AACT Herbal Dietary Supplement Section Abstracts September 2020

1. Drug-Drug Interactions Between Cannabidiol and Lithium. Singh RK, Dillon B, Tatum DA, Van Poppel KC, Bonthius DJ.

Child Neurol Open. 2020 Aug 13;7:2329048X20947896. doi: 10.1177/2329048X20947896. eCollection 2020 Jan-Dec.

Epidiolex® (Cannabidiol- CBD) is approved for epilepsy associated with Dravet syndrome (DS) and Lennox-Gastaut syndrome (LGS) in patients over 2 years of age. Common side effects include somnolence and diarrhea. Recent studies have demonstrated interactions between cannabidiol and several other antiseizure medications. However, little is known regarding interactions between cannabidiol and other classes of medications. We discuss an autistic patient with LGS and significant psychiatric comorbidities who was being treated with multiple antiseizure and psychiatric medications, including lithium, when CBD was added to his medical regimen. Several weeks after initiating CBD therapy, he developed hypersomnolence, ataxia and decreased oral intake and was found to have lithium toxicity. Lithium was discontinued and his symptoms resolved. He remains on CBD and 2 other antiseizure medications, seizure-free with improved behavior. We review mechanisms of action and pharmacokinetics of CBD and discuss possible explanations for lithium toxicity in this patient.

DOI: 10.1177/2329048X20947896
PMCID: PMC7427002
PMID: 32851114

2. Cannabidiol (CBD) in Dietary Supplements: Perspectives on Science, Safety, and Potential Regulatory Approaches. Walker LA, Koturbash I, Kingston R, ElSohly MA, Yates CR, Gurley BJ, Khan I.

J Diet Suppl. 2020;17(5):493-502. doi: 10.1080/19390211.2020.1777244. Epub 2020 Jun 16.

The proliferation in the last few years of cannabidiol (CBD)-containing products in the U.S. markets has been greatly accelerated by changes in the regulatory environment, and by perceptions of their health benefits and presumed safety. The result has been aggressive marketing of many types of products, some of dubious quality, making or implying drug-type claims. The recent approval by the U.S. Food and Drug Administration (FDA) of CBD in the form of Epidiolex®, further complicates the regulatory picture. In addition, a number of studies suggest that, at least at high doses, there may be serious adverse effects or drug interactions associated with CBD. At present, CBD-containing products do not meet the strict definition of dietary supplements, but the FDA is continuing to consider some framework under which they might be allowed. Meanwhile, FDA has adopted a "risk-based" enforcement policy. Possible approaches to a new framework for regulation of CBD products as dietary supplements are discussed here, including expanded research emphasis, a robust corporate stewardship program, and a rigorous adverse event reporting program.

DOI: 10.1080/19390211.2020.1777244
PMID: 32543246

3. Cannabidiol and Other Cannabinoids: From Toxicology and Pharmacology to the Development of a Regulatory Pathway. Koturbash I, MacKay D.

J Diet Suppl. 2020;17(5):487-492. doi: 10.1080/19390211.2020.1796886. Epub 2020 Jul 25.

Cannabidiol (CBD) is a non-psychotropic constituent of Cannabis sativa that has grown in popularity during the last decade. CBD is the active component of EPIDIOLEX®, a U.S. Food and Drug Administration (FDA)-approved drug designed for the treatment of drug-resistant pediatric epileptic seizures associated with several rare syndromes. Furthermore, CBD has been proposed as a treatment for a number of other diseases for which clinical trials are now ongoing. Accumulating evidence indicates that the number of "CBD-containing" products, available mostly online, is growing exponentially. However, the U.S. FDA currently prohibits sales of CBD as a dietary supplement (DS) or ingredient in conventional food. Further, clear federal regulatory and quality oversight does not exist, which has led to an uncontrolled CBD market that, in turn, threatens to result in negative health effects experienced by a trusting public. Thus, there are open questions demanding answers in the very near future: For which medical purposes is CBD provably effective? Can it be used safely as a non-prescription product? At what level? Is a hemp extract that contains CBD a different ingredient than isolated CBD? Is CBD safe for everyone? What is a future path for hemp products with CBD as well as for other cannabinoids? Should CBD be allowed as a drug only, or is there a way for hemp extracts to be listed as a dietary supplement and food ingredient? This Special Issue, the first of its kind on CBD and other phytocannabinoids, is devoted to answering those and other questions by publishing articles in the fields of pharmacology, toxicology, and regulation.

