PMID: 33136556

13. An Unusual Culprit of Drug-Induced Pancreatitis. Weissman S, Lo A, Patel R, Mehta TI, Singh V, Aziz M, Belyayeva A, Cherian J, Amrutiya V, Atoot A, Hassan A, Sotiriadis J, Atoot A, Tabibian JH.

Dig Dis Sci. 2020 May;65(5):1549-1552. doi: 10.1007/s10620-019-05864-4. Epub 2019 Sep 30.

Acute pancreatitis is a potentially life-threatening condition and a common indication for hospitalization. Gallstones and alcohol account for the majority of cases, but various, less appreciated etiologies also exist. In recent years, medi-cations have been increasingly recognized as an etiologic culprit for acute pancreatitis, though still only responsible for 0.1–2% of all cases [1]. Albeit very rare, case reports have also implicated homeopathic medications as potential causes of acute pancreatitis [2, 3]. Here we present the case of a 51-year-old man who experienced an episode of acute pancreatitis secondary to Sambucol, an extract of black elderberry (Sambucus mexicana) often used to treat flu-like symptoms and provide immunological benefits [4]. This represents, to our knowledge, the first case of black elderberry-induced acute pancreatitis and serves to illus-trate the importance of maintaining a broad differential and taking a thorough history, including homeopathic and other alternative remedies, in patients presenting with acute pan-creatitis of unclear etiology.

DOI: 10.1007/s10620-019-05864-4
PMID: 31571105 [Indexed for MEDLINE]

14. Gardenia Fruit-Related Blue-Gray Skin Pigmentation. Mizawa M, Andoh T, Shimizu T.

JAMA Dermatol. 2020 Mar 1;156(3):351-353. doi: 10.1001/jamadermatol.2019.4682.

Gardenia Fruit-Related Blue-Gray Skin Pigmentation.

DOI: 10.1001/jamadermatol.2019.4682
PMID: 32022833 [Indexed for MEDLINE]

Gardenia fruit is widely used in herbal medicine, and it has choleretic, sedative, diuretic, anti-inflammatory, and antipyretic effects.[1] An ingredient of gardenia fruit is attracting attention as a possible cause of mesenteric phlebosclerosis, which is characterized by fibrotic change or calcification of the mesenteric vein and the bronze coloration of the colonic membrane.[2] Mesenteric phlebosclerosis may cause abdominal pain, stool abnormalities, and bowel obstruction, but it is often asymptomatic. It is suggested that genipin, a metabolite of geniposide (the major ingredient of gardenia fruit) is involved in the bronze coloration. Herein, we describe a patient who took the extract of gardenia fruit for 7 years, developed skin pigmentation complicated with mesenteric phlebosclerosis.

15. Review: Usnic acid-induced hepatotoxicity and cell death. Kwong SP, Wang C.

Environ Toxicol Pharmacol. 2020 Nov;80:103493. doi: 10.1016/j.etap.2020.103493.
Epub 2020 Sep 19.

Increasing prevalence of herbal and dietary supplement-induced hepatotoxicity has been reported worldwide. Usnic acid (UA) is a well-known hepatotoxin derived from lichens. Since 2000, more than 20 incident reports have been received by the US Food and Drug Administration after

intake of UA containing dietary supplement resulting in severe complications. Scientists and clinicians have been studying the cause, prevention and treatment of UA-induced hepatotoxicity. It is now known that UA decouples oxidative phosphorylation, induces adenosine triphosphate (ATP) depletion, decreases glutathione (GSH), and induces oxidative stress markedly leading to lipid peroxidation and organelle stress. In addition, experimental rat liver tissues have shown massive vacuolization associated with cellular swellings. Additionally, various signaling pathways, such as c-JNK N-terminal kinase (JNK), store-operated calcium entry, nuclear erythroid 2-related factor 2 (Nrf2), and protein kinase B/mammalian target of rapamycin (Akt/mTOR) pathways are stimulated by UA causing beneficial or harmful effects. Nevertheless, there are controversial issues, such as UA-induced inflammatory or anti-inflammatory responses, cytochrome P450 detoxifying UA into non-toxic or transforming UA into reactive metabolites, and unknown mechanism of the formation of vacuolization and membrane pore. This article focused on the previous and latest comprehensive putative mechanistic findings of UA-induced hepatotoxicity and cell death. New insights on controversial issues and future perspectives are also discussed and summarized.

DOI: 10.1016/j.etap.2020.103493
PMID: 32961280

16. Acute Liver Failure Caused by Use of Fat Burner: A Case Report. Ferreira GSA, Watanabe ALC, Trevizoli NC, Jorge FMF, Diaz LGG, Couto CF, Lima LV, Raupp DRL, Araujo BE.

