AACT Herbal Dietary Supplements Special Interest Group Abstracts July 2016

1. **Cushing in a Leaf: Endocrine Disruption From a Natural Remedy.** Martini C, Zanchetta E, Di Ruvo M, Nalesso A, Battocchio M, Gentilin E, Degli Uberti E, Vettor R, Zatelli MC.

J Clin Endocrinol Metab. 2016 May 24:jc20161490. [Epub ahead of print]

BACKGROUND: Information regarding the safety of herbal drugs is often not reported. We describe the case of a 65-year-old woman referred to us for a iatrogenic hypercortisolism, who denied any previous steroid consumption. She reported only a chronic application of a phytocosmetic cream, containing ethanol extract of the Cardiospermum halicacabum (CH) plant. Adrenal insufficiency occurred after the cream application was stopped. CH is used in traditional and Western medicine for its documented anti-inflammatory properties. Once the presence of synthetic glucocorticoids was ruled out in the phytocosmetic product, we investigated whether and how its chronic application could have caused the iatrogenic hypercortisolism. METHODS: Liquid chromatography high-resolution mass spectrometry (LC-HRMS) was performed to exclude the presence of known glucocorticoids in the cream. ELISA assay and Western blot analysis were employed to assess ACTH secretion and the glucocorticoid receptor expression respectively in murine ACTH-secreting pituitary adenoma cells AtT-20/D16v-F2, treated with dexamethasone, CH tincture, and mifepristone alone or in combination. To detect specific interaction of CH extract with the glucocorticoid receptor, we performed a dual-luciferase reporter assay in HEK293 cells. RESULTS: In AtT-20/D16v-F2 cells CH extract showed to significantly reduce basal and CRH-induced ACTH secretion and the glucocorticoid receptor expression, similarly to dexamethasone; these effects were counteracted by mifepristone. In HEK293 cells dexamethasone significantly induced luciferase activity after 24 and 36 hour treatment, CH tincture only after 36 hours and these effects were antagonized by mifepristone. CONCLUSIONS: CH extract displays a glucocorticoid-like activity, by means of a direct binding to the glucocorticoid receptor.

DOI: 10.1210/jc.2016-1490
PMID: 27218272 [PubMed - as supplied by publisher]

2. **Case report: a rare case of attempted homicide with Gloriosa superba seeds.** Kande Vidanalage CJ, Ekanayeka R, Wijewardane DK.

BMC Pharmacol Toxicol. 2016 Jun 21;17(1):26. doi: 10.1186/s40360-016-0069-6.

BACKGROUND: Gloriosa superba, well known as the glory lily or superb lily, is a tropical climbing plant that features an exotic red flower. The plant is poisonous because of high concentrations of colchicine in all parts of the plant. It is commercially grown for use in Ayurveda medicine and as a cash crop for extracting colchicine in India and Africa. It is a wild plant in Sri Lanka and commercial cultivation is rare. Accidental and suicidal poisonings with Gloriosa tubers are well known and reported. There are no case reports of poisoning by Gloriosa seeds in Sri Lanka. Google and PubMed searches showed no reported cases of poisoning with seeds or their use with homicidal intent in other parts of the world. CASE PRESENTATION: A 27-year-old man was brought to hospital with profuse vomiting and diarrhea after drinking coriander tea, which is a common traditional treatment for common cold. The family members suspected poisoning by Gloriosa because they had seeds at home and the victim's sister-in-law who had made the herbal tea went missing from home. They were able to identify Gloriosa seeds, which looked similar to coriander, in the pot. The patient developed shock and respiratory distress and needed ventilation and intensive care. He also developed mild renal impairment, and thrombocytopenia. He developed massive generalised alopecia while recovering from acute illness. Full recovery was achieved after 15 days of hospital care. CONCLUSIONS: There are many poisonous plants in Asian countries. This case highlights the possibility of accidental or intentional use of Gloriosa seeds or its extracts to cause potentially fatal poisoning. It would be difficult to identify Gloriosa as the cause of poisoning

without any background information because of multiple complications that can mimic a systemic infection. This case is a good example of the use of plants as biological weapons.

DOI: 10.1186/s40360-016-0069-6
PMCID: PMC4915169
PMID: 27324655 [PubMed - in process]

3. **Drug-Induced Liver Injury: Highlights from a Review of the 2015 Literature.** Sarges P, Steinberg JM, Lewis JH.

Drug Saf. 2016 May 3. [Epub ahead of print]