DOI: 10.1080/19390211.2020.1796886
PMID: 32715797

4. Time for Change: Stepping Up the FDA's Regulation of Dietary Supplements to Promote Consumer Safety and Awareness. Kennett G.

J Law Health. 2019;33(1):47-78.

People are often looking for that quick fix when it comes to their health. With dietary supplements so readily available on the market, the public assume that they have been through rigorous testing. Dietary supplements are not tested as much as consumers believe. The Food and Drug Administration (FDA) does not initiate the same type of testing and analysis for supplements as it does for food, drink and medication. Given that people are now choosing supplemental meal replacements and the like, as opposed to whole foods, regulations drastically need to be stepped up in an effort to emphasise public safety. An authoritative body needs to stop manufacturers from taking advantage of an already vulnerable marketplace. I suggest a new form of regulation that takes the pressure away from the FDA and into the hands of someone who wholly focuses on the supplement market. Dietary supplements have revolutionised the "health" world; however, the only way that the market can keep growing is through enacting more stringent rules and regulations--at the same time allowing consumers to maintain their autonomy and freedom when purchasing.

PMID: 31841617 [Indexed for MEDLINE]

5. Drug-induced liver injury in older people. Lucena MI, Sanabria J, García-Cortes M, Stephens C, Andrade RJ.

Lancet Gastroenterol Hepatol. 2020 Sep;5(9):862-874. doi: 10.1016/S2468-1253(20)30006-6.

Drug-induced liver injury (DILI) is a rare, unpredictable, and potentially serious adverse reaction. It is induced by many drugs, herbs, and dietary supplements and represents a diagnostic challenge to clinicians. Older people (aged 65 years and older) are often polymedicated, and their declining physiological function affects drug pharmacokinetics. There is no consistent evidence that age is a general risk factor for DILI; however, age might be a risk factor with specific medications, with antimicrobials and cardiovascular drugs being the most likely medications to cause DILI in older people. Ageing influences DILI phenotypes, making cholestatic damage and chronic DILI more likely. In older people with DILI, comorbidities act as confounding causes and account for higher mortality unrelated to the liver. There are no specific therapies for DILI and supportive measures are still the mainstay of management. This Review highlights current advances and gaps in DILI epidemiology, mechanisms, and diagnosis that are pertinent to older individuals.

DOI: 10.1016/S2468-1253(20)30006-6
PMID: 32818465 [Indexed for MEDLINE]

6. Acute liver injury following turmeric use in Tuscany: an analysis of the Italian Phytovigilance database and systematic review of case reports. Lombardi N, Crescioli G, Maggini V, Ippoliti I, Menniti-Ippolito F, Gallo E, Brilli V, Lanzi C, Mannaioni G, Firenzuoli F, Vannacci A.

Br J Clin Pharmacol. 2020 Jul 13. doi: 10.1111/bcp.14460. Online ahead of print.

AIMS: Several cases of acute non-infectious cholestatic hepatitis recently appeared in Italy following consumption of Curcuma longa-containing dietary supplements. The aim of this research was to describe the Tuscan (Italy) cases of acute hepatitis and to compare them with similar cases of hepatotoxicity published in literature by performing a systematic review. METHODS: Records of Tuscan cases of acute hepatitis were obtained from the Italian Phytovigilance system. Each spontaneous report was analysed in order to collect all relevant clinical information of patients and information concerning the Curcuma longa-containing dietary supplement. Moreover, both the RUCAM and WHO-UMC systems were used to evaluate the causal relationship between the use of dietary supplement and acute hepatitis. A systematic literature review was performed in MEDLINE and Embase and all case-reports and case-series published in English were included. RESULTS: Seven cases of acute hepatitis occurring in Tuscany up to September 2019 are described. In all cases, hepatotoxicity was associated with Curcuma longa formulations with high bioavailability and high dosage of curcumin/curcuminoids. The causal relationship was also supported by the positive dechallenge observed in most cases. In the 22 cases identified through the systematic review, the majority of patients were concomitantly exposed to at least one other medication and 16 of them experienced a positive dechallenge. CONCLUSIONS: Within the frame of poorly controlled and regulated products, such as dietary supplements, the evaluation of Italian cases of Curcuma longa-induced acute hepatitis and the systematic review of literature confirmed the association between Curcuma longa and liver injury.

