

1. German Kava Ban Lifted by Court: The Alleged Hepatotoxicity of Kava (*Piper methysticum*) as a Case of Ill-Defined Herbal Drug Identity, Lacking Quality Control, and Misguided Regulatory Politics. Kuchta K, Schmidt M, Nahrstedt A.

Planta Med. 2015 Dec;81(18):1647-53. doi: 10.1055/s-0035-1558295. Epub 2015 Dec 22.

Abstract: Kava, the rhizome and roots of *Piper methysticum*, are one of the most important social pillars of Melanesian societies. They have been used for more than 1000 years in social gatherings for the preparation of beverages with relaxing effects. During the colonial period, extract preparations found their way into Western medicinal systems, with experience especially concerning the treatment of situational anxiety dating back more than 100 years. It therefore came as a surprise when the safety of kava was suddenly questioned based on the observation of a series of case reports of liver toxicity in 1999 and 2000. These case reports ultimately led to a ban of kava products in Europe - a ban that has been contested because of the poor evidence of risks related to kava. Only recently, two German administrative courts decided that the decision of the regulatory authority to ban kava as a measure to ensure consumer safety was inappropriate and even associated with an increased risk due to the higher risk inherent to the therapeutic alternatives. This ruling can be considered as final for at least the German market, as no further appeal has been pursued by the regulatory authorities. However, in order to prevent further misunderstandings, especially in other markets, the current situation calls for a comprehensive presentation of the cardinal facts and misconceptions concerning kava and related drug quality issues.

PMID: 26695707 [PubMed - in process]

2. Acute liver failure associated with *Garcinia cambogia* use. Corey R, Werner KT, Singer A, Moss A, Smith M, et. al.

Ann Hepatol. Jan-Feb 2016;15(1):123-6

Abstract: Millions of Americans regularly use herbal supplements, but many are unaware of the potential hidden dangers. Numerous supplements have been associated with hepatotoxicity and, indeed dietary/herbal supplements represent an increasingly common source of acute liver injury. We report a case of acute liver failure requiring liver transplantation associated with the use of *Garcinia cambogia*, a supplement widely promoted for weight loss. When patients present with acute hepatitis or liver failure from an unknown etiology, a careful history of supplement use should be performed.

PMID: 26626648 [PubMed - in process]

3. Cholestatic liver injury secondary to artemisinin. Kumar S.

Hepatology. 2015 Sep;62(3):973-4. doi: 10.1002/hep.27900. Epub 2015 Jul 22.

Abstract: Herbal and dietary supplements (HDS) are an important cause of liver injury. Also known as Qinghaosu, artemisinin is a widely used Chinese herbal supplement with activity against malarial organisms, including those resistant to chloroquine. Artemisinin-derivative based combination therapy is U.S. Food and Drug Administration approved and recommended by the World Health Organization (WHO) for treatment of malaria. Liver injury associated with the use of artemisinin is extraordinarily rare. This report describes a case of severe liver injury secondary to artemisinin monotherapy.

PMID: 25980398 [PubMed - indexed for MEDLINE]

4. The Role of Adverse Event Reporting in the FDA Response to a Multistate Outbreak of Liver Disease Associated with a Dietary Supplement. Klontz KC, DeBeck HJ, LeBlanc P, Mogen KM, Wolpert BJ, et. al.

Public Health Rep. 2015 Sep-Oct;130(5):526-32.

Abstract: OBJECTIVE: Liver disease is a potential complication from using dietary supplements. This study investigated an outbreak of non-viral liver disease associated with the use of OxyELITE Pro(TM), a dietary supplement used for weight loss and/or muscle building. METHODS: Illness details were ascertained from MedWatch reports submitted to the U.S. Food and Drug Administration (FDA) describing consumers who ingested OxyELITE Pro alone or in combination with other dietary supplements. FDA's Forensic Chemistry Center analyzed samples of OxyELITE Pro. RESULTS: From February 2012 to February 2014, FDA received 114 reports of adverse events of all kinds involving consumers who ingested OxyELITE Pro. The onset of illness for the first report was December 2010 and for the last report was January 2014. Thirty-three states, two foreign nations, and Puerto Rico submitted reports. Fifty-five of the reports (48%) described liver disease in the absence of viral infection, gallbladder disease, autoimmune disease, or other known causes of liver damage. A total of 33 (60%) of these patients were hospitalized, and three underwent liver transplantation. In early 2013, OxyELITE Pro products entered the market with a formulation distinct from products sold previously. The new formulation replaced 1,3-dimethylamylamine with aegeline. However, the manufacturer failed to submit to FDA a required "new dietary ingredient" notice for the use of aegeline in OxyELITE Pro products. Laboratory analysis identified no drugs, poisons, pharmaceuticals, toxic metals, usnic acid, N-Nitroso-fenfluramine, pyrrolizidine alkaloids, aristocholic acid, or phenethylamines in the products. CONCLUSIONS: Vigilant surveillance is required for adverse events linked to the use of dietary supplements.

PMCID: PMC4529836 [Available on 2016-09-01]

PMID: 26327730 [PubMed - indexed for MEDLINE]

5. A case of hepatotoxicity induced by adulterated "Tiger king", a Chinese herbal medicine containing sildenafil. Nissan R, Poperno A, Stein GY, Shapira B, Fuchs S, et. al.

Curr Drug Saf. 2015 Nov 12. [Epub ahead of print]

Abstract: Detection of phosphodiesterase type 5 inhibitors and their analogues in "100% natural" or "herbal" supplements have been described in numerous reports. However, few reports have been published in relation to actual harm caused by counterfeit erectile dysfunction herbal supplements. We describe a case of a 65-year old male admitted to a tertiary hospital with acute liver toxicity, possibly induced by adulterated "Chinese herbal" supplement "Tiger King" for sexual enhancement. Chemical analysis of the tablets discovered the presence of therapeutic doses of sildenafil with no other herbal components. Other medications were excluded as potential causes of the hepatic impairment. According to the Naranjo adverse drug reaction scale and the Roussel Uclaf Causality Assessment Method (RUCAM) the probability of association of Hepatotoxicity with Sildenafil was "possible" and "probable" respectively (Naranjo score of 4, RUCAM score of 7). Within three days of admission, the patient's clinical status and liver function improved without any specific treatment. His liver function tests normalized 30 days post discharge. Further pharmacovigilance actions should be taken by regulatory authorities and pharmaceutical companies in order to determine the relation between sildenafil and hepatotoxicity. This case emphasizes the importance of raising public awareness on the potential dangers of "Tiger king" in particular, and other counterfeit medications or herbal supplements of unknown origin.