Transplant Proc. 2020 Jun;52(5):1409-1412. doi: 10.1016/j.transproceed.2020.01.072. Epub 2020 Mar 17.

Acute liver failure is a rare condition consisting of abrupt and extensive hepatocyte injury, leading to significant liver dysfunction associated with a high mortality. Liver transplantation is the most effective treatment in severe cases. The most common cause of acute liver failure in Western countries is drug-induced liver injury caused by prescription drugs and herbal and dietary supplements. Thermogenics, or fat burners, are a category of dietary supplements that claim to increase the resting metabolic rate, leading to weight loss. There are previous reports of acute liver failure associated with specific thermogenic formulations. We report the case of a 36-year-old male patient who developed jaundice 7 days after he started taking a thermogenic dietary supplement (Thermo Gun), with progressive deterioration of hepatic function and development of hepatic encephalopathy 19 days after the beginning of the symptoms. He had a Model for End-Stage Liver Disease score of 38 and fulfilled 4 of the King's College Criteria for poor prognosis in patients with acute liver failure. He underwent liver transplantation, receiving a graft from a cadaveric donor, and is alive with good liver graft function 2 years after the transplant. No possible causes for acute liver injury were identified other than the use of the supplement, which contained N-acetyl-L-tyrosine; 1,3,7-trimenthylxanthine; white willow; and 1-hydroxypholedrine. We found no previous reports in the literature of acute liver failure associated with those particular substances. This manuscript is compliant with the Helsinki Congress and the Istanbul Declaration.

DOI: 10.1016/j.transproceed.2020.01.072

PMID: 32192741 [Indexed for MEDLINE]

17. Kratom induced severe cholestatic liver injury histologically mimicking primary biliary cholangitis: A case report. Gandhi D, Ahuja K, Quade A, Batts KP, Patel L.

World J Hepatol. 2020 Oct 27;12(10):863-869. doi: 10.4254/wjh.v12.i10.863.

BACKGROUND: Kratom is a psychoactive substance that is isolated from the plant Mitragyna speciosa. The leaves can be chewed fresh or dried, smoked, or infused similar to herbal teas. The plant leaves have been used by natives of Southeast Asia for centuries. The substance has been used for its stimulant activity at low doses, and as an opium substitute at higher doses due to a morphine like effect. CASE SUMMARY: A 37-year-old female with a history of depression and obesity (body mass index: 32) presented to emergency room with a week-long history of nausea, decreased appetite, fatigue, and two days of jaundice. On admission bilirubin was markedly elevated. Her condition was thought to be due to consumption of Kratom 2 wk before onset of symptoms. Liver biopsy showed changes mimicking primary biliary cholangitis. Patient's symptoms and jaundice improved quickly. CONCLUSION: The use of Kratom has been on the rise in recent years across the United States and Europe. Several case reports have associated adverse health impact of Kratom-containing products including death due to its ability to alter levels of consciousness. Only a few case reports have highlighted the hepatotoxic effects of Kratom. Even fewer reports exist describing the detailed histopathological changes.

DOI: 10.4254/wjh.v12.i10.863
PMCID: PMC7643221
PMID: 33200023

18. Biotin Interference and Laboratory Testing: Possible Implications/Ramifications for Emergency Medicine. Nowak RM, DeMasi D, Murn A, Neuenschwander J.

Ann Emerg Med. 2020 Sep;76(3):369-370. doi: 10.1016/j.annemergmed.2020.04.029.

DOI: 10.1016/j.annemergmed.2020.04.029
PMID: 32828334 [Indexed for MEDLINE]

19. Reliable identification and quantification of anabolic androgenic steroids in dietary supplements by using gas chromatography coupled to triple quadrupole mass spectrometry. Micalizzi G, Huszti K, Pálinkás Z, Mandolfino F, Martos É, Dugo P, Mondello L, Utczás M.

Drug Test Anal. 2020 Sep 22. doi: 10.1002/dta.2929. Online ahead of print.

