

AACT Herbal Dietary Supplements SIG Abstracts May 2018

1. Recommended Approaches for Pharmacokinetic Natural Product-Drug Interaction

Research: a NaPDI Center Commentary. Paine MF, Shen DD, McCune JS.

Drug Metab Dispos. 2018 May 7. pii: dmd.117.079962. doi: 10.1124/dmd.117.079962. [Epub ahead of print]

Sales of botanical dietary supplements and other purported medicinal natural products (NPs) have escalated over the past ~25 years, increasing the potential for NPs to precipitate clinically significant pharmacokinetic interactions with United States Food and Drug Administration (FDA)-approved medications (NP-drug interactions or NPDI). Published NPDI studies to date often lack consistency in design, implementation, and documentation, which present difficulties in assessing the clinical significance of the results. Common hurdles include large variability in the admixture composition of phytoconstituents between and within batches of a given NP, limited knowledge on the pharmacokinetics of precipitant NP constituents, and use of animal and/or in vitro models which, in some cases, are not mechanistically appropriate for extrapolation to humans. The National Center for Complementary and Integrative Health has created a Center of Excellence for Natural Product-Drug Interaction (NaPDI Center) to address these unmet research needs. The NaPDI Center has two overarching goals: 1) develop Recommended Approaches to guide researchers in the proper conduct of NPDI studies, which will evolve over time concurrent with emerging technologies and new research data; and 2) apply the Recommended Approaches in evaluating four model NPs as precipitants of NPDI with clinically relevant object drugs. The major objectives of this commentary are to 1) explain the rationale for creating the NaPDI Center; 2) describe the Decision Trees developed by the NaPDI Center to enhance the planning, rigor, and consistency of NPDI studies; and 3) provide a framework for communicating results to the multidisciplinary scientists interested in the NaPDI Center's Interaction Projects.

DOI: 10.1124/dmd.117.079962

PMID: 29735755

2. Complementary and Alternative Medicine Use in United States Adults With Liver Disease. Henson JB, Brown CL, Chow SC, Muir AJ.

J Clin Gastroenterol. 2017 Jul;51(6):564-570. doi: 10.1097/MCG.0000000000000617.

GOALS: To describe the complementary and alternative medicine (CAM) use in US adults with liver disease. **BACKGROUND:** The prevalence and patterns of CAM use among US adults with liver disease have not been well characterized. The 2012 National Health Interview Survey is considered the most current and comprehensive source of information on CAM use in US adults. **STUDY:** Using the results of the 2012 National Health Interview Survey, the prevalence of CAM use, most common modalities used, reasons for CAM use, perceived benefits, perceived helpfulness and importance, and disclosure of CAM to health care providers were compared between adults with and without liver disease. **RESULTS:** Of the 647 adults with liver disease, 41% reported using CAM in the prior year, compared with 33% of adults without liver disease. The most common modality was herbs and supplements (23%), and 3% of respondents reported consumption of a potentially hepatotoxic substance in the previous 30 days. Only a small proportion of CAM therapies were used specifically for liver disease, with milk thistle being the most common. Among respondents with liver disease, CAM was used more commonly for anxiety or depression, fatigue, and substance use. The majority believed that these therapies improved health. Nearly one-third of therapies were not reported to health care providers, mostly due to failure of the provider to ask. **CONCLUSIONS:** CAM use, particularly herbs and supplements, is prevalent among US adults with liver disease. Many do not disclose their CAM use to their providers, despite some using potentially hepatotoxic substances.

DOI: 10.1097/MCG.0000000000000617

PMID: 27479144 [Indexed for MEDLINE]

3. Naturally complex: Perspectives and challenges associated with Botanical Dietary Supplement

Safety assessment. Shipkowski KA, Betz JM, Birnbaum LS, Bucher JR, Coates PM, Hopp DC, MacKay D, Oketch-Rabah H, Walker NJ, Welch C, Rider CV.

Food Chem Toxicol. 2018 Apr 4. pii: S0278-6915(18)30209-6. doi: 10.1016/j.fct.2018.04.007. [Epub ahead of print]

DOI: 10.1016/j.fct.2018.04.007

PMID: 29626579

4. China to roll back regulations for traditional medicine despite safety concerns. Cyranoski D.

Nature. 2017 Nov 29;551(7682):552-553. doi: 10.1038/nature.2017.23038.

DOI: 10.1038/nature.2017.23038

PMID: 29189784 [Indexed for MEDLINE]

5. Herbal Highs: Review on Psychoactive Effects and Neuropharmacology. Graziano S, Orsolini L, Rotolo MC, Tittarelli R, Schifano F, Pichini S.

Curr Neuropharmacol. 2017;15(5):750-761. doi: 10.2174/1570159X14666161031144427.

