AACT Herbal Dietary Supplement Section Abstracts March 2020

1. The scoop on brain health dietary supplement products containing huperzine A. Crawford C, Wang YH, Avula B, Bae JY, Khan IA, Deuster PA.

Clin Toxicol (Phila). 2020 Jan 28:1-6. doi: 10.1080/15563650.2020.1713337. [Epub ahead of print]

Context: Public health concerns are emerging surrounding huperzine A commonly found in dietary supplements. We sought to determine the actual content of products claiming to contain huperzine A and whether the ingredients on the supplement facts labels matched the analyses.Methods: We identified and analyzed 22 dietary supplement products listing huperzine A on product labels. We found these products were listed in Natural Medicines and Dietary Supplement Databases and being queried by Military Service Members for enhanced mental focus, alertness and energy. Analyses were conducted by using Liquid Chromatography-Quadrupole Time of Flight Mass Spectrometry.Results: Sixteen (73%) products had at least one ingredient claimed on the supplement facts label not detected through analysis. Compounds not reported on the label were detected in 16 (73%) products analyzed. Nine products (41%) listed ingredients not meeting the regulations for being a dietary supplement ingredient according to the FDA. Ingredients of most concern detected include stimulants: demelverine, 1,5-dimethylhexylamine, 1,3-dimethylhexylamine, N-phenethyl dimethylamine, halostachine, higenamine, noopept, β-PEA, vinpocetine, sulbutiamine; and hordenine, currently on the FDA advisory list. Quantitative analysis showed the presence of huperzine A in the range from detected under the limits of quantification (DUL) to 267.1 µg/serving. Only two supplements showed huperzine A content within 10% of the declared amount.Conclusions: In a study of dietary supplements claiming to contain huperzine A, we found products that had at least one ingredient claimed on the supplement facts label not detected through analysis. Moreover, some ingredients not on the label could be dangerous and likely do not meet the definition of a dietary supplement ingredient according to the FDA. Quantitative analysis of huperzine A showed the amount detected was not in line with what appeared on the product label. Consumers should be aware of deceptive label claims and warned not to purchase products containing potentially dangerous ingredients.

DOI: 10.1080/15563650.2020.1713337
PMID: 31990212

2. Pharmacological profiles of compounds in preworkout supplements ("boosters"). Rickli A, Hoener MC, Liechti ME.

Eur J Pharmacol. 2019 Sep 15;859:172515. doi: 10.1016/j.ejphar.2019.172515. Epub 2019 Jun 29.

Preworkout supplements ("boosters") are used to enhance physical and mental performance during workouts. These products may contain various chemical substances with undefined pharmacological activity. We investigated whether substances that are contained in commercially available athletic multiple-ingredient preworkout supplements exert amphetamine-type activity at norepinephrine, dopamine, and serotonin transporters (NET, DAT, and SERT, respectively). We assessed the in vitro monoamine transporter inhibition potencies of the substances using human embryonic kidney 293 cells that expressed the human NET, DAT, and SERT. The phenethylamines β-phenethylamine, N-methylphenethylamine, β-methylphenethylamine, N-benzylphenethylamine, N-methyl-β-methylphenethylamine, and methylsynephrine inhibited the NET and less potently the DAT similarly to D-amphetamine. β-phenethylamine was the most potent, with IC50 values of 0.05 and 1.8 µM at the NET and DAT, respectively. These IC50 values were comparable to D-amphetamine (IC50 = 0.09 and 1.3 µM, respectively). The alkylamines 1,3-dimethylbutylamine and 1,3-dimethylamylamine blocked the NET but not the DAT. Most of the phenethylamines interacted with trace amine-associated receptor 1, serotonin 5-hydroxytryptamine-1A receptor, and adrenergic α1A and α2A receptors at submicromolar concentrations.

None of the compounds blocked the SERT. In conclusion, products that are used by athletes may contain substances with mainly noradrenergic amphetamine-type properties.

DOI: 10.1016/j.ejphar.2019.172515
PMID: 31265842 [Indexed for MEDLINE]

3. The Supplement Adulterant β-Methylphenethylamine Increases Blood Pressure by Acting at Peripheral Norepinephrine Transporters. Schindler CW, Thorndike EB, Rice KC, Partilla JS, Baumann MH.

J Pharmacol Exp Ther. 2019 Jun;369(3):328-336. doi: 10.1124/jpet.118.255976. Epub 2019 Mar 21.

β-Methylphenethylamine [(BMPEA), 2-phenylpropan-1-amine] is a structural isomer of amphetamine (1-phenylpropan-2-amine) that has been identified in preworkout and weight loss supplements, yet little information is available about its pharmacology. Here, the neurochemical and cardiovascular effects of BMPEA and its analogs, N-methyl-2-phenylpropan-1-amine (MPPA) and N,N-dimethyl-2-phenylpropan-1-amine (DMPPA), were compared with structurally related amphetamines. As expected, amphetamine and methamphetamine were potent substrate-type releasing agents at dopamine transporters (DATs) and norepinephrine transporters (NETs) in rat brain synaptosomes. BMPEA and MPPA were also substrates at DATs and NETs, but they were at least 10-fold less potent than amphetamine. DMPPA was a weak substrate only at NETs. Importantly, the releasing actions of BMPEA and MPPA were more potent at NETs than DATs. Amphetamine produced significant dose-related increases in blood pressure (BP), heart rate (HR), and locomotor activity in conscious rats fitted with surgically implanted biotelemetry transmitters. BMPEA, MPPA, and DMPPA produced increases in BP that were similar to the effects of amphetamine, but the compounds failed to substantially affect HR or activity. The hypertensive effect of BMPEA was reversed by the α-adrenergic antagonist prazosin but not the ganglionic blocker chlorisondamine. Radioligand binding at various G protein-coupled receptors did not identify nontransporter sites of action that could account for cardiovascular effects of BMPEA or its analogs. Our results show that BMPEA, MPPA, and DMPPA are biologically active. The compounds are unlikely to be abused due to weak effects at DATs, but they could produce adverse cardiovascular effects via substrate activity at peripheral NET sites.

DOI: 10.1124/jpet.118.255976
PMCID: PMC6533570
PMID: 30898867 [Indexed for MEDLINE]

4. Aminorex identified in horse urine following consumption of Barbarea vulgaris; a preliminary report. Maylin G, Fenger C, Machin J, Kudrimoti S, Eisenberg R, Green J, Tobin T.

Ir Vet J. 2019 Dec 23;72:15. doi: 10.1186/s13620-019-0153-5. eCollection 2019.

Background: Aminorex, (RS)-5- Phenyl-4,5-dihydro-1,3-oxazol-2-amine, is an amphetamine-like anorectic and in the United States a Drug Enforcement Administration [DEA] Schedule 1 controlled substance. Aminorex in horse urine is usually present as a metabolite of Levamisole, an equine anthelmintic and immune stimulant. Recently, Aminorex identifications have been reported in horse urine with no history or evidence of Levamisole administration. Analysis of the urine samples suggested a botanical source, directing attention to the Brassicaceae plant family, with their contained GlucoBarbarin and Barbarin as possible sources of Aminorex. Since horsepersons face up to a 1 year suspension and a $10,000.00 fine for an Aminorex identification, the existence of natural sources of Aminorex precursors in equine feedstuffs is of importance to both individual horsepersons and the industry worldwide. Results: Testing the hypothesis that Brassicaceae plants could give rise to Aminorex identifications in equine urine we botanically identified and harvested flowering Kentucky Barbarea vulgaris, ("Yellow Rocket") in May 2018 in Kentucky and administered the plant orally to two horses. Analysis of post-administration urine samples yielded Aminorex, showing that consumption of Kentucky Barbarea

vulgaris can give rise to Aminorex identifications in equine urine. Conclusions: Aminorex has been identified in post administration urine samples from horses fed freshly harvested flowering Kentucky Barbarea vulgaris, colloquially "Yellow Rocket". These identifications are consistent with occasional low concentration identifications of Aminorex in equine samples submitted for drug testing. The source of these Aminorex identifications is believed to be the chemically related Barbarin, found as its precursor GlucoBarbarin in Kentucky Barbarea vulgaris and related Brassicaceae plants worldwide.

DOI: 10.1186/s13620-019-0153-5
PMCID: PMC6929286
PMID: 31890155

5. Cholestatic liver injury induced by food additives, dietary supplements and parenteral nutrition. Vilas-Boas V, Gijbels E, Jonckheer J, De Waele E, Vinken M.

Environ Int. 2020 Mar;136:105422. doi: 10.1016/j.envint.2019.105422. Epub 2019 Dec 26.

Cholestasis refers to the accumulation of toxic levels of bile acids in the liver due to defective bile secretion. This pathological situation can be triggered by drugs, but also by ingredients contained in food, food supplements and parenteral nutrition. This paper provides an overview of the current knowledge on cholestatic injury associated with such ingredients, with particular emphasis on the underlying mechanisms of toxicity.

DOI: 10.1016/j.envint.2019.105422
PMID: 31884416

6. United States Pharmacopeia (USP) comprehensive review of the hepatotoxicity of green tea extracts. Oketch-Rabah HA, Roe AL, Rider CV, Bonkovsky HL, Giancaspro GI, Navarro V, Paine MF, Betz JM, Marles RJ, Casper S, Gurley B, Jordan SA, He K, Kapoor MP, Rao TP, Sherker AH, Fontana RJ, Rossi S, Vuppalanchi R, Seeff LB, Stolz A, Ahmad J, Koh C, Serrano J, Low Dog T, Ko R.

Toxicol Rep. 2020 Feb 15;7:386-402. doi: 10.1016/j.toxrep.2020.02.008. eCollection 2020.

As part of the United States Pharmacopeia's ongoing review of dietary supplement safety data, a new comprehensive systematic review on green tea extracts (GTE) has been completed. GTEs may contain hepatotoxic solvent residues, pesticide residues, pyrrolizidine alkaloids and elemental impurities, but no evidence of their involvement in GTE-induced liver injury was found during this review. GTE catechin profiles vary significantly with manufacturing processes. Animal and human data indicate that repeated oral administration of bolus doses of GTE during fasting significantly increases bioavailability of catechins, specifically EGCG, possibly involving saturation of first-pass elimination mechanisms. Toxicological studies show a hepatocellular pattern of liver injury. Published adverse event case reports associate hepatotoxicity with EGCG intake amounts from 140 mg to ~1000 mg/day and substantial inter-individual variability in susceptibility, possibly due to genetic factors. Based on these findings, USP included a cautionary labeling requirement in its Powdered Decaffeinated Green Tea Extract monograph that reads as follows: "Do not take on an empty stomach. Take with food. Do not use if you have a liver problem and discontinue use and consult a healthcare practitioner if you develop symptoms of liver trouble, such as abdominal pain, dark urine, or jaundice (yellowing of the skin or eyes)."

DOI: 10.1016/j.toxrep.2020.02.008
PMCID: PMC7044683
PMID: 32140423

7. Ashwagandha-induced liver injury: A case series from Iceland and the US Drug-Induced Liver Injury Network. Björnsson HK, Björnsson ES, Avula B, Khan IA, Jonasson JG, Ghabril M, Hayashi PH, Navarro V.

Liver Int. 2020 Jan 28. doi: 10.1111/liv.14393. [Epub ahead of print]
BACKGROUND & AIMS: Ashwagandha (Withania somnifera) is widely used in Indian Ayurvedic medicine. Several dietary supplements containing ashwagandha are marketed in the US and Europe, but only one case of drug-induced liver injury (DILI) due to ashwagandha has been published. The aim of this case series was to describe the clinical phenotype of suspected ashwagandha-induced liver injury. METHODS: Five cases of liver injury attributed to ashwagandha-containing supplements were identified; three were collected in Iceland during 2017-2018 and two from the Drug-Induced Liver Injury Network (DILIN) in 2016. Other causes for liver injury were excluded. Causality was assessed using the DILIN structured expert opinion causality approach. RESULTS: Among the five patients, three were males; mean age was 43 years (range 21-62). All patients developed jaundice and symptoms such as nausea, lethargy, pruritus and abdominal discomfort after a latency of 2-12 weeks. Liver injury was cholestatic or mixed (R ratios 1.4-3.3). Pruritus and hyperbilirubinaemia were prolonged (5-20 weeks). No patient developed hepatic failure. Liver tests normalized within 1-5 months in four patients. One patient was lost to follow-up. One biopsy was performed, showing acute cholestatic hepatitis. Chemical analysis confirmed ashwagandha in available supplements; no other toxic compounds were identified. No patient was taking potentially hepatotoxic prescription medications, although four were consuming additional supplements, and in one case, rhodiola was a possible causative agent along with ashwagandha. CONCLUSIONS: These cases illustrate the hepatotoxic potential of ashwagandha. Liver injury is typically cholestatic or mixed with severe jaundice and pruritus, but self-limited with liver tests normalizing in 1-5 months.

DOI: 10.1111/liv.14393
PMID: 31991029

8. The hepatotoxicity of Polygonum multiflorum: The emerging role of the immune-mediated liver injury. Rao T, Liu YT, Zeng XC, Li CP, Ou-Yang DS.

Acta Pharmacol Sin. 2020 Mar 2. doi: 10.1038/s41401-020-0360-3. [Epub ahead of print]

Herbal and dietary supplements (HDS)-induced liver injury has been a great concern all over the world. Polygonum multiflorum Thunb., a well-known Chinese herbal medicine, is recently drawn increasing attention because of its hepatotoxicity. According to the clinical and experimental studies, P. multiflorum-induced liver injury (PM-DILI) is considered to be immune-mediated idiosyncratic liver injury, but the role of immune response and the underlying mechanisms are not completely elucidated. Previous studies focused on the direct toxicity of PM-DILI by using animal models with intrinsic drug-induced liver injury (DILI). However, most epidemiological and clinical evidence demonstrate that PM-DILI is immune-mediated idiosyncratic liver injury. The aim of this review is to assess current epidemiological, clinical and experimental evidence about the possible role of innate and adaptive immunity in the idiosyncratic hepatotoxicity of P. multiflorum. The potential effects of factors associated with immune tolerance, including immune checkpoint molecules and regulatory immune cells on the individual's susceptibility to PM-DILI are also discussed. We conclude by giving our hypothesis of possible immune mechanisms of PM-DILI and providing suggestions for future studies on valuable biomarkers identification and proper immune models establishment.

