

AACT Herbal Dietary Supplements SIG Abstracts July 2018

1. Botanicals and Hepatotoxicity. Roytman MM, Poerzgen P, Navarro V.

Clin Pharmacol Ther. 2018 Jun 19. doi: 10.1002/cpt.1097. [Epub ahead of print]

The use of botanicals, often in the form of multi-ingredient herbal dietary supplements (HDS), has grown tremendously in the past three decades despite their unproven efficacy. This is paralleled by an increase in dietary supplement-related health complications, notably hepatotoxicity. This article reviews the demographics and motivations of dietary supplement (DS) consumers and the regulatory framework for DS in the US and other developed countries. It examines in detail three groups of multi-ingredient HDS associated with hepatotoxicity: OxyElite Pro (two formulations), green tea extract-based DS, and "designer anabolic steroids." These examples illustrate the difficulties in identifying and adjudicating causality of suspect compound(s) of multi-ingredient HDS-associated liver injury in the clinical setting. The article outlines future directions for further study of HDS-associated hepatotoxicity as well as measures to safeguard the consumer against it.

DOI: 10.1002/cpt.1097

PMID: 29920648

2. Herbal assault: liver toxicity of herbal and dietary supplements.

Lancet Gastroenterol Hepatol. 2018 Mar;3(3):141. doi: 10.1016/S2468-1253(18)30011-6.

DOI: 10.1016/S2468-1253(18)30011-6

PMID: 29870727

3. Effect of Green Tea Supplements on Liver Enzyme Elevation: Results from a Randomized Intervention Study in the United States. Yu Z, Samavat H, Dostal AM, Wang R, Torkelson CJ, Yang CS, Butler LM, Kensler TW, Wu AH, Kurzer MS, Yuan JM.

Cancer Prev Res (Phila). 2017 Oct;10(10):571-579. doi: 10.1158/1940-6207.CAPR-17-0160. Epub 2017 Aug 1.

Liver injury effects of green tea-based products have been reported in sporadic case reports. However, no study has examined systematically such adverse effects in an unbiased manner. We examined the potential effects of a high, sustained oral dose of green tea extract (GTE) on liver injury measures in a randomized, placebo-controlled, double-blinded phase II clinical trial, which enrolled 1,075 women with the original aim to assess the effect of daily GTE consumption for 12 months on biomarkers of breast cancer risk. The current analysis examined the effect of GTE consumption on liver injury in 1,021 participants (513 in GTE and 508 in placebo arm) with normal baseline levels of liver enzymes. Among women in the GTE arm, alanine aminotransferase (ALT) increased by 5.4 U/L [95% confidence interval (CI), 3.6-7.1] and aspartate aminotransferase increased by 3.8 U/L (95% CI, 2.5-5.1), which were significantly higher than those among women in the placebo arm (both $P < 0.001$). Overall, 26 (5.1%) women in GTE developed moderate or more severe abnormalities in any liver function measure during the intervention period, yielding an OR of 7.0 (95% CI, 2.4-20.3) for developing liver function abnormalities as compared with those in the placebo arm. ALT returned to normal after dechallenge and increased again after one or more rechallenges with GTE. The rise-fall pattern of liver enzyme values following the challenge-dechallenge cycles of GTE consumption strongly implicates the effect of high-dose GTE on liver enzyme elevations.

DOI: 10.1158/1940-6207.CAPR-17-0160

PMID: 28765194 [Indexed for MEDLINE]

4. Acute liver injury following Garcinia cambogia weight-loss supplementation: case series and literature review. Crescioli G, Lombardi N, Bettiol A, Marconi E, Risaliti F, Bertoni M, Menniti Ippolito F, Maggini V, Gallo E, Firenzuoli F, Vannacci A.

Intern Emerg Med. 2018 May 25. doi: 10.1007/s11739-018-1880-4. [Epub ahead of print]

Herbal weight-loss supplements are sold as self-medication products, and are often used under the misconception that their natural origin guarantees their safety. Food supplements are not required to provide any benefit/risk profile evaluation before marketing; however, possible risks associated with use of herbal extracts in food supplements are becoming more and more documented in the literature. Some herbs are listed as the leading cause of herb-induced liver injury, with a severe or potentially lethal clinical course, and unpredictable herb-drug interactions. Garcinia cambogia (GC) extract and GC-containing products are some of the most popular dietary supplements currently marketed for weight loss. Here, we present four cases of acute liver failure in women taking GC extract for weight loss, and a

literature review of clinical evidences about hepatic toxicity in patients taking dietary supplements containing GC extract.

DOI: 10.1007/s11739-018-1880-4

PMID: 29802521

5. Aloe vera-induced acute liver injury: A case report and literature review. Parlati L, Voican CS, Perlemuter K, Perlemuter G.

Clin Res Hepatol Gastroenterol. 2017 Sep;41(4):e39-e42. doi: 10.1016/j.clinre.2016.10.002. Epub 2016 Nov 14.

Recent data suggest that herbal and dietary supplements are the second most common cause of liver injury. We herein report a case of acute liver injury in a 68-year old female caused by ingestion of Aloe vera. Upon discontinuation of the oral Aloe vera, liver function tests (LFT) returned to normal levels. Thus, it is crucial to consider the use of herbal products as causative agents of acute liver injury.

DOI: 10.1016/j.clinre.2016.10.002

PMID: 27856182 [Indexed for MEDLINE]

6. Drug interaction study of flavonoids toward CYP3A4 and their quantitative structure activity relationship (QSAR) analysis for predicting potential effects. Li Y, Ning J, Wang Y, Wang C, Sun C, Huo X, Yu Z, Feng L, Zhang B, Tian X, Ma X.

Toxicol Lett. 2018 Sep 15;294:27-36. doi: 10.1016/j.toxlet.2018.05.008. Epub 2018 May 9.

The high risk of herb-drug interactions (HDIs) mediated by the herbal medicines and dietary supplements which containing abundant flavonoids had become more and more frequent in our daily life. In our study, the inhibition activities of 44 different structures of flavonoids toward human CYPs were systemically evaluated for the first time. According to our results, a remarkable structure-dependent inhibition behavior toward CYP3A4 was observed in vitro. Some flavonoids such as licoflavone (12) and irilone (30) exhibited the selective inhibition toward CYP3 A4 rather than other major human CYPs. To illustrate the interaction mechanism, the inhibition kinetics of various compounds was further performed. Sophoranone (1), apigenin (10), baicalein (11), 5,4'-dihydroxy-3,6,7,8,3'-pentamethoxyflavone (15), myricetin (23) and kushenol K (38) remarkably inhibited the CYP3 A4-catalyzed bufalin 5'-hydroxylation reaction, with K_i values of 2.17 ± 0.29 , 6.15 ± 0.39 , 9.18 ± 3.40 , 2.30 ± 0.36 , 5.00 ± 2.77 and 1.35 ± 0.25 μM , respectively. Importantly, compounds 1, 11, 15, 23 and 38 could significantly inhibit the metabolism of some clinical drugs in vitro, and these drug-drug interactions (DDIs) of myricetin (23) or kushenol K (38) with clinical drug diazepam were further verified in human primary hepatocytes, respectively. Finally, a quantitative structure-activity relationship (QSAR) of flavonoids with their inhibitory effects toward CYP3 A4 was established using computational methods. Our findings illustrated the high risk of herb-drug interactions (HDIs) caused by flavonoids and revealed the vital structures requirement of natural flavonoids for the HDIs with clinical drugs eliminated by CYP3 A4. Our research provided the useful guidance to safely and rationally use herbal medicines and dietary supplements containing rich natural flavonoids components.

DOI: 10.1016/j.toxlet.2018.05.008

PMID: 29753067

7. Hepatoprotective effects of berberine on acetaminophen-induced hepatotoxicity in mice. Zhao Z, Wei Q, Hua W, Liu Y, Liu X, Zhu Y.

Biomed Pharmacother. 2018 Jul;103:1319-1326. doi: 10.1016/j.biopha.2018.04.175. Epub 2018 May 7.

Acetaminophen (APAP) hepatotoxicity remains the leading cause of drug-induced liver injury due to the lack of safe and effective therapeutic agents. Berberine (BBR) is a natural alkaloid derived from traditional medicine *Rhizoma Coptidis* and possesses various pharmacological properties. The aim of this study was to explore the hepatoprotective effects and underlying mechanisms of BBR on APAP-induced hepatotoxicity. Our results indicated that BBR pretreatment significantly ameliorated APAP-induced hepatic pathological abnormalities and attenuated the elevations of serum aminotransferases and liver/body weight ratio. Compared to APAP group, BBR notably increased the levels of hepatic UDP-glucuronosyltransferases and sulfotransferases, whereas failed to ameliorate APAP-induced GSH depletion. Pretreatment with BBR significantly reduced hepatic MDA and MPO levels, inhibited JNK phosphorylation and up-regulated the expression of nuclear Nrf-2 and its downstream gene Mn-SOD. Additionally, BBR obviously prevented APAP-induced DNA fragmentation. Furthermore, BBR pretreatment dramatically reduced the expression of pro-inflammatory cytokines, HMGB1, p-p65 and cleaved caspase-1 and inhibited the infiltration of macrophages and neutrophils. Taken these results together, BBR exhibits notable preventive effects on APAP-induced hepatotoxicity by inhibiting oxidative stress, hepatocyte necrosis and inflammatory response.

DOI: 10.1016/j.biopha.2018.04.175

PMID: 29864914

8. Suicide Attempt by Ingestion of Rotenone-Containing Plant Extracts in French Polynesia: A Case Report.

Torrents R, Domangé B, Schmitt C, Boulamery A, De Haro L, Simon N.

Wilderness Environ Med. 2017 Sep;28(3):278-279. doi: 10.1016/j.wem.2017.03.017. Epub 2017 Jul 26.

DOI: 10.1016/j.wem.2017.03.017

PMID: 28754293 [Indexed for MEDLINE]

9. Hemorrhagic Stroke in a Young Healthy Male Following Use of Pre-Workout Supplement Animal Rage XL.

Harris BF, Winn C, Ableman TB.

Mil Med. 2017 Sep;182(9):e2030-e2033. doi: 10.7205/MILMED-D-17-00013.

So-called "pre-workout" supplements are substances marketed as natural dietary supplements with claims of helping athletes achieve more focused and intense workouts. The use of such products remains popular among American youth as a whole, but is especially high among active duty service members. Supplements are minimally regulated by the Food and Drug Administration (FDA), and unlike pharmaceuticals, supplements are often brought to market without any testing to show neither efficacy nor safety. Several case reports have documented serious adverse events and raise the question of whether supplement use was a causative factor. Reported events occurring after use of pre-workout supplements include, among others, ischemic stroke, hemorrhagic stroke, myocardial infarction, hepatitis, and death. Here, we present the case of a healthy 25-year-old active duty male who experienced a bilateral cerebellar hemorrhagic stroke occurring shortly after taking a supplement named Animal Rage XL. Hemorrhagic stroke occurring in a healthy 25-year-old male with no risk factors is exceedingly rare. This is the first known case of stroke temporally associated with this particular supplement, which is currently available for purchase at military exchanges. Additionally, several of the active ingredients in this supplement have been shown to cause hypertension, tachycardia, and vasospasm. All of these effects could increase the likelihood and severity of a hemorrhagic stroke. The investigated ingredients in this abstract include β -phenethylamine, creatine-monophosphate, and caffeine.

DOI: 10.7205/MILMED-D-17-00013

PMID: 28885973 [Indexed for MEDLINE]

10. Ayurveda metallic-mineral 'Bhasma'-associated severe liver injury. Philips CA, Paramaguru R, Augustine P.

BMJ Case Rep. 2018 Jun 29;2018. pii: bcr-2018-225590. doi:10.1136/bcr-2018-225590.

Ayurveda Bhasma is a metallic-mineral preparation homogenised with herbal juices or decoctions and modified with heat treatment to apparently detoxify the heavy metals. It is widely recommended for the treatment of many disease conditions by practitioners of complementary and alternative medicine in the absence of good quality clinical trial evidence on its safety and efficacy. Heavy metal-induced liver injury is widely reported in the literature, and heavy metal adulteration of non-Bhasma-related Ayurveda and herbal products has been well described. We report a patient who developed severe liver injury requiring listing for liver transplantation for improved survival, after consumption of Bhasma for dyspepsia. This case describes the first documented case and toxicology analysis of Ayurveda Bhasma associated with severe drug-induced liver injury. Physicians must be alert regarding patient's use of supposedly safe Ayurveda Bhasma that may promote acute severe liver injury in the absence of other known aetiologies.

DOI: 10.1136/bcr-2018-225590

PMID: 29960971

11. Phytophotodermatitis related to carrot extract-containing sunscreen. Bosanac SS, Clark AK, Sivamani RK.

Dermatol Online J. 2018 Jan 15;24(1). pii: 13030/qt2nv2d1n0.

Phytophotodermatitis is a clinical diagnosis from phototoxicity of the skin induced by contact with plants or their extracts. Phytophotodermatitis may present with burning, erythema, patches, plaques, vesicles, bullae, or hyperpigmented patches in well-demarcated and unusual shapes. Inquiring about occupation, hobbies, and plant or plant extract contact is essential to establishing the diagnosis. Herein we present a case of phytophotodermatitis after use of carrot extract-containing sunscreen presenting as a hyperpigmented patch in a geometric distribution with accentuation of pigment within the dynamic rhytides.

PMID: 29469776 [Indexed for MEDLINE]

12. Beau's lines. Lin X, Wu S.

QJM. 2017 Oct 1;110(10):669-670. doi: 10.1093/qjmed/hcx122.

DOI: 10.1093/qjmed/hcx122
PMID: 29016930 [Indexed for MEDLINE]

13. The use of complementary and alternative medicines during breastfeeding: results from the Herbal supplements in Breastfeeding Investigation (HaBIT) study. Bettiol A, Lombardi N, Marconi E, Crescioli G, Bonaiuti R, Maggini V, Gallo E, Mugelli A, Firenzuoli F, Ravaldi C, Vannacci A.

Br J Clin Pharmacol. 2018 May 16. doi: 10.1111/bcp.13639. [Epub ahead of print]

AIMS: The use of complementary and alternative medicines (CAMs) during breastfeeding is increasing, mainly because of their presumed greater safety compared with conventional medications. However, CAMs can cause serious adverse effects, and there is limited high-quality evidence supporting their use during lactation. In Italy, specific investigations on the attitude of lactating women towards CAMs are lacking. The Herbal supplements in Breastfeeding Investigation (HaBIT) study aimed to explore attitudes to and knowledge on CAMs among lactating women. **METHODS:** A web-based survey was conducted over a 6-year period among lactating women resident in Tuscany, Italy. Data on lactating behaviour, CAMs use during pregnancy or breastfeeding, and women's knowledge about the efficacy and safety of CAMs were collected. **RESULTS:** A total of 388 lactating women answered the questionnaire. The majority of them were primiparae, with a high educational level. Of these, 204 women declared themselves to have used CAMs during breastfeeding. Moreover, 61% and 48% of subjects reported also using CAMs before and during pregnancy, respectively. A significant proportion of subjects were unable to identify correctly the types of CAMs they were using. Seventy-three per cent of women were convinced that CAMs were equally safe or safer than conventional medications; nevertheless, 65% of women admitted to have no scientific information about the potential risks of CAMs, and 14 CAMs users reported that they had experienced side effects. **CONCLUSIONS:** These results demonstrate the need for healthcare providers to increase the awareness of breastfeeding women about CAMs. Further research is needed to support the evidence base for nonpharmaceutical approaches for symptom control during breastfeeding.

DOI: 10.1111/bