AACT Herbal Dietary Supplement Section Abstracts November 2019

1. A health risk for consumers: the presence of adulterated food supplements in the Netherlands. Biesterbos JWH, Sijm DTHM, van Dam R, Mol HGJ.

Food Addit Contam Part A Chem Anal Control Expo Risk Assess. 2019 Sep;36(9):1273-1288. doi: 10.1080/19440049.2019.1633020. Epub 2019 Jul 11.

The use of food supplements is increasing. They are marketed as beneficial for health, well-being, physical or mental condition and performance, or to prevent diseases. Producers add synthetic compounds or illicit herbal material to food supplements to claim desired effects. Claims made to support marketing without scientific evidence are, however, illegal. Intake of adulterated food supplements may lead to serious adverse effects. The aim of this paper is to report the results of analyses of (adulterated) food supplements conducted by the Netherlands Food and Consumer Product Safety Authority between October 2013 and October 2018. In total, 416 supplements were analysed of which 264 (64%) contained one or more pharmacological active substances or plant toxins, such as caffeine, synephrine, sildenafil, icariin, sibutramine, higenamine, hordenine, phenethylamine, methylsynephrine, DMAA, phenolphthalein, octopamine and ephedrine. When compared to dose levels that are considered safe, daily doses of the substances in the food supplements were sometimes much higher, causing a risk for consumers who are unaware of the presence of these pharmacologically active substances. In many cases, neither food nor medicines legislation (easily) enables enforcement actions. This means that some products containing pharmacologically active substances (i.e. synthetic medicines and their illicit analogues), stay available on the market. An undesirable situation because for many of these substances no detailed toxicity data are available.

DOI: 10.1080/19440049.2019.1633020
PMID: 31294678 [Indexed for MEDLINE]

2. Potential of Herb-Drug / Herb Interactions between Substrates and Inhibitors of UGTs Derived from Herbal Medicines. Liu D, Zhang L, Duan LX, Wu JJ, Hu M, Liu ZQ, Wang CY.

Pharmacol Res. 2019 Oct 30:104510. doi: 10.1016/j.phrs.2019.104510. [Epub ahead of print]

Herbal medicines are widely used as alternative or complementary therapies worldwide to treat and prevent chronic diseases. However, herbal medicines coadministration with therapeutic drugs may cause dramatic clinical herb-drug/herb interactions (HDIs/HHIs) that may result in low drug efficacy or serious toxic reactions. Phase II metabolism enzyme UDP glucuronosyltransferases (UGTs) play a significant detoxification role in vivo. Most drugs and non-drug xenobiotics undergo phase II metabolic transformations to be more polar compounds that are more easily excreted. Herbal medicines are a mixed and chemically varied group that includes flavonoids, stilbenes, coumarins, quinones, and terpenes, which are potential substrates and inhibitors of UGTs. Although increasing studies about glucuronidation metabolism and the inhibition toward UGTs of many herbal medicines have been reported, it is still difficult to determine which compounds from herbal medicines are substrates or inhibitors of UGTs. This article gives an overview of UGTs studies, which mainly focuses on glucuronidation of herbal constituents as substrates catalyzed by UGTs, potential herbal inhibitors for UGTs. We summarize the negative effects of UGT1A polymorphism and single nucleotide polymorphisms (SNPs), relevant clinical situations of HDIs/HHIs induced by inhibition of UGTs, and propose establishing classification criteria for inhibitors. Finally, we also discuss future research and strategic directions to advance the understanding of the potential HDIs/HHIs and suggest some additional studies revealing more information on UGT-mediated HDIs/HHIs.

DOI: 10.1016/j.phrs.2019.104510
PMID: 31678209

3. Roles of Renal Drug Transporter in Drug Disposition and Renal Toxicity. Yang X, Han L.

Adv Exp Med Biol. 2019;1141:341-360. doi: 10.1007/978-981-13-7647-4_7.

The kidney plays an important role in maintaining total body homeostasis and eliminating toxic xenobiotics and metabolites. Numerous drugs and their metabolites are ultimately eliminated in the urine. The reabsorption and secretion functions of the nephron are mediated by a variety of transporters located in the basolateral and luminal membranes of the tubular cells. In the past decade, many studies indicated that transporters play important roles in drug pharmacokinetics and demonstrated the impact of renal transporters on the disposition of drugs, drug-drug interactions, and nephrotoxicities. Here, we focus on several important renal transporters and their roles in drug elimination and disposition, drug-induced nephrotoxicities and potential clinical solutions.

DOI: 10.1007/978-981-13-7647-4_7
PMID: 31571169 [Indexed for MEDLINE]

4. Roles of Hepatic Drug Transporters in Drug Disposition and Liver Toxicity. Pan G

Adv Exp Med Biol. 2019;1141:293-340. doi: 10.1007/978-981-13-7647-4_6.