PMID: 26560492 [PubMed - as supplied by publisher]

6. Acute hepatitis induced by a Chinese herbal product Qibao Meiran Wan: a case study. Li X, Qu C, He Q, Chen W, Zhang X, et. al.

Int J Clin Exp Med. 2015 Jul 15;8(7):11624-7. eCollection 2015.

Abstract: Qibao Meiran Wan is a Chinese herbal product sold as a therapy for tonifying the liver and kidney, dizziness, premature graying of hair, backache, constipation, and night sweats. It is widely available in Chinese pharmacies and drugstores and is sold without prescription. We describe a case of acute liver injury in a 26-year-old Chinese man who developed symptomatic hepatitis 1 month after starting Qibao Meiran Wan. There was no evidence of viral hepatitis, Epstein-Barr virus, cytomegalovirus, autoimmune hepatitis, or Budd-Chiari syndrome. The liver injury slowly resolved over 20 days after discontinuing the herbal product. Herbal toxicity was later confirmed by a liver biopsy. Qibao Meiran Wan contains a mixture of several plants including *Polygonum multiflorum*, which was previously associated with hepatotoxicity. To our knowledge, this is the first report of hepatotoxicity by Qibao Meiran Wan. Clinicians treating patients with acute hepatitis of unclear etiology should pay attention to the consumption of Qibao Meiran Wan.

PMCID: PMC4565378

PMID: 26379995 [PubMed]

7. **Further Concerns About Glutamine: A Case Report on Hyperammonemic Encephalopathy.**

Cioccarelli L, Gautschi M, Etter R, Weck A, Takala J.

Crit Care Med. 2015 Oct;43(10):e458-60. doi: 10.1097/CCM.0000000000001151.

Abstract: OBJECTIVE: We report a case of a woman with hyperammonemic encephalopathy following glutamine supplementation. DESIGN: Case report. INTERVENTIONS: Plasma amino acid analysis suggestive of a urea cycle defect and initiation of a treatment with lactulose and the two ammonia scavenger drugs sodium benzoate and phenylacetate. Together with a restricted protein intake ammonia and glutamine plasma levels decreased with subsequent improvement of the neurological status. MEASUREMENTS AND MAIN RESULTS: Massive catabolism and exogenous glutamine administration may have contributed to hyperammonemia and hyperglutaminemia in this patient. CONCLUSION: This case adds further concerns regarding glutamine administration to critically ill patients and implies the importance of monitoring ammonia and glutamine serum levels in such patients.

PMID: 26035146 [PubMed - indexed for MEDLINE]

8. **To chew or not to chew: that's the question.** Yildiz H, Komuta M, Monsalve C, Starkel P, Lefebvre C.

Acta Clin Belg. 2015 Sep 16:2295333715Y0000000070. [Epub ahead of print]

Abstract: A 25-year-old Somali man was referred to the department of internal medicine because of nausea, vomiting and jaundice of recent onset. On physical examination, he was frankly icteric without clinical signs of chronic liver disease. Laboratory data showed evidence of acute hepatitis. Viral serologic tests for hepatitis A, B, C and E were negative. Antinuclear antibodies (ANA) were positive (titre 1 : 1280; speckled pattern, NV < 1 : 40) as well anti-actin antibodies (titre 75UA, NV < 20). A liver biopsy was performed and showed a feature compatible with toxic hepatitis. On further questioning, the patient admitted to daily chew Khat when he was living in Somalia. We concluded to Khat-induced toxic hepatitis together with high-titre anti-nuclear antibody mimicking serologic patterns of auto-immune hepatitis.

PMID: 26374255 [PubMed - as supplied by publisher]

9. **Start me up! Recurrent ventricular tachydysrhythmias following intentional concentrated caffeine ingestion.** Laskowski LK, Henesch JA, Nelson LS, Hoffman RS, Smith SW.

Clin Toxicol (Phila). 2015;53(8):830-3.

Abstract: CONTEXT: Nearly pure caffeine is sold as a "dietary supplement," with instructions to ingest 1/64th to 1/16th of one teaspoon (50-200 mg). We report a patient with refractory cardiac dysrhythmias treated with defibrillation, beta-adrenergic blockade, and hemodialysis to highlight concentrated caffeine's dangers. CASE DETAILS: A 20-year-old woman presented with severe agitation, tremor, and vomiting approximately 1-2 h after suicidal ingestion of concentrated caffeine (powder and tablets). Within minutes, ventricular fibrillation commenced. Defibrillation, intubation, and amiodarone administration achieved return of spontaneous circulation (ROSC). Shortly thereafter, she developed pulseless ventricular tachycardia (VTach), with ROSC after defibrillation and lidocaine. She subsequently experienced 23 episodes of pulseless VTach, each responsive to defibrillation. Activated charcoal was administered via orogastric tube. An esmolol infusion was started. Hemodialysis was initiated once she was hemodynamically stable. She was extubated the following day, continued on oral metoprolol, and transferred to psychiatry on hospital day seven, achieving full neurological recovery. Serum caffeine concentrations performed approximately six and 18 h post-ingestion (pre/post-dialysis) were 240.8 mcg/mL and 150.7 mcg/mL. DISCUSSION: Severe caffeine toxicity can produce difficult to treat, life-threatening dysrhythmias. Concentrated caffeine, marketed for dietary supplementation, presents a substantial public health risk that demands action to limit consumer availability.

PMID: 26279469 [PubMed - indexed for MEDLINE]

10. An Unusual Etiology for Bidirectional Ventricular Tachycardia. Yun-Tao Zhao, MD, PhD, Lei Wang, MD, Zhong Yi, MD, PhD

Can J Cardiol. 2015 Nov 18. doi: 10.1016/j.cjca.2015.06.024. [Epub ahead of print]

Abstract: Bidirectional ventricular tachycardia is a rare variety of tachycardia with a morphologically distinct presentation. The QRS axis and/or morphology alternate in the frontal plane leads. We report a patient with bidirectional ventricular tachycardia in association with aconitine poisoning.

PMID: 26604120 [PubMed - as supplied by publisher]

11. Herbal Cardiotoxicity: Can Mother Nature Hurt the Heart? Pollak PT.

Can J Cardiol. 2015 Oct 30. pii: S0828-282X(15)01374-4. doi: 10.1016/j.cjca.2015.08.024. [Epub ahead of print]

(editorial accompanying above case report)

PMID: 26604119 [PubMed - as supplied by publisher]

12. Successful Rescue of a Patient with Acute Aconitine Poisoning Complicated by Polycystic Renal Hemorrhage. Chen X, Wu R, Jin H, Gao R, Yang B, Wang Q.

J Nippon Med Sch. 2015;82(5):257-61. doi: 10.1272/jnms.82.257.

Abstract: INTRODUCTION: Aconitine is a highly toxic diterpenoid alkaloid, produced by plants of the Aconitum genus, that is still used in Chinese herbal medicines. Aconitine poisoning remains common in China and other parts of Asia. CASE REPORT: A 48-year-old man received a diagnosis of aconitine poisoning after ingesting herbal medicinal wine made with caowu, which is made from Aconitum kusnezoffii roots, and was admitted to our hospital's emergency department. Electrocardiography and thoracoabdominal computed tomography showed cardiovascular toxicity from aconitine poisoning along with polycystic renal hemorrhaging. Because the arrhythmia was not controlled with lidocaine, blood

purification with a reduced dosage of heparin was performed to treat the arrhythmia and to avoid increasing the bleeding of the polycystic renal hemorrhage. The patient recovered from aconitine poisoning and polycystic kidney hemorrhage. **CONCLUSIONS:** This case significantly advances our understanding of hemoperfusion with reduced heparin for the treatment of ventricular arrhythmia caused by aconitine poisoning.

PMID: 26568394 [PubMed - in process]

13. *Cryptostegia grandiflora* Toxicity Manifesting as Hyperkalemia, Complete Heart Block and Thrombocytopenia. Sangle SA, Inamdar S, Deshmukh V.

J Assoc Physicians India. 2015 May;63(5):79-81.

Abstract: Cardiac glycosides are widely available in botanic products and other naturally occurring substances worldwide. Accidental consumption of it leads to digitalis toxicity with varied systemic manifestations. We describe a case of consumption of extract of leaves of the Indian rubber vine plant (*Cryptostegia grandiflora*) which led to gastrointestinal, cardiac, electrolyte, and hematological disturbances.

PMID: 26591155 [PubMed - indexed for MEDLINE]

14. A case of Mobitz type II atrioventricular block due to *Nerium oleander* poisoning successfully managed with digoxin-specific Fab antibody fragments. Tatlısu MA, Çekirdekçi Eİ, Akyüz Ş, Nurkalem Z

Türk Kardiyol Dern Ars. 2015 Oct;43(7):648-50. doi: 10.5543/tkda.2015.65848.

Abstract: *Nerium oleander* is a popular ornamental plant grown in many tropical and subtropical countries and in the Mediterranean region. It is dangerous because it has been shown to contain several types of cardiac glycosides, and hence can cause cardiac arrhythmias resembling digoxin in their toxicologic manifestations. We report a patient presenting to our hospital with Mobitz type II atrioventricular block after drinking herbal tea prepared from oleander leaves. Three hours after admission, a 200-mg empiric dose of digoxin-specific Fab antibody fragments was administered intravenously over 30 minutes. A 12-lead electrocardiogram (ECG) revealed sinus rhythm at the end of infusion. After 72 hours, the patient was discharged without any symptoms.

PMID: 26536992 [PubMed - in process]

15. Star fruit toxicity: a cause of both acute kidney injury and chronic kidney disease: a report of two cases. Abeysekera RA, Wijetunge S, Nanayakkara N, Wazil AW, Ratnatunga NV, et. al.

BMC Res Notes. 2015 Dec 17;8(1):796. doi: 10.1186/s13104-015-1640-8.

Abstract: **BACKGROUND:** Star fruit (*Averrhoa carambola*) is commonly consumed as a herbal remedy for various ailments in tropical countries. However, the dangers associated with consumption of star fruit are not commonly known. Although star fruit induced oxalate nephrotoxicity in those with existing renal impairment is well documented, reports on its effect on those with normal renal function are infrequent. We report two unique clinical presentation patterns of star fruit nephrotoxicity following consumption of the fruit as a remedy for diabetes mellitus-the first, in a patient with normal renal function and the second case which we believe is the first reported case of chronic kidney disease (CKD) due to prolonged and excessive consumption of star fruits. **CASE PRESENTATION:** The first patient is a 56-year-old female diabetic patient who had normal renal function prior to developing acute kidney injury (AKI) after consuming large amount of star fruit juice at once. The second patient, a 60-year-old male, also diabetic presented with acute on chronic renal failure following ingestion of a significant number of star fruits in a

short duration with a background history of regular star fruit consumption over the past 2-3 years. Both had histologically confirmed oxalate induced renal injury. The former had histological features of acute tubulo-interstitial disease whilst the latter had acute-on-chronic interstitial disease; neither had histological evidence of diabetic nephropathy. Both recovered over 2 weeks without the need for haemodialysis. CONCLUSION: These cases illustrate the importance of obtaining the patient's detailed history with respect to ingestion of herbs, traditional medication and health foods such as star fruits especially in AKI or CKD of unknown cause.

PMCID: PMC4683968

PMID: 26680759 [PubMed - in process]

16. Clinically Relevant Pharmacokinetic Herb-drug Interactions in Antiretroviral Therapy. Fasinu PS, Gurley BJ, Walker LA.

Curr Drug Metab. 2015;17(1):52-64.

Abstract: For healthcare professionals, the volume of literature available on herb-drug interactions often makes it difficult to separate experimental/potential interactions from those deemed clinically relevant. There is a need for concise and conclusive information to guide pharmacotherapy in HIV/AIDS. In this review, the bases for potential interaction of medicinal herbs with specific antiretroviral drugs are presented, and several botanicals are discussed for which clinically relevant interactions in humans are established. Such studies have provided, in most cases, sufficient ground to warrant the avoidance of concurrent administration of antiretroviral (ARVs) drugs with St John's wort (*Hypericum perforatum*), black pepper (*Piper* species) and grapefruit juice. Other botanicals that require caution in the use with antiretrovirals include African potato (*Hypoxis hemerocallidea*), ginkgo (*Ginkgo biloba*), ginseng (*Panax* species), garlic (*Allium sativum*), goldenseal (*Hydrastis canadensis*) and kava kava (*Piper methysticum*). The knowledge of clinically significant herb-drug interaction will be important in order to avoid herb-induced risk of sub-therapeutic exposure to ARVs (which can lead to viral resistance) or the precipitation of toxicity (which may lead to poor compliance and/or discontinuation of antiretroviral therapy).

PMID: 26526838 [PubMed - in process]

17. Combined DNA, toxicological and heavy metal analyses provides an auditing toolkit to improve pharmacovigilance of traditional Chinese medicine (TCM). Coghlan ML, Maker G, Crighton E, Haile J, Murray DC, et. al.

Sci Rep. 2015 Dec 10;5:17475. doi: 10.1038/srep17475.

Abstract: Globally, there has been an increase in the use of herbal remedies including traditional Chinese medicine (TCM). There is a perception that products are natural, safe and effectively regulated, however, regulatory agencies are hampered by a lack of a toolkit to audit ingredient lists, adulterants and constituent active compounds. Here, for the first time, a multidisciplinary approach to assessing the molecular content of 26 TCMs is described. Next generation DNA sequencing is combined with toxicological and heavy metal screening by separation techniques and mass spectrometry (MS) to provide a comprehensive audit. Genetic analysis revealed that 50% of samples contained DNA of undeclared plant or animal taxa, including an endangered species of *Panthera* (snow leopard). In 50% of the TCMs, an undeclared pharmaceutical agent was detected including warfarin, dexamethasone, diclofenac, cyproheptadine and paracetamol. Mass spectrometry revealed heavy metals including arsenic, lead and cadmium, one with a level of arsenic >10 times the acceptable limit. The study showed 92% of the TCMs examined were found to have some form of contamination and/or substitution. This study demonstrates that a combination of molecular methodologies can provide an effective means by which to audit complementary and alternative medicines.

PMCID: PMC4675079

PMID: 26658160 [PubMed - in process]

18. Metabolomics and its application to the evaluation of the efficacy and toxicity of traditional Chinese herb medicines. Shi J, Cao B, Wang XW, Aa JY, Duan JA, et. al

J Chromatogr B Analyt Technol Biomed Life Sci. 2015 Nov 24. pii: S1570-0232(15)30233-6. doi: 10.1016/j.jchromb.2015.10.014. [Epub ahead of print]

Abstract: Traditional Chinese herb medicines (TCHMs) have been used in the treatment of a variety of diseases for thousands of years in Asian countries. The active components of TCHMs usually exert combined synergistic therapeutic effects on multiple targets, but with less potential therapeutic effect based on routine indices than Western drugs. These complex effects make the assessment of the efficacy of TCHMs and the clarification of their underlying mechanisms very challenging, and therefore hinder their wider application and acceptance. Metabolomics is a crucial part of systems biology. It allows the quantitative measurement of large numbers of the low-molecular endogenous metabolites involved in metabolic pathways, and thus reflects the fundamental metabolism status of the body. Recently, dozens of metabolomic studies have been devoted to prove the efficacy/safety, explore the underlying mechanisms, and identify the potential biomarkers to access the action targets of TCHMs, with fruitful results. This article presents an overview of these studies, focusing on the progress made in exploring the pharmacology and toxicology of various herbal medicines.

PMID: 26657802 [PubMed - as supplied by publisher]

19. Toxicity of Botanical Medicines: An Overlooked Global Health Problem. Marcus DM, Grollman AP.

Am J Public Health. 2016 Jan;106(1):16-7. doi: 10.2105/AJPH.2015.302937. Epub 2015 Nov 12.

ABSTRACT: Botanical remedies are used worldwide, especially in regions where a strong culture of traditional healing exists and access to conventional health care is limited. The belief that herbal remedies are safe, based primarily on their long history of use, is no longer tenable in view of extensive documentation of their adverse effects. Although extracts of *Aristolochia* sp. plants have been used in botanicals for more than 2000 years, the profound toxicity of their active principles, aristolochic acids (AAs), was recognized only 20 years ago.(1) Aristolochic acids concentrate in the renal cortex, where they cause aristolochic acid nephropathy (AAN): interstitial tubulonephritis, renal failure, and carcinomas of the upper urinary tract.

PMID: 26562106 [PubMed - in process]

20. Differentiation between two "fang ji" herbal medicines, *Stephania tetrandra* and the nephrotoxic *Aristolochia fangchi*, using hyperspectral imaging. Tankeu S, Vermaak I, Chen W, Sandasi M, Viljoen A.

Phytochemistry. 2015 Nov 26. pii: S0031-9422(15)30109-6. doi: 10.1016/j.phytochem.2015.11.008. [Epub ahead of print]

Abstract: *Stephania tetrandra* ("hang fang ji") and *Aristolochia fangchi* ("guang fang ji") are two different plant species used in Traditional Chinese Medicine (TCM). Both are commonly referred to as "fang ji" and *S. tetrandra* is mistakenly substituted and adulterated with the nephrotoxic *A. fangchi* as they have several morphological similarities. *A. fangchi* contains aristolochic acid, a carcinogen that causes urothelial carcinoma as well as aristolochic acid nephropathy (AAN). In Belgium, 128 cases of AAN was reported while in China, a further 116 cases with end-stage renal disease were noted. Toxicity issues associated with species substitution and adulteration necessitate the development of reliable methods for

the quality assessment of herbal medicines. Hyperspectral imaging in combination with partial least squares discriminant analysis (PLS-DA) is suggested as an effective method to distinguish between *S. tetrandra* and *A. fangchi* root powder. Hyperspectral images were obtained in the wavelength region of 920-2514nm. Reduction of the dimensionality of the data was done by selecting the discrimination information range (964-1774nm). A discrimination model with a coefficient of determination (R^2) of 0.9 and a root mean square error of prediction (RMSEP) of 0.23 was created. The constructed model successfully identified *A. fangchi* and *S. tetrandra* samples inserted into the model as an external validation set. In addition, adulteration detection was investigated by preparing incremental adulteration mixtures of *S. tetrandra* with *A. fangchi* (10-90%). Hyperspectral imaging showed the ability to accurately predict adulteration as low as 10%. It is evident that hyperspectral imaging has tremendous potential in the development of visual quality control methods which may prevent cases of aristolochic acid nephropathy in the future.

