

## AACT Herbal Dietary Supplements SIG Abstracts May 2017

**1. Perioperative Risks of Dietary and Herbal Supplements.** Levy I, Attias S, Ben-Arye E, Goldstein L, Matter I, Somri M, Schiff E.

World J Surg. 2017 Apr;41(4):927-934. doi: 10.1007/s00268-016-3825-2.

**BACKGROUND:** Patients undergoing surgery often use Dietary and Herbal Supplements (DHS). We explored the risk of DHS-drug interactions in the perioperative setting. **METHODS:** In this cross-sectional prospective study, participants hospitalized for surgery completed a questionnaire regarding DHS use. We used pharmacological databases to assess DHS-drug interactions. We then applied univariate and multivariate logistic regression analyses to characterize patients at risk for DHS-drug interactions. **RESULTS:** Of 526 interviewees, 230 (44%) patients reported DHS use, with 16.5% reporting using DHS that could potentially interact with anesthesia. Twenty-four (10%) patients used DHS that could potentially interact with antithrombotic drugs taken perioperatively. The medical files of three patients included reports of intraoperative bleeding. The patient files of only 11% of DHS users documented DHS use. **CONCLUSIONS:** DHS use poses a significant health risk due to potential interactions. Guidelines should emphasize perioperative management of DHS use.

DOI: 10.1007/s00268-016-3825-2

PMID: 27878352

**2. Bleeding risk of dietary supplements: A hidden nightmare for cardiac surgeons.** Bedi HS, Tewarson V, Negi K.

Indian Heart J. 2016 Sep;68 Suppl 2:S249-S250. doi: 10.1016/j.ihj.2016.03.028. Epub 2016 Apr 6.

We report a 55-year-old man who underwent off-pump bypass surgery and had diffuse oozing and bruising postoperatively. His hematological profile had been normal preoperatively and he had been off antiplatelets for a week prior to surgery. Postoperatively, a detailed talk revealed that he had been on dietary supplements containing fish oil and garlic - both of which are known to affect platelet function. It behooves the surgeon and anesthetist to screen all patients preoperatively for the possibility of intake of any dietary supplements taken by the patient.

DOI: 10.1016/j.ihj.2016.03.028

PMCID: PMC5067726 [Available on 2017-09-01]

PMID: 27751305

**3. Commonly Used Dietary Supplements on Coagulation Function during Surgery.** Wang CZ, Moss J, Yuan CS.

Medicines (Basel). 2015 Sep;2(3):157-185. Epub 2015 Jul 27.

**BACKGROUND:** Patients who undergo surgery appear to use dietary supplements significantly more frequently than the general population. Because they contain pharmacologically active compounds, dietary supplements may affect coagulation and platelet function during the perioperative period through direct effects, pharmacodynamic interactions, and pharmacokinetic interactions. However, in this regard, limited studies have been conducted that address the pharmacological interactions of dietary supplements. To avoid possible bleeding risks during surgery, information of potential complications of dietary supplements during perioperative management is important for physicians. **METHODS:** Through a systematic database search of all available years, articles were identified in this review if they included dietary supplements and coagulation/platelet function, while special attention was paid to studies published after 1990. **RESULTS:** Safety concerns are reported in commercially available dietary supplements. Effects of the most commonly used natural products on blood coagulation and platelet function are systematically reviewed, including 11 herbal medicines (echinacea, ephedra, garlic, ginger, ginkgo, ginseng, green tea, kava, saw palmetto, St John's wort, and valerian) and 4 other dietary supplements (coenzyme Q10, glucosamine and chondroitin sulfate, fish oil, and vitamins).

Bleeding risks of garlic, ginkgo, ginseng, green tea, saw palmetto, St John's wort, and fish oil are reported. Cardiovascular instability was observed with ephedra, ginseng, and kava. Pharmacodynamic and pharmacokinetic interactions between dietary supplements and drugs used in the perioperative period are discussed. **CONCLUSIONS:** To prevent potential problems associated with the use of dietary supplements, physicians should be familiar with the perioperative effects of commonly used dietary supplements. Since the effects of dietary supplements on coagulation and platelet function are difficult to predict, it is prudent to advise their discontinuation before surgery.

DOI: 10.3390/medicines2030157

PMCID: PMC4777343

PMID: 26949700

**4. 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 Jul;82(11-12):1030-8. doi: 10.1055/s-0042-107800. Epub 2016 Jun 3.

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 [Indexed for MEDLINE]

**5. Fatal *Taxus baccata* ingestion with perimortem serum taxine B quantification.** Arens AM, Anaebere TC, Horng H, Olson K.

Clin Toxicol (Phila). 2016 Nov;54(9):878-880. Epub 2016 Jul 20.