Hepatic drug transporters are mainly distributed in parenchymal liver cells (hepatocytes), contributing to drug's liver disposition and elimination. According to their functions, hepatic transporters can be roughly divided into influx and efflux transporters, translocating specific molecules from blood into hepatic cytosol and mediating the excretion of drugs and metabolites from hepatic cytosol to blood or bile, respectively. The function of hepatic transport systems can be affected by interspecies differences and inter-individual variability (polymorphism). In addition, some drugs and disease can redistribute transporters from the cell surface to the intracellular compartments, leading to the changes in the expression and function of transporters. Hepatic drug transporters have been associated with the hepatic toxicity of drugs. Gene polymorphism of transporters and altered transporter expressions and functions due to diseases are found to be susceptible factors for drug-induced liver injury (DILI). In this chapter, the localization of hepatic drug transporters, their regulatory factors, physiological roles, and their roles in drug's liver disposition and DILI are reviewed.

DOI: 10.1007/978-981-13-7647-4_6
PMID: 31571168 [Indexed for MEDLINE]

5. Complementary and Alternative Medicine-related Drug-induced Liver Injury in Asia. Philips CA, Augustine P, Rajesh S, Y PK, Madhu D.

J Clin Transl Hepatol. 2019 Sep 28;7(3):263-274. doi: 10.14218/JCTH.2019.00024. Epub 2019 Sep 2.

The use of complementary and alternative medicines (CAMs) for treatment of acute and chronic diseases is on the rise world over, especially in Asian countries, and mostly in China and India. Drug-induced liver injury (DILI) due to CAM is increasingly reported in the literature from multiple centers all around the world and with large-number patient series published from the West, mostly based on nation-wide DILI networks and multicenter collaboration. Comprehensive DILI networks are lacking among major Asian countries with high incidence of CAM practices. Chinese medical societies dealing with drug toxicity, CAM practice and hepatobiliary disease have adopted an integrated approach to establishing identification, diagnosis and treatment of CAM-related DILI, representing a systematic approach that could be iterated by other countries for improving patient outcomes. In this exhaustive review, we provide published data on CAM-related DILI in Asia, with detail on incidences along with analysis of patient

population and their clinical outcomes. Concise and clear discussion on commonly implicated CAM agents in major Asian countries and associated chemical and toxicology analyses as well as descriptions of liver biopsy findings are discussed with future directions.

DOI: 10.14218/JCTH.2019.00024
PMCID: PMC6783675
PMID: 31608219

6. Early Administration of N-acetylcysteine in the Treatment of Clove Oil Ingestion. Kim A, Farkas AN, Dewar SB, Abesamis MG.

J Pediatr Gastroenterol Nutr. 2018 Aug;67(2):e38-e39. doi: 10.1097/MPG.0000000000001988.

DOI: 10.1097/MPG.0000000000001988
PMID: 29601442 [Indexed for MEDLINE]

7. Danger of Herbal Tea: A Case of Acute Cholestatic Hepatitis Due to Artemisia annua Tea. Ruperti-Repilado FJ, Haefliger S, Rehm S, Zweier M, Rentsch KM, Blum J, Jetter A, Heim M, Leuppi-Taegtmeyer A, Terracciano L, Bernsmeier C.

Front Med (Lausanne). 2019 Oct 11;6:221. doi: 10.3389/fmed.2019.00221. eCollection 2019.

Background: Artemisia annua is a Chinese medicinal herb. Artemisinin-derivatives are recommended as part of a combination treatment for uncomplicated malaria. Herbal and dietary supplements (HDS) are increasingly used worldwide and HDS-induced liver injury is becoming a growing concern. Case Report: We present the first case of severe acute cholestatic hepatitis due to the intake of Artemisia annua tea as chemoprophylaxis for malaria in a patient returning from Ethiopia. The patients presented with jaundice, elevated transaminases, and parameters of cholestasis (total bilirubin 186.6 μmol/L, conjugated bilirubin 168.5 μmol/L). A liver biopsy showed a portal hepatitis with lymphocytic infiltration of the bile ducts and diffuse intra-canalicular and intra-cytoplasmic bilirubinostasis. The toxicologic analysis of the Artemisia tea revealed the ingredients arteannuin b, deoxyartemisin, campher, and scopoletin. There were no other identifiable etiologies of liver disease. The Roussel Uclaf Causality Assessment Method (RUCAM) score assessed a "probably" causal relationship. Sequencing of genes encoding for hepatic transporters for bile acid homeostasis (BSEP, MDR3, and FIC1) found no genetic variants typically associated with hereditary cholestasis syndromes. Normalization of bilirubin occurred 3 months after the onset of disease. Conclusion: The use of artemisinin-derivatives for malaria prevention is ineffective and potentially harmful and should thus be discouraged. Moreover, the case demonstrates our as yet inadequate understanding of the pathophysiology and susceptibility to HDS induced liver injury.

DOI: 10.3389/fmed.2019.00221
PMCID: PMC6798169
PMID: 31681778

8. A Callosal Catastrophe: Toxic Leukoencephalopathy Associated with Thermogenic Weight Loss Supplement Use. Mahdavi ZK, Narayan R, Mainali S, Greenberg BM, Aiyagari V, McDonagh DL.

Neurocrit Care. 2018 Dec;29(3):504-507. doi: 10.1007/s12028-017-0473-9.