Numerous publications contributed to the expanding knowledge base about drug-induced liver injury (DILI) in 2015. New findings from the US Drug Induced Liver Injury Network (DILIN) in their most recently updated registry include a 1-to 3-week delay in the appearance of acute DILI from short-course antibiotics such as cefazolin. They corroborated the finding that acute DILI in patients with underlying liver disease was far more severe and potentially fatal than in patients without liver disease. The only drug that seemed to have an increased risk of hepatotoxicity in these patients was azithromycin. While nearly one in six patients with acute DILI had persistently elevated liver tests at 6 months, and results for 75 % of these patients continued to be abnormal at 12 months, most of these "chronic" injury cases were relatively minor and the result of cholestatic hepatotoxins. Newly described DILI agents include tolvaptan, as well as some new direct-acting antiviral protease inhibitors for chronic hepatitis C. The latter have been associated with serious acute hepatitis, hyperbilirubinemia, and decompensation. Herbal hepatotoxicity continues to be increasingly reported, although applying causality assessment to these cases can, in fact, be more challenging than with prescription drugs. As important as cases with DILI, the class of PCSK9 inhibitors used to lower low-density lipoprotein (LDL) cholesterol have not been associated with significant liver injury, in contrast with other lipid-lowering agents. With respect to pharmacologic DILI risk factors, new data show that drugs metabolized by cytochrome P450 enzymes had a nearly four times higher likelihood of causing DILI. Interestingly, high lipophilicity, which was previously felt to be a risk factor for DILI, was not found to be associated, although more study is needed to confirm this observation. While human leukocyte antigen (HLA) genotypes have been linked to several specific agents, the role of such testing in the general population remains undefined due to the currently low positive and negative predictive values of the available tests. New DILI biomarkers, specifically microRNA-122 and keratin-18, among others, appear to have the necessary predictive value to determine the prognosis and outcome of patients with paracetamol (acetaminophen [AAP])-induced acute liver failure (ALF), and may be of great benefit in deciding who requires N-Acetyecysteine (NAC), and for what duration. Treatment options for other forms of DILI remain limited; no firm conclusions can currently be drawn for the use of NAC in non-AAP ALF.

DOI: 10.1007/s40264-016-0427-8
PMID: 27142208 [PubMed - as supplied by publisher]

4. **Severe Acute Hepatocellular Injury Attributed to OxyELITE Pro: A Case Series.** Heidemann LA, Navarro VJ, Ahmad J, Hayashi PH, Stolz A, Kleiner DE, Fontana RJ.

Dig Dis Sci. 2016 May 3. [Epub ahead of print]

BACKGROUND/AIM: Herbal and dietary supplement (HDS) hepatotoxicity is increasingly being reported in the USA. This case series describes the presenting clinical features and outcomes of seven patients with liver injury attributed to OxyELITE Pro enrolled in the Drug-Induced Liver Injury Network (DILIN) study. METHODS: The 6-month outcomes of patients with hepatotoxicity attributed to OxyELITE Pro enrolled in the DILIN prospective registry between 2004 and 2015 are presented. RESULTS: Six of the seven patients (86 %) presented in 2013 with symptoms of

hepatitis and acute hepatocellular injury. The median duration of OxyELITE Pro use was 18 weeks (range 5-102 weeks). Median age was 36 years (range 28-62), 86 % were female, and 43 % were Asian. One patient had rash, none had eosinophilia, and three had antinuclear antibody reactivity. The median peak ALT was 2242 U/L, alkaline phosphatase 284 U/L and bilirubin 15.0 mg/dL. Six patients (86 %) were hospitalized, three developed acute liver failure and two underwent liver transplantation. DILIN causality scores for OxyELITE Pro were definite in 1,highly likely in 3, probable in 2, and possible in 1. Four of the five patients without liver transplant recovered completely within 6 months, while one patient had mild residual ALT elevations. CONCLUSIONS: Seven cases of severe acute hepatocellular injury attributed to OxyELITE Pro are reported. These results reinforce the need to assess for HDS supplement use in patients presenting with unexplained acute hepatitis and point to the need for additional regulatory oversight of HDS products.

DOI: 10.1007/s10620-016-4181-7
PMID: 27142670 [PubMed - as supplied by publisher]

5. **Acute Hepatitis after Ingestion of a Preparation of Chinese Skullcap and Black Catechu for Joint Pain.** Papafragkakis C, Ona MA, Reddy M, Anand S.

Case Reports Hepatol. 2016;2016:4356749. doi: 10.1155/2016/4356749. Epub 2016 Apr 10.

Many herbal preparations are routinely used and have been occasionally associated with a wide range of side effects, from mild to severe. Chinese skullcap and black catechu are herbal medications commonly used for their hepatoprotective and other properties. We report a case of acute toxic hepatitis associated with ingestion of Chinese skullcap and black catechu in one preparation for the alleviation of joint pain.

DOI: 10.1155/2016/4356749
PMCID: PMC4842037
PMID: 27144042 [PubMed]

6. **Coca: The History and Medical Significance of an Ancient Andean Tradition.** Biondich AS, Joslin JD.

Emerg Med Int. 2016;2016:4048764. doi: 10.1155/2016/4048764. Epub 2016 Apr 7.

Coca leaf products are an integral part of the lives of the Andean peoples from both a cultural and traditional medicine perspective. Coca is also the whole plant from which cocaine is derived. Coca products are thought to be a panacea for health troubles in regions of South America. This review will examine the toxicology of whole coca and will also look at medicinal applications of this plant, past, present, and future.

DOI: 10.1155/2016/4048764
PMCID: PMC4838786
PMID: 27144028 [PubMed]

7. **hERG Channel Blocking Ipecac Alkaloids Identified by Combined In Silico - In Vitro Screening.** Kratz JM, Mair CE, Oettl SK, Saxena P, Scheel O, Schuster D, Hering S, Rollinger JM.