**INTRODUCTION:** Common yew (*Taxus baccata*) is a common decorative evergreen shrub with potentially fatal toxicity hallmarked by seizure, arrhythmia and cardiovascular collapse if ingested. Taxine B has been identified as one of the most cardiotoxic taxine alkaloids in *Taxus* spp, and another alkaloid, 3,5-dimethoxyphenol (3,5-DMP), is used as a marker of ingestion. We present a fatal case of ingestion of yew with perimortem serum and gastric taxine B, and 3,5-DMP concentrations. **CASE PRESENTATION:** A 22-year-old woman was brought to the emergency department (ED) from a nearby botanical garden after she was found apneic and pulseless after a witnessed generalized tonic clonic seizure. The patient was found to have a wide complex rhythm with persistent cardiovascular collapse and expired despite maximal supportive care in the ED. A baggie of plant material was found on the patient, identified as *Taxus baccata*. Perimortem serum and gastric samples were analyzed to quantify serum and gastric taxine B and 3,5-DMP concentrations. **RESULTS:** Perimortem serum showed a 3,5-DMP concentration of 86.9 ng/mL, and taxine B of 80.9 ug/mL. **CONCLUSION:** We report a perimortem serum and gastric taxine B and 3,5-DMP concentrations in a fatal case of *T. baccata* toxicity.

DOI: 10.1080/15563650.2016.1209765

PMID: 27436403 [Indexed for MEDLINE]

**6. Dietary supplement for energy and reduced appetite containing the  $\beta$ -agonist isopropyltopamine leads to heart problems and hospitalisations.** Bovee TF, Mol HG, Bienenmann-Ploum ME, Heskamp HH, Van Bruchem GD, Van Ginkel LA, Kooijman M, Lasaroms JJ, Van Dam R, Hoogenboom RL.

Food Addit Contam Part A Chem Anal Control Expo Risk Assess. 2016 May;33(5):749-59. doi: 10.1080/19440049.2016.1167965. Epub 2016 Apr 19.

In 2013 the Dutch authorities issued a warning against a dietary supplement that was linked to 11 reported adverse reactions, including heart problems and in one case even a cardiac arrest. In the UK a 20-year-old woman, said to have overdosed on this supplement, died. Since according to the label the product was a herbal mixture, initial LC-MS/MS analysis focused on the detection of plant toxins. Yohimbe alkaloids, which are not allowed to be present in herbal preparations according to Dutch legislation, were found at relatively high levels (400-900 mg kg<sup>-1</sup>). However, their presence did not explain the adverse health effects reported. Based on these effects the supplement was screened for the presence of a  $\beta$ -agonist, using three different biosensor assays, i.e. the validated competitive radioligand  $\beta$ 2-adrenergic receptor binding assay, a validated  $\beta$ -agonists ELISA and a newly developed multiplex microsphere (bead)-based  $\beta$ -agonist assay with imaging detection (MAGPIX®). The high responses obtained in these three biosensors suggested strongly the presence of a  $\beta$ -agonist. Inspection of the label indicated the presence of N-isopropyltopamine. A pure standard of this compound was bought and shown to have a strong activity in the three biosensor assays. Analysis by LC-full-scan high-resolution MS confirmed the presence of this 'unknown known'  $\beta$ 3-agonist N-isopropyltopamine, reported to lead to heart problems at high doses. A confirmatory quantitative analysis revealed that one dose of the preparation resulted in an intake of 40-60 mg, which is within the therapeutic range of this compound. The case shows the strength of combining bioassays with chemical analytical techniques for identification of illegal pharmacologically active substances in food supplements.

**7. Case reports of aconite poisoning in mainland China from 2004 to 2015: A retrospective analysis.** Li H, Liu L, Zhu S, Liu Q.

J Forensic Leg Med. 2016 Aug;42:68-73. doi: 10.1016/j.jflm.2016.05.016. Epub 2016 May 25.

Aconitum species have long been used in key traditional medicines in China, but cases of fatal aconite poisoning have also been reported. This paper presents a review of 40 single and multi-person cases of fatal aconite poisoning. The cases involved 53 victims in mainland China described in 27 case reports published between January 2004 and September 2015. We summarize the details of the case reports in order to highlight the features of fatal aconite-poisoning cases in China, including victims' sex and age, route of intoxication, clinical symptoms, medicolegal autopsy findings, and results of toxicological analysis. Our results indicate a need for legal medical experts encountering cases of fatal aconite poisoning to pay increased attention to the methods used for collecting biological samples. In addition, prevention strategies should focus on increasing public awareness regarding the potential toxicity of Aconitum, harm caused by medicinal liquors containing aconitine, and possibility of Aconitum alkaloids accumulating in the body.

DOI: 10.1016/j.jflm.2016.05.016

PMID: 27266651 [Indexed for MEDLINE]

**8. A botanical, phytochemical and ethnomedicinal review of the genus Mitragyna korth: Implications for products sold as kratom.** Brown PN, Lund JA, Murch SJ.

J Ethnopharmacol. 2017 Apr 18;202:302-325. doi: 10.1016/j.jep.2017.03.020. Epub 2017 Mar 19.

**ETHNOPHARMACOLOGICAL RELEVANCE:** The genus Mitragyna (Rubiaceae) has been traditionally used in parts of Africa, Asia and Oceania. In recent years, there has been increased interest in species of Mitragyna with the introduction of products to western markets and regulatory uncertainty. **AIM OF THE STUDY:** This paper reviewed the traditional ethnomedicinal uses of leaves for species belonging to the genus Mitragyna with reference to the botany and known chemistry in order to highlight areas of interest for products currently being sold as kratom.