DOI: 10.1038/s41401-020-0360-3
PMID: 32123300

9. Aloe-emodin induces hepatotoxicity by the inhibition of multidrug resistance protein 2. Liu DM, Yang D, Zhou CY, Wu JS, Zhang GL, Wang P, Wang F, Meng XL.

Phytomedicine. 2019 Dec 9;68:153148. doi: 10.1016/j.phymed.2019.153148. [Epub ahead of print]

BACKGROUND: Aloe-emodin (AE) is among the primary bioactive anthraquinones present in traditional Chinese medicinal plants such as Rheum palmatum L. Multidrug resistance protein 2 (ABCC2/MRP2) is an important efflux transporter of substances associated with cellular oxidative stress. However, the effects of traditional Chinese medicine on this protein remain unclear. PURPOSE: The aim of this research is to study the role of ABCC2 in AE-induced hepatotoxicity. METHODS: The expression of ABCC2 protein and mRNA levels were analyzed by Western-Blotting and qRT-PCR, respectively. The intracellular oxidative stress caused by AE was evaluated by quantifying the levels of intracellular reactive oxygen species, malondialdehyde, glutathione reduced and oxidized glutathione. The levels of adenosine triphosphate, mitochondrial membrane potential and mitochondrial DNA were explored to evaluate the effects of AE on mitochondrial function. The effects of AE on cell apoptosis and cell cycle were detected by flow cytometry. To further clarify the key role of ABCC2 in AE induced cytotoxicity, we used pCI-neo-ABCC2 plasmid to over express ABCC2 protein, and small interfering RNA was used to knockdown ABCC2 in HepG2 cells. Additionally, we investigated the impact of AE on ABCC2 degradation pathway and the hepatotoxic effects of AE in mice. RESULTS: AE was found to inhibit ABCC2 transport activity, downregulate ABCC2 expression and altered intracellular redox balance. Induction of oxidative stress resulted in depletion of intracellular glutathione reduced, mitochondria dysfunction and activation of apoptosis. ABCC2 overexpression significantly reduced AE-induced intracellular oxidative stress and cell death, which was enhanced by ABCC2 knockdown. Furthermore, AE was observed to promote ABCC2 degradation through induction of autophagy and hepatotoxicity was induced in mice by promoting ABCC2 degradation. CONCLUSIONS: The inhibition of ABCC2 is a novel effect of AE that triggers oxidative stress and apoptosis. These findings are helpful in understanding the toxicological effects of AE-containing medicinal plants.

DOI: 10.1016/j.phymed.2019.153148
PMID: 32028185

10. Suspected Hepatotoxicity With a Supercritical Carbon Dioxide Extract of Artemisia annua in Grapeseed Oil Used in New Zealand. Savage RL, Hill GR, Barnes J, Kenyon SH, Tatley MV.

Front Pharmacol. 2019 Dec 20;10:1448. doi: 10.3389/fphar.2019.01448. eCollection 2019.

A case series of hepatotoxicity associated with an extract of Artemisia annua L. was identified through the New Zealand spontaneous adverse drug reaction reporting system. A. annua extract, produced using a supercritical carbon dioxide extraction method and formulated with grapeseed oil, has been marketed in New Zealand as a natural product for joint health. As of 31 January 2019, the New Zealand Pharmacovigilance Centre had received 29 reports of hepatic adverse reactions occurring in patients taking A. annua extract in grapeseed oil. The case reports were assessed for patient and adverse reaction characteristics, patterns of A. annua extract use and causality (based on the WHO-UMC system for standardized case causality assessment). Patients were aged 47 to 93 years (median 67). Time to onset of hepatotoxicity from starting A. annua extract was 7 days to approximately 12 months in the 23 reports with this information. Nineteen of these reports indicated onset within 12 weeks. A. annua extract was the sole suspect medicine in 27 reports. A few patients had possible predisposing conditions. Twenty-seven patients were reported to have recovered or improved on stopping A. annua extract. Nine patients required hospital admission. The pattern of hepatic injury varied. Jaundice, often with pruritus and dark urine, was experienced by 16 patients. There was considerable consistency across case reports from various reporters. We assessed the case reports as a series using the Bradford Hill guidelines for causal inference and concluded that there was a safety signal of a causal association between the A. annua extract and hepatotoxicity sufficient to be communicated and investigated further.

DOI: 10.3389/fphar.2019.01448
PMCID: PMC6933422
PMID: 31920644

11. Idiosyncratic drug-induced liver injury in patients: Detection, severity assessment, and regulatory implications. Watkins PB.

Adv Pharmacol. 2019;85:165-193. doi: 10.1016/bs.apha.2019.02.004. Epub 2019 Apr 30.