Planta Med. 2016 May 4. [Epub ahead of print]

Human ether-a-go-go-related gene channel blocking is associated with QT interval prolongation and increased risk of potentially fatal arrhythmias. As natural products keep increasing in popularity, there is an urgent need for studies assessing human ether-a-go-go-related gene channel-related cardiotoxic risks. We selected 49 plant species based on the results of a

pharmacophore-based virtual screening campaign, in parallel with a literature data survey concerning highly consumed herbal medicines with reported cardiac liabilities. Lead-like enhanced extracts were prepared, an initial in vitro screening was performed at 100 μg/mL by voltage clamp on Xenopus oocytes, and five human ether-a-go-go-related gene channel blocking extracts were identified. In accordance to the six virtually predicted alkaloids, the root extract of Carapichea ipecacuanha inhibited human ether-a-go-go-related gene channel currents by 32.5%. A phytochemical workflow resulted in the isolation and identification of five out of the six virtually predicted alkaloids. All isolates blocked human ether-a-go-go-related gene channel currents to different extents. The major ipecac constituents emetine (1) and cephaeline (2) showed IC50 values of 21.4 and 5.3 μM, respectively, measured by whole-cell patch clamp in HEK293 cells. This is the first report on human ether-a-go-go-related gene channel blockers from C. ipecacuanha. Its roots and rhizomes are used to produce different pharmacopeial ipecac preparations that are mainly used as emetics for poisoning treatment. Our findings raise further questions regarding the safety and over-the-counter appropriateness of these herbal products.

DOI: 10.1055/s-0042-105572
PMID: 27145237 [PubMed - as supplied by publisher]

8. **Pharmacokinetics of hERG Channel Blocking Voacangine in Wistar Rats Applying a Validated LC-ESI-MS/MS Method.** Mair CE, de Miranda Silva C, Grienke U, Kratz JM, Carreño F, Zimmermann ES, de Araújo BV, Dalla Costa T, Rollinger JM.

Planta Med. 2016 Jun 3. [Epub ahead of print]

Herbal preparations from Voacanga africana are used in West and Central African folk medicine and are also becoming increasingly popular as a legal high in Europe. Recently, the main alkaloid voacangine was found to be a potent human ether-à-go-go-related gene channel blocker in vitro. Blockage of this channel might imply possible cardiotoxicity. Therefore, the aim of this study was to characterise voacangine in vivo to assess its pharmacokinetics and to estimate if further studies to investigate its cardiotoxic risk are required. Male Wistar rats received different doses of voacangine as a pure compound and as a hydro-ethanolic extract of V. africana root bark with a quantified amount of 9.71% voacangine. For the obtained data, a simultaneous population pharmacokinetics model was successfully developed, comprising a two-compartment model for i.v. dosing and a one-compartmental model with two first-order absorption rates for oral dosing. The absolute bioavailability of voacangine was determined to be 11-13%. Model analysis showed significant differences in the first absorption rate constant for voacangine administered as a pure compound and voacangine from the extract of V. africana. Taking into account the obtained low bioavailability of voacangine, its cardiotoxic risk might be neglectable in healthy consumers, but may have a serious impact in light of drug/drug interactions and impaired health conditions.

DOI: 10.1055/s-0042-107800
PMID: 27257769 [PubMed - as supplied by publisher]

9. **Induction of P-glycoprotein expression and activity by Aconitum alkaloids: Implication for clinical drug-drug interactions.** Wu J, Lin N, Li F, Zhang G, He S, Zhu Y, Ou R, Li N, Liu S, Feng L, Liu L, Liu Z, Lu L.

Sci Rep. 2016 May 3;6:25343. doi: 10.1038/srep25343.

The Aconitum species, which mainly contain bioactive Aconitum alkaloids, are frequently administered concomitantly with other herbal medicines or chemical drugs in clinics. The potential risk of drug-drug interactions (DDIs) arising from co-administration of Aconitum alkaloids and other drugs against specific targets such as P-glycoprotein (P-gp) must be evaluated. This study focused on the effects of three representative Aconitum alkaloids: aconitine (AC), benzoylaconine (BAC), and aconine, on the expression and activity of P-gp. We observed that Aconitum alkaloids increased P-gp expression in LS174T and Caco-2 cells in the order AC>BAC>aconine. Nuclear

receptors were involved in the induction of P-gp. AC and BAC increased the P-gp transport activity. Strikingly, intracellular ATP levels and mitochondrial mass also increased. Furthermore, exposure to AC decreased the toxicity of vincristine and doxorubicin towards the cells. In vivo, AC significantly up-regulated the P-gp protein levels in the jejunum, ileum, and colon of FVB mice, and protected them against acute AC toxicity. Taken together, the findings of our in vitro and in vivo experiments indicate that AC can induce P-gp expression, and that co-administration of AC with P-gp substrate drugs may cause DDIs. Our findings have important implications for Aconitum therapy in clinics.

DOI: 10.1038/srep25343
PMCID: PMC4853792
PMID: 27139035 [PubMed - in process]

10. **A randomized, double-blind, multicenter, placebo-controlled clinical study on the efficacy and safety of Shenmai injection in patients with chronic heart failure.** Xian S, Yang Z, Lee J, Jiang Z, Ye X, Luo L, Jin L, Yang T, Ye S, Lu D.

J Ethnopharmacol. 2016 Jun 20;186:136-42. doi: 10.1016/j.jep.2016.03.066. Epub 2016 Apr 1.