**MATERIALS AND METHODS:** A literature search was conducted using Web of Science, Google Scholar, the Royal Museum for Central Africa, Internet Archive, Hathi Trust, and Biodiversity Heritage Library search engines in the spring of 2015, fall of 2016 and winter of 2017 to document uses of bark, leaf and root

material. RESULTS: Leaves of *M. speciosa* (kratom) had the most common documented ethnomedicinal uses as an opium substitute or remedy for addiction. Other species of *Mitragyna* were reportedly used for treating pain, however the mode of preparation was most often cited as topical application. Other uses of *Mitragyna* included treatment of fever, skin infections, and as a mild anxiolytic. CONCLUSIONS: *Mitragyna* species have been used medicinally in various parts of the world and that there is significant traditional evidence of use. Modern products that include formulations as topical application of liniments, balms or tinctures may provide effective alternatives for treatment of certain types of pains. Future research is required to establish safety and toxicology limits, medicinal chemistry parameters and the potential for different physiological responses among varying genetic populations to support regulatory requirements for *Mitragyna* spp.

DOI: 10.1016/j.jep.2017.03.020  
PMID: 28330725

### **9. An Integrated View of Aristolochic Acid Nephropathy: Update of the Literature.** Jadot I, Declèves AE, Nortier J, Caron N.

Int J Mol Sci. 2017 Jan 29;18(2). pii: E297. doi: 10.3390/ijms18020297.

The term "aristolochic acid nephropathy" (AAN) is used to include any form of toxic interstitial nephropathy that is caused either by ingestion of plants containing aristolochic acids (AA) as part of traditional phytotherapies (formerly known as "Chinese herbs nephropathy"), or by the environmental contaminants in food (Balkan endemic nephropathy). It is frequently associated with urothelial malignancies. Although products containing AA have been banned in most of countries, AAN cases remain regularly reported all over the world. Moreover, AAN incidence is probably highly underestimated given the presence of AA in traditional herbal remedies worldwide and the weak awareness of the disease. During these two past decades, animal models for AAN have been developed to investigate underlying molecular and cellular mechanisms involved in AAN

pathogenesis. Indeed, a more-in-depth understanding of these processes is essential to develop therapeutic strategies aimed to reduce the global and underestimated burden of this disease. In this regard, our purpose was to build a broad overview of what is currently known about AAN. To achieve this goal, we aimed to summarize the latest data available about underlying pathophysiological mechanisms leading to AAN development with a particular emphasis on the imbalance between vasoactive factors as well as a focus on the vascular events often not considered in AAN.

DOI: 10.3390/ijms18020297  
PMCID: PMC5343833  
PMID: 28146082 [Indexed for MEDLINE]

### **10. Sodium-Glucose Cotransporter 2 (SGLT2) Inhibitors from Natural Products: Discovery of Next-Generation Antihyperglycemic Agents.** Choi CI.

Molecules. 2016 Aug 27;21(9). pii: E1136. doi: 10.3390/molecules21091136.

Diabetes mellitus is a chronic condition associated with the metabolic impairment of insulin actions, leading to the development of life-threatening complications. Although many kinds of oral antihyperglycemic agents with different therapeutic mechanisms have been marketed, their undesirable adverse effects, such as hypoglycemia, weight gain, and hepato-renal toxicity, have increased demand for the discovery of novel, safer antidiabetic drugs. Since the important roles of the sodium-glucose cotransporter 2 (SGLT2) for glucose homeostasis in the kidney were recently elucidated, pharmacological inhibition of SGLT2 has been considered a promising therapeutic target for the treatment of type 2 diabetes. Since the discovery of the first natural SGLT2 inhibitor, phlorizin, several synthetic glucoside analogs have been developed and introduced into the market. Furthermore, many efforts to find new active constituents with SGLT2 inhibition from natural products are still ongoing. This review introduces the history of research on the development of early-generation SGLT2 inhibitors, and recent progress on the discovery of novel candidates for SGLT2 inhibitor from several natural products that are widely used in traditional herbal medicine.

DOI: 10.3390/molecules21091136

PMID: 27618891 [Indexed for MEDLINE]

**11. Thujone inhibits the function of  $\alpha 7$ -nicotinic acetylcholine receptors and impairs nicotine-induced memory enhancement in one-trial passive avoidance paradigm.** Sultan A, Yang KS, Isaev D, Nebrisi EE, Syed N, Khan N, Howarth CF, Sadek B, Oz M.