BACKGROUND: A new trend among users of new psychoactive substances' the consumption of "herbal highs": plant parts containing psychoactive substances. Most of the substances extracted from herbs, in old centuries were at the centre of religious ceremonies of ancient civilizations. Currently, these herbal products are mainly sold by internet web sites and easily obtained since some of them have no legal restriction.

OBJECTIVE: We reviewed psychoactive effects and neuropharmacology of the most used "herbal highs" with characterized active principles, with studies reporting mechanisms of action, pharmacological and subjective effects, eventual secondary effects including intoxications and/or fatalities **Method:** The PubMed database was searched using the following key words: herbal highs, *Argyrea nervosa*, *Ipomoea violacea* and *Rivea corymbosa*; *Catha edulis*; *Datura stramonium*; *Piper methysticum*; *Mitragyna speciosa*. **RESULTS:** Psychoactive plants here reviewed have been known and used from ancient times, even if for some of them limited information still exist regarding subjective and neuropharmacological effects and consequent eventual toxicity when plants are used alone or in combination with "classical" drugs of abuse.

CONCLUSION: Some "herbal highs" should be classified as harmful drugs since chronic administration has been linked with addiction and cognitive impairment; for some others taking into consideration only the recent trends of abuse, studies investigating these aspects are lacking.

DOI: 10.2174/1570159X14666161031144427

PMCID: PMC5771051

PMID: 27799032 [Indexed for MEDLINE]

6. Suspected Driving Under the Influence Case Involving Mitragynine. Wright TH.

J Anal Toxicol. 2018 Apr 27. doi: 10.1093/jat/bky028. [Epub ahead of print]

Mitragynine is a novel psychoactive substance (NPS) that has emerged as a designer opioid being distributed on the street. Mitragynine, also known as kratom, has dose-dependent pharmacological effects and possesses both stimulant-like and sedative effects due to dual-binding of α -adrenergic and μ -opioid receptors. This herbal remedy readily available online has caused adverse effects including tachycardia, agitation, tremors, hallucination and death; however, this is the first reported suspected driving under the influence case involving mitragynine. Additional testing outside of the normal routine protocol for suspected impaired driving cases was performed based on the admission of kratom use from the suspect to the drug recognition expert (DRE) officer. Based on the evaluation, the DRE officer concluded that the driver was under the influence of a central nervous system stimulant and cannabis. An alkaline drug screen identified mitragynine in a 37-year-old female driver who was suspected of driving under the influence after nearly striking an oncoming vehicle. A blood amphetamine concentration was quantified at 0.052 mg/L and mitragynine and citalopram were reported qualitatively. The goal of this case study is to provide demographic history, adverse effects and a DRE evaluation in a driver known to have abused mitragynine.

DOI: 10.1093/jat/bky028

PMID: 29718282

7. Histologic Characterization of Kratom Use-Associated Liver Injury. Rivero M, Chang M, Soldevila-Pico C, Lai J, Liu X.

Gastroenterology Res. 2018 Feb;11(1):79-82. doi: 10.14740/gr990e. Epub 2018 Feb 23.

Kratom is an herbal product derived from the leaves of Southeast Asian *Mitragyna speciosa* trees. It has traditionally been used by indigenous people to relieve fatigue and manage pain, diarrhea, or opioid withdrawal. The use of kratom has become more commonplace in the United States for similar purposes. Only rare reports of kratom liver toxicity exist in the literature but without histologic characterization. Herein, we report one case of kratom use-associated liver toxicity in a 38-year-old patient. The patient complained of dark colored urine and light colored stools after using kratom. He had unremarkable physical examination. Laboratory testing at presentation revealed elevated alanine aminotransferase (389 U/L), aspartate aminotransferase (220 U/L), total bilirubin (5.1 mg/dL), and alkaline phosphatase (304 U/L). There was no serology evidence of viral hepatitis A, B, and C. The acetaminophen level at presentation was below detectable limits. Ultrasound examination of the right upper quadrant revealed normal echogenicity and contour of the liver without bile ductal dilatation or disease of the gallbladder. The patient underwent liver biopsy 4 days after the initial presentation which revealed a pattern of acute cholestatic liver injury including zone 3 hepatocellular and canalicular cholestasis, focal hepatocyte dropout, mild portal inflammation, and bile duct injury. Kratom was stopped, the patient improved clinically and biochemically and was discharged 8 days after the initial presentation. To our best knowledge, this is the first case report detailing the histology of kratom use-associated liver injury.

DOI: 10.14740/gr990e

PMCID: PMC5827910

PMID: 29511414

8. Hepatotoxicity Associated with Use of the Weight Loss Supplement *Garcinia cambogia*: A Case Report and Review of the Literature. Kothadia JP, Kaminski M, Samant H, Olivera-Martinez M.

Case Reports Hepatol. 2018 Mar 12;2018:6483605. doi: 10.1155/2018/6483605. eCollection 2018.