ETHNOPHARMACOLOGICAL RELEVANCE: Shenmai injection (SMI) is a traditional Chinese herbal medicine extracted from Panax ginseng (Panax ginseng C.A. Mey, steamed and dry) and Ophiopogon japonicus (Ophiopogon japonicus (L.f.) Ker-Gawl, root). It has been widely used for the treatment of chronic heart failure (CHF) in China. However, the evidence supporting its effects remains unclear due to lack of high quality trials. The aim of this study was to investigate the efficacy and safety of SMI in CHF patients with coronary artery disease (CAD). MATERIALS AND METHODS: This double-blind, multicenter study randomized 240 eligible patients equally to receive SMI or placebo (100ml/day) in addition to standard medicines for the treatment of CHF. The primary endpoint was the New York Heart Association (NYHA) functional classification. The secondary endpoints were 6-min walking distance (6MWD), short-form 36 (SF-36) hearth survey score, traditional Chinese medicines (TCM) syndrome score, left ventricular ejection fractions (LVEF) and B-type natriuretic peptide (BNP) level. RESULTS: During treatment of 1 week, the NYHA functional classification was gradually improved in both groups, but the SMI group demonstrated a significantly greater improvement compared with the placebo group ($p=0.001$). Moreover, the improvement in patients received SMI was superior to those in control group with respect to 6MWD, SF-36 score and TCM syndrome score. Treatment with SMI within 1 week was well tolerated with no apparent safety concerns. CONCLUSIONS: The integrative treatment with standard medicines plus SMI can further improve NYHA functional classification for patients with CHF and CAD. Therefore, SMI could be recommended in the combination therapy for CHF accompanied with CAD.

DOI: 10.1016/j.jep.2016.03.066
PMID: 27045864 [PubMed - in process]

11. **Caffeine toxicity in forensic practice: possible effects and under-appreciated sources.** Musgrave IF, Farrington RL, Hoban C, Byard RW.

Forensic Sci Med Pathol. 2016 Jun 25. [Epub ahead of print]

Caffeine is considered a very safe stimulant and is widely consumed in a variety of forms, from pure caffeine to beverages and foods. Typically, death is only seen when gram quantities of caffeine are consumed, usually in suicide attempts. Even in this scenario, death is rare. However, there are special populations that need to be considered in forensic presentations, who may be at greater risk. These include poor metabolizers, people with liver disease, and people with cardiac conditions, who can die as a result of caffeine intake at levels well below what is ordinarily considered toxic. Also, caffeine intake may be hidden. For example, herbal medicines with substantial caffeine content may not disclose these concentrations on their product label. The role

of caffeine in medicolegal deaths is yet to be defined, however, herbal medicines and herbal weight loss supplements may represent an underappreciated source of caffeine in this context.

DOI: 10.1007/s12024-016-9786-9
PMID: 27344159 [PubMed - as supplied by publisher]

12. **The current state of research on ayahuasca: A systematic review of human studies assessing psychiatric symptoms, neuropsychological functioning, and neuroimaging.** Dos Santos RG, Balthazar FM, Bouso JC, Hallak JE.

J Psychopharmacol. 2016 Jun 10. pii: 0269881116652578. [Epub ahead of print]

RATIONALE: In recent decades, the use of ayahuasca (AYA) - a β-carboline- and dimethyltryptamine-rich hallucinogenic botanical preparation traditionally used by Northwestern Amazonian tribes for ritual and therapeutic purposes - has spread from South America to Europe and the USA, raising concerns about its possible toxicity and hopes of its therapeutic potential. Thus, it is important to analyze the acute, subacute, and long-term effects of AYA to assess its safety and toxicity. OBJECTIVES: The purpose of this study was to conduct a systematic review of human studies assessing AYA effects on psychiatric symptoms, neuropsychological functioning, and neuroimaging. METHODS: Papers published until 16 December 2015 were included from PubMed, LILACS and SciELO databases following a comprehensive search strategy and pre-determined set of criteria for article selection. RESULTS: The review included 28 full-text articles. Acute AYA administration was well tolerated, increased introspection and positive mood, altered visual perceptions, activated frontal and paralimbic regions and decreased default mode network activity. It also improved planning and inhibitory control and impaired working memory, and showed antidepressive and antiaddictive potentials. Long-term AYA use was associated with increased cortical thickness of the anterior cingulate cortex and cortical thinning of the posterior cingulate cortex, which was inversely correlated to age of onset, intensity of prior AYA use, and spirituality. Subacute and long-term AYA use was not associated with increased psychopathology or cognitive deficits, being associated with enhanced mood and cognition, increased spirituality, and reduced impulsivity. CONCLUSIONS: Acute, subacute, and long-term AYA use seems to have low toxicity. Preliminary studies about potential therapeutic effects of AYA need replication due to their methodological limitations.

DOI: 10.1177/0269881116652578
PMID: 27287824 [PubMed - as supplied by publisher]

13. **Herbal medicines: challenges in the modern world. Part 1. Australia and New Zealand.** Barnes J, McLachlan AJ, Sherwin CM, Enioutina EY.

Expert Rev Clin Pharmacol. 2016 Jul;9(7):905-15. doi:10.1586/17512433.2016.1171712. Epub 2016 Apr 12.

As in many developed countries, herbal medicines (HMs) are widely used in Australia and New Zealand (NZ). The popularity of HM continues to rise. Western, Asian and indigenous HMs are used, reflecting the cultural diversity of people in this region. HMs in Australia are regulated on a risk-based system with many HMs identified as being low risk. The legislation was reviewed in 2015 and proposals for change are under consideration. In NZ, it is recognised that current regulations for HMs and other natural health products (NHPs) do not adequately protect public health. NZ is entering a phase of regulatory change for this sector, and proposals for a 'light-touch' regulatory framework for NHPs are planned to be introduced into legislation during 2016.

DOI: 10.1586/17512433.2016.1171712
PMID: 27070431 [PubMed - in process]

14. **Herbal medicines: challenges in the modern world. Part 2. European Union and**

Russia. Sammons HM, Gubarev MI, Krepkova LV, Bortnikova VV, Corrick F, Job KM, Sherwin CM, Enioutina EY.

Expert Rev Clin Pharmacol. 2016 May 27:1-11. [Epub ahead of print]

INTRODUCTION: Herbal medicines (HMs) have been well known to people of the European Union (EU) and Russia for centuries. Currently, Western HMs can be classified into two categories, plant-derived conventional medicines and dietary supplements. Interest to HMs has grown rapidly in all countries during the past two decades. AREAS COVERED: The main goal of this review article is to present the history of HMs in the EU and Russia, forms of modern HMs, including Oriental Medicines that are popular among consumers of both countries. Additional discussion points comprise safety and adulteration issues associated with HMs, including regulatory changes and new legislative measures undertaken by the authorities. Materials available from legislative and governmental websites, PubMed and news media were used. Expert commentary: Due to cultural diversities in the EU and Russia, traditional HMs of other regions, particularly Chinese Traditional and Ayurvedic medicines, are also popular. Recently, dietary supplements containing multiple herbal and other natural products have flooded the EU and Russian markets. Pharmacovigilance in these markets is challenging in terms of establishing quality and safety of ingredients, determining efficacy, and defining risks of herb-herb and herb-drug interactions. Both the EU and Russia have introduced new legislation aimed to overcome these deficiencies.

DOI: 10.1080/17512433.2016.1189326
PMID: 27171366 [PubMed - as supplied by publisher]

15. **Herbal medicines: challenges in the modern world. Part 3. China and Japan**. Teng L, Zu Q, Li G, Yu T, Job KM, Yang X, Di L, Sherwin CM, Enioutina EY.

Expert Rev Clin Pharmacol. 2016 Jun 8:1-9. [Epub ahead of print]

INTRODUCTION: Medicinal plants, and formulations prepared from them, have been used in China and Japan for thousands of years. Nowadays, ancient formulations of Traditional Chinese and Kampo (Japanese) Medicines coexist with Western herbal medicines (HMs) and complement each other. HMs are used for the treatment of mild and chronic diseases, as an adjunct therapy, to improve wellbeing and delay aging, or as healthy (functional) foods. AREAS COVERED: This article, a third part in a series of reviews, is focusing on history, use and regulation of the traditional and modern HMs in Japan and China. Materials available from legislative and governmental websites, PubMed and news media were used. Expert commentary: HMs are heavily regulated in both countries, often in a similar manner as conventional pharmaceutical drugs. The majority of herbal formulations are sold as over-the-counter medications supplied with leaflets describing indications and appropriate dosages for patients of different ages. Medical practitioners prescribe herbal formulations that are tailored to the needs of particular patients. Both countries had problems with adverse drug reactions and toxicity of single herbs and herbal formulations that have been investigated by authorities, and some drugs have been removed from the market.

DOI: 10.1080/17512433.2016.1195263
PMID: 27232545 [PubMed - as supplied by publisher]

16. **Scientific and Regulatory Perspectives in Herbal and Dietary Supplement Associated Hepatotoxicity in the United States.** Avigan MI, Mozersky RP, Seeff LB.

Int J Mol Sci. 2016 Mar 3;17(3). pii: E331. doi: 10.3390/ijms17030331.

In the United States (US), the risk of hepatotoxicity linked to the widespread use of certain herbal products has gained increased attention among regulatory scientists. Based on current US law, all dietary supplements sold domestically, including botanical supplements, are regulated by the Food

and Drug Administration (FDA) as a special category of foods. Under this designation, regulatory scientists do not routinely evaluate the efficacy of these products prior to their marketing, despite the content variability and phytochemical complexity that often characterizes them. Nonetheless, there has been notable progress in the development of advanced scientific methods to qualitatively and quantitatively measure ingredients and screen for contaminants and adulterants in botanical products when hepatotoxicity is recognized.

DOI: 10.3390/ijms17030331
PMCID: PMC4813193
PMID: 26950122 [PubMed - in process]

17. **Systematic Review of Adverse Effects from Herbal Drugs Reported in Randomized Controlled Trials.** Lee JY, Jun SA, Hong SS, Ahn YC, Lee DS, Son CG.

Phytother Res. 2016 May 16. doi: 10.1002/ptr.5647. [Epub ahead of print]

Herbal drugs have become a popular form of healthcare, raising concerns about their safety. This study aimed to characterize the adverse effects of herbal drugs through a systematic review of results reported in randomized controlled trials (RCTs). Using eight electronic databases including PubMed, the Cochrane library and six Korean medical databases, the frequency of reported toxicity was recorded based on drug composition and indication. Among 4957 potentially relevant articles, 242 papers comprised of 244 studies met our inclusion criteria; these included 111 studies of a single herb and 133 of multiple herbs. These studies accounted for a total 15 441 participants (male = 5590; female = 9851; 7383 for single and 8058 for multiple herb studies). There were 480 cases (3.1%) of adverse events (344 for single, 136 for multiple herb studies; $p < 0.01$). A total of 259 cases reported blood test abnormalities, including five cases of abnormality in hepatic functional enzymes. The most frequently reported adverse event was digestive symptoms (44.3%), followed by nervous system symptoms (17.3%) and behaviors such as loss of appetite (16.3%). This is the first systematic review of adverse effects of herbal drugs among clinical studies, and the results indicate that herbal drugs are relatively safe.