Toxicology. 2017 Apr 7. pii: S0300-483X(17)30103-8. doi: 10.1016/j.tox.2017.04.005. [Epub ahead of print]

Effects of thujone, a major ingredient of absinthe, wormwood oil and some herbal medicines, were tested on the function of  $\alpha 7$  subunit of the human nicotinic acetylcholine ( $\alpha 7$  nACh) receptor expressed in *Xenopus* oocytes using the two-electrode voltage-clamp technique. Thujone reversibly inhibited ACh (100 $\mu$ M)-induced currents with an IC<sub>50</sub> value of 24.7 $\mu$ M. The effect of thujone was not dependent on the membrane potential and did not involve Ca(2+)-dependent Cl(-) channels expressed endogenously in oocytes. Inhibition by thujone was not reversed by increasing ACh concentrations. Moreover, specific binding of [(125)I]  $\alpha$ -bungarotoxin was not altered by thujone. Further experiments in SH-EP1 cells expressing human  $\alpha 7$  nACh receptor indicated that thujone suppressed choline induced Ca(2+) transients in a concentration-dependent manner. In rat hippocampal CA3-dentate gyrus synapses, nicotine-induced enhancement of long-term potentiation was also inhibited by thujone. Furthermore, the results observed in in-vivo one-trial passive avoidance paradigm show that thujone (1.25mg/kg, i.p.) significantly impaired nicotine-induced enhancement of learning and memory in Wistar rats. Collectively, our results indicate that thujone inhibits the function of the  $\alpha 7$ -nACh receptor and impairs cellular and behavioral correlates of cholinergic modulation of learning and memory.

DOI: 10.1016/j.tox.2017.04.005

PMID: 28395994

**12. Mania Induced by *Garcinia cambogia*: A Case Series.** Hendrickson BP, Shaikh N, Occhiogrosso M, Penzner JB.

Prim Care Companion CNS Disord. 2016 Apr 28;18(2). doi: 10.4088/PCC.15101890. eCollection 2016.

**To the Editor:** Despite that the putative mechanism of action of the weight loss supplement *Garcinia cambogia* is considered to be serotonergic, literature about its psychiatric effects is limited. We report 3 stable, euthymic adults whose mania emerged when they began taking *G.cambogia*.

DOI: 10.4088/PCC.15101890

PMCID: PMC4956425

PMID: 27486540 [Indexed for MEDLINE]

**13. [Red yeast-rice-induced muscular injuries: Analysis of French pharmacovigilance database and literature review].** [Article in French] Philibert C, Bres V, Jean-Pastor MJ, Guy C, Lebrun-Vignes B, Robin P, Pinzani V, Hillaire-Buys D.

Therapie. 2016 Oct 27. pii: S0040-5957(16)30054-3. doi: 10.2515/therapie/2015053. [Epub ahead of print]

Red yeast rice (RYR) is a dietary supplement containing monacolins obtained by fermentation of *Monascus purpureus* strains. Because of its structural homology with lovastatin, monacolin K inhibits HMG-CoA reductase and shows hypocholesterolemic properties comparable to synthetic statins. We studied all cases of myopathy involving RYR reported in the French national pharmacovigilance database (6 cases) and in scientific literature (9 cases). Among these cases, 9 showed elevated creatine kinase, 3 rhabdomyolysis and 2 myalgia. Recent studies seem to show good efficacy of the RYR, however, our work reports the existence of related muscular disorders. In addition, dietary supplements currently available on the market may show considerable variability of formulation and/or the presence of contaminants. When clinicobiological disorders occur, physicians should consider the eventual use of an herbal treatment.

DOI: 10.2515/therapie/2015053

PMID: 28277227

**14. Survival after profound acidosis and rhabdomyolysis due to dietary supplement use.** Pourmand A, Li A, Yiu A, Mazer-Amirshahi M, Shokoohi H.

Am J Emerg Med. 2016 Nov;34(11):2259.e1-2259.e3. doi: 10.1016/j.ajem.2016.05.052. Epub 2016 May 24.

DOI: 10.1016/j.ajem.2016.05.052

PMID: 27260553 [Indexed for MEDLINE]

**15. Beneficial Effects of Silymarin After the Discontinuation of CCl<sub>4</sub>-Induced Liver Fibrosis.** Clichici S, Olteanu D, Filip A, Nagy AL, Oros A, Mircea PA.

J Med Food. 2016 Aug;19(8):789-97. doi: 10.1089/jmf.2015.0104. Epub 2016 Jul 21.

Silymarin (Si) is a herbal product with hepatoprotective potential, well-known for its antioxidant, anti-inflammatory, and immunomodulatory properties. We have recently demonstrated that the usual therapeutic doses of Si are capable of inhibiting the progression of incipient liver fibrosis. We aimed at further investigating the benefits of Si administration upon liver alterations after the hepatotoxin discontinuation, using CCl<sub>4</sub> to induce liver injuries on rats. CCl<sub>4</sub> administration induces first of all oxidative stress, but other mechanisms, such as inflammation and liver fibrosis are also triggered. Fifty Wistar rats were randomly divided into five groups (n = 10). The control group received sunflower oil twice a week for 8 weeks. Carboxymethyl cellulose group received sunflower oil twice a week, for 8 weeks and CMC daily, for the next 2 weeks. CCl<sub>4</sub> group received CCl<sub>4</sub> in sunflower oil, by gavage, twice a week, for 8 weeks. CCl<sub>4</sub> + Si 50 group received CCl<sub>4</sub> twice a week, for 8 weeks, and then 50 mg/body weight (b.w.) Silymarin for the next 2 weeks. CCl<sub>4</sub> + Si 200 group was similar to the previous group, but with Si 200 mg/b.w. Ten weeks after the experiment had begun, we assessed inflammation (IL-6, MAPK, NF- $\kappa$ B, pNF- $\kappa$ B), fibrosis (hyaluronic acid), TGF- $\beta$ 1, MMP-9, markers of hepatic stellate cell activation ( $\alpha$ -SMA expression), and proliferative capacity (proliferating cell nuclear antigen). Our data showed that Silymarin administered after the toxic liver injury is capable of reducing inflammation and liver fibrosis. The benefits were more important for the higher dose than for the usual therapeutic dose.