BACKGROUND: The use of weight loss drugs and dietary supplements is common, but safety profiles for these drugs are largely unknown. Reports of toxicity have been published, and the use of these agents should be considered in clinical differential diagnoses. METHODS: We report the case of a patient with toxic leukoencephalopathy and hyponatremia associated with oral consumption of a thermogenic dietary supplement and essential oils. RESULTS: A 30-year-old woman presented after 2 days of headache, blurred vision, photophobia, vomiting, and hand spasms. She was taking a thermogenic dietary

supplement daily for 6 months as well as a number of essential oils. Examination revealed mild right sided ataxia and diffuse hyperreflexia. Neuroimaging demonstrated bilaterally symmetric T2 hyperintensities of the corpus callosum and periventricular white matter. Approximately 18 h after admission she became unresponsive with brief extensor posturing and urinary incontinence. She partially recovered, but 1 h later became unresponsive with dilated nonreactive pupils and extensor posturing (central herniation syndrome). She was intubated, hyperventilated, and given hyperosmotic therapy. Emergent imaging showed diffuse cerebral edema. Intracranial pressure was elevated but normalized with treatment; she regained consciousness the following day. She was extubated one day later and discharged on hospital day 5. She was seen 2 months later with no further symptoms and a normal neurologic examination. CONCLUSIONS: The pathophysiology of this patient's hyponatremia and toxic leukoencephalopathy is unknown. However, physicians must be aware of the association between thermogenic dietary supplements and toxic leukoencephalopathy. Vigilance for life-threatening complications including hyponatremia and cerebral edema is critical.

DOI: 10.1007/s12028-017-0473-9
PMID: 29047014 [Indexed for MEDLINE]

9. Ocular complications of Garcinia cambogia extract diet pills: Case report. Cho HK, Han YS, Park JM.

Eur J Ophthalmol. 2019 Oct 3:1120672119872364. doi: 10.1177/1120672119872364. [Epub ahead of print]

BACKGROUND: Garcinia cambogia contains hydroxycitric acid. Hydroxycitric acid is a potent competitive inhibitor of adenosine triphosphate citrate lyase which is a key enzyme in the synthesis of fatty acids. Hydroxycitric acid also regulates the level of serotonin. In these regards, hydroxycitric acid has been reported to exhibit weight loss activity. Adverse reactions of G. cambogia from numerous clinical studies demonstrated relatively mild reactions. However, there are some complications of G. cambogia reported in the past: acute liver injury, acute hepatitis, and hepatic failure. However, ocular complications of G. cambogia have not been reported yet. CASE PRESENTATION: A 35-year-old female visited our clinic with decreased vision in the left eye and ocular pain in both eyes for the last 6 days. She also complained of headache, dizziness, and nausea. She had taken G. cambogia extract more than the recommended dose. There was myopic shift with anterior chamber shallowing in both eyes, especially in the left eye. Moreover, swelling and retinal folds of peripapillary retinal nerve fiber layer and macula were observed in both eyes. These ocular complications of G. cambogia extract resolved after discontinuation of the extract and topical and oral steroid treatment. Herein, we report the first case of ocular complications of G. cambogia extract diet pill assessed with optical coherence tomography of optic disk and macula along with dual Scheimpflug analyzer. CONCLUSION: It is necessary that physicians dealing with obesity advice patients about possible visual disturbance of this extract when taken in overdose so that they can see an ophthalmologist immediately.

DOI: 10.1177/1120672119872364
PMID: 31578090

10. Unknowing ingestion of Brugmansia suaveolens leaves presenting with signs of anticholinergic toxicity: a case report. Jayawickreme KP, Janaka KVC, Subasinghe SASP.

J Med Case Rep. 2019 Oct 30;13(1):322. doi: 10.1186/s13256-019-2250-1.

BACKGROUND: Brugmansia suaveolens is the commonest species under the Solanacea ("Angels Trumpet" in English; "Attana" in Sinhalese) plant family in Sri Lanka. It contains alkaloids like scopolamine, atropine and hyoscyamine which can cause an anticholinergic toxindrome. There have been a few reported cases of accidental ingestion of Brugmansia seeds among children, seeds being the most

toxic part, but no such reported cases of Brugmansia leaves poisoning among adults. CASE PRESENTATION: A 60-year-old-female Sinhalese presented with acute confusion, delirium, and agitation. She had ingested a herbal drink made from leaves of an unknown plant from her garden prior to onset of symptoms. She had urinary retention, mydriasis and sinus tachycardia. She was managed supportively with activated charcoal and hydration and the delirium completely resolved within 15 hours. The presented unkown plant leaves were identified as Brugmansia suaveolens. CONCLUSION: Although seeds are the most toxic plant part in most cases of Brugmansia poisoning, leaves also have a significant degree of toxicity. It is important that medical professionals promptly recognize the features of anticholinergic syndrome, and have a high index to suspect Brugmansia poisoning and start prompt treatment. It is also important to improve awareness of toxic plants among the general community to prevent toxicities and fatalities.

DOI: 10.1186/s13256-019-2250-1
PMCID: PMC6819485
PMID: 31665073

11. Pill-Induced Esophagitis From Intake of Dietary Supplements. O'Donnell C, Tandon P, Govardhanam V, Habal F.

ACG Case Rep J. 2019 Jun 25;6(6):e00106. doi: 10.14309/crj.0000000000000106. eCollection 2019 Jun.