DOI: 10.1002/ptr.5647
PMID: 27196988 [PubMed - as supplied by publisher]

18. **Use of Medicinal Plants with Teratogenic and Abortive Effects by Pregnant Women in a City in Northeastern Brazil.** Araújo CR, Santiago FG, Peixoto MI, Oliveira JO, Coutinho Mde S.

Rev Bras Ginecol Obstet. 2016 Mar;38(3):127-31. doi: 10.1055/s-0036-1580714. Epub 2016 Mar 29.

Purpose The purpose of this study is to verify the use of medicinal plants by pregnant women treated at four Basic Health Units and at a public maternity facility in Brazil's northeast. Methods This is a cross-sectional, quantitative study, performed between February and April 2014. The subjects were 178 pregnant women, aged 18 to 42 years. To collect data, a structured questionnaire with dichotomous and multiple choice questions was used. To verify the correlation between the variables, Pearson's chi-square test was used. Results The study showed that 30.9% of the pregnant women used medicinal plants, and boldo was the most cited (35.4%). All the plants utilized, except lemongrass, have toxic effects in pregnancy, according to Resolution SES/RJ N° 1757. There was no statistically significant correlation between social class and use of medicinal plants. Conclusion The health of the study participants and their unborn children is at risk due to the inappropriate use of medicinal plants.

DOI: 10.1055/s-0036-1580714
PMID: 27022784 [PubMed - in process]

19. **Adulteration of herbal sexual enhancers and slimmers: The wish for better sexual well-being and perfect body can be risky.** Skalicka-Woźniak K, Georgiev MI, Orhan IE.

Food Chem Toxicol. 2016 Jun 20. pii: S0278-6915(16)30199-5. doi:10.1016/j.fct.2016.06.018. [Epub ahead of print]

The popularity of herbal medicines and dietary supplements is increasing all over the world due to the many side-effects assigned to synthetic drugs. Herbal remedies should be considered as safe, with no side-effects, but unfortunately, even if they are labelled as natural, large numbers of adulterants, not only with toxic heavy metals but also with undeclared synthetic substances, have been detected up to date. In this review, the most frequent instances of adulteration of herbal medicines and dietary supplements acting as sexual enhancers and slimming products are thoroughly discussed. The great success of synthetic phosphodiesterase type-5 (PDE-5) inhibitory drugs like sildenafil, vardenafil and tadalafil, used for the treatment of erectile dysfunction has made them, as well as their unapproved analogues, popular as adulterants in herbal dietary supplements. The second group among blockbuster products are herbal preparations for slimming purpose, as obesity and gaining weight are major problems worldwide. Here, sibutramine hydrochloride monohydrate, an anti-obesity drug which inhibits serotonergic and noradrenergic reuptake, seems to be the most common adulterant. Together with large numbers of its analogues, thyroid hormones, anorexigens, diuretics, stimulants, and laxative agents are also detected in most of tested diet supplements.

DOI: 10.1016/j.fct.2016.06.018
PMID: 27338710 [PubMed - as supplied by publisher]

20. **Involvement of herbal medicine as a cause of mesenteric phlebosclerosis: results from a large-scale nationwide survey.** Shimizu S, Kobayashi T, Tomioka H, Ohtsu K, Matsui T, Hibi T.

J Gastroenterol. 2016 May 24. [Epub ahead of print]

BACKGROUND: Mesenteric phlebosclerosis (MP) is a rare disease characterized by venous calcification extending from the colonic wall to the mesentery, with chronic ischemic changes from venous return impairment in the intestine. It is an idiopathic disease, but increasing attention has been paid to the potential involvement of herbal medicine, or Kampo, in its etiology. Until now, there were scattered case reports, but no large-scale studies have been conducted to unravel the clinical characteristics and etiology of the disease. METHODS: A nationwide survey was conducted using questionnaires to assess possible etiology (particularly the involvement of herbal medicine), clinical manifestations, disease course, and treatment of MP. RESULTS: Data from 222 patients were collected. Among the 169 patients (76.1 %), whose history of herbal medicine was obtained, 147 (87.0 %) used herbal medicines. The use of herbal medicines containing sanshishi (gardenia fruit, Gardenia jasminoides Ellis) was reported in 119 out of 147 patients (81.0 %). Therefore, the use of herbal medicine containing sanshishi was confirmed in 70.4 % of 169 patients whose history of herbal medicine was obtained. The duration of sanshishi use ranged from 3 to 51 years (mean 13.6 years). Patients who discontinued sanshishi showed a better outcome compared with those who continued it. CONCLUSIONS: The use of herbal medicine containing sanshishi is associated with the etiology of MP. Although it may not be the causative factor, it is necessary for gastroenterologists to be aware of the potential risk of herbal medicine containing sanshishi for the development of MP.