The use of herbal and dietary supplements for weight loss is becoming increasingly common as obesity is becoming major health problem in the United States. Despite the popularity of these natural supplements, there are no guidelines for their therapeutic doses and their safety is always a concern. *Garcinia cambogia* extract with its active ingredient "hydroxycitric acid" is a component of many weight loss regimens. It suppresses fatty acid biosynthesis and decreases appetite. However, its prolonged use in weight maintenance is unknown. Here we describe a case of acute hepatitis after the use of *Garcinia cambogia* for weight loss.

DOI: 10.1155/2018/6483605

PMCID: PMC5867608

PMID: 29721342

9. Hepatic veno-occlusive disease related to *Gynura segetum*: A case report. Sun Z, Kang J, Zhang Y.

Medicine (Baltimore). 2018 Apr;97(17):e0552. doi: 10.1097/MD.000000000010552.

INTRODUCTION: Hepatic veno-occlusive disease (HVOD), as known as hepatic sinusoidal obstruction syndrome (HSOS), is an obliterative venulitis of the terminal hepatic venules, which is responsible for considerable mortality. The potential mechanism is destruction of hepatic sinusoidal endothelial cells (SEC), with sloughing and downstream occlusion of terminal hepatic venules. Here, we report a case of HVOD who have a history of ingestion of *Gynura segetum* for 1 month. The patient presents for abdominal pain and distension. He was diagnosed for HVOD using computerized tomography (CT) and ultrasonography of liver. And then best supportive care was added. However, without liver transplantation for financial reason, he died in 1 month after discharged from hospital. **CONCLUSIONS:** We think portal flow reversal was a characteristic imaging findings of HVOD, which can be listed as a specific diagnostic criterion of HVOD. Once the condition was worsening, liver transplantation should be considered as the first choice of treatment planning.

DOI: 10.1097/MD.000000000010552

PMID: 29703039 [Indexed for MEDLINE]

10. Acute toxic hepatitis induced by a herbal medicine : Anchusa Boraginaceae. Cagin YF, Seckin Y, Firat F, Samdanci E.

Acta Gastroenterol Belg. 2017 Oct-Dec;80(4):533-536.

BACKGROUND AND AIM: Herbal treatments are becoming increasingly popular in many countries. Anchusa Boraginaceae (also called Tort plant and beef tongue) is commonly used as a herbal medicine in Elazig region as diuretic and in the treatment of ulcers, and it is stated that this has no adverse effect. We report a case of acute hepatitis associated with long time use of high doses of Anchusa Boraginaceae. **CASE:** A 43-year-old male patient is drinking water of Anchusa Boraginaceae that is boiling for 14 days to dissolve the stones in the gallbladder. He had no medical history and did not take any other drugs or toxins. Two weeks later ; he admitted with developed tea colored like urine and yellowing of the body. Three weeks later; he was referred to the our department from the epicenter. Blood tests showed aspartate aminotransferase : 37 U/L, alanine aminotransferase : 66 U/L, gama glutamyl transferase : 23 U/L, total bilirubin : 16.9 mg/dL, direct bilirubin : 12 mg/dL, and INR : 1.3 Viral and autoimmune hepatitis were eliminated. Upper abdominal ultrasound was normal. After the herbal medicine was stopped on admission, the patient's laboratory tests didn't recover. Then; the support treatment was performed. The clinical and the laboratory values returned to normal after 2 months after the acute episode. **CONCLUSIONS:** The consumption of herbal medicines containing Anchusa Boraginaceae can induce toxic hepatitis. Recovery can be complete after discontinuation. This case report highlights the risk and lytic effect on gallstone associated with Anchusa Boraginaceae.

PMID: 29560651

11. Pyridoxine Toxicity Small Fiber Neuropathy With Dysautonomia: A Case Report. Bacharach R, Lowden M, Ahmed A.

J Clin Neuromuscul Dis. 2017 Sep;19(1):43-46. doi: 10.1097/CND.000000000000172.

Pyridoxine (vitamin B6) toxicity is a well-known cause of primary sensory, length-dependent, axonal polyneuropathy. Although sensory symptoms predominate, autonomic symptoms have also been reported in some cases. To date, there is no objective evidence of autonomic dysfunction reported in the literature. We present the case of a 41-year-old woman with 2 years of progressive burning pain, numbness, tingling, and weakness in a stocking-glove distribution who was found to have severe pyridoxine toxicity. Concurrent presence of large and small fiber nerve dysfunction was noted in the form of abnormal electromyography/ nerve conduction study demonstrating a chronic sensory polyneuropathy and autonomic testing demonstrating abnormal responses to quantitative sweat testing and cardiovagal function testing. This case highlights the need for consideration of small fiber nerve damage by obtaining autonomic testing in cases of pyridoxine toxicity.