DOI: 10.1111/bcp.14460
PMID: 32656820

7. Turmeric supplement induced hepatotoxicity: a rare complication of a poorly regulated substance. Suhail FK, Masood U, Sharma A, John S, Dhamoon A.

Clin Toxicol (Phila). 2020 Mar;58(3):216-217. doi: 10.1080/15563650.2019.1632882. Epub 2019 Jul 4.

DOI: 10.1080/15563650.2019.1632882

PMID: 31271321 [Indexed for MEDLINE]

8. Acute Severe Liver Injury Related to Long-Term Garcinia cambogia Intake. Ferreira V, Mathieu A, Soucy G, Giard JM, Erard-Poinsot D.

ACG Case Rep J. 2020 Aug 11;7(8):e00429. doi: 10.14309/crj.0000000000000429. eCollection 2020 Aug.

Herbal and dietary supplements are frequently used as weight loss supplements. However, they account for 20% of drug-induced liver injury. Garcinia cambogia's (GC) active compound, hydroxycitric acid, can be found among those supplements. We report a 26-year-old woman who had been taking GC for 7 months when she presented with subacute liver failure and ultimately required a liver transplantation. This report highlights the risk of liver injury after long-term use of GC and demonstrates the importance of considering a close and prolonged monitoring of patients in a tertiary liver transplant center.

DOI: 10.14309/crj.0000000000000429
PMCID: PMC7423904
PMID: 32821764

9. Cryptogenic Intracranial Hemorrhagic Strokes Associated with Hypervitaminosis E and Acutely Elevated α-Tocopherol Levels. Le NK, Kesayan T, Chang JY, Rose DZ.

J Stroke Cerebrovasc Dis. 2020 May;29(5):104747. doi: 10.1016/j.jstrokecerebrovasdis.2020.104747. Epub 2020 Mar 6.

OBJECTIVES: Up to 41% of intracerebral hemorrhages (ICH) are considered cryptogenic despite a thorough investigation to determine etiology. Certain over-the-counter supplements may increase proclivity to bleeding, and we hypothesize that specifically vitamin E may have an association with ICH and acutely elevated serum levels of α-tocopherol. Our aim is to report 3 cases of recently admitted patients with hypervitaminosis E and otherwise cryptogenic ICH. METHODS: At our institution between January and December 2018, 179 patients were admitted with ICH with 73 imputed to be "cryptogenic" (without clear etiology as per Structural vascular lesions, Medication, Amyloid angiopathy, Systemic disease, Hypertension, or Undetermined and Hypertension, Amyloid angiopathy, Tumor, Oral anticoagulants, vascular Malformation, Infrequent causes, and Cryptogenic criteria). Of these, we found 3 (4.1%) clearly admitted to consistent use of vitamin E supplementation for which α-tocopherol levels were checked. We describe the clinical presentation and course of these patients and their etiologic and diagnostic evaluations including neuroimaging and α-tocopherol laboratory data. RESULTS: All patients in this series were consistently consuming higher than recommended doses of vitamin E and developed acute ICH. The first 2 patients both had subcortical (thalamic) intraparenchymal hemorrhages while the third had an intraventricular hemorrhage. Serum α-tocopherol levels in patient A, B, and C were elevated at 30.8, 46.7, and 23.3 mg/L, respectively (normal range 5.7-19.9 mg/L) with a mean of 33.6 mg/L. No clear alternate etiologies to their ICH could be conclusively determined despite thorough workups. CONCLUSIONS: In patients with cryptogenic ICH, clinicians should consider hypervitaminosis E and check serum α-tocopherol level during admission. Reviewing the patient's pharmacologic history, including over-the-counter supplements such as vitamin E, may help identify its association, and its avoidance in the future may mitigate risk. With its known vitamin K antagonism, hypo-prothrombinemic effect, cytochrome p-450 interaction, and antiplatelet activity, vitamin E may not be as benign as presumed. Its consumption in nonrecommended doses may increase ICH risk, which may be underestimated and under-reported.