DOI: 10.1007/s00535-016-1218-9
PMID: 27220772 [PubMed - as supplied by publisher]

21. **Acute Disseminated Encephalomyelitis after Oral Therapy with Herbal Extracts: A Case Report.** Kaymakamzade B, Karabudak R, Kurne AT, Nurlu G.

Balkan Med J. 2016 May;33(3):366-9. doi: 10.5152/balkanmedj.2016.140420. Epub 2016 May 1.

BACKGROUND: Acute disseminated encephalomyelitis (ADEM) is a rare demyelinating disease of the central nervous system, commonly attributed to infections or vaccinations. Toxic or allergenic compounds can also trigger a response in the immune system and may cause demyelination. We present a case with ADEM after using oral herbal medications.
CASE REPORT: A 25 year-old male developed bilateral central facial palsy and severe quadriparesis after taking herbal drugs (containing echinacea and many other herbal ingredients) for two weeks. He had used the extract to increase his potency and reproductivity. He had no past history of recent immunization or viral infection. The clinical findings, cerebrospinal fluid (CSF) analysis and brain magnetic resonance imaging (MRI) were compatible with ADEM. The neurological findings were improved after seven doses of pulse methylprednisolone treatment. To our knowledge, this is the third report in the literature that links herbal therapy and demyelinating disease. CONCLUSION: Most of the ADEM cases related to herbal therapy in the literature similarly used echinacea. It is our opinion that other ingredients of the herbal extract used by our case, besides echinacea, could have the potential to cause a trigger in the immune system. Further studies are needed to clarify the immunological effects of different kinds of herbal compounds, as well as the effects of different parts of the plants and the results of various dosages. Moreover, ingredients should also be tested for toxicity, adverse effects and drug interactions.

DOI: 10.5152/balkanmedj.2016.140420
PMCID: PMC4899001
PMID: 27308086 [PubMed]

22. **Oral exposure to aristolochic acid I induces gastric histological lesions with non-specific renal injury in rat.** Pu XY, Shen JY, Deng ZP, Zhang ZA.

Exp Toxicol Pathol. 2016 Jun;68(6):315-20. doi: 10.1016/j.etp.2016.03.003. Epub 2016 Mar 24.

Many Aristolochia species herbal drugs, used for diseases treatment since antiquity, contain active component aristolochic acid mixture, which consists of aristolochic acid I and II. However, it remains unclear whether aristolochic acid I is gastrotoxic, though evidence has shown that aristolochic acid mixture is nephrotoxic, carcinogenic, and genotoxic. The present study aimed to investigate the gastrotoxicity in rats treated with aristolochic acid I alone. Four groups of rats were orally administrated with vehicle (1% NaHCO3), or 30mg, 60mg, and 90mg/kg/day of aristolochic acid I for twelve days. The results showed that aristolochic acid I can induce obvious body weight loss, forestomach injury characterized by necrosis, ulcer, hyperkeratosis, and hyperplasia of epithelial cells. The severity of these forestomach lesions was presented in a dose-dependent mode. Meanwhile, only non-specific, slight renal tubule degeneration, and occasionally single necrotic epithelial cell were found in aristolochic acid I-treated rats' kidney. These resulst indicated aristolochic acid I had obvious gastrotoxicity, and such aristolochic acid I-induced forestomach toxicity probably presented much prior to kidney injury. Such irritation lesions may play a partial role in gastric cancer development of rats induced by aristolochic acid. Therefore, these results expanded our understanding on the digestive system toxicity of aristolochic acid I.

DOI: 10.1016/j.etp.2016.03.003
PMID: 27019954 [PubMed - in process]

23. **Evaluation of herbal product use and possible herb-drug interactions in Turkish elderly**. Turkmenoglu FP, Kutsal YG, Dolgun AB, Diker Y, Baydar T.

Complement Ther Clin Pract. 2016 May;23:46-51. doi: 10.1016/j.ctcp.2016.03.004. Epub 2016 Mar 18.

OBJECTIVES: To determine the prevalence and documentation of the use of herbal remedies by individuals aged ≥65 years and to evaluate possible adverse reactions and herb-drug interactions. METHOD: Using a cross-sectional research design, data were collected from 1418 participants (age range 65-95 years) via interview-based questionnaires. RESULTS: The prevalence of herbal use among older adults was 30% (n = 426); 64% (n = 274) used more than one prescription medication, and polyherbacy was reported by 47.5% (n = 202) of participants. Some participants used herbal products that are known to interfere with conventional drugs used to treat chronic diseases, such as cardiac glycosides, diuretics, anticoagulants, antidiabetics, anticonvulsants, and monoamine oxidase inhibitors. CONCLUSION: To ensure good patient care, it is important that healthcare professionals are aware of possible health complications associated with the concomitant use of herbs and medications.

DOI: 10.1016/j.ctcp.2016.03.004
PMID: 27157958 [PubMed - in process]

23. **Potential hazards of toxic metals found in toothpastes commonly used in Nigeria.**
Orisakwe OE, Okolo KO, Igweze ZN, Ajaezi GC, Udowelle NA.

Rocz Panstw Zakl Hig. 2016;67(2):197-204.