The aim of the present research was the identification and quantification of specific anabolic androgenic steroids (AASs) and other sterane structured compounds in dietary supplements (DSs). The adulteration of DSs by these compounds is of a particular concern in athletes, because it might lead to a positive doping result. The research was focused on the optimization of a

highly sensitive and selective GC-based analytical strategy using triple quadrupole MS as detector. Chromatographic method and multiple reaction monitoring (MRM) transitions of 28 target compounds were optimized. Sample clean-up was carried out by using a solid phase extraction (SPE) procedure, while the derivatization of AASs was performed by using N-methyl-N-(trimethylsilyl)-trifluoroacetamide (MSTFA). The method was validated, and the following parameters were investigated: linearity range, limit of detection, accuracy, and precision expressed in terms of intra-day precision. The calibration curves were evaluated by using regression model and resulting in a good determination coefficients ($R2 \geq 0.9912$). The residuals were scattered randomly around zero. The limits of detection (LODs) were lower than 7.0 ng g-1 or ng ml-1 . The accuracy assessment was evaluated in different forms of DSs characterized by high sample-to-sample variability (liquid, powder, tablet, capsule, protein, and herbal-based). Intra-day assay precision was in all cases lower than 20%. The developed analytical method was successfully applied to the analysis of 67 commercially available dietary supplements. In five cases, one or more steroid-type compounds were found in the concentration of 5 ng g-1 -100 μg g-1 , which might result adverse analytical findings in athletes.

DOI: 10.1002/dta.2929
PMID: 32959986

20. Toxicokinetics and Toxicodynamics of Ayahuasca Alkaloids N,N-Dimethyltryptamine (DMT), Harmine, Harmaline and Tetrahydroharmine: Clinical and Forensic Impact. Brito-da-Costa AM, Dias-da-Silva D, Gomes NGM, Dinis-Oliveira RJ, Madureira-Carvalho Á.

Pharmaceuticals (Basel). 2020 Oct 23;13(11):E334. doi: 10.3390/ph13110334.

Ayahuasca is a hallucinogenic botanical beverage originally used by indigenous Amazonian tribes in religious ceremonies and therapeutic practices. While ethnobotanical surveys still indicate its spiritual and medicinal uses, consumption of ayahuasca has been progressively related with a recreational purpose, particularly in Western societies. The ayahuasca aqueous concoction is typically prepared from the leaves of the N,N-dimethyltryptamine (DMT)-containing Psychotria viridis, and the stem and bark of Banisteriopsis caapi, the plant source of harmala alkaloids. Herein, the toxicokinetics and toxicodynamics of the psychoactive DMT and harmala alkaloids harmine, harmaline and tetrahydroharmine, are comprehensively covered, particularly emphasizing the psychological, physiological, and toxic effects deriving from their concomitant intake. Potential therapeutic utility, particularly in mental and psychiatric disorders, and forensic aspects of DMT and ayahuasca are also reviewed and discussed. Following administration of ayahuasca, DMT is rapidly absorbed and distributed. Harmala alkaloids act as potent inhibitors of monoamine oxidase A (MAO-A), preventing extensive first-pass degradation of DMT into 3-indole-acetic acid (3-IAA), and enabling sufficient amounts of DMT to reach the brain. DMT has affinity for a variety of serotonergic and non-serotonergic receptors, though its psychotropic effects are mainly related with the activation of serotonin receptors type 2A (5-HT2A). Mildly to rarely severe psychedelic adverse effects are reported for ayahuasca or its alkaloids individually, but abuse does not lead to dependence or tolerance. For a long time, the evidence has pointed to potential psychotherapeutic benefits in the treatment of depression, anxiety, and substance abuse disorders; and although misuse of ayahuasca has been

diverting attention away from such clinical potential, research onto its therapeutic effects has now strongly resurged.

DOI: 10.3390/ph13110334
PMID: 33114119

21. Inhibition and induction of CYP enzymes in humans: an update. Hakkola J, Hukkanen J, Turpeinen M, Pelkonen O.

Arch Toxicol. 2020 Nov;94(11):3671-3722. doi: 10.1007/s00204-020-02936-7. Epub 2020 Oct 27.

The cytochrome P450 (CYP) enzyme family is the most important enzyme system catalyzing the phase 1 metabolism of pharmaceuticals and other xenobiotics such as herbal remedies and toxic compounds in the environment. The inhibition and induction of CYPs are major mechanisms causing pharmacokinetic drug-drug interactions. This review presents a comprehensive update on the inhibitors and inducers of the specific CYP enzymes in humans. The focus is on the more recent human in vitro and in vivo findings since the publication of our previous review on this topic in 2008. In addition to the general presentation of inhibitory drugs and inducers of human CYP enzymes by drugs, herbal remedies, and toxic compounds, an in-depth view on tyrosine-kinase inhibitors and antiretroviral HIV medications as victims and perpetrators of drug-drug interactions is provided as examples of the current trends in the field. Also, a concise overview of the mechanisms of CYP induction is presented to aid the understanding of the induction phenomena.