DOI: 10.1089/jmf.2015.0104

PMID: 27441792 [Indexed for MEDLINE]

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

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

Regul Toxicol Pharmacol. 2017 Mar 27;86:292-302. doi: 10.1016/j.yrtph.2017.03.019. [Epub ahead of print]

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

DOI: 10.1016/j.yrtph.2017.03.019

PMID: 28347763

**17. Toxic pyrrolizidine alkaloids in herbal medicines commonly used in Ghana.** Letsyo E, Jerz G, Winterhalter P, Beuerle T.

J Ethnopharmacol. 2017 Apr 18;202:154-161. doi: 10.1016/j.jep.2017.03.008. Epub 2017 Mar 8.

**ETHNOPHARMACOLOGICAL RELEVANCE:** Herbal medicines have been used for centuries for the management and treatment of various ailments due to the belief that they pose only little or no health risk and side effects, and also, in part, due to their availability, affordability and/or self-supply. However, the increasing information over the recent years on the occurrence of pyrrolizidine alkaloids (PAs) in honey, herbal food and tea products has raised concerns about the safety of herbal medicines with respect to contamination. To this day, little is known on the occurrence of toxic PAs in herbal medicines, especially in tropical West Africa. The aim of this study was therefore to determine the PA content of 70 well-known and widely patronized plant-derived medicinal preparations, which are commercialized in Ghana and some West African countries, in order to ascertain their potential health risk. **MATERIALS AND METHODS:** PAs of the herbal medicinal products, sourced from specialized drugstores and mostly regulatory approved, were analyzed for their PA content by a HPLC-ESI-MS/MS sum parameter method. **RESULTS:** The results show that a total of 60% of the analyzed herbal products were PA positive, indicating an average PA-concentration of 25.0µg/kg. The maximum PA level (1290.0µg/kg) was attributed to a regulatory-approved herbal medicine not known, according to the list of declared ingredients, to contain PA-plant parts. Interestingly, higher PA content (average, 30.2µg/kg) was detected in regulatory-approved herbal medicines, in contrast to lower amount (average, 8.0µg/kg) detected in non-regulatory-approved products. **CONCLUSION:** The findings of this study clearly demonstrate that herbal medicines containing PA plants as ingredients, as well as some of those containing plant species not known to produce PAs, are likely to contain hepatotoxic PA at levels higher than the daily dose in food and herbal medicinal products proposed by the European Medicines Agency (i.e. 0.35µg PA per day for 50kg adult and 0.14µg PA per day for 20kg children). Hence, regulatory authorities are advised to carry out more rigorous quality control tests with respect to PAs so as to minimize the exposure of the consumers to these toxic compounds.

DOI: 10.1016/j.jep.2017.03.008

PMID: 28284793

### **18. Hepatotoxicity induced by greater celandine (*Chelidonium majus* L.): a review of the literature.**

Pantano F, Mannocchi G, Marinelli E, Gentili S, Graziano S, Busardò FP, di Luca NM.

Eur Rev Med Pharmacol Sci. 2017 Mar;21(1 Suppl):46-52.

The available literature assessing *Chelidonium majus* L. (CM) hepatotoxicity potential, and its risk to benefit assessment has been reviewed in this paper. Identification of significant scientific literature was performed via the following research databases: Cochrane Central, Google Scholar, EMBASE, Medline, Science Direct, Scopus, Web of Science, using the following keywords: "*Chelidonium majus*", "greater celandine", "Hepatotoxicity", "Liver" "Injury", "Toxicity" individually investigated and then again in association. CM named also greater celandine, swallow-wort, or bai-qu-cai (Chinese), has been used for a long time in traditional Chinese medicine and phytotherapy. Its extracts have been claimed to display a wide variety of biological activities: antimicrobial, anti-inflammatory, spasmolytic, antineoplastic, hepatoprotective, and analgesic. Moreover, herbal medicine suggests this plant have numerous additional effects which have not yet been scientifically evaluated, such as antitussive, diuretic, and eye-regenerative. However, despite its claimed hepatoprotective effects, several hepatotoxicity cases have been reported to be probably or highly probably connected with CM exposure, after their evaluation through liver-targeted causality assessment methods. CM hepatotoxicity has been defined as a distinct form of herb-induced liver injury (HILI), due to an idiosyncratic reaction of the metabolic type. This evidence has to be considered in relationship with the absence of considerable benefits of CM therapy. Therefore, the risk to benefit ratio of the use of herbal products containing greater celandine can actually be considered as negative.

PMID: 28379595

### **19. Sildenafil-associated hepatotoxicity: a review of the literature.** Graziano S, Montana A, Zaami S, Rotolo MC, Minutillo A, Busardò FP, Marinelli E.

Eur Rev Med Pharmacol Sci. 2017 Mar;21(1 Suppl):17-22.