DOI: 10.1016/j.jstrokecerebrovasdis.2020.104747
PMID: 32151478 [Indexed for MEDLINE]

10.Hypercalcemia from hypervitaminosis A in a child with autism. O'Neal S, Foster TP, Bhatt A, Lossius MN, Dayton K.

J Pediatr Endocrinol Metab. 2020 Jul 13:/j/jpem.ahead-of-print/jpem-2020-0075/jpem-2020-0075.xml. doi: 10.1515/jpem-2020-0075. Online ahead of print.

Objectives Vitamin A is essential for normal cellular physiology and is often taken as a dietary supplement. Hypervitaminosis A can lead to hypercalcemia by increasing osteoclasts and subsequent bone resorption. Dietary supplements including vitamin A are new popular treatment stategies for autism. Case presentation We report a five-year old boy with autism spectrum disorder presenting with severe abdominal pain and bilateral lower extremity pain, who was found to have persistent hypercalcemia due to hypervitaminosis A. The patient ingested over 700 times the recommended intake of Vitamin A per day for age. Retention of vitamin A in the liver and adipose tissue causes toxic levels of retinoids and hypercalcemia. Conclusions Acute treatment included intravenous rehydration, furosemide, and calcitonin. Pamidronate was the definitive treatment for hypercalcemia from hypervitaminosis A due to its osteoclast inhibition and long biologic half-life. Parents should be counseled on risks of toxicity and absence of evidence showing benefits of vitamin A therapy for autism.

DOI: 10.1515/jpem-2020-0075
PMID: 32658863

11. Bodybuilding supplements leading to copper toxicity, encephalopathy, fulminant hepatic failure and rhabdomyolysis. Richards JR, Scheerlinck PH, Owen KP, Colby DK.

Am J Emerg Med. 2020 Jun 2:S0735-6757(20)30460-5. doi: 10.1016/j.ajem.2020.05.096. Online ahead of print.

Millions of people worldwide use nutritional and dietary supplements, such as vitamins and minerals. These and other performance-enhancing substances are also used by high school, college, and professional athletes, bodybuilders, and amateur sports enthusiasts. The constituents of these supplements and their metabolites may be harmful and not listed on the product label. We present a case report of a 32-year-old bodybuilder using myriad nutritional, performance-enhancing, and weight-loss supplements with life-threatening encephalopathy, hepatic failure, rhabdomyolysis, and copper toxicity mimicking Wilson's disease. Emergency physicians and nurses should be aware of these potential deleterious effects and inquire about supplement use by patients with unexplained multiorgan failure. Family, friends, or acquaintances should be asked to bring the actual products to the hospital for analysis.

DOI: 10.1016/j.ajem.2020.05.096
PMID: 32532617

12. Death from cardiac glycoside "pong-pong" following use as weight-loss supplement purchased on Internet. Nordt SP, Hendrickson M, Won K, Miller MJ, Swadron SP, Cantrell FL.

Am J Emerg Med. 2020 Aug;38(8):1698.e5-1698.e6. doi: 10.1016/j.ajem.2020.04.063. Epub 2020 Apr 21.

Cerbera odollam or "pong-pong" tree contains cardiac glycosides similar to digoxin, oleander and yellow oleander. Cerbera odollam is a common method of suicide in South East Asia and has also been used as a weight loss supplement. We present a case of a 33-year-old female presenting with lethargy, vomiting, bradycardia, severe hyperkalemia of 8.9 mEq/L, slow atrial fibrillation followed by cardiovascular collapse following the ingestion of "pong-pong", the kernel of Cerbera odollam, as a weight loss supplement. Despite the administration of a total of nine vials of digoxin-specific Fab the patient could not be resuscitated. Clinicians should be aware of natural cardiac glycosides being uses as weight-loss agents and consider acute cardiac glycoside poisoning in patients with hyperkalemia, abnormal cardiovascular signs, symptoms and abnormal ECG findings.