DOI: 10.1097/CND.000000000000172

PMID: 28827489 [Indexed for MEDLINE]

12. Fatal Folic Acid Toxicity in Humans. Devnath GP, Kumaran S, Rajiv R, Shaha KK, Nagaraj A.

J Forensic Sci. 2017 Nov;62(6):1668-1670. doi: 10.1111/1556-4029.13489. Epub 2017 Mar 6.

Folic acid is B-9 vitamin. Folic acid is prescribed commonly for pregnant women to prevent neural tube defects in the fetus, patients under chemotherapy, pernicious anemia and to reduce the risk of stroke and cardiovascular disease. Acute or chronic ingestion of a large dose of folic acid generally manifests as neurological complications, which are reversible. In this present case, a 23-year-old pregnant woman committed suicide by consuming folic acid tablets and succumbed to death within 36 h. Postmortem toxicological analysis detected folic acid in viscera. Death following acute consumption of folic acid is rare and has been not reported in the literature, to the best of our knowledge.

DOI: 10.1111/1556-4029.13489

PMID: 28261784 [Indexed for MEDLINE]

13. How much is too much? Two contrasting cases of excessive vitamin D supplementation. Kim S, Stephens LD, Fitzgerald RL.

Clin Chim Acta. 2017 Oct;473:35-38. doi: 10.1016/j.cca.2017.08.004. Epub 2017 Aug 8.

BACKGROUND: In this report, we describe 2 contrasting cases of hypervitaminosis D. **CASE PRESENTATION:** Patient 1 was a 75-y old man who developed symptomatic hypercalcemia (peak serum calcium concentration of 15.3mg/dl; reference range: 8.5-10.6mg/dl), cardiac injury, and a high total serum vitamin D concentration of 243ng/ml (30-80ng/ml) as a result of daily consumption of prescribed 50,000IU ergocalciferol (vitamin D2) and 500mg calcium-citrate for 1y. Patient 2 was a 60-y old woman who consumed 40,000IU of cholecalciferol (vitamin D3) daily for >10months with a peak total serum vitamin D concentration of 479ng/ml (30-80ng/ml), but did not present with symptoms related to vitamin D toxicity. **CONCLUSION:** These cases demonstrate that individual responses to supraphysiologic concentrations of vitamin D for extended periods of time vary widely, and that defining a toxic concentration of this vitamin is difficult. The different outcomes in these two patients, despite months of high-dose vitamin D therapy, demonstrates that individual patient pharmacodynamics determine clinical sequelae.

DOI: 10.1016/j.cca.2017.08.004

PMID: 28801091 [Indexed for MEDLINE]

14. Critical elevation of international normalized ratio in an elderly woman using a natural health product. Pottie K, Premji K, Cheskey SL.

Can Fam Physician. 2017 Jul;63(7):536-537.

We present the clinical case of an older woman taking warfarin who experienced a critically elevated international normalized ratio (INR) possibly associated with a multivitamin supplement.

PMCID: PMC5507228

PMID: 28701443 [Indexed for MEDLINE]

15. Acute-on-chronic subdural hematoma in a patient taking Red Clover herbal supplement: A case report. Hall S, Walshe E, Ajayi C, Boyle K, Griffith C.

Surg Neurol Int. 2018 Feb 21;9:43. doi: 10.4103/sni.sni_174_17. eCollection 2018.

Background: Herbal supplements are commonly used, however, their side-effect profiles are poorly understood and not subject to the same scrutiny as prescribed medications. Some herbal supplements such as St Johns' Wort are accepted to interfere with clotting pathways, however others, including Red Clover have theoretical bleeding risks based on coumarin content with very little underlying evidence. **Case Description:** This case reports a 65-year-old woman who suffered a spontaneous acute-on-chronic subdural hemorrhage with a significant postoperative re-hemorrhage. She had no other risk factors for coagulopathy other than a history of taking Red Clover supplements for postmenopausal symptoms. Her normal INR combined with an intraoperative thromboelastogram confirmed a coagulopathy which was more consistent with anti-platelet effects than coumarin toxicity. After tranexamic acid and platelet transfusions she had no further bleeding and made an uneventful recovery. **Conclusion:** This case highlights another risk factor for intracranial hemorrhage and the importance of a thorough drug history. The mechanism of Red Clover induced coagulopathy appears to be mediated through anti-platelet actions, which is consistent with in-vitro evidence reporting its role in preventing platelet adhesion.

DOI: 10.4103/sni.sni_174_17

PMCID: PMC5843970

PMID: 29541484

16. Probiotics and infective endocarditis in patients with hereditary hemorrhagic telangiectasia: a clinical case and a review of the literature. Boumis E, Capone A, Galati V, Venditti C, Petrosillo N.

BMC Infect Dis. 2018 Feb 1;18(1):65. doi: 10.1186/s12879-018-2956-5.