Idiosyncratic Drug-Induced Liver Injury (IDILI) is a rare but potentially life-threatening event that is caused by drugs that, at usual therapeutic doses, do not cause any biochemical or clinical evidence of liver injury in the majority of treated patients. The most common clinical phenotypes of IDILI are "acute hepatitis," "mixed hepatocellular-cholestatic hepatitis," and "cholestatic hepatitis" and these are distinguished by clinical, biochemical and histologic characteristics. Anti-microbials, herbals and dietary supplements are now the agents most often implicated in the US Drug-Induced Liver Injury Network registry. There are several scales that have been used to characterize the severity of IDILI events. There are no reliable means to accurately predict the course of an IDILI event at presentation. In clinical trials, the "gold standard" liver safety signal is the occurrence of "Hy's Law Cases." Making the diagnosis of IDILI, and when a patient is taking multiple drugs, identifying the most likely culprit can be challenging, but many drugs cause IDILI with characteristic clinical and biochemical presentations, or "signatures." In a clinical trial, it is sometimes possible to identify an overlooked "signature" of IDILI by characterizing more minor, asymptomatic, and transient elevations in liver chemistries. This observation can be helpful in assessing causation in rare serious liver events occurring in the clinical trial, or first recognized post-marketing.

DOI: 10.1016/bs.apha.2019.02.004
PMID: 31307586 [Indexed for MEDLINE]

12. Evaluating kratom alkaloids using PHASE. Ellis CR, Racz R, Kruhlak NL, Kim MT, Zakharov AV, Southall N, Hawkins EG, Burkhart K, Strauss DG, Stavitskaya L.

PLoS One. 2020 Mar 3;15(3):e0229646. doi: 10.1371/journal.pone.0229646. eCollection 2020.

Kratom is a botanical substance that is marketed and promoted in the US for pharmaceutical opioid indications despite having no US Food and Drug Administration approved uses. Kratom contains over forty alkaloids including two partial agonists at the mu opioid receptor, mitragynine and 7-hydroxymitragynine, that have been subjected to the FDA's scientific and medical evaluation. However, pharmacological and toxicological data for the remaining alkaloids are limited. Therefore, we applied the Public Health Assessment via Structural Evaluation (PHASE) protocol to generate in silico binding profiles for 25 kratom alkaloids to facilitate the risk evaluation of kratom. PHASE demonstrates that kratom alkaloids share structural features with controlled opioids, indicates that several alkaloids bind to the opioid, adrenergic, and serotonin receptors, and suggests that mitragynine and 7-hydroxymitragynine are the strongest binders at the mu opioid receptor. Subsequently, the in silico binding profiles of a subset of the alkaloids were experimentally verified at the opioid, adrenergic, and serotonin receptors using radioligand binding assays. The verified binding profiles demonstrate the ability of PHASE to identify potential safety signals and provide a tool for prioritizing experimental evaluation of high-risk compounds.

DOI: 10.1371/journal.pone.0229646
PMID: 32126112

13. A counterfeit multivitamin product inducing severe bleeding disorders in humans. Peña-Acevedo L, Zuluaga AF, Aristizabal-Solis A.

Clin Toxicol (Phila). 2020 Jan 10:1-3. doi: 10.1080/15563650.2019.1703999. [Epub ahead of print]

Context: During a period of 6 months, 36 people reported to health authorities in the Department of Antioquia, Colombia, presenting episodes of bleeding in varying magnitude and locations in the body and alterations in coagulation tests, after having taken a falsified dietary supplement. The identification of the first four cases were to the cell-phone line at the Drug and Poison Research Information Center (CIEMTO). The successive presentation of cases with similar manifestations, taking the same product, served to suspect a possible common link.Case details: All of the patients needed hospitalization, the administration of blood products and / or vitamin K to reverse the clinical manifestations, and to stop the oral consumption of the falsified supplement. For each patient there was a full recovery of coagulation and improvement of haemorrhagic manifestations after the first week of management. The Food and Drug administration of Colombia (INVIMA), withdrew the product from the market, alerted the medical community and the general public and conducted an investigation that finally showed warfarin as a the main contaminant in the dietary supplement.Conclusion: This cases series emphasize the importance of the Poison Control Center to detect promptly potential new exposure of hazards to hundreds of products to the population, some of them fraudulent.

DOI: 10.1080/15563650.2019.1703999
PMID: 31922430

14. A 'Natural' thyroid storm! Mohebbi MR, Chen AT.

J Clin Pharm Ther. 2019 Oct;44(5):813-814. doi: 10.1111/jcpt.12996. Epub 2019 Jun 18.

WHAT IS KNOWN AND OBJECTIVE: Over the counter supplements are often taken for granted during medication reconciliation in the emergency department. Supplements are not regulated by FDA, and some can be potentially dangerous. CASE SUMMARY: We report a case of thyrotoxicosis secondary to over the counter bovine thyroid supplements. Our patient presented with atrial fibrillation with rapid ventricular response refractory to calcium channel blockers. Had we not known about the supplement, the course of treatment would have been different with potential adverse outcome. WHAT IS NEW AND CONCLUSION: Natural thyroid supplements are marketed as over the counter products and are largely unregulated. Thyroid extracts have been found to have disparaging inconsistencies in composition, delivering anywhere from non-existent to supratherapeutic doses. Thyroid supplements should be regulated considering the potential side effects.