BACKGROUND: Toothpastes have multi-functional configurations as oral care products. They can however constitute a pos- sible source, amongst others, of toxic metal exposure in public health. Indeed, the public health impact of personal hygiene and consumer products is largely unknown. OBJECTIVE: To determine the level of toxic metals (lead, cadmium, cobalt, chromium, nickel) in toothpastes available in Nigeria, (home produced and imported), and assess the potential risk to the people. MATERIAL AND METHOD: The samples of toothpastes commonly used in Nigeria were tested. Using a market basket protocol thirty five different brands of toothpaste were used. Samples were digest by addition of 10 mL mixture of conc. nitric and hydrochloric acids (HCl:HNO , 3:1), followed by heating to dryness. 20 mL deionized water was added, stirred and filtered. The filtrate was made up in standard volumetric flask and lead, cadmium, chromium, cobalt and nickel concentrations were determined using the atomic absorption spectrophotometry 205A. The daily intake of metals and target hazard quotient (THQ) were then calculated. RESULTS: Pepsodent and Flodent had the highest levels of lead at respectively 23.575 and 18.092 mg/kg while Colgate Herbal had the highest nickel of 18.535 mg/kg. The daily intake estimates of all imported toothpaste samples were below the stated upper limits (UL). All target hazard quotients were also found to be below one. CONCLUSIONS: Although the UL, THQ and daily intake rates were all normal, the high levels of lead in some of the tooth- pastes an important concern to public health suggesting that pre-marketing safety studies of toothpastes may be worthwhile for the regulatory authorities.

PMID: 27289516 [PubMed - in process]

24. **Data on heavy metals and selected anions in the Persian popular herbal distillates.**
Keshtkar M, Dobaradaran S, Soleimani F, Karbasdehi VN, Mohammadi MJ, Mirahmadi R, Ghasemi FF.

Data Brief. 2016 May 12;8:21-5. doi: 10.1016/j.dib.2016.05.005. eCollection 2016.

In this data article, we determined the concentration levels of heavy metals including Pb, Co, Cd, Mn, Mg, Fe and Cu as well as selected anions including [Formula: see text] , [Formula: see text], [Formula: see text] and [Formula: see text] in the most used and popular herbal distillates in Iran. It is well known that heavy metals may pose a serious health hazard due to their bioaccumulation

throughout the trophic chain ("Heavy metals (Cd, Cu, Ni and Pb) content in two fish species of Persian Gulf in Bushehr Port, Iran" (Dobaradaran et al., 2013) [1]; "Comparative investigation of heavy metal, trace, and macro element contents in commercially valuable fish species harvested off from the Persian Gulf" (Abadi et al., 2015) [2]) as well as some other environmental pollutions, "Assessment of sediment quality based on acid-volatile sulfide and simultaneously extracted metals in heavily industrialized area of Asaluyeh, Persian Gulf: concentrations, spatial distributions, and sediment bioavailability/toxicity" (Arfaeinia et al., 2016) [3]. The concentration levels of heavy metals and anions in herbal distillates samples were determined using flame atomic absorption spectrometry (FAAS, Varian AA240, Australia) and a spectrophotometer (M501 Single Beam Scanning UV/VIS, UK) respectively.

DOI: 10.1016/j.dib.2016.05.005
PMCID: PMC4885015
PMID: 27274526 [PubMed]

25. **A review on the elemental contents of Pakistani medicinal plants: Implications for folk medicines**. Aziz MA, Adnan M, Begum S, Azizullah A, Nazir R, Iram S.

J Ethnopharmacol. 2016 Jul 21;188:177-92. doi: 10.1016/j.jep.2016.05.011. Epub 2016 May 10.

ETHNOPHARMACOLOGICAL RELEVANCE: Substantially, plants produce chemicals such as primary and secondary metabolites, which have significant applications in modern therapy. Indigenous people mostly rely on traditional medicines derived from medicinal plants. These plants have the capacity to absorb a variety of toxic elements. The ingestion of such plants for medicinal purpose can have imperative side effects. Hence, with regard to the toxicological consideration of medicinal plants, an effort has been made to review the elemental contents of ethno medicinally important plants of Pakistan and to highlight the existing gaps in knowledge of the safety and efficacy of traditional herbal medications. MATERIALS AND METHODS: Literature related to the elemental contents of ethno medicinal plants was acquired by utilizing electronic databases. We reviewed only macro-elemental and trace elemental contents of 69 medicinal plant taxa, which are traditionally used in Pakistan for the treatment of sundry ailments, including anemia, jaundice, cancer, piles, diarrhea, dysentery, headache, diabetes, asthma, blood purification, sedative and ulcer. RESULTS: A majority of plants showed elemental contents above the permissible levels as recommended by the World health organization (WHO). As an example, the concentrations of Cadmium (Cd) and Lead (Pb) were reportedly found higher than the WHO permissible levels in 43 and 42 medicinal plants, respectively. More specifically, the concentrations of Pb (54ppm: Silybum marianum) and Cd (5.25ppm: Artemisia herba-alba) were found highest in the Asteraceae family. CONCLUSIONS: The reported medicinal plants contain a higher amount of trace and toxic elements. Intake of these plants as traditional medicines may trigger the accumulation of trace and toxic elements in human bodies, which can cause different types of diseases. Thus, a clear understanding about the nature of toxic substances and factors affecting their concentrations in traditional medicines are essential prerequisites for efficacious herbal therapeutics with lesser or no side effects.

DOI: 10.1016/j.jep.2016.05.011
PMID: 27174080 [PubMed - in process]