BACKGROUND: In the last decades, probiotics have been widely used as food supplements because of their putative beneficial health effects. They are generally considered safe but rare reports of serious infections caused by bacteria included in the definition of probiotics raise concerns on their potential pathogenic role in patients with particular predisposing factors. Patients with hereditary hemorrhagic telangiectasia (HHT) are exposed to infections because of telangiectasias and arteriovenous malformations (AVMs). We describe what is, to our knowledge, the first case of infective endocarditis (IE) caused by *Lactobacillus rhamnosus* in a patient with HHT. A systematic review of the relevant medical literature is presented. **CASE PRESENTATION:** A patient with HHT and an aortic bioprosthesis was admitted because of prolonged fever not responding to antibiotics. The patient had a history of repeated serious infections with hospitalizations and prolonged use of antibiotics, and used to assume large amounts of different commercial products containing probiotics. Weeks before the onset of symptoms the patient had been treated with nasal packings and with surgical closure of a nasal bleeding site because of recurrent epistaxis. A diagnosis of IE of the aortic bioprosthesis was made. All blood cultures were positive for *L. rhamnosus*. The patients responded to a cycle of 6 weeks of amoxicillin/clavulanate plus gentamicin. A systematic review of IE linked to consumption of probiotics, and of infective endocarditis in patients with HHT was conducted. 10 cases of IE linked to probiotics consumption and 6 cases of IE in patients with HHT were found. **CONCLUSIONS:** Consumption of probiotics can pose a risk of serious infections in patients with particular predisposing factors. Patients with HHT can be considered at risk because of their predisposition to infections. Prophylaxis with antibiotics before nasal packings in patients with HHT can be considered.

DOI: 10.1186/s12879-018-2956-5

PMCID: PMC5796351

PMID: 29390976 [Indexed for MEDLINE]

17. Serotonin Syndrome from 5-Hydroxytryptophan Supplement Ingestion in a 9-Month-Old Labrador Retriever. Jennifer H, Mariana P, Karyn B.

J Med Toxicol. 2017 Jun;13(2):183-186. doi: 10.1007/s13181-017-0600-1. Epub 2017 Feb 16.

INTRODUCTION: 5-Hydroxytryptophan (5-HTP) supplements are available over the counter and labeled as sleeping aids and anxiolytics for human use. 5-HTP is a serotonin precursor and overdose can lead to serotonin syndrome. **CASE REPORT:** A 9-month-old female Labrador retriever was evaluated after ingestion of a 5-HTP supplement. Signs of agitation developed within 1 h of ingestion, and emesis was attempted by the owner with 3% hydrogen peroxide (H₂O₂) orally. On presentation, the dog was obtunded, bilaterally mydriatic and salivating. Physical exam revealed tachypnea, tachycardia, hyperthermia, and hypertension. Eighteen hours post presentation, the dog developed melena, hematemesis, and pigmenturia. A hemogram revealed mild anemia with evidence of oxidative erythrocyte damage (eccentricocytes, Heinz bodies, and siderocytes). A chemistry panel revealed markedly elevated creatine kinase and hyperbilirubinemia, supporting hemolytic anemia. A urinalysis revealed pigmenturia. Hemolytic anemia was presumed to be caused by oxidative damage secondary to gastrointestinal ulceration and circulatory embolism of H₂O₂. Treatment included fluid therapy, a mannitol constant rate infusion, antiemetics, gastroprotectants, and cyproheptadine as a serotonin antagonist. The patient responded well to treatment and was discharged within 48 h of presentation. **DISCUSSION:** Serotonin syndrome is an increasingly common toxic syndrome in veterinary medicine with the availability of over-the-counter medications that alter serotonin metabolism. The importance of appropriate client education regarding emesis with H₂O₂ is highlighted.

DOI: 10.1007/s13181-017-0600-1

PMCID: PMC5440317 [Available on 2018-06-01]

PMID: 28210931 [Indexed for MEDLINE]

18. Pneumonitis with Diffuse Alveolar Hemorrhage Induced by Sho-seiryu-to. Tsuchiya K, Toyoshima M, Suda T.

Intern Med. 2017 Oct 1;56(19):2623-2626. doi: 10.2169/internalmedicine.8779-16. Epub 2017 Sep 6.

A 78-year-old man presented with acute-onset fever and dyspnea. He had been taking Sho-seiryu-to for allergic rhinitis. A chest radiograph showed diffuse bilateral ground-glass opacities with subpleural sparing, crazy-paving pattern, and traction bronchiectasis. The patient's bronchoalveolar lavage fluid was bloody and transbronchial lung biopsy specimens showed alveolitis, organising pneumonia, and type 2 alveolar epithelial cell proliferation. There were no clinical and laboratory findings suggestive of respiratory tract infection or

connective tissue disease. Based on the clinical course and the exclusion of other etiologies, Sho-seiryu-to-induced pneumonitis with diffuse alveolar hemorrhage was considered. The patient's pneumonitis resolved after the discontinuation of the drug and the administration of systemic corticosteroid therapy.

DOI: 10.2169/internalmedicine.8779-16
PMCID: PMC5658529
PMID: 28883249 [Indexed for MEDLINE]

19. Rapid onset of multiple concurrent squamous cell carcinomas associated with the use of an arsenic-containing traditional medicine for chronic plaque psoriasis. Siefring ML, Lu D, States JC, Van Hoang M.

BMJ Case Rep. 2018 Mar 30;2018. pii: bcr-2017-222645. doi:10.1136/bcr-2017-222645.

We report a case of a 46-year-old Vietnamese man who developed widespread, numerous and concurrent cutaneous squamous cell carcinomas (SCCs) in non-sun exposed skin areas after taking a traditional medicine (TM) formulation for chronic plaque psoriasis. The SCC lesions began to develop within 12-15 months after beginning the arsenic-containing TM. The patient experienced both acute and chronic symptoms consistent with arsenic exposure. Laboratory investigation of a collected hair sample showed a significant arsenic level. The TM formulation used by the patient was tested and demonstrated an extremely high concentration of arsenic.

DOI: 10.1136/bcr-2017-222645
PMCID: PMC5884260
PMID: 29602886

20. Principal component analysis of synthetic adulterants in herbal supplements advertised as weight loss drugs. Dastjerdi AG, Akhgari M, Kamali A, Mousavi Z.

Complement Ther Clin Pract. 2018 May;31:236-241. doi: 10.1016/j.ctcp.2018.03.007. Epub 2018 Mar 15.

OBJECTIVE: Obesity is one of the major problems in many countries. Herbal drugs are widely used to treat obesity. Unfortunately the majority of herbal weight loss drugs are adulterated with active pharmaceutical ingredients. The purpose of the present study was to analyse herbal weight loss drugs for the general search for pharmaceuticals. **METHODS:** sixty one herbal weight loss drugs that were collected from herb shops and internet in Kermanshah, Iran were analysed qualitatively using gas chromatography/mass spectrometry. **RESULTS:** Of the 61 weight loss products sampled, 72% were found to be adulterated with tramadol, caffeine, fluoxetine, rizatriptan, venlafaxine and methadone. **CONCLUSION:** Herbal weight loss products were adulterated with controlled and legitimate drugs. Patients should be aware of the danger of using adulterated supplements.

DOI: 10.1016/j.ctcp.2018.03.007
PMID: 29705461

21. Chromatographic fingerprinting through chemometric techniques for herbal slimming pills: A way of adulterant identification. Shekari N, Vosough M, Tabar Heidar K.

Forensic Sci Int. 2018 May;286:213-222. doi: 10.1016/j.forsciint.2018.03.022. Epub 2018 Mar 19.

In the current study, gas chromatography-mass spectrometry (GC-MS) fingerprinting of herbal slimming pills assisted by chemometric methods has been presented. Deconvolution of two-way chromatographic signals of nine herbal slimming pills into pure chromatographic and spectral patterns was performed. The peak clusters were resolved using multivariate curve resolution-alternating least squares (MCR-ALS) by employing appropriate constraints. It was revealed that more useful chemical information about the composition of the slimming pills can be obtained by employing sophisticated GC-MS method coupled with proper chemometric tools yielding the extended number of identified constituents. The thorough fingerprinting of the complex mixtures proved the presence of some toxic or carcinogen components, such as toluene, furfural, furfuryl alcohol, styrene, itaconic anhydride, citraconic anhydride, trimethyl phosphate, phenol, pyrocatechol, p-propenylanisole and pyrogallol. In addition, some samples were shown to be

adulterated with undeclared ingredients, including stimulants, anorexiants and laxatives such as phenolphthalein, amfepramone, caffeine and sibutramine.

DOI: 10.1016/j.forsciint.2018.03.022

PMID: 29602149

22. A Review of the Toxicity of Compounds Found in Herbal Dietary Supplements. Hudson A, Lopez E, Almalki AJ, Roe AL, Calderón AI.

Planta Med. 2018 Apr 19. doi: 10.1055/a-0605-3786. [Epub ahead of print]

Use of herbal dietary supplements by the public is common and has been happening for centuries. In the United States, the Food and Drug Administration has a limited scope of regulation over marketed herbal dietary supplements, which may contain toxic botanical compounds that pose a public health risk. While the Food and Drug Administration has made efforts to prohibit the sale of unsafe herbal dietary supplements, numerous reports have proliferated of adverse events due to these supplements. This literature review investigates bioactive plant compounds commonly used in herbal dietary supplements and their relative toxicities. Using primarily the National Library of Medicine journal database and SciFinder for current reports, 47 toxic compounds in 55 species from 46 plant families were found to demonstrate harmful effects due to hepatic, cardiovascular, central nervous system, and digestive system toxicity. This review further contributes a novel and comprehensive view of toxicity across the botanical dietary market, and investigates the toxicity of the top ten botanical dietary supplements purchased in the United States of America to gauge the exposure risk of toxicity to the public. The criteria of measuring toxicity in this review (plant compound, family, quantity, and toxicity effects) across the entire market in the United States, with special attention to those supplements whose exposure to the consumer is maximal, provides a unique contribution to the investigation of botanical supplements.