DOI: 10.1111/jcpt.12996
PMID: 31211437 [Indexed for MEDLINE]

15. Severe transient myopathy in a patient with progressive multiple sclerosis and high-dose biotin. Maillart E, Mochel F, Acquaviva C, Maisonobe T, Stankoff B.

Neurology. 2019 May 28;92(22):1060-1062. doi: 10.1212/WNL.0000000000007576. Epub 2019 Apr 26.

Daily high-dose biotin has been suggested to improve disability in patients with progressive multiple sclerosis (P-MS) in a small controlled trial conducted in France. The supposed mechanisms of action supporting high-dose biotin are (1) the support of myelin repair through acetyl-CoA carboxylase activation by enhancing fatty acid synthesis and (2) the protection against axonal degeneration related to hypoxia through enhanced energy production. In the trial, safety was good, with incidence of adverse events similar in both groups, and few serious adverse events (SAE). Here, we report a detailed SAE: a transient myopathy resembling multiple acyl-coenzyme A dehydrogenase deficiency (MADD) or riboflavin transporter defects, reversible upon biotin withdrawal.

DOI: 10.1212/WNL.0000000000007576
PMID: 31028130 [Indexed for MEDLINE]

16.Use of vitamin D drops leading to kidney failure in a 54-year-old man. Auguste BL, Avila-Casado C, Bargman JM.

CMAJ. 2019 Apr 8;191(14):E390-E394. doi: 10.1503/cmaj.180465.

DOI: 10.1503/cmaj.180465
PMCID: PMC6453674 [Available on 2020-04-08]
PMID: 30962197 [Indexed for MEDLINE]

17. Acute tea tree oil intoxication in a pet cockatiel (Nymphicus hollandicus): a case report. Vetere A, Bertocchi M, Pelizzone I, Moggia E, Travaglino C, Della Grotta M, Casali S, Gerosa S, Strada L, Filia K, Casalini J, Parmigiani E, Di Ianni F.

BMC Vet Res. 2020 Jan 31;16(1):29. doi: 10.1186/s12917-020-2255-4.

BACKGROUND: Phytotherapy is becoming a more and more common practice, not only for personal care but also for pet care. Nevertheless, we often have to deal with substances on which, in most cases, very little literature is available, even more so if the species of interest are the exotic ones. In particular, the essential oil from the Melaleuca leaves, because of its antinflammatory and antibacterial properties, is widely used and very little is known about its potential toxicity on pet birds. The present paper describes the first case of Tea tree oil intoxication in a pet bird. CASE PRESENTATION: A one-year-old, 80 g male cockatiel (Nymphicus hollandicus) was presented for clinical examination due to a serious despondency episode after the application of 3 drops of tea tree oil (Melaleuca alternifoglia) directly on the cutis of its right wing. The subject was urgently hospitalized and blood tests were performed.Serum biochemical values showed severe liver damage and slight renal involvement, complete blood count (CBC) parameters indicated a moderate neutrophilia a moderate neutropenia. Warm subcutaneous fluids and vitamin (VIT) B12 were administered, and after 8 h of fluid therapy the clinical condition of the patient improved. The subject was discharged after 48 h of hospitalization, in stable conditions. CONCLUSIONS: Toxicosis are relatively common in bird pets and a number of cases are reported in literature, concerning heavy metals intoxications and toxic plants ingestion. However, in literature there are no described cases regarding Melaleuca oil intoxication in pet birds, but it has been reported in humans (mainly by ingestion) as well as in dogs, cats and rats. We hope that this first case report can be an initial aid in the knowledge of this potential toxicosis and therefore in the clinical veterinary practice of pet birds.

DOI: 10.1186/s12917-020-2255-4
PMCID: PMC6995176
PMID: 32005244

18. Weight loss supplement causing acute heart block in a child. O'Brien DR, Szymczuk V, Albaro CA.

Cardiol Young. 2020 Jan;30(1):131-133. doi: 10.1017/S104795111900283X. Epub 2020 Jan 6.

A 16-year-old male was admitted to the paediatric ICU with acute onset of vomiting, somnolence, and chest pain, and electrocardiogram showing 2nd degree heart block after ingesting an Aleurites moluccana (Candlenut) seed as a herbal weight loss supplement. Electrocardiogram showed progressively worsening heart block with down-sloping of the ST segments, resembling digoxin toxicity. After 2 days of ICU observation, his symptoms began to improve and eventually resolved. The side effects of herbal supplements are often unknown but by analysing cases such as these, physicians can develop a better understanding of these substances to help guide management.

DOI: 10.1017/S104795111900283X
PMID: 31902376

19. Thrombocytopenia Caused by a Tea Beverage of Taxus yunnanensis (Chinese Yew). Ubukawa K, Kameoka Y, Guo YM, Nara M, Watanabe A, Fujishima M, Fujishima N, Yoshioka T, Takahashi N.