Cases of pill-induced esophagitis can be associated with significant acute symptoms leading to hospitalization and have resulted in mediastinal penetration and hemorrhage. Clinicians often consider the diagnosis in patients taking classically associated medications. However, because many patients take dietary supplements, it is important to consider these as a potential etiology in a patient presenting with esophageal symptoms. We present a case of pill-induced esophagitis in a 40-year-old woman after the ingestion of l-arginine, selenium, and vitamin E supplements. Literature review revealed 6 cases of l-arginine-induced esophagitis reported, and no previous cases associated with vitamin E or selenium.

DOI: 10.14309/crj.0000000000000106
PMCID: PMC6722335
PMID: 31616773

12. Case report of sudden death in a twin infant given melatonin supplementation: A challenging interpretation of postmortem toxicology. Shimomura ET, Briones AJ, Gordon CJ, Warren WS, Jackson GF.

Forensic Sci Int. 2019 Nov;304:109962. doi: 10.1016/j.forsciint.2019.109962. Epub 2019 Sep 26.

Melatonin (MEL) is a neurohormone in humans produced in a number of locations. Starting with the amino acid tryptophan, MEL is produced through a number of enzymatic steps that includes serotonin as an intermediate compound. The primary production of MEL is in the pineal gland located in the brain. It is directly associated with the the suprachiasmatic nucleus (SCN) located in the hypothalamus. In young and adult humans, the blood levels of MEL are typically in the picogram levels and produced in a cyclic schedule highly regulated by light detected in the retina by intrinsically photosensitive retinal ganglion cells (ipRGCs), resulting in production primarily during periods of darkness. During periods of light, MEL levels are typically very low or undetectable. Basal levels of MEL in infants have been observed to be either undetectable or also in the picogram levels, although some medical treatment has involved administration of exogenous MEL resulting in peak levels in the nanogram range. MEL is considered to be well tolerated and there have been limited reports of toxicity. In this case, an infant was found unresponsive and cause of death was ruled as Undetermined. Melatonin was detected in the peripheral blood at a concentration of 1,400ng/mL.

DOI: 10.1016/j.forsciint.2019.109962

PMID: 31610334

13. Cardiac toxicity of Triptergium wilfordii Hook F. may correlate with its inhibition to hERG channel. Zhao W, Xiao L, Pan L, Ke X, Zhang Y, Zhong D, Xu J, Cao F, Wu L, Chen Y.

Heliyon. 2019 Oct 9;5(10):e02527. doi: 10.1016/j.heliyon.2019.e02527. eCollection 2019 Oct.

Tripterygium wilfordii Hook F. (TWHF) is a Chinese traditional medicine with cardiac toxicities. However, the mechanism of acute cardiac toxicity is not very clear. By using patch clamp techniques, we found that 0.05 mg/ml and 0.1 mg/ml of the aqueous crude extract of TWHF inhibit 21.4 ± 1.6% and 86.7 ± 5.7% (n = 5) of hERG current Amplitudes (IhERG) respectively. We further found that Celastrol, one of main components of TWHF, inhibits hERG with an IC50 of 0.83 μM. Additional mutagenesis studies show that mutations of T623A, S624A and F656A significantly alter the inhibition and S624A has the strongest effect, supported by our docking model. Our data suggest that inhibition of hERG channel activity by Celastrol contributed to TWHF cardiotoxicity.

DOI: 10.1016/j.heliyon.2019.e02527
PMCID: PMC6812191
PMID: 31667381

14. Acute myocardial infarction in yellow oleander poisoning. Anandhi D, Prakash Raju KNJ, Basha MH, Pandit VR.

J Postgrad Med. 2018 Apr-Jun;64(2):123-126. doi: 10.4103/jpgm.JPGM_141_17.

Self-harm by consuming yellow oleander seeds has become more frequent in South Asian countries, especially Sri Lanka and in southern parts of India. Yellow oleander poisoning usually presents with gastrointestinal, cardiovascular, and neurological manifestations as well as electrolyte abnormalities. Cardiac effects can manifest as nearly any type of dysrhythmia and sudden death with very few premonitory signs. To our knowledge yellow oleander poisoning related acute myocardial infarction has not yet been reported. We report a 37-year-old man with yellow oleander poisoning who had normal sinus rhythm at presentation but within few hours developed acute ST-segment myocardial infarction.

DOI: 10.4103/jpgm.JPGM_141_17
PMCID: PMC5954810
PMID: 28862240 [Indexed for MEDLINE]

15. Podophyllin Toxicity with Systemic Manifestations in a Young Male. Jha M, Goyal SR, Sharma SC.

J Assoc Physicians India. 2019 Aug;67(8):89-90.

Podophyllin poisoning is a rare but a fatal poisoning with a long term systemic and neurological sequela. There has been no case report reported in an adult in India. We present a 28-year-old young male with podophyllin poisoning. This report confirms the transient central neurotoxicity of podophyllin and persistent peripheral neurotoxicity of podophyllin.