PMID: 26632529 [PubMed - as supplied by publisher]

21. An integrated system for identifying the hidden assassins in traditional medicines containing aristolochic acids. Wu L, Sun W, Wang B, Zhao H, Li Y, et. al.

Sci Rep. 2015 Aug 13;5:11318. doi: 10.1038/srep11318.

Abstract: Traditional herbal medicines adulterated and contaminated with plant materials from the Aristolochiaceae family, which contain aristolochic acids (AAs), cause aristolochic acid nephropathy. Approximately 256 traditional Chinese patent medicines, containing Aristolochiaceae materials, are still being sold in Chinese markets today. In order to protect consumers from health risks due to AAs, the hidden assassins, efficient methods to differentiate Aristolochiaceae herbs from their putative substitutes need to be established. In this study, 158 Aristolochiaceae samples representing 46 species and four genera as well as 131 non-Aristolochiaceae samples representing 33 species, 20 genera and 12 families were analyzed using DNA barcodes based on the ITS2 and psbA-trnH sequences. Aristolochiaceae materials and their non-Aristolochiaceae substitutes were successfully identified using BLAST1, the nearest distance method and the neighbor-joining (NJ) tree. In addition, based on sequence information of ITS2, we developed a Real-Time PCR assay which successfully identified herbal material from the Aristolochiaceae family. Using Ultra High Performance Liquid Chromatography-Mass Spectrometer (UHPLC-HR-MS), we demonstrated that most representatives from the Aristolochiaceae family contain toxic AAs. Therefore, integrated DNA barcodes, Real-Time PCR assays using TaqMan probes and UHPLC-HR-MS system provides an efficient and reliable authentication system to protect consumers from health risks due to the hidden assassins (AAs).

PMCID: PMC4535178

PMID: 26270958 [PubMed - in process]

22. Hepatotoxicity of Pyrrolizidine Alkaloids. Neuman MG, Cohen L, Opris M, Nanau RM, Hyunjin J.

J Pharm Pharm Sci. 2015 Nov;18(4):825-43.

Abstract: PURPOSE: This article aimed 1) to review herbal medicine containing pyrrolizidine alkaloids (PA)-induced toxicities of the liver; 2) to encourage the recognition and prevention of common problems encountered when using complementary and alternative medicine and 3) to review the toxic effects of herbal remedies containing PAs. DESIGN AND METHODS: We performed a systematic literature search using the PubMed and Google Scholar engines. The search was not restricted to languages. We also provide an interpretation of the data. CONCLUSIONS: Herbal remedies containing PAs can induce liver damage, including hepato- sinusoidal obstruction syndrome or veno-occlusive disease. Preventing overdose and monitoring long-term use of such remedies may avoid glutathione depletion leading to mitochondrial injury, and therefore avoid liver cell damage. Moreover, immediately stopping the herbal medication prevents further harm to the liver. Chronic consumption of hepatotoxicants can lead to cancer

formation and promotion. The role of active metabolites in PA-induced liver toxicity and their mechanism of action require further investigation.

PMID: 26626258 [PubMed - in process]

23. Pyrrolizidine and tropane alkaloids in teas and the herbal teas peppermint, rooibos and chamomile in the Israeli market. Shimshoni JA, Duebecke A, Mulder PP, Cuneah O, Barel S.

Food Addit Contam Part A Chem Anal Control Expo Risk Assess. 2015 Dec;32(12):2058-67. doi: 10.1080/19440049.2015.1087651. Epub 2015 Oct 15.

Abstract: Dehydro pyrrolizidine alkaloids (dehydro PAs) are carcinogenic phytotoxins prevalent in the Boraginaceae, Asteraceae and Fabaceae families. Dehydro PAs enter the food and feed chain by co-harvesting of crops intended for human and animal consumption as well as by carry-over into animal-based products such as milk, eggs and honey. Recently the occurrence of dehydro PAs in teas and herbal teas has gained increasing attention from the EU, due to the high levels of dehydro PAs found in commercially available teas and herbal teas in Germany and Switzerland. Furthermore, several tropane alkaloids (TAs, e.g. scopolamine and hyoscyamine) intoxications due to the consumption of contaminated herbal teas were reported in the literature. The aim of the present study was to determine the dehydro PAs and TAs levels in 70 pre-packed teabags of herbal and non-herbal tea types sold in supermarkets in Israel. Chamomile, peppermint and rooibos teas contained high dehydro PAs levels in almost all samples analysed. Lower amounts were detected in black and green teas, while no dehydro PAs were found in fennel and melissa herbal teas. Total dehydro PAs concentrations in chamomile, peppermint and rooibos teas ranged from 20 to 1729 µg/kg. Except for black tea containing only mono-ester retrorsine-type dehydro PAs, all other teas and herbal teas showed mixed patterns of dehydro PA ester types, indicating a contamination by various weed species during harvesting and/or production. The TA levels per teabag were below the recommended acute reference dose; however, the positive findings of TAs in all peppermint tea samples warrant a more extensive survey. The partially high levels of dehydro PAs found in teas and herbal teas present an urgent warning letter to the regulatory authorities to perform routine quality control analysis and implement maximum residual levels for dehydro PAs.

PMID: 26365752 [PubMed - in process]

24. Risk assessment on the use of herbal medicinal products containing pyrrolizidine alkaloids. Allgaier C, Franz S.

Regul Toxicol Pharmacol. 2015 Nov;73(2):494-500. doi:10.1016/j.yrtph.2015.09.024. Epub 2015 Sep 21.