Intern Med. 2019 Nov 1;58(21):3153-3156. doi: 10.2169/internalmedicine.2967-19. Epub 2019 Jul 10.

A 53-year-old woman presented at our hospital due to nasal bleeding and petechiae with profound thrombocytopenia (0.4×109/L). Her platelet count returned to the normal range immediately following a platelet transfusion. In this case, tea brewed from Taxus yunnanensis was the only suspected agent ingested prior to the onset of thrombocytopenia while all other etiologies for thrombocytopenia were excluded. A re-exposure test to Taxus yunnanensis resulted in the recurrence of acute thrombocytopenia. The association of thrombocytopenia with substances other than drugs has so far only been rarely described and to the best of our knowledge, this is the first reported case of thrombocytopenia caused by Taxus yunnanensis.

DOI: 10.2169/internalmedicine.2967-19
PMCID: PMC6875462
PMID: 31292386 [Indexed for MEDLINE]

20. Green Breast Milk Following Ingestion of Blue-Green Algae: A Case Report. Naor N, Fridman E, Kouadio F, Merlob P, Linder N.

Breastfeed Med. 2019 Apr;14(3):203-204. doi: 10.1089/bfm.2018.0184. Epub 2019 Feb 20.

Breast milk is an excellent nutritional source for newborns, and a change in its color can be alarming to both mother and physician, and may prevent breastfeeding. Different colors of breast milk have been reported such as blood-stained, blue, and bluish-green. We present the first case of green breast milk caused by maternal ingestion of blue-green algae pills immediately before and after delivery. The score on the Naranjo Adverse Drug Reaction Probability Scale was 5, indicating a probable adverse drug reaction. Laboratory analysis yielded no other abnormalities in the milk. The mother stopped taking the supplement, and the milk returned to its normal appearance 3 days later. This report should alert physicians to include supplement intake as part of the anamnesis for new mothers who present with breast milk changes.

DOI: 10.1089/bfm.2018.0184
PMID: 30785777 [Indexed for MEDLINE]

21. Commercial Cannabinoid Oil-Induced Stevens-Johnson Syndrome. Yin HY, Hadjokas N, Mirchia K, Swan R, Alpert S.

Case Rep Ophthalmol Med. 2020 Feb 19;2020:6760272. doi: 10.1155/2020/6760272. eCollection 2020.

Purpose: To report an unusual presentation of commercial cannabidiol (CBD) oil-induced Stevens-Johnson Syndrome/toxic epidermal necrolysis (SJS-TEN). Methods: A 56-year-old woman presented with acute onset of a diffuse, blistering, maculopapular rash with over 30% total body surface area (BSA) involvement two days after taking CBD oil sublingually for chronic pain. Biopsy confirmed SJS-TEN. Ophthalmology was consulted and mild eye involvement was found. She was started on topical

cyclosporine, prednisone, moxifloxacin, and erythromycin ointment to prevent progression, which was successful. She was otherwise treated with supportive therapy in the intensive care burn unit and ultimately passed away from septic shock. Conclusion: In this case, we described an unusual drug-induced SJS from a commercial, non-FDA-regulated cannabis product. The use of a commercial CBD product should be cautioned due to potential for series of drug reactions to the cannabis product and the risk for reaction to other unregulated other pharmacological components.

DOI: 10.1155/2020/6760272
PMCID: PMC7053463
PMID: 32148986

22. Severe Methemoglobinemia Secondary to Ferula asafoetida Ingestion in an Infant: A Case Report. Al-Qahtani S, Abusham S, Alhelali I.

Saudi J Med Med Sci. 2020 Jan-Apr;8(1):56-59. doi: 10.4103/sjmms.sjmms_5_18. Epub 2019 Dec 23.

Methemoglobinemia is an increase in the methemoglobin levels in the blood. Infants are more susceptible to develop secondary methemoglobinemia because of the limited activity of methemoglobin reductase B enzyme. We report a case of life-threatening methemoglobinemia secondary to ingestion of Ferula asafoetida herbal remedy in an infant who presented with cyanosis and severe respiratory distress. The patient had two brothers who had a glucose-6-phosphate dehydrogenase deficiency and the patient's deficiency status was unknown, and thus, methylene blue was not initiated whereas ascorbic acid was unavailable. Accordingly, the patient was successfully treated with hyperoxia. Based on this case, the authors suggest that the use of F. asafoetida as an herbal remedy should be avoided in infants, and pediatricians should be aware of such toxicity and inform parents appropriately.

DOI: 10.4103/sjmms.sjmms_5_18
PMCID: PMC6945318
PMID: 31929780

23. Factors Related to Disclosure and Nondisclosure of Dietary Supplements in Primary Care, Integrative Medicine, and Naturopathic Medicine. Guzman JR, Paterniti DA, Liu Y, Tarn DM.

