AACT Herbal Dietary Supplement Section Abstracts January 2022

1. Herbal and dietary supplement-induced liver injury in Taiwan: comparison with conventional drug-induced liver injury. Huang YS, Chang TT, Peng CY, Lo GH, Hsu CW, Hu CT, Huang YH

Hepatol Int. 2021 Dec;15(6):1456-1465. doi: 10.1007/s12072-021-10241-3. Epub 2021 Aug 11.

BACKGROUND AND AIMS: Whether herbal and dietary supplements (HDS) are safer than Western conventional drugs is controversial. The aim of this study was to explore the characteristics and risk factors for HDS-induced liver injury (HILI) in Taiwan. METHODS: This is a 9-year multi-center prospective study conducted in Taiwan from 2011 to 2019. Patients with HILI were compared to those with conventional drug-induced liver injury (CILI). RESULTS: A total of 1,297 patients were enrolled, of whom 285 (22.0%) had HILI and 1,012 (78.0%) had CILI. Compared to the CILI group, the HILI group had higher initial serum alanine aminotransferase, alkaline phosphatase (ALP), peak ALP and bilirubin levels, and higher rates of jaundice, ascites, encephalopathy, coagulopathy, sepsis and acute liver failure. In addition, the HILI group had a higher mortality rate than the CILI group (12.6 vs. 8.0%, p = 0.016). Hepatitis B carrier status, elevated baseline liver biochemical tests and the use of crude herbs (without processing) were associated with an increased risk of HILI-related mortality (adjusted hazard ratios [95% confidence intervals]: 2.90 [1.43-5.99], 2.40 [1.01-5.68] and 2.94 [1.45-5.97], respectively). CONCLUSIONS: HDS are popular and incriminated in more than one-fifth of drug-induced liver injuries in Taiwan. The patients with HILI were more severe than those with CILI in terms of liver biochemical tests, complications and mortality. Hepatitis B carriers, those with elevated baseline liver tests and crude herb users may have a higher risk of HILI-related mortality. The prudent use of HDS is suggested in these high-risk subjects.

DOI: 10.1007/s12072-021-10241-3
PMID: 34382132 [Indexed for MEDLINE]

2. Drug adulteration of sexual enhancement supplements: a worldwide insidious public health threat. Yéléhé-Okouma M, Pape E, Humbertjean L, Evrard M, El Osta R, Petitpain N, Gillet P, El Balkhi S, Scala-Bertola J.

Fundam Clin Pharmacol. 2021 Oct;35(5):792-807. doi: 10.1111/fcp.12653. Epub 2021 Mar 8.

Worldwide, the consumption of dietary supplements for the enhancement of sexual performance is common. Consumers are generally fond of these products because they often want to avoid drugs, preferring "natural" than "chemical" solutions. This is challenging, as many of these supplements labelled "herbal" or "natural" are actually adulterated with drugs, mainly phosphodiesterase-5 inhibitors. This phenomenon is facilitated by fewer demanding regulations for marketing supplements. Thus, consumers may be widely exposed to serious adverse events, such as acute liver injury, kidney failure, pulmonary embolism, stroke or even death. We aim to warn physicians about this issue. This multidisciplinary review simultaneously deals with clinical consequences of this phenomenon, analytical toxicology and regulation. Indeed, after outlining this worldwide issue and highlighting that a drug-adulterated dietary supplement is actually a falsified drug, we discuss its main contributing factors. Then, we describe some examples of adverse events of which a case of sildenafil-tadalafil-induced ischaemic stroke that benefited medical care in our hospital. Furthermore, we present some means to avoid adulteration and discuss their limitations that may be explained by the heterogeneity of the regulation of dietary supplements between countries. Doing so, we point out the requirement of a global harmonization of this regulation for an efficient eradication of this public health threat. Meanwhile, dietary supplements should be considered adulterated until proven otherwise. Thus, we encourage physicians to investigate these products in the drug histories of their patients, especially when clinical conditions cannot be explained by classical aetiologies.

DOI: 10.1111/fcp.12653
PMID: 33484004 [Indexed for MEDLINE]

3. Characterization of pregnancies exposed to St. John's wort and their outcomes: A claims data analysis. Schäfer W, Wentzell N, Schink T, Haug U.