Abstract: Pyrrolizidine alkaloids (PA) are common plantal toxins directed against insect herbivores. Unsaturated PAs are known to be hepatotoxic. Many of the PAs are in addition mutagenic and some may possibly be carcinogenic for humans. The risk of an exposure to PAs associated with their occurrence in herbal medicinal products and in foodstuff is under current discussion. The present risk assessment for herbal medicinal products containing PAs is based on a margin of safety derivation for foodstuff indicating that a life-long exposure to maximally 0.007 µg/kg bw/day is not expected to be associated with safety concerns. This approach offers a possibility to estimate the potential risk of PA-containing herbal medicinal products irrespective of the route of administration. It assumes PA levels in the final herbal medicinal product below 0.01 ppm and considers for dermal administration a 100% skin penetration of the PAs reflecting a worst-case scenario. As a result, the calculated margins of safety show a potential exposure using herbal medicinal products 70-, 45.5-, and 19.3-fold lower on a one-day base and 608-, 396-, and 168- fold lower on a one-year base for adults, children aged 12 years, and children aged 4 years, respectively, than the thresholds considered acceptable for foodstuff.

PMID: 26399164 [PubMed - in process]

25. **Critical review of resveratrol in xenobiotic-induced hepatotoxicity.** McGill MR, Du K, Weemhoff JL, Jaeschke H.

Food Chem Toxicol. 2015 Dec;86:309-18. doi: 10.1016/j.fct.2015.11.003. Epub 2015 Nov 10.

Abstract: Use of natural products is increasingly popular. In fact, many patients with liver diseases self-medicate with herbal supplements. Resveratrol (RSV), in particular, is a common natural product that can reduce injury in experimental models of liver disease. Xenobiotic hepatotoxicity is a particularly important area-of-need for therapeutics. Drug-induced liver injury, for example, is the most common cause of acute liver failure (ALF) and ALF-induced deaths in many countries. Importantly, RSV protects against hepatotoxicity in animal models in vivo caused by several drugs and chemicals and may be an effective intervention. Although many mechanisms have been proposed to explain the protection, not all are consistent with other data. Furthermore, RSV suffers from other issues, including limited bioavailability due to extensive hepatic metabolism. The purpose of this article is to summarize recent findings on the protective effects of RSV in xenobiotic-induced liver injury and other forms of liver injury and to provide a critical review of the underlying mechanisms. New mechanisms that are more consistent with data emerging from the toxicology field are suggested. Efforts to move RSV into clinical use are also considered. Overall, RSV is a promising candidate for therapeutic use, but additional studies are needed to better understand its effects.

PMID: 26561740 [PubMed - in process]

26. **Progress on mechanism of Tripterygium wilfordii-induced liver injury and detoxification mechanism of licorice.** Cao LJ, Yan M, Li HD, Zhang BK, Fang PF.

Zhongguo Zhong Yao Za Zhi. 2015 Jul;40(13):2537-41.

Abstract: Tripterygium wilfordii has exhibited multiple pharmacological activities, such as anti-inflammatory, immune modulation, anti-tumor and anti-fertility. T. wilfordii have been used for the therapy of inflammation and autoimmune diseases including rheumatoid arthritis, immune complex nephritis and systemic lupus erythematosus clinically. However, it is well known that T. wilfordii has small margin between the therapeutic and toxic doses and could cause serious injury on digestive, reproductive and urogenital systems. Among all the organs, liver is one of the most remarkable targets of T. wilfordii-induced toxicities, and the damage is more serious than others. It is generally accepted that T. wilfordii-induced liver injury is a result of the combined effects of toxic elements of T. wilfordii. It is reported in several studies that the mechanism of T. wilfordii-induced liver injury may be related to lipid peroxidation, cell apoptosis and immune damage, and so on. Licorice is one of the most commonly used Chinese herbal medicine, with effects of heat-clearing and detoxicating, anti-inflammatory and hepatoprotective, reconciling various drugs, and so on. Licorice often accompany T. wilfordii in clinical application which can significantly reduce the liver injury induced by T. wilfordii. The attenuated effect is exact, but the mechanism is still a lack of in-depth study. This paper reviews the studies on T. wilfordii-induced liver injury and the related mechanism as well as licorice and other traditional Chinese medicine accompany T. wilfordii to reduce the injury in recent years, so as to provide reference for related research in the future.

PMID: 26697674 [PubMed - in process]

27. **Adverse Psychiatric Effects Associated with Herbal Weight-Loss Products.** Bersani FS, Coviello M, Imperatori C, Francesconi M, Hough CM, et al.

Biomed Res Int. 2015;2015:120679. doi: 10.1155/2015/120679. Epub 2015 Sep 17.

Abstract: Obesity and overeating are among the most prevalent health concerns worldwide and

individuals are increasingly using performance and image-enhancing drugs (PIEDs) as an easy and fast way to control their weight. Among these, herbal weight-loss products (HWLPs) often attract users due to their health claims, assumed safety, easy availability, affordable price, extensive marketing, and the perceived lack of need for professional oversight. Reports suggest that certain HWLPs may lead to onset or exacerbation of psychiatric disturbances. Here we review the available evidence on psychiatric adverse effects of HWLPs due to their intrinsic toxicity and potential for interaction with psychiatric medications.

PMCID: PMC4589574

PMID: 26457296 [PubMed - in process]

28. Speciation and bioavailability of lead in complementary medicines. Bolan S, Naidu R, Kunhikrishnan A, Seshadri B, Ok YS, et. al.

Sci Total Environ. 2016 Jan 1;539:304-12. doi: 10.1016/j.scitotenv.2015.08.124. Epub 2015 Sep 11.

Abstract: Complementary medicines have associated risks which include toxic heavy metal(loid) and pesticide contamination. The objective of this study was to examine the speciation and bioavailability of lead (Pb) in selected complementary medicines. Six herbal and six ayurvedic medicines were analysed for: (i) total heavy metal(loid) contents including arsenic (As), cadmium (Cd), Pb and mercury (Hg); (ii) speciation of Pb using sequential fractionation and extended x-ray absorption fine structure (EXAFS) techniques; and (iii) bioavailability of Pb using a physiologically-based in vitro extraction test (PBET). The daily intake of Pb through the uptake of these medicines was compared with the safety guidelines for Pb. The results indicated that generally ayurvedic medicines contained higher levels of heavy metal(loid)s than herbal medicines with the amount of Pb much higher than the other metal(loid)s. Sequential fractionation indicated that while organic-bound Pb species dominated the herbal medicines, inorganic-bound Pb species dominated the ayurvedic medicines. EXAFS data indicated the presence of various Pb species in ayurvedic medicines. This implies that Pb is derived from plant uptake and inorganic mineral input in herbal and ayurvedic medicines, respectively. Bioavailability of Pb was higher in ayurvedic than herbal medicines, indicating that Pb added as a mineral therapeutic input is more bioavailable than that derived from plant uptake. There was a positive relationship between soluble Pb fraction and bioavailability indicating that solubility is an important factor controlling bioavailability. The daily intake values for Pb as estimated by total and bioavailable metal(loid) contents are likely to exceed the safe threshold level in certain ayurvedic medicines. This research demonstrated that Pb toxicity is likely to result from the regular intake of these medicines which requires further investigation.