PMID: 31562731 [Indexed for MEDLINE]

16. What do we know about health risks related to thebaine in food? Eisenreich A, Sachse B, Gürtler R, Dusemund B, Lindtner O, Schäfer B.

Food Chem. 2019 Oct 14;309:125564. doi: 10.1016/j.foodchem.2019.125564. [Epub ahead of print]

Opium alkaloids such as morphine and thebaine occur in the latex of Papaver somniferum varieties. Some varieties are used for both, pharmaceutical opium alkaloid generation and poppy seed production for food use. Poppy seeds can be contaminated with opium alkaloid-containing latex, e.g. during harvesting. In recent years, poppy seed contamination with opium alkaloids, including thebaine, gave repeatedly reasons for concern in Europe. So far, risk assessments regarding opium alkaloids in poppy seeds were mainly based on the morphine level, whereas other opium alkaloids thereunder thebaine could not be finally evaluated due to lack of data. However, available limited data indicate that thebaine exhibits a higher acute toxic potential than morphine. Therefore, exposure to thebaine by consumption of poppy seed-containing food could pose a health risk. Here, we discuss the recent knowledge regarding thebaine's toxicological profile available for the assessment of potential health risks associated with its consumption via food.

DOI: 10.1016/j.foodchem.2019.125564
PMID: 31670127

17. Prevalence and Knowledge of Potential Interactions Between Over-the-Counter Products and Apixaban. Tarn DM, Barrientos M, Wang AY, Ramaprasad A, Fang MC, Schwartz JB.

J Am Geriatr Soc. 2019 Oct 28. doi: 10.1111/jgs.16193. [Epub ahead of print]

BACKGROUND: Direct-acting oral anticoagulants (DOACs), such as apixaban, are the most commonly prescribed anticoagulants, with advantages in that they do not require routine monitoring. However, less frequent contact with healthcare professionals may contribute to poor patient knowledge about potential interactions between over-the-counter (OTC) products and DOACs. OBJECTIVE: Determine the prevalence of use of OTC products (OTC medications and dietary supplements) with potentially serious apixaban interactions and assess patient knowledge of potential interactions. DESIGN: Cross-sectional survey. SETTING: Academic-affiliated outpatient medical practices in northern and southern California. PARTICIPANTS: A total of 791 English- or Spanish-speaking patients prescribed apixaban. MEASUREMENTS: Use and knowledge of OTC medications and dietary supplements with potentially serious apixaban interactions. RESULTS: Almost all respondents (n = 771; 97.5%) reported OTC product use. Of respondents, 33% (n = 266) took at least one OTC product with potentially serious apixaban interactions daily/most days and 53 (6.7%) took multiple products (mean = 2.6 [SD = 2.6]). Aspirin was taken daily by 116 (14.7%; of which 75 [64.7%] also consumed other potentially interacting OTC products), and some days/as needed by an additional 82 (10.4%). Ibuprofen and naproxen were taken daily/most days by 14 (1.8%) and occasionally by 225 (28.5%). Dietary supplements with potentially serious interactions were taken daily/most days by 160 (20.2%). Approximately 66% of respondents were either uncertain or incorrect about the potential for increased bleeding from combining nonsteroidal anti-inflammatory drugs and apixaban. Less knowledge about OTC products with potentially serious interactions was associated with greater OTC product use (odds ratio = 0.54; 95% confidence interval = 0.35-0.85). CONCLUSION: Significant numbers of patients take OTC products (particularly dietary supplements) with potentially serious interactions with the DOAC apixaban and appear to lack knowledge about potentially harmful interactions. Interventions are needed to educate patients and healthcare providers about potential dangers of taking interacting OTC products in combination with apixaban, and data are needed on outcomes associated with concomitant apixaban-OTC product use.

DOI: 10.1111/jgs.16193
PMID: 31658372

18. Fish Oil and Perioperative Bleeding. Akintoye E, Sethi P, Harris WS, Thompson PA, Marchioli R, Tavazzi L, Latini R, Pretorius M, Brown NJ, Libby P, Mozaffarian D.

Circ Cardiovasc Qual Outcomes. 2018 Nov;11(11):e004584. doi: 10.1161/CIRCOUTCOMES 118.004584.