DOI: 10.1055/a-0605-3786

PMID: 29672820

23. Traditional Chinese Medicine and Herb-induced Liver Injury: Comparison with Drug-induced Liver Injury. Jing J, Teschke R.

J Clin Transl Hepatol. 2018 Mar 28;6(1):57-68. doi: 10.14218/JCTH.2017.00033. Epub 2017 Oct 27.

Cases of suspected herb-induced liver injury (HILI) caused by herbal Traditional Chinese Medicines (TCMs) and of drug-induced liver injury (DILI) are commonly published in the scientific literature worldwide. As opposed to the multiplicity of botanical chemicals in herbal TCM products, which are often mixtures of several herbs, conventional Western drugs contain only a single synthetic chemical. It is therefore of interest to study how HILI by TCM and DILI compare with each other, and to what extent results from each liver injury type can be transferred to the other. China is among the few countries with a large population using synthetic Western drugs as well as herbal TCM. Therefore, China is well suited to studies of liver injury comparing drugs with TCM herbs. Despite some concordance, recent analyses of liver injury cases with verified causality, using the Roussel Uclaf Causality Assessment Method, revealed major differences in HILI caused by TCMs as compared to DILI with respect to the following features: HILI cases are less frequently observed as compared to DILI, have a smaller proportion of females and less unintentional rechallenge events, and present a higher rate of hepatocellular injury features. Since many results were obtained among Chinese residents who had access to and had used Western drugs and TCM herbs, such ethnic homogeneity supports the contention that the observed differences of HILI and DILI in the assessed population are well founded.

24. Risk assessment of pyrrolizidine alkaloids in food of plant and animal origin. Dusemund B, Nowak N, Sommerfeld C, Lindtner O, Schäfer B, Lampen A.

Food Chem Toxicol. 2018 Mar 7;115:63-72. doi: 10.1016/j.fct.2018.03.005. [Epub ahead of print]

Acute liver toxicity, specifically in the form of hepatic veno-occlusive disease (HVOD), is known from reports on human poisonings following ingestions of 1,2-unsaturated pyrrolizidine alkaloids (PAs) containing herbs. Recently PA exposure via common foods contaminated via PA-producing plants raised concern, especially regarding the potential of genotoxicity and carcinogenicity. The

health risks related to the estimated exposures to PAs from food were assessed. With respect to common foods, herbal teas and teas are the main sources through which consumers can be exposed to PAs. For high long-term consumption of these foods a possible health concern has been revealed in the assessment of chronic risks referring to a BMDL10 of 237 µg/kg bw per day recently established by EFSA based on model averaging for data on riddelliine. However, acute health damage from acute or short-term intake of PAs via common food is considered to be unlikely. Food supplements on the basis of PA-producing plants may significantly contribute to PA exposures and their intake is associated with risks of acute and chronic toxicity. However, no health risks have to be expected from the consumption of food supplements based on oil-based preparations of PA-producing plants, which were described to be free of PAs.

DOI: 10.1016/j.fct.2018.03.005

PMID: 29524571

25. Risk assessment for pyrrolizidine alkaloids detected in (herbal) teas and plant food supplements.

Chen L, Mulder PPJ, Louisse J, Peijnenburg A, Wesseling S, Rietjens IMCM.

Regul Toxicol Pharmacol. 2017 Jun;86:292-302. doi: 10.1016/j.yrtph.2017.03.019. Epub 2017 Mar 27.

Pyrrolizidine alkaloids (PAs) are plant metabolites present in some botanical preparations, with especially 1,2-unsaturated PAs being of concern because they are genotoxic carcinogens. This study presents an overview of tumour data on PAs and points of departure (PODs) derived from them, corroborating that the BMDL10 for lasiocarpine represents a conservative POD for risk assessment. A risk assessment using this BMDL10 and mean levels of PAs reported in literature for (herbal) teas, indicates that consumption of one cup of tea a day would result in MOE values lower than 10 000 for several types of (herbal) teas, indicating a priority for risk management for these products. A refined risk assessment using interim relative potency (REP) factors showed that based on the mean PA levels, 7(54%) of 13 types of (herbal) teas and 1 (14%) of 7 types of plant food supplements (PFS) resulted in MOE values lower than 10 000, indicating a priority for risk management also for these products in particular. This includes both preparations containing PA-producing and non-PA-producing plants. Our study provides insight in the current state-of-the art and limitations in the risk assessment of PA-containing food products, especially (herbal) teas and PFS, indicating that PAs in food presents a field of interest for current and future risk management.