PMID: 26363725 [PubMed - in process]

29. Contamination of soil, medicinal, and fodder plants with lead and cadmium present in mine-affected areas, Northern Pakistan. Nawab J, Khan S, Shah MT, Qamar Z, Din I, et. al.

Environ Monit Assess. 2015 Sep;187(9):605. doi: 10.1007/s10661-015-4807-9. Epub 2015 Sep 1.

Abstract: This study aimed to investigate the lead (Pb) and cadmium (Cd) concentrations in the soil and plants (medicinal and fodder) grown in chromite mining-affected areas, Northern Pakistan. Soil and plant samples were collected and analyzed for Pb and Cd concentrations using atomic absorption spectrometer. Soil pollution load indices (PLIs) were greater than 2 for both Cd and Pb, indicating high level of contamination in the study area. Furthermore, Cd concentrations in the soil surrounding the mining sites exceeded the maximum allowable limit (MAL) (0.6 mg kg⁻¹), while the concentrations of Pb were lower than the MAL (350 mg kg⁻¹) set by State Environmental Protection Administration (SEPA) for agriculture soil. The concentrations of Cd and Pb were significantly higher ($P < 0.001$) in the soil of the mining-contaminated sites as compared to the reference site, which can be attributed to the dispersion of toxic heavy metals, present in the bed rocks and waste of the mines. The concentrations of Pb and Cd in majority of medicinal and fodder plant species grown in surrounding areas of mines were higher than their

MALs set by World Health Organization/Food Agriculture Organization (WHO/FAO) for herbal (10 and 0.3 mg kg⁻¹), respectively) and edible (0.3 and 0.2 mg kg⁻¹), respectively) plants. The high concentrations of Cd and Pb may cause contamination of the food chain and health risk.

PMID: 26324064 [PubMed - in process]

30. "Wild cannabis": A review of the traditional use and phytochemistry of *Leonotis leonurus*.

Nsuala BN, Enslin G, Viljoen A.

J Ethnopharmacol. 2015 Nov 4;174:520-39. doi: 10.1016/j.jep.2015.08.013. Epub 2015 Aug 18.

Abstract: ETHNOPHARMACOLOGICAL RELEVANCE: *Leonotis leonurus*, locally commonly known as "wilde dagga" (=wild cannabis), is traditionally used as a decoction, both topically and orally, in the treatment of a wide variety of conditions such as haemorrhoids, eczema, skin rashes, boils, itching, muscular cramps, headache, epilepsy, chest infections, constipation, spider and snake bites. The dried leaves and flowers are also smoked to relieve epilepsy. The leaves and flowers are reported to produce a mild euphoric effect when smoked and have been said to have a similar, although less potent, psychoactive effect to cannabis. AIM OF THE REVIEW: To amalgamate the botanical aspects, ethnopharmacology, phytochemistry, biological activity, toxicity and commercial aspects of the scientific literature available on *L. leonurus*. METHODS: An extensive review of the literature from 1900 to 2015 was carried out. Electronic databases including Scopus®, SciFinder®, Pubmed®, Google Scholar® and Google® were used as data sources. All abstracts, full-text articles and books written in English were considered. RESULTS: The phytochemistry of particularly the non-volatile constituents of *L. leonurus* has been comprehensively investigated due to interest generated as a result of the wide variety of biological effects reported for this plant. More than 50 compounds have been isolated and characterised. *L. leonurus* contains mainly terpenoids, particularly labdane diterpenes, the major diterpene reported is marrubiin. Various other compounds have been reported by some authors to have been isolated from the plant, including, in the popular literature only, the mildly psychoactive alkaloid, leonurine. Leonurine has however, never been reported by any scientific analysis of the extracts of *L. leonurus*. CONCLUSION: Despite the publication of various papers on *L. leonurus*, there is still, however, the need for definitive research and clarification of other compounds, including alkaloids and essential oils from *L. leonurus*, as well as from other plant parts, such as the roots which are extensively used in traditional medicine. The traditional use by smoking also requires further investigation as to how the chemistry and activity are affected by this form of administration. Research has proven the psychoactive effects of the crude extract of *L. leonurus*, but confirmation of the presence of psychoactive compounds, as well as isolation and characterization, is still required. Deliberate adulteration of *L. leonurus* with synthetic cannabinoids has been reported recently, in an attempt to facilitate the marketing of these illegal substances, highlighting the necessity for refinement of appropriate quality control processes to ensure safety and quality. Much work is therefore still required on the aspect of quality control to ensure safety, quality and efficacy of the product supplied to patients, as this plant is widely used in South Africa as a traditional medicine. Commercially available plant sources provide a viable option for phytochemical research, particularly with regard to the appropriate validation of the plant material (taxonomy) in order to identify and delimit closely related species such as *L. leonurus* and *L. nepetifolia* which are very similar in habit.

PMID: 26292023 [PubMed - in process]

31. Determination of the inhibitory effect of green tea extract on glucose-6-phosphate

dehydrogenase based on multi-layer capillary enzyme micro-reactor. Camara MA, Tian M, Liu X, Liu X, Wang Y, Yang J, Yang L.