Background Fish oil is among the most common natural supplements for treatment of hypertriglyceridemia or prevention of cardiovascular disease. However, concerns about theoretical bleeding risk have led to recommendations that patients should stop taking fish oil before surgery or delay in elective procedures for patients taking fish oil by some health care professionals. Methods and Results We tested the effect of fish oil supplementation on perioperative bleeding in a multinational, placebo-controlled trial involving 1516 patients who were randomized to perioperative fish oil (eicosapentaenoic acid+docosahexaenoic acid; 8-10 g for 2-5 days preoperatively, and then 2 g/d postoperatively) or placebo. Primary outcome was major perioperative bleeding as defined by the Bleeding Academic Research Consortium. Secondary outcomes include perioperative bleeding per thrombolysis in myocardial infarction and International Society on Thrombosis and Hemostasis definitions, chest tube output, and total units of blood transfused. Participants' mean (SD) age was 63 (13) years, and planned surgery included coronary artery bypass graft (52%) and valve surgery (50%). The primary outcome occurred in 92 patients (6.1%). Compared with placebo, risk of Bleeding Academic Research Consortium bleeding was not higher in the fish oil group: odds ratio, 0.81; 95% CI, 0.53-1.24; absolute risk difference, 1.1% lower (95% CI, -3.0% to 1.8%). Similar findings were seen for secondary bleeding definitions. The total units of blood transfused were significantly lower in the fish oil group compared with placebo (mean, 1.61 versus 1.92; P<0.001). Evaluating achieved plasma phospholipid omega-3 polyunsaturated fatty acids levels with supplementation (on the morning of surgery), higher levels were associated with lower risk of Bleeding Academic Research Consortium bleeding, with substantially lower risk in the third (odds ratio, 0.30 [95% CI, 0.11-0.78]) and fourth (0.36 [95% CI, 0.15-0.87]) quartiles, compared with the lowest quartile. Conclusions Fish oil supplementation did not increase perioperative bleeding and reduced the number of blood transfusions. Higher achieved n-3-PUFA levels were associated with lower risk of bleeding. These novel findings support the need for reconsideration of current recommendations to stop fish oil or delay procedures before cardiac surgery. Clinical Trial Registration URL: https://www.clinicaltrials.gov . Unique identifier: NCT00970489.

DOI: 10.1161/CIRCOUTCOMES.118.004584
PMCID: PMC6376981
PMID: 30571332 [Indexed for MEDLINE]

19. The Scheduling of Kratom and Selective Use of Data. Griffin OH, Webb ME.

J Psychoactive Drugs. 2018 Apr-Jun;50(2):114-120. doi: 10.1080/02791072.2017.1371363. Epub 2017 Sep 22.

Kratom is a traditional drug from Southeast Asia that has been an emerging new substance in the United States. On August 30, 2016, the DEA announced the intention to emergency schedule kratom into Schedule I. To support this decision, the DEA cited an increase in drug seizures of kratom and an increase in calls to poison control concerning kratom. However, a short time later, on October 12, 2016, the DEA withdrew the intent to schedule kratom after public and congressional backlash. The withdrawal by the DEA was somewhat unprecedented. To better understand both decisions, the current article examines the evidence the DEA cited to support their decision to emergency schedule kratom and the degree and type of media coverage of kratom to determine if a media-driven drug panic occurred.

DOI: 10.1080/02791072.2017.1371363
PMID: 28937941 [Indexed for MEDLINE]

20. How does cannabidiol (CBD) influence the acute effects of delta-9-tetrahydrocannabinol (THC) in humans? A systematic review. Freeman AM, Petrilli K, Lees R, Hindocha C, Mokrysz C, Curran HV, Saunders R, Freeman TP.

Neurosci Biobehav Rev. 2019 Sep 30;107:696-712. doi: 10.1016/j.neubiorev.2019.09.036. [Epub ahead of print]

The recent liberalisation of cannabis regulation has increased public and scientific debate about its potential benefits and risks. A key focus has been the extent to which cannabidiol (CBD) might influence the acute effects of delta-9-tetrahydrocannabinol (THC), but this has never been reviewed systematically. In this systematic review of how CBD influences the acute effects of THC we identified 16 studies involving 466 participants. Ten studies were judged at low risk of bias. The findings were mixed, although CBD was found to reduce the effects of THC in several studies. Some studies found that CBD reduced intense experiences of anxiety or psychosis-like effects of THC and blunted some of the impairments on emotion and reward processing. However, CBD did not consistently influence the effects of THC across all studies and outcomes. There was considerable heterogeneity in dose, route of administration and THC:CBD ratio across studies and no clear dose-response profile emerged. Although findings were mixed, this review suggests that CBD may interact with some acute effects of THC.

DOI: 10.1016/j.neubiorev.2019.09.036
PMID: 31580839

21. Analysis of cannabinoids in urine samples of short-term and long-term consumers of hemp seed products. Baeck S, Kim B, Cho B, Kim E.

Forensic Sci Int. 2019 Oct 21;305:109997. doi: 10.1016/j.forsciint.2019.109997. [Epub ahead of print]

With the increasing consumption of hemp seed products, it is important to establish whether biological samples from consumers contain trace cannabinoids that could mistakenly be attributed to cannabis abuse. Thus, we analyzed whether the cannabinoids, 11-nor-9-carboxy-tetrahydrocannabinol, cannabidiol, and cannabinol, can be detected in the urine of short-term (1 week) and long-term (12 weeks) consumers of hemp seed products. Using three hemp seed products that have recently been highly distributed in Korea, subjects consumed 30 g of hemp seeds (Group A, 53.1 (±0.5) μg THC and Group B, 124.81 (±1.5) μg THC) or 2 capsules of hemp seed oil (Group C, 11.1 μg THC) once a day at 10am. In the short-term study, the hemp seed product was consumed for 7 days, after which a single urine sample was collected. In the long-term study, the hemp seed product was consumed for 12 weeks, and urine samples were collected at 7 day intervals. For screening of the urine samples, we used COBAS C311, and for the confirmatory analysis we used gas chromatography/mass spectrometry. In the screening, all 64 samples from the short-term study were below the detection cutoff level of 25 ng/mL. In the long-term study, out of the 480 samples, 3 samples from 2 participants were above the cutoff level, but these samples were all negative in screening. In conclusion, our study demonstrated that when hemp seed products sold in Korea are consumed in normal quantities over the short- or long-term, urine samples do not test positive for cannabinoids.

DOI: 10.1016/j.forsciint.2019.109997
PMID: 31670217

22. Toxicological Aspects and Determination of the Main Components of Ayahuasca: A Critical Review. Simão AY, Gonçalves J, Duarte AP, Barroso M, Cristóvão AC, Gallardo E.

Medicines (Basel). 2019 Oct 18;6(4). pii: E106. doi: 10.3390/medicines6040106.

Ayahuasca is a psychoactive beverage prepared traditionally from a mixture of the leaves and stems of Psychotria viridis and Banisteriopsis caapi, respectively, being originally consumed by indigenous Amazonian tribes for ritual and medicinal purposes. Over the years, its use has spread to other populations as a means to personal growth and spiritual connection. Also, the recreational use of its isolated compounds has become prominent. The main compounds of this tea-like preparation are N,N-dimethyltryptamine (DMT), β-Carbolines, and harmala alkaloids, such as harmine, tetrahydroharmine,

and harmaline. The latter are monoamine-oxidase inhibitors and are responsible for DMT psychoactive and hallucinogenic effects on the central nervous system. Although consumers defend its use, its metabolic effects and those on the central nervous system are not fully understood yet. The majority of studies regarding the effects of this beverage and of its individual compounds are based on in vivo experiments, clinical trials, and even surveys. This paper will not only address the toxicological aspects of the ayahuasca compounds but also perform a comprehensive and critical review on the analytical methods available for their determination in biological and non-biological specimens, with special focus on instrumental developments and sample preparation approaches.

DOI: 10.3390/medicines6040106
PMID: 31635364

23. The Fever Tree: from Malaria to Neurological Diseases. Eyal S.

Toxins (Basel). 2018 Nov 23;10(12). pii: E491. doi: 10.3390/toxins10120491.

This article describes the discovery and use of the South American cinchona bark and its main therapeutic (and toxic) alkaloids, quinine and quinidine. Since the introduction of cinchona to Europe in the 17th century, it played a role in treating emperors and peasants and was central to colonialism and wars. Over those 400 years, the medical use of cinchona alkaloids has evolved from bark extracts to chemical synthesis and controlled clinical trials. At the present time, the use of quinine and quinidine has declined, to a large extent due to their toxicity. However, quinine is still being prescribed in resource-limited settings, in severe malaria, and in pregnant women, and quinidine made a limited comeback in the treatment of several cardiac and neurological syndromes. In addition, the article presents more recent studies which improved our understanding of cinchona alkaloids' pharmacology. The knowledge gained through these studies will hopefully lead to a wider use of these drugs in precision medicine and to design of new generation, safer quinine and quinidine derivatives.

DOI: 10.3390/toxins10120491
PMCID: PMC6316520
PMID: 30477182 [Indexed for MEDLINE]

24. Treatment of lead and arsenic poisoning in anuric patients - a case report and narrative review of the literature. Hsiao CY, Gresham C, Marshall MR.

BMC Nephrol. 2019 Oct 17;20(1):374. doi: 10.1186/s12882-019-1561-1.

BACKGROUND: Heavy metal poisoning can cause debilitating illness if left untreated, and its management in anuric patients poses challenges. Literature with which to guide clinical practice in this area is rather scattered. CASE PRESENTATION: We present a case of symptomatic lead and arsenic poisoning from use of Ayurvedic medicine in a 28-year-old man with end-stage kidney disease on chronic hemodialysis. We describe his treatment course with chelating agents and extracorporeal blood purification, and review the relevant literature to provide general guidance. CONCLUSION: Cumulative clinical experience assists in identifying preferred chelators and modalities of extracorporeal blood purification when managing such patients. However, a larger body of real-world or clinical trial evidence is necessary to inform evidence-based guidelines for the management of heavy metal poisoning in anuric patients.

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PMCID: PMC6796459
PMID: 31623560

25 Collective exposure to lead from an approved natural product-derived drug in Korea.
Lim DY, Kang WY, Ahn JS, Cho S, Kim S, Moon JD, Lee BC, Park WJ.

Ann Occup Environ Med. 2019 Aug 26;31:e20. doi: 10.35371/aoem.2019.31.e20. eCollection 2019.

Background: In Asian countries, including Korea, lead poisoning caused by traditional herbal medicines is often observed in the clinic. However, there have been no reports thus far of lead poisoning caused by drugs that were approved by the Korea Food and Drug Administration (KFDA). Here, we describe seven patients who ingested a problematic natural product-derived drug (NPD). Case presentation: In July 2018, seven patients visited a university hospital after ingesting an NPD, S. capsules. These patients complained of various symptoms, and their blood lead levels (BLLs) were elevated relative to those of the general population (arithmetic mean: 19.5 ± 11.6 μg/dL, range: 6.28-35.25 μg/dL). The total doses and BLLs were directly proportional to each other among the patients ($r = 0.943$, $p = 0.001$). After the patients discontinued drug intake, their BLLs decreased gradually. The capsule was confirmed to contain lead above the standard value (arithmetic mean: 2,547 ± 1,821.9 ppm). Conclusion: This incident highlights the need to strengthen standards for the management of NPD ingredients in Korea. NPDs are more likely to be contaminated than other drugs. Thorough management by the KFDA is essential to prevent a recurrence. Moreover, systematic health care is needed for many patients who have taken problematic NPDs.

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PMCID: PMC6779882
PMID: 31620297

26. Subacute Arsenic Neuropathy: Clinical and Electrophysiological Observations. Valappil AV, Mammen A.

J Neurosci Rural Pract. 2019 Jul;10(3):529-532. doi: 10.1055/s-0039-1695693. Epub 2019 Oct 9.

We report a patient who developed subacute peripheral neuropathy following ingestion of a traditional medicine for obesity. A 9-year-old girl who had a residual equinus varus deformity and sphincter disturbance due to pelvic ganglioneuroma presented with subacute sensorimotor peripheral neuropathy of 2 weeks duration. Her symptoms started 3 weeks after she started taking a locally made traditional medicine for obesity. She had no other systemic features of arsenic toxicity. She had Mee's lines on her nails and high serum arsenic levels and 24-hour urine levels confirmed the diagnosis of arsenic neuropathy. Nerve conduction study on admission demonstrated axonal sensorimotor neuropathy with slowed conduction velocity. She was not given any specific treatment and recovery was slow. At 18 months, she showed complete recovery and electrodiagnostic parameters returned to normal values. Arsenic is a known ingredient of many Indian ethnic remedies and possibility of arsenic neuropathy should be thought of in patients presenting with acute or sub-acute peripheral neuropathy of unknown etiology.

DOI: 10.1055/s-0039-1695693
PMCID: PMC6785343
PMID: 31602157

27. Supplement Use and Behaviors of Athletes Affiliated With an Australian State-Based Sports Institute. Waller MC, Kerr DA, Binnie MJ, Eaton E, Wood C, Stenvers T, Gucciardi DF, Goodman C, Ducker KJ.

Int J Sport Nutr Exerc Metab. 2019 Sep 1;29(5):518-525. doi:10.1123/ijsnem.2018-0336.

The authors aimed to update knowledge of the use of supplements among Australian athletes at a state-based sports institute. The authors conducted a cross-sectional survey using an online questionnaire to assess the influence of age, sports category, and scholarship category on supplement use. Of 94 completed questionnaires, 82 (87%) indicated supplements in the previous 12 months (mean = 4.9 ± 3.3). No

significant difference in supplement usage rate was identified when considering age, scholarship category, or sport category. The most frequently used supplements were sports drinks (70%), caffeine (48%), protein powder (42%), and sports bars (42%). Recovery (63%), health maintenance (59%), and improved energy (50%) were the most frequently reported rationale to use supplements. Allied health professionals and credible online resources were the predominant sources of influence regarding use. However, athletes from lower scholarship categories were more likely to have social media, parents, and siblings influence usage, and age was inversely related to increased influence from parents, social media, physicians not associated with the institute, the Internet, and siblings. Older athletes and those on higher scholarships were more likely to source supplements from training facilities and sports nutrition staff outside of the institute or direct from a supplier, whereas those on lower scholarships tended to rely more on family and friends for their supplements. Findings from this study show a high prevalence of supplement use and are the first to show an influence of social media, particularly in younger athletes. Opportunities exist to optimize how athletes are informed regarding supplement use and organizational and supplement policy.

DOI: 10.1123/ijsnem.2018-0336
PMID: 30859854 [Indexed for MEDLINE]

28. Retrospective self-reported dietary supplement use by Australian military personnel during deployment to Iraq and Afghanistan: results from the Middle East Area of Operations Health Study. Lui CW, Waller M, Bell A, van der Pols JC.

Appl Physiol Nutr Metab. 2019 Jun;44(6):674-680. doi: 10.1139/apnm-2018-0576. Epub 2018 Nov 23.

The use of dietary supplements is popular among military personnel. However, there is a lack of understanding about the changes in use during deployment and the specific factors associated with such changes. This study retrospectively examined changes in the pattern of supplement use among Australian veterans during their deployment to Iraq (n = 8848) and Afghanistan (n = 6507) between 2001 and 2009 and identified work-related circumstances that were associated with these changes. The frequency of use of supplements at present and during deployment was assessed. Multiple logistic regression analysis was used to compare the use of supplements among different groups and among those with different deployment experiences. The study found that overall use of supplements was highest on deployment to Afghanistan (27.8%) compared with deployment to Iraq (22.0%, $p < 0.001$) or after deployment (current use, 21.2%; $p < 0.001$). Personnel who were younger or who were at the rank of noncommissioned officer were more likely to use dietary supplements. Men were more likely to use body-building supplements, whereas women more often used weight-loss supplements. Those veterans who did not report using supplements regularly on deployment were far less likely to use them subsequently. Combat exposure, mixed duty cycles, and working long hours during deployment were associated with higher supplement use. The findings confirmed that supplement use in the military reflects the unique demands and stressors of defence service.

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