Reprod Toxicol. 2021 Jun;102:90-97. doi: 10.1016/j.reprotox.2021.04.005. Epub 2021 May 4.

Little is known about the utilization of St. John's wort (Hypericum perforatum L.) during pregnancy. In Germany, certain preparations of St. John's wort can be reimbursed by statutory health insurances, facilitating to investigate exposure to St. John's wort based on claims data. We therefore aimed to characterize pregnancies exposed to St. John's wort and to explore potential malformations in the babies. Using claims data from the German Pharmacoepidemiological Research Database (GePaRD), pregnancies exposed to St. John's wort during at least one trimester between 2006 and 2016 and the corresponding babies were identified. Exposure was identified via outpatient dispensations. Pregnancies were characterized regarding timing of exposure, use of other antidepressants, pregnancy outcomes and the occurrence of major malformations in the babies (not considering codes for musculoskeletal and other malformations due to low data quality in this regard). Out of 496 pregnancies with a dispensation of St. John's wort during pregnancy, 420 (85 %) had a dispensation during the first trimester. There was a dispensation of other antidepressants before pregnancy in 21 % (during pregnancy: 12 %). Eleven percent of pregnancies ended in non-live births. In 312 babies linked to 305 pregnancies, major malformations were coded in 18 babies (5.8 %), of which 17 were exposed in the first trimester. The crude relative risk of major malformations for babies exposed during the first vs. the second or third trimester only was 3.56 (0.48-26.17). Our results suggest that only in a minority of pregnancies, St. John's wort is used as an alternative to other antidepressants. Even though the relatively high rates of non-live births and major malformations after exposure to St. John's wort during the first trimester need to be interpreted with caution, the findings are striking and generate hypotheses that merit further investigation.

DOI: 10.1016/j.reprotox.2021.04.005
PMID: 33961968 [Indexed for MEDLINE]

4. Important considerations for drugs, nutritional, and herbal supplements in pediatric solid organ transplant recipients. Pilch NA, Sell ML, McGhee W, Venkataramanan R.

Pediatr Transplant. 2021 Feb;25(1):e13881. doi: 10.1111/petr.13881. Epub 2020 Nov 3.

Pediatric transplant recipients are on multiple prescription and non-prescription drugs. Many patients also use dietary, nutritional, and herbal supplements. This manuscript researched formulations of immunosuppressive drugs currently available and presents information on generic immunosuppressive drugs, commonly used non-prescription medications, dietary supplements, and herbal supplements. Immunosuppressive drugs are available in various formulations. Not all formulations are interchangeable. A number of FDA-approved generic formulations are available commercially in the United States. Generally generic formulations produce similar blood concentration vs time profiles compared to brand name products in adults and are considered to be bioequivalent. NSAID should be avoided in transplant patients due to potential drug interactions and increased risk associated with NSAID use; and appropriate doses of acetaminophen should be used for treatment of pain. Over-the-counter medications, such as guaifenesin and dextromethorphan, antihistamine medications, including diphenhydramine, loratadine, cetirizine, and fexofenadine, can be safely used in pediatric solid organ transplant population. Many safe and effective over-the-counter options exist for stool softening and as laxative. Diarrhea can lead to an increase in calcineurin inhibitor levels. Food can alter the absorption of immunosuppressive drugs. Several herbal products can alter immune status of the patients or alter the blood concentration of immunosuppressive drugs or may produce renal or hepatic toxicities and should be avoided in pediatric transplant recipients. It is important to educate pediatric transplant recipients and their families about not only immunosuppressive drug therapy but also about non-prescription drugs, dietary, and herbal supplement use.

DOI: 10.1111/petr.13881
PMID: 33142023 [Indexed for MEDLINE]

5. Case 38-2021: A 76-Year-Old Woman with Abdominal Pain, Weight Loss, and Memory Impairment. Willett LL, Bromberg GK, Chung R, Leaf RK, Goldman RH, Dickey AK.

N Engl J Med. 2021 Dec 16;385(25):2378-2388. doi: 10.1056/NEJMcpc2107354.