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PMCID: PMC7603454
PMID: 33111191

22. Important considerations for drugs, nutritional, and herbal supplements in pediatric solid organ transplant recipients. Pilch NA, Sell ML, McGhee W, Venkataramanan R.

Pediatr Transplant. 2020 Nov 3:e13881. doi: 10.1111/petr.13881. Online ahead of print.

Pediatric transplant recipients are on multiple prescription and non-prescription drugs. Many patients also use dietary, nutritional, and herbal supplements. This manuscript researched formulations of immunosuppressive drugs currently available and presents information on generic immunosuppressive drugs, commonly used non-prescription medications, dietary supplements, and herbal supplements. Immunosuppressive drugs are available in various formulations. Not all formulations are interchangeable. A number of FDA-approved generic formulations are available commercially in the United States. Generally generic formulations produce similar blood concentration vs time profiles compared to brand name products in adults and are considered to be bioequivalent. NSAID should be avoided in transplant patients due to potential drug interactions and increased risk associated with NSAID use; and appropriate doses of acetaminophen should be used for treatment of pain. Over-the-counter medications, such as

guaifenesin and dextromethorphan, antihistamine medications, including diphenhydramine, loratadine, cetirizine, and fexofenadine, can be safely used in pediatric solid organ transplant population. Many safe and effective over-the-counter options exist for stool softening and as laxative. Diarrhea can lead to an increase in calcineurin inhibitor levels. Food can alter the absorption of immunosuppressive drugs. Several herbal products can alter immune status of the patients or alter the blood concentration of immunosuppressive drugs or may produce renal or hepatic toxicities and should be avoided in pediatric transplant recipients. It is important to educate pediatric transplant recipients and their families about not only immunosuppressive drug therapy but also about non-prescription drugs, dietary, and herbal supplement use.

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PMID: 33142023

23. Arrhythmogenic foods - A growing medical problem. Woosley RL.

Trends Cardiovasc Med. 2020 Jul;30(5):310-312. doi: 10.1016/j.tcm.2019.08.007. Epub 2019 Aug 24.

Comment in: Trends Cardiovasc Med. 2020 Jul;30(5):313-314.

Arrhythmogenic ingredients in our diet such as mushrooms, licorice, toxic honey, liquid protein drinks, etc. have long been recognized as rare but important considerations in the differential diagnosis of arrhythmias. Anecdotal reports of torsades de pointes (TdP), arrhythmias and/or sudden death and small studies in normal subjects have suggested that simple ingredients such as grapefruit juice or ingredients in energy drinks marketed as dietary supplements could have direct arrhythmogenic actions, especially in patients with congenital long QT syndrome (cLQTS). Two recent studies that employed the industry-standard "thorough QT" trial design leave no doubt that grapefruit juice and some energy drinks can prolong the QTc interval and to exceed 500 msec. in some patients with cLQTS, a threshold known to signal imminent danger. These reports raise numerous clinically important questions such as which other patients may be at risk of arrhythmias. For example, patients with multiple clinical risk factors for TdP (hypokalemia, bradycardia, female sex, etc.) may be at risk from these and possibly other dietary ingredients ingested by millions of people each day. It is essential that further research evaluate the safety of these and similar food products and that vulnerable patients, especially those with cLQTS, be warned of this serious and emerging threat.

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PMID: 31477495 [Indexed for MEDLINE]

24. Review of Published Bitter Orange Extract and p-Synephrine Adverse Event Clinical Study Case Reports. Stohs SJ, Ray SD.

J Diet Suppl. 2020;17(3):355-363. doi: 10.1080/19390211.2019.1577936. Epub 2019 Mar 5.

p-Synephrine is the primary active ingredient in bitter orange (Citrus aurantium) extract and is present in other citrus species. This review summarizes all known case reports that have been published regarding adverse events associated with multi-ingredient dietary supplements containing bitter orange extract. A common characteristic of all the case studies was the assumption that if bitter orange extract is listed on the label of the product it is the most likely cause of any adverse effect, although in no case was the presence of p-synephrine determined or a direct link demonstrated. No case study reviewed the existing published literature, and all failed to note that numerous clinical studies have not demonstrated adverse effects at commonly used doses. Most studies did not indicate the composition of the product involved, and no study analyzed the product in question. In no case was a direct correlation between the event and p-synephrine made. Although p-synephrine and ephedrine have some structural similarity, the structural differences result in markedly different pharmacokinetic, physiological, and pharmacological effects, and thus the effects produced by ephedrine cannot be extrapolated to p-synephrine.

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