Sildenafil citrate (Viagra®) is a vasoactive agent available worldwide since 1998 for the treatment of male erectile dysfunction. It is a selective phosphodiesterase type 5-enzyme inhibitor able to potentiate the

downstream effects of nitric oxide on smooth muscle relaxation and vasodilation through its effects on the cyclic guanosine monophosphate (c-GMP) pathway in the erectile tissue of the penis. When sildenafil is orally administered, it is rapidly absorbed with a maximum plasma concentration achieved within 1 h and has a terminal half-life of between 3 to 6 h. The drug is extensively and rapidly metabolized by the liver, primarily by the CYP3A4 enzyme. Although the drug is well tolerated, specific adverse events have been observed, like flushing, headaches, dyspepsia, and visual disturbances. Liver toxicity related to sildenafil consumption has been considered a very rare event. However, in the last decade, some cases of sildenafil-associated hepatotoxicity have been reported. Furthermore, some hepatic intoxications have been reported after the intake of "natural" or "herbal" aphrodisiac supplements sold through Internet, sex shops, social media, and by word-of-mouth found to contain sildenafil and other phosphodiesterase type 5 (PDE-5) inhibitors. Studies investigating a possible link between sildenafil use and liver damage are limited, and the underlying mechanism responsible for hepatotoxicity is still missing. Studies in animals evidence that the hematopoietic function of the liver may have severely been affected as a result of a probable toxic effect of sildenafil. Here, the studies reporting liver toxicity by sildenafil in humans and in animals are reported and discussed.

PMID: 28379598

**20. Hidden Risks of Alternative Medicines: A Case of Boldo-Induced Hepatotoxicity.** Ribeiro RJ, Silvestre C, Duarte C.

J Diet Suppl. 2017 Mar 4;14(2):186-190. Epub 2016 Aug 30.

The alternative medicines are commonly used, especially herbal ones. Among them, boldo is traditionally used for symptomatic treatment of dyspepsia and mild gastrointestinal spasmodic disorders. Nevertheless, the number of reported cases of possible hepatotoxicity of some of these products has increased, including one report of boldo-induced hepatitis. We present the case of a 72-year-old female patient who has developed jaundice and increased serum levels of liver enzymes, after repeated consumption of boldo leaves infusion, during 2 weeks. After exclusion of common causes of hepatobiliary pathology, boldo-induced hepatotoxicity was considered probable. Interrupting of ingestion led to clinical and laboratorial recovery. This case proves the value of research in the alternative medicines' use. Ingestion of boldo, particularly in elderly patients with biliary tract disorders, may be the cause of otherwise unexplained jaundice or abnormal values of liver enzymes.

DOI: 10.1080/19390211.2016.1207123

PMID: 27576017 [Indexed for MEDLINE]

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

Acta Clin Belg. 2016 Jun;71(3):187-9. doi: 10.1179/2295333715Y.0000000070. Epub 2016 Feb 5.

A 25-year-old Somalian 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.

DOI: 10.1179/2295333715Y.0000000070

PMID: 26374255 [Indexed for MEDLINE]

**22. A Case of Idiopathic Mesenteric Phlebosclerosis with Progressive Intestinal Necrosis.** Kayano H, Nomura E, Hiraiwa S, Kuramoto T, Yatabe K, Machida T, Tajiri T, Mukai M, Makuuchi H.

Tokai J Exp Clin Med. 2016 Jun 20;41(2):70-5.

The patient was a 39-year-old woman who was referred to our department from her previous doctor with a 2-day history of right abdominal pain. Abdominal computed tomography showed wall thickening associated



with calcification in the ascending colon. Contrast enhancement in the same portion of the intestinal wall was rather poor. Fluid accumulation was also seen around the intestine, so emergency surgery was performed under a provisional diagnosis of intestinal necrosis. Intestinal necrosis due to idiopathic mesenteric phlebosclerosis was diagnosed from postoperative histopathological tests. Idiopathic mesenteric phlebosclerosis displays a chronic course and in most cases conservative treatment is indicated. Bowel obstruction is common among patients who require surgical treatment, but rare cases such as the present one are also seen in which intestinal necrosis occurs. In recent years, an association with herbal medicine has been indicated as one potential cause of this disease, and this entity should be kept in mind when patients with acute abdomen and a history of taking herbal medicines are encountered.

PMID: 27344996 [Indexed for MEDLINE]

### **23. Facial eschar following a single application of black salve.** Laskey D, Tran M.

Clin Toxicol (Phila). 2017 Apr 20;1-2. doi: 10.1080/15563650.2017.1312428. [Epub ahead of print]

A previously healthy 86-year-old male was transported by ambulance to the trauma bay of the emergency department (ED) for profuse bleeding from the left temple. The ambulance crew raised concern that the volume and force of the bleed may suggest arterial involvement. The patient reported having applied a natural topical remedy to a mole two weeks prior at the recommendation of a naturopath. The patient described progressive blackening and swelling of the area in the days following the single application of the product. After gaining control of the bleeding in the ED, the area was found to have a raised, 2 cm eschar.