DOI: 10.1056/NEJMcpc2107354
PMID: 34910867 [Indexed for MEDLINE]

6. Turmeric-Induced Hepatotoxicity: Report of 2 Cases. Sohal A, Alhankawi D, Sandhu S, Chintanaboina J.

Int Med Case Rep J. 2021 Dec 22;14:849-852. doi: 10.2147/IMCRJ.S333342. eCollection 2021.

The use of herbal and dietary supplements is rising in the United States. Turmeric has been one of the most popular supplements recently, used widely for various conditions such as arthritis, digestive disorder, and liver conditions. Although rarely reported, hepatotoxicity can happen with turmeric use. Here, we present 2 cases of drug-induced liver injury due to turmeric use with the complete resolution after cessation.

DOI: 10.2147/IMCRJ.S333342
PMCID: PMC8711139
PMID: 34992472

7. Herbal hepatitis due to use of alternative medicines for Lyme disease. Perrillo RP, Burton JR Jr, Westbrook LM.

Proc (Bayl Univ Med Cent). 2021 Oct 19;35(1):104-105. doi: 10.1080/08998280.2021.1974272. eCollection 2022.

Lyme disease often leaves patients with chronic symptoms of fatigue, easy confusion, and even cardiac arrhythmias. We report a case in which Lyme disease was treated with an herbal mixture due to protracted symptoms despite intravenous antibiotics. This mixture was associated with hepatotoxicity. General providers should be aware of the fact that homeopathic remedies may be associated with hepatotoxicity, and herbalists need better understanding of the safety risks of the individual components in remedy mixtures.

DOI: 10.1080/08998280.2021.1974272
PMCID: PMC8682861
PMID: 34970053

8. Drug-induced hepatocellular injury due to herbal supplement ashwagandha. Ireland PJ, Hardy T, Burt AD, Donnelly M.

J R Coll Physicians Edinb. 2021 Dec;51(4):363-365. doi: 10.4997/JRCPE.2021.409.

A 39-year-old female presented with a one-week history of jaundice and nausea after taking an over-the-counter herbal supplement containing ashwagandha root extract. Initial investigations revealed a hepatocellular pattern of liver enzyme abnormality with jaundice. Investigations, including viral serology, liver specific autoantibodies and an ultrasound scan of the abdomen, were unremarkable. Liver biopsy showed an acute cholestatic hepatitis with confluent necrosis but no features of chronicity. These histopathological findings differ to that of a previously reported case. Review of recent literature revealed that some clinical features and the time course of liver injury were similar to previous reports of ashwagandha drug-induced liver injury (DILI). The patient received treatment with ursodeoxycholic acid. We compare this case to previous reported cases of ashwagandha DILI and discuss the biochemical and histopathological features of ashwagandha DILI, therapeutic strategies and the importance of recognising herbal supplements as a possible cause of DILI.

DOI: 10.4997/JRCPE.2021.409
PMID: 34882134

9. [No harm, no foul? Adverse events in pediatric complementary and alternative medicine use]. [Article in Dutch] Rake JP, Vos BO, Vlieger AM.

Ned Tijdschr Geneeskd. 2021 Oct 28;165:D6099.

In the Netherlands, children are frequently using complementary and alternative medicine (CAM), but data on adverse events are scarce. A three-year registration amongst Dutch pediatricians found 32 cases of adverse events associated with pediatric CAM use. Twenty-two children experienced adverse events that were indirectly related to the CAM treatment, such as delaying or stopping a regular treatment or diagnosis or using an unnecessary (deficient) diet. These indirect effects involved many different therapies. Nine children experienced direct adverse events such as toxicity of an ingested substance or harm due to body manipulation. Direct effects occurred after using herbal medicine, high dose vitamins or supplements, and manual-based manipulation. The authors advise physicians to be aware of potential side-effects of CAM treatment in children and inform parents regarding its use. A list of ten recommendations for parents considering the use of CAM for their children is presented.

PMID: 34854635 [Indexed for MEDLINE]

10. Probing the Hidden Role of Mitochondrial DNA Damage and Dysfunction in the Etiology of Aristolochic Acid Nephropathy. Chan W, Ham YH.