Biomed Chromatogr. 2015 Dec 10. doi: 10.1002/bmc.3669. [Epub ahead of print]

Abstract: Natural herbal medicines are an important source of enzyme inhibitors for the discovery of new drugs. A number of natural extracts such as green tea have been used in prevention and treatment of diseases due to their low-cost, low toxicity and good performance. The present study reports an online assay of the activity and inhibition of the green tea extract of the Glucose 6-phosphate dehydrogenase (G6PDH) enzyme using multi-layer capillary electrophoresis based immobilized enzyme micro-reactors (CE-IMERs). The multi-layer CE-IMERs were produced with layer-by-layer electrostatic assembly, which can easily enhance the enzyme loading capacity of the micro-reactor. The activity of the G6PDH enzyme was determined and the enzyme inhibition by the inhibitors from green tea extract was investigated using online assay of the multi-layer CE-IMERs. The Michaelis constant (K_m) of the enzyme, the IC_{50} and K_i values of the inhibitors were achieved and found to agree with those obtained using offline assays. The results show a competitive inhibition of green tea extract on the G6PDH enzyme. The present study provides an efficient and easy-to-operate approach for determining G6PDH enzyme reaction and the inhibition of green tea extract, which may be beneficial in research and the development of natural herbal medicines.

PMID: 26659432 [PubMed - as supplied by publisher]

32. Bottle gourd (*Lagenaria siceraria*) juice poisoning. Verma A, Jaiswal S.

World J Emerg Med. 2015;6(4):308-9. doi: 10.5847/wjem.j.1920-8642.2015.04.011.

Abstract: BACKGROUND: Bottle gourd (*Lagenaria siceraria*) is popularly known as lauki, ghia or dudhi in India. Its consumption is advocated by traditional medicine healers for controlling diabetes mellitus, hypertension, liver diseases, weight loss and other diseases. However, in last few years there have been reports of suspected toxicity due to consumption of its juice leading to severe vomiting and upper gastrointestinal bleeding. As emergency physicians we need to be aware of this very rare poisoning specially in India. METHODS: We present a case of a 52-year-old woman who presented with multiple episodes of hematemesis and shock to the emergency department (ED) after consuming bottle gourd juice. The patient was resuscitated and stabilized with fluids, proton pump inhibitors and antiemetics and shifted to the intensive care unit (ICU) under the care of a gastroenterology team for urgent endoscopy and further management. RESULTS: The patient received intravenous fluids, antibiotics, antiemetics, and antacids and underwent upper gastroenterologic endoscopy during the hospitalization. She was discharged in a stable condition 4 days later. CONCLUSIONS: As a member of the Cucurbitaceae family, bottle gourd contains toxic tetracyclic triterpenoid compounds called cucurbitacins which are responsible for the bitter taste and toxicity. There is no known antidote for this toxicity, and clinicians treat such patients symptomatically only. It is important to educate the public about the harmful effects of this potentially life-threatening toxicity.

PMCID: PMC4677076

PMID: 26693268 [PubMed]

33. Herbal Remedies Use by Breast Cancer Patients in the West Bank of Palestine. Jaradat NA, Shawahna R, Eid AM, Al-Ramahi R, Asma MK, Zaid AN.

J Ethnopharmacol. 2015 Dec 3. pii: S0378-8741(15)30251-8. doi:10.1016/j.jep.2015.11.050. [Epub ahead of print]

Abstract: ETHNOPHARMACOLOGICAL RELEVANCE: Recent ethnopharmacological surveys showed that herbal remedies are the most preferred modality of complementary and alternative medicine (CAM). In Palestine as in many other countries, herbal remedies are widely used in the treatment of many diseases. AIM OF THE STUDY: The aim of this study was to investigate the use of herbal remedies by women living with breast cancer in the West Bank of Palestine. METHODS: This study was a questionnaire based cross-sectional descriptive study on the use of herbal remedies by breast cancer patients in the West Bank. A questionnaire was distributed to 115 patients at outpatient cancer clinics in

face to face interviews. RESULTS: The study had a response rate of 89.6%. Of all respondents, 68% were herbal remedies users. Women with breast cancer used 46 plant species belonging to 32 families. Of these, Brassicaceae and Lamiaceae were the most prevalent. Ephedra alata was the most commonly used plant species in the treatment of breast cancer. Leaves and seeds were the most commonly used parts and decoction was the most commonly used method of preparation. Herbal remedies users were more likely to use herbal remedies instead of chemotherapy. The most commonly stated reason for using herbal remedies was the belief in boosting the patient's immune system to fight cancer. CONCLUSION: The use of herbal remedies is prevalent in breast cancer patients in Palestine. The use of herbal remedies was associated with educational level, time since diagnosis, type of surgery use, and use of endocrine therapy. It was apparent that the majority of users were satisfied with herbal remedies use. Clinical trials and pharmacological tests are required to be established for the presence of side effects, toxicity and efficacy for these herbal remedies.

PMID: 26656536 [PubMed - as supplied by publisher]

34. Treatment of nausea in pregnancy: a cross-sectional multinational web-based study of pregnant women and new mothers. Heitmann K, Holst L, Lupattelli A, Maltepe C, Nordeng H.

BMC Pregnancy Childbirth. 2015 Dec 1;15(1):321. doi: 10.1186/s12884-015-0746-2.

Abstract: BACKGROUND: The factors related to the treatment of nausea during pregnancy have not yet been investigated in several countries simultaneously. The present study aimed to describe differences in self-reported nausea during pregnancy and the patterns of use for both conventional and herbal medicines across countries. The factors related to nausea and its treatment and the relationships between different self-reported co-morbidities and nausea were also investigated. METHODS: This cross-sectional study used data collected by a web-based questionnaire distributed between October 2011 and February 2012 in several countries within five regions: Western, Northern, and Eastern Europe, North America, and Australia. Women who were pregnant or had a child less than one year old were eligible to participate. RESULTS: A total of 9113 women were included in the study, whereof 6701 (73.5 %) had experienced nausea during pregnancy. Among respondents with nausea, conventional medicines were used by 1201 (17.9 %) women and herbal medicines by 556 (8.3 %) women. The extent of self-reported nausea and its treatment varied by country. Education, working status, and folic acid use were significantly associated with the use of conventional medicines against nausea. Respondents who had nausea also had a high burden of co-morbidity. CONCLUSION: The prevalence of nausea was high across all participating countries but its treatment varied, possibly due to cultural differences and differences in attitudes towards medicines. A high degree of co-morbidity was found among respondents with nausea.

PMCID: PMC4667480

PMID: 26628289 [PubMed - in process]