DOI: 10.1080/15563650.2017.1312428

PMID: 28426257

### **24. Contact dermatitis caused by panthenol used for aftercare treatment of a new tattoo.** Bregnbak D, Johansen JD, Zachariae C.

Contact Dermatitis. 2016 Jul;75(1):50-2. doi: 10.1111/cod.12544.

DOI: 10.1111/cod.12544

PMID: 27264289 [Indexed for MEDLINE]

### **25. Safety of herbal medicine use during chemotherapy in patients with ovarian cancer: a "bedside-to-bench" approach.** Ben-Arye E, Lavie O, Samuels N, Khamaisie H, Schiff E, Raz OG, Mahajna J.

Med Oncol. 2017 Apr;34(4):54. doi: 10.1007/s12032-017-0910-9. Epub 2017 Feb 25.

In this study, we explored herbal supplements used by patients during chemotherapy and test for herb-drug interactions and response of cancer cells to treatment. Patients with gynecological cancer referred to a complementary and integrative medicine (CIM) service were asked about their use of herbal medicine during chemotherapy. The leading five clinically relevant herbs selected for cytotoxicity analysis included the following: wheatgrass (*Triticum aestivum*), European mistletoe (*Viscum album*), ginger (*Zingiber officinale*), Ephedra (*Ephedra campylopoda*), and Oriental mistletoe (*Viscum cruciatum*). Cytotoxicity was examined using XTT assays in cisplatin-sensitive and resistant ovarian cancer cell lines (A2780, A2780CisR), and non-cancer kidney cells (HEK-293). The effect of the selected herbs on carboplatin and paclitaxel cytotoxicity was tested as well. Pro-apoptotic effects were tested using Poly(ADP-ribose) polymerase (PARP) cleavage. Of 98 patients referred to the CIM service, 42 (42.9%) reported using/intending to use herbal products during chemotherapy. European mistletoe and ginger exhibited significant anti-cancer activity in cisplatin-sensitive and resistant ovarian cells. Wheatgrass and ephedra reduced cytotoxicity of carboplatin on cisplatin-sensitive ovarian cancer cells, while ginger, European and Oriental mistletoe increased chemosensitivity in both cancer cell lines. Wheatgrass, European mistletoe, and ginger increased sensitivity to cisplatin-resistant cells treated with carboplatin and paclitaxel. No effect was observed with the addition of any of the herbs on non-cancerous embryonic kidney cells (HEK-293). Herbal medicine use by patients with ovarian cancer may influence anti-cancer activity of chemotherapy. Integrative physicians can provide "bedside-to-bench" guidance on the safety of these products.

DOI: 10.1007/s12032-017-0910-9  
PMID: 28238155 [Indexed for MEDLINE]

**26. Traditional medicine preparations and health risks: time to revisit their regulatory status.** De Capitani EM.

Clin Toxicol (Phila). 2017 Feb;55(2):79-80. doi: 10.1080/15563650.2016.1260138.

Epub 2016 Nov 24.

DOI: 10.1080/15563650.2016.1260138  
PMID: 27882778 [Indexed for MEDLINE]

**27. Management of chronic pain using complementary and integrative medicine.** Chen L, Michalsen A.

BMJ. 2017 Apr 24;357:j1284. doi: 10.1136/bmj.j1284.

Complementary and integrative medicine (CIM) encompasses both Western-style medicine and complementary health approaches as a new combined approach to treat a variety of clinical conditions. Chronic pain is the leading indication for use of CIM, and about 33% of adults and 12% of children in the US have used it in this context. Although advances have been made in treatments for chronic pain, it remains inadequately controlled for many people. Adverse effects and complications of analgesic drugs, such as addiction, kidney failure, and gastrointestinal bleeding, also limit their use. CIM offers a multimodality treatment approach that can tackle the multidimensional nature of pain with fewer or no serious adverse effects. This review focuses on the use of CIM in three conditions with a high incidence of chronic pain: back pain, neck pain, and rheumatoid arthritis. It summarizes research on the mechanisms of action and clinical studies on the efficacy of commonly used CIM modalities such as acupuncture, mind-body system, dietary interventions and fasting, and herbal medicine and nutrients.

PMID: 28438745

**28. Vitamin D supplements poison dozens of Danish children.** Stafford N.

BMJ. 2016 Aug 16;354:i4534. doi: 10.1136/bmj.i4534.

**29. Dietary supplementation is more prevalent among adults with arthritis in the United States population.** Wilson PB.

Complement Ther Med. 2016 Dec;29:152-157. doi: 10.1016/j.ctim.2016.10.004. Epub 2016 Oct 6.