DOI: 10.1016/j.ajem.2020.04.063
PMID: 32387148 [Indexed for MEDLINE]

13. An Intentional Aconite Overdose: A Case Report. Wood C, Coulson J, Thompson J, Bonner S.

J Crit Care Med (Targu Mures). 2020 May 6;6(2):124-129. doi: 10.2478/jccm-2020-0016. eCollection 2020 Apr.

BACKGROUND: Aconite is one of the most toxic known herbs, widely used for centuries as an essential Chinese medicine, but also for deliberate poisoning throughout history. Clinically indicated in herbal medicine for a range of ailments from headaches to muscle spasm, unfortunately the narrow therapeutic window may lead to a range of toxic presentations. The mechanism of action of the pharmacologically active compounds in Aconite relate to the activation of voltage gated sodium channels within a range of tissue including myocardial, neuronal and smooth muscle leading to persistent cellular activity. CASE PRESENTATION: We report on a rare case of a fifty year old male with intentional aconite overdose presenting with refractory cardiovascular instability from persistent life threatening arrhythmias, respiratory failure and seizure activity. CONCLUSION: An overview of Aconite, its history, pharmacological effects, treatment of overdose and outcomes is presented.

DOI: 10.2478/jccm-2020-0016
PMCID: PMC7216026
PMID: 32426520

14. A young man with orange hands. Constantinescu SM, Morelle J.

Eur J Intern Med. 2019 Oct;68:76. doi: 10.1016/j.ejim.2019.07.012. Epub 2019 Jul 30.

DOI: 10.1016/j.ejim.2019.07.012
PMID: 31375252 [Indexed for MEDLINE]

15. Herbal supplements interactions with oral oestrogen-based contraceptive metabolism and transport. Hlengwa N, Muller CJF, Basson AK, Bowles S, Louw J, Awortwe C.

Phytother Res. 2020 Jul;34(7):1519-1529. doi: 10.1002/ptr.6623. Epub 2020 Feb 3.

The increased use of herbal supplements as complementary or alternative medicines has become a clinical conundrum due to the potential for herb-drug interactions. This is exacerbated by an increased supply of new herbal supplements in the market claiming various health advantages. These herbal supplements are

available as over-the-counter self-medications. Herbal supplements are generally perceived as efficacious without side effects commonly associated with conventional drugs. However, despite regulations, claims related to their therapeutic effects are mostly unsupported by scientific evidence. These products often lack suitable product quality controls, labelled inadequately and with batch to batch variations, potentially compromising the safety of the consumer. Amongst health practitioners, the greatest concern is related to the lack of chemical characterization of the active compounds of the herbal supplements. The interaction between these different active components and their concomitant effects on other conventional drugs is generally not known. This review will focus on herbal supplements with the potential to effect pharmacokinetic and pharmacodynamic properties of oestrogen-based oral contraceptives. The use of herbal supplements for weight management, depression, and immune boosting benefits were selected as likely herbal supplements to be used concomitantly by women on oral contraceptives.

DOI: 10.1002/ptr.6623
PMID: 32017271 [Indexed for MEDLINE]

16. Safety Concerns of Skin, Hair and Nail Supplements in Retail Stores. Perez-Sanchez AC, Burns EK, Perez VM, Tantry EK, Prabhu S, Katta R.

Cureus. 2020 Jul 30;12(7):e9477. doi: 10.7759/cureus.9477.

BACKGROUND: Dietary supplements promoted for "skin, hair, and nail" health are becoming increasingly popular, although there is a lack of regulatory oversight. As no centralized database or repository for these supplements is available, the aim of this study was to provide an overview of supplements in a sample of retail stores, with a focus on safety concerns. METHODS: Dermatology supplements were defined as those that featured the words "skin", "hair", "nails", "beauty", or "glow" in the product name or tagline. Seven stores including drug, grocery, department, and cosmetics stores were surveyed within a three-mile radius. Data were extracted from the Supplement Facts label of each product. RESULTS: A total of 176 separate supplements were identified, containing a total of 255 distinct ingredients. These included vitamins, minerals, food extracts, botanicals, animal products (collagen, fish oils), amino acids, a hormone, and distinct microbial strains. CONCLUSION: This survey of "dermatology" supplements available in local retailers raised several safety concerns, including potential interactions, teratogenicity risks, a lack of independent third-party testing, lack of warning labels, and nutrient "overdosing". Given limited regulation of dietary supplements, it is imperative that physicians educate patients on the potential risks. These include risks related to supplement ingredients and dosages, as well as risks related to the lack of regulatory oversight. Patients must also be educated about the multiple gaps in our knowledge of dietary supplements, especially in terms of efficacy and long-term safety.