DOI: 10.1016/j.yrtph.2017.03.019

PMID: 28347763 [Indexed for MEDLINE]

26. Plant toxins and acute medicinal plant poisoning in children: A systematic literature review.

Ghorani-Azam A, Sepahi S, Riahi-Zanjani B, Alizadeh Ghamsari A, Mohajeri SA, Balali-Mood M.

J Res Med Sci. 2018 Mar 27;23:26. doi: 10.4103/jrms.JRMS_629_17. eCollection 2018.

Background: For many years, medicinal plants and herbal therapy have been widely used in different societies for the treatment of various diseases. Besides their therapeutic potency, some of the medicinal plants have strong toxicity in human, especially in children and elderly. Despite common beliefs that natural products are safe, there have been few reports on their toxicities.

Materials and Methods: In the present study, we aimed to systematically review the literature wherein acute plant poisoning and herbal intoxication have been reported in pediatric patients. After literature search and selection of the appropriate documents, the desired data were extracted and described qualitatively. Results: A total of 127 articles with overall 1453 intoxicated cases were collected. The results of this study showed that some medicinal plants can cause acute poisoning and complications such as hepatic and renal failure in children. Conclusion: The findings of this survey showed that acute plant poisoning can be life-threatening in children, and since a single-ingested dose of toxic plants can cause acute poisoning, parents should be aware of these toxic effects and compare the side effects of self-medication with its potential benefits.

DOI: 10.4103/jrms.JRMS_629_17

PMCID: PMC5894275

PMID: 29692823

27. Nephrotoxicity and Chinese Herbal Medicine. Yang B, Xie Y, Guo M, Rosner MH, Yang H, Ronco C.

Clin J Am Soc Nephrol. 2018 Apr 3. pii: CJN.11571017. doi: 10.2215/CJN.11571017. [Epub ahead of print]

Chinese herbal medicine has been practiced for the prevention, treatment, and cure of diseases for thousands of years. Herbal medicine involves the use of natural compounds, which have relatively complex active ingredients with varying degrees of side effects. Some of these herbal medicines are known to cause nephrotoxicity, which can be overlooked by physicians and patients due to the belief that herbal medications are innocuous. Some of the nephrotoxic components from herbs are aristolochic acids and other plant alkaloids. In addition, anthraquinones, flavonoids, and glycosides from herbs also are known to cause kidney toxicity. The kidney manifestations of nephrotoxicity associated with herbal medicine include acute kidney injury, CKD, nephrolithiasis, rhabdomyolysis, Fanconi syndrome, and urothelial carcinoma. Several factors contribute to the nephrotoxicity of herbal medicines, including the intrinsic toxicity of herbs, incorrect processing or storage, adulteration, contamination by heavy metals, incorrect dosing, and interactions between herbal medicines and medications. The exact incidence of kidney injury due to nephrotoxic herbal medicine is not known. However, clinicians should consider herbal medicine use in patients with unexplained AKI or progressive CKD. In addition, exposure to herbal medicine containing aristolochic acid may increase risk for future uroepithelial cancers, and patients require appropriate postexposure screening.

DOI: 10.2215/CJN.11571017

PMID: 29615394

28. Toxic metals in ayurvedic preparations from a public health lead poisoning cluster investigation.

Mikulski MA, Wichman MD, Simmons DL, Pham AN, Clottey V, Fuortes LJ.

Int J Occup Environ Health. 2018 Mar 12:1-6. doi: 10.1080/10773525.2018.1447880.

[Epub ahead of print]

Background Herbal formulations, traditional medicine, and complementary and alternative medicine are used by the majority of the world's population. Toxicity associated with use of Ayurvedic products due to metal content is an increasingly recognized potential public health problem. Objectives Report on toxic metals content of Ayurvedic products obtained during an investigation of lead poisoning among users of Ayurvedic medicine. Methods Samples of Ayurvedic formulations were analyzed for metals and metalloids following established US. Environmental Protection Agency methods. Results Lead was found in 65% of 252 Ayurvedic medicine samples with mercury and arsenic found in 38 and 32% of samples, respectively. Almost half of samples containing mercury, 36% of samples containing lead and 39% of samples containing arsenic had concentrations of those metals per pill that exceeded, up to several thousand times, the recommended daily intake values for pharmaceutical impurities. Conclusions Lack of regulations regarding manufacturing and content or purity of Ayurvedic and other herbal formulations poses a significant global public health problem.

DOI: 10.1080/10773525.2018.1447880

PMID: 29528276