**OBJECTIVES:** Sparse data are available to describe the prevalence of dietary supplementation among individuals with arthritis. Using a nationally representative sample, this investigation assessed the prevalence of dietary supplement use among Americans self-reporting arthritis. **SETTING AND DESIGN:** Data from 4606 participants of the 2011-2012 National Health and Nutrition Examination Survey were analyzed, including from 1170 participants self-reporting arthritis. Participants reported dietary supplementation over the past 30 days. **RESULTS:** Approximately 62.5% of adults with arthritis reported taking at least one dietary supplement, which was greater than the 49.0% among individuals without arthritis ( $P < 0.001$ ). Arthritis was not independently associated with higher odds of supplement use (odds ratio = 1.12, 95% confidence interval [CI] = 0.88-1.42) in a multivariate logistic regression model. Among individuals with arthritis, supplement use was more prevalent in older adults ( $\geq 50$  years), non-Hispanic whites, those with greater education, and those with health insurance. Among 721 participants with arthritis that were taking at least one supplement, 15.1% (95% CI = 12.8-17.8%) indicated at least one of their supplements was 'for healthy joints, arthritis', compared to only 7.7% (95% CI = 6.4-9.3%) of participants without arthritis ( $P < 0.001$ ). Glucosamine and/or chondroitin were the most common types of supplements used to improve joint health in arthritis. **CONCLUSIONS:** Given that roughly three out of five individuals with arthritis regularly use dietary supplements, health practitioners should be prepared to discuss potential benefits and risks of supplementation for the management of pain and function in arthritis.

DOI: 10.1016/j.ctim.2016.10.004  
PMID: 27912939 [Indexed for MEDLINE]

**30. Dietary Intakes and Supplement Use in Pre-Adolescent and Adolescent Canadian Athletes.** Parnell JA, Wiens KP, Erdman KA.

Nutrients. 2016 Aug 26;8(9). pii: E526. doi: 10.3390/nu8090526.

Young athletes experience numerous dietary challenges including growth, training/competition, unhealthy food environments, and travel. The objective was to determine nutrient intakes and supplement use in pre-adolescent and adolescent Canadian athletes. Athletes (n = 187) aged 11-18 years completed an on-line 24-h food recall and dietary supplement questionnaire. Median energy intake (interquartile range) varied from 2159 kcal/day (1717-2437) in 11-13 years old females to 2905 kcal/day (2291-3483) in 14-18 years old males. Carbohydrate and protein intakes were 8.1 (6.1-10.5); 2.4 (1.6-3.4) in males 11-13 years, 5.7 (4.5-7.9); 2.0 (1.4-2.6) in females 11-13 years, 5.3 (4.3-7.4); 2.0 (1.5-2.4) in males 14-18 y and 4.9 (4.4-6.2); 1.7 (1.3-2.0) in females 14-18 years g/kg of body weight respectively. Median vitamin D intakes were below the recommended dietary allowance (RDA) and potassium was below the adequate intake (AI) for all athlete groups. Females 14-18 years had intakes below the RDA for iron 91% (72-112), folate 89% (61-114) and calcium 84% (48-106). Multivitamin-multiminerals, vitamin C, vitamin D, vitamin-enriched water, protein powder, sport foods, fatty acids, probiotics, and plant extracts were popular supplements. Canadian pre-adolescent and adolescent athletes could improve their dietary intakes by focusing on food sources of calcium, vitamin D, potassium, iron, and folate. With the exceptions of vitamin D and carbohydrates during long exercise sessions, supplementation is generally unnecessary.

DOI: 10.3390/nu8090526  
PMCID: PMC5037513  
PMID: 27571101 [Indexed for MEDLINE]

**31. Use and Factors Associated With Herbal/Botanical and Nonvitamin/Nonmineral Dietary Supplements Among Women of Reproductive Age: An Analysis of the Infant Feeding Practices Study II.** Budzynska K, Filippelli AC, Sadikova E, Low Dog T, Gardiner P.

J Midwifery Womens Health. 2016 Jul;61(4):419-26. doi: 10.1111/jmwh.12482. Epub 2016 Jun 23.

**INTRODUCTION:** Little is known about the changes in prevalence of dietary supplement use in pregnancy, postpartum, and in a comparison group of nonpregnant women. **METHODS:** We conducted a secondary analysis of the Infant Feeding Practices II study. The purpose of this study is to report the prevalence of herbal or botanical and nonvitamin, nonmineral dietary supplement use by US women with respect to demographic, behavioral, and health factors. We compared pregnant and postpartum women to a comparison group of nonpregnant women who had not given birth in the past 12 months. Our main outcome was the prevalence of dietary supplements. Multiple logistic regression models were used to examine factors associated with herbal or botanical and nonvitamin, nonmineral dietary supplement use during reproductive age, pregnancy, and postpartum. **RESULTS:** The total sample included 1444 women assessed during the prenatal period, 1422 from the postpartum period, and 1517 women in a comparison group. In terms of herb or botanical use, 15% of the prenatal group, 16% of the postpartum group, and 22% of the comparison group reported using herbs or botanicals. The most frequently used nonvitamin, nonmineral supplement was omega-3 fatty acid. Among the total prenatal group and comparison group, women eating 5 or more servings of fruits or vegetables were less likely to report using herbs or botanicals. Women in the comparison group self-identifying as black were 4 times as likely to report using herbs or botanicals compared to participants self-identifying as white. In addition, women identifying as a race other than white were almost twice as likely to report herb or botanical use across all study groups. **DISCUSSION:** This is one of the rare studies that shows the changing prevalence of herbs or botanicals and nonvitamin, nonmineral dietary supplement use in women in the reproductive stage of their lives.

DOI: 10.1111/jmwh.12482  
PMID: 27336953 [Indexed for MEDLINE]