DOI: 10.7759/cureus.9477
PMCID: PMC7455464
PMID: 32874806

17. Aristolochia Herbs and Iatrogenic Disease: The Case of Portland's Powders. Tomlinson T, Fernandes A, Grollman AP.

Yale J Biol Med. 2020 Jun 29;93(2):355-363. eCollection 2020 Jun.

Aristolochia herbals have a 2500-year history of medicinal use. We focused this article on Portland's Powders, an 18th-century British gout medicine containing Aristolochia herbs. The powders constitute an 18th-century iteration of an herbal remedy, which was used, with variations, since at least the fifth century BCE. The use of Portland's Powders in Great Britain may appear to be an unusual choice for investigating a public health problem currently widespread in Asia. Yet it exemplifies long-term medicinal use of Aristolochia herbs, reflecting our argument that aristolochic acid nephropathy (AAN) is a historically persistent iatrogenic disease. Moreover, we provide compelling evidence that individuals taking Portland's Powders for gout would have ingested toxic quantities of aristolochic acid, which causes AAN and cancer. Several factors, including long history of use, latency of toxic effects, and lack of effective regulation, perpetuate usage of Aristolochia herbals to the present day.

PMCID: PMC7309663
PMID: 32607094

18. FDA Targets Illegal Hangover Relief. Voelker R.

JAMA. 2020 Sep 1;324(9):832. doi: 10.1001/jama.2020.15849.

DOI: 10.1001/jama.2020.15849
PMID: 32870284 [Indexed for MEDLINE]

19. Potential Risk of Food-Drug Interactions: Citrus Polymethoxyflavones and Flavanones as Inhibitors of the Organic Anion Transporting Polypeptides (OATP) 1B1, 1B3, and 2B1. Bajraktari-Sylejmani G, Weiss J.

Eur J Drug Metab Pharmacokinet. 2020 Jul 13. doi: 10.1007/s13318-020-00634-4. Online ahead of print.

BACKGROUND AND OBJECTIVES: Citrus flavonoids are not only components of daily nutrition, they are also promoted as dietary supplements and are important ingredients in traditional medicines. Interactions of flavonoids with synthetic drugs represent an often neglected issue. We therefore investigated in vitro whether the polymethoxyflavones nobiletin, sinensetin, and tangeretin and the flavonoid rutinosides didymin, hesperidin, and narirutin can inhibit human organic anion transporting polypeptides (OATP) 1B1, 1B3, and 2B1, which are important transporters mediating drug-drug and food-drug interactions. METHODS: Inhibition was investigated by quantifying the decreased uptake of the fluorescent OATP1B1 and OATP1B3 substrate 8-fluorescein-cAMP in HEK293 cells overexpressing OATP1B1 or OATP1B3 and of the fluorescent OATP2B1 substrate 4',5'-dibromofluorescein in HEK293 cells overexpressing OATP2B1. RESULTS: We demonstrate that all flavonoids investigated inhibit OATP2B1 in the lower micromolar range (IC50 between 1.6 and 14.2 μM), but only the polymethoxyflavones also inhibit OATP1B1 and 1B3 (IC50 between 2.1 and 21 μM). CONCLUSIONS: All flavonoids investigated might contribute to the intestinal OATP2B1-based interactions with drugs observed with citrus juices or fruits. In contrast, the concentration of the polymethoxyflavones after consumption of citrus juices or fruits is most likely too low to reach relevant systemic concentrations and thus to inhibit hepatic OATP1B1 and OATP1B3, but there might be a risk when they are consumed as medicines or as dietary supplements.

DOI: 10.1007/s13318-020-00634-4
PMID: 32661908