Chem Res Toxicol. 2021 Aug 16;34(8):1903-1909. doi: 10.1021/acs.chemrestox.1c00175. Epub 2021 Jul 13.

Aristolochic acid nephropathy (AAN) is a unique type of progressive renal interstitial fibrotic disease caused by prolonged exposure to aristolochic acids (AAs) through AA-containing herbal medicines or AA-tainted food. Despite decades of research and affecting millions of people around the world, the pathophysiology of AAN remains incompletely understood. In this study, we tested the potential causative role of mitochondrial dysfunction in AAN development. Our findings revealed AA exposure induces an exposure concentration and duration dependent lowering of adenosine triphosphate in both cultured human kidney and liver cells, highlighting an AA exposure effect on mitochondrial energy production in the kidney and liver, which both are highly metabolically active and energy-demanding organs. Analysis with liquid chromatography-tandem mass spectrometry coupled with stable isotope dilution method detected high levels of mutagenic 8-oxo-2'-deoxyguanosine and 7-(deoxyadenosine-N6-yl)-aristolactam adduct on mitochondrial DNA isolated from AA-treated cells, unmasking a potentially important causative, but previously unknown role of mitochondrial DNA mutation in the pathophysiology of AAN development.

DOI: 10.1021/acs.chemrestox.1c00175
PMID: 34255491 [Indexed for MEDLINE]

11. Systematic investigation on the distribution of four hidden toxic Aconitum alkaloids in commonly used Aconitum herbs and their acute toxicity. Huang YF, He F, Cui H, Zhang YY, Yang HY, Liang ZS, Dai W, Cheng CS, Xie Y, Liu L, Liu ZQ, Zhou H.

J Pharm Biomed Anal. 2022 Jan 20;208:114471. doi: 10.1016/j.jpba.2021.114471. Epub 2021 Nov 16.

Yunaconitine (YAC), crassicauline A (CCA), 8-deacetylyunaconitine (DYA), and 8-deacetylcrassicauline A (DCA), as hidden toxic Aconitum alkaloids, are detected in some products of processed Aconitum carmichaelii lateral root and poisoning cases. The distribution and toxicity of these four components in Aconitum herbs should be further systematically studied for medication safety. This study developed a new UHPLC-QQQ-MS/MS method to determine ten Aconitum alkaloids, including aconitine, mesaconitine, hypaconitine, benzoylaconine, benzoylmesaconine, benzoylhypaconine, YAC, CCA, DYA, and DCA, for Aconitum herbs simultaneously. YAC and CCA were founded in some samples of unprocessed A. carmichaelii lateral root (7.04%), A. carmichaelii root (9.43%), A. brachypodum root (6.00%), and A. ouvrardianum root (100%). Four hidden toxic Aconitum alkaloids were detected in processed A. carmichaelii lateral root (2.56%) and A. vilmorinianum root (100%). Four hidden toxic Aconitum alkaloids played significant roles in the classification of Aconitum herbs by OPLS-DA analysis. The acute toxicity test was performed by up-and-down procedure (UDP). The oral administration of the half lethal dose (LD50) of YAC, CCA, DYA, and DCA to female ICR mice was 2.37 mg/kg, 5.60 mg/kg, 60.0 mg/kg, and 753 mg/kg, respectively. The LD50 by intravenous injection was 0.200 mg/kg, 0.980 mg/kg, 7.60 mg/kg, and 34.0 mg/kg, respectively. The LD50 of unprocessed A. carmichaelii lateral root, A. vilmorinianum root, and A. brachypodum root to mice orally was 1.89 g/kg, 0.950 g/kg, and 0.380 g/kg, respectively. Symptoms of Aconitum alkaloid poisoning in mice were decreased activity, fur erect, palpebral edema, vomiting,

polypnea, and convulsions. The main change of organs was flatulence. No poisoning or death occurred in mice at the maximum dosage (27.0 g/kg) of A. ouvrardianum root orally. To better control the quality and safety of Aconitum herbs, this study provides favorable support for improving the existing standards to strengthen the supervision of the four hidden toxic Aconitum alkaloids.

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PMID: 34814080 [Indexed for MEDLINE]