J Fam Med Dis Prev. 2019;5(4). doi: 10.23937/2469-5793/1510109. Epub 2019 Aug 8.

Background: Patients infrequently disclose use of dietary supplements to providers. Little is known about factors that motivate patients to disclose supplement use. The study aimed to identify reported factors motivating patients' disclosure and nondisclosure of dietary supplement use and explore differences based on type of supplement and provider practice. Methods: Mixed methods study combining qualitative content analysis of semi-structured interviews with statistical analyses to assess differences in identified factors by provider practice type and supplement type. Seventy-eight English-speaking patients who reported taking 466 dietary supplements in the previous 30 days were recruited from primary care and Complementary and Alternative Medicine (CAM), and Integrative Medicine (IM) offices in Southern California. Results: We identified nine themes related to disclosure and nine related to nondisclosure of dietary supplement use. Major themes were features of the office visit, circumstances in patient health and medical care, and provider/patient characteristics. The most commonly raised theme promoting disclosure of supplement use was provider inquiry. Patients associate disclosure with having concerns about a supplement but also with annual physical exams and some routine topics of discussion, including self-care, lab results, and new medication prescriptions. Themes related to nondisclosure included lack of provider inquiry, features of the office visit, such as supplements being unrelated to the visit purpose, and patients' convictions that supplements are safe or not important to discuss. Themes did not vary by supplement type. Primary care patients were more likely than CAM/IM patients to attribute nondisclosure to convictions that supplements were beneficial, not worth mentioning, or equivalent to food ($p \leq 0.001$). Conclusions: When providers fail to ask directly about dietary supplement use,

disclosure is often an impromptu decision that is driven by the content of provider-patient interactions. Ensuring disclosure of dietary supplement use to prevent potential drug-supplement interactions or adverse health outcomes likely requires consistent, proactive provider queries about supplement use.

DOI: 10.23937/2469-5793/1510109
PMCID: PMC7015169
PMID: 32051918

24. Herb-drug interactions: a novel algorithm-assisted information system for pharmacokinetic drug interactions with herbal supplements in cancer treatment. Ziemann J, Lendeckel A, Müller S, Horneber M, Ritter CA.

Eur J Clin Pharmacol. 2019 Sep;75(9):1237-1248. doi: 10.1007/s00228-019-02700-6. Epub 2019 Jun 1.

PURPOSE: To develop a system to estimate the risk of herb-drug interactions that includes the available evidence from clinical and laboratory studies, transparently delineates the algorithm for the risk estimation, could be used in practice settings and allows for adaptation and update. METHODS: We systematically searched Drugbank, Transformer, Drug Information Handbook, European and German Pharmacopoeia and MEDLINE for studies on herb-drug interactions of five common medicinal plants (coneflower, ginseng, milk thistle, mistletoe and St. John's wort). A diverse set of data were independently extracted by two researchers and subsequently analysed by a newly developed algorithm. Results are displayed in the form of interaction risk categories. The development of the algorithm was guided by an expert panel consensus process. RESULTS: From 882 publications retrieved by the search, 154 studies were eligible and provided 529 data sets on herbal interactions. The developed algorithm prioritises results from clinical trials over case reports over in vitro investigations and considers type of study, consistency of study results and study outcome for clinical trials as well as identification, permeability, bioavailability, and interaction potency of an identified herbal perpetrator for in vitro investigations. Risk categories were assigned to and dynamically visualised in a colour-coded matrix format. CONCLUSIONS: The novel algorithm allows to transparently generate and dynamically display herb-drug interaction risks based on the available evidence from clinical and laboratory pharmacologic studies. It provides health professionals with readily available and easy updatable information about the risk of pharmacokinetic interactions between herbs and oncologic drugs.

DOI: 10.1007/s00228-019-02700-6
PMID: 31154477 [Indexed for MEDLINE]

25. Toxicity of Herbs, Vitamins, and Supplements. Charen E, Harbord N.

Adv Chronic Kidney Dis. 2020 Jan;27(1):67-71. doi: 10.1053/j.ackd.2019.08.003.

In the United States, the Food and Drug Administration regulates the efficacy and safety of pharmaceutical drugs. This government agency was formed in direct response to a mass poisoning and more than 100 deaths from kidney failure due to a medicinal toxic alcohol exposure. In contrast, the Food and Drug Administration also regulates the use of vitamins, minerals, herbs, or botanicals as dietary supplements, banning specific medical claims but requiring no documentation of efficacy. Safety of dietary supplements is only ensured through reporting of adverse events and rarely through intervention. Consumers should be aware that supplements may in fact contain actual pharmaceuticals or nothing of value and have significant toxic potential. Toxicity due to Chinese herbal medicines, aristolochic acid, amygdalin, hypervitaminosis D, and heavy metal contamination is reviewed.

DOI: 10.1053/j.ackd.2019.08.003
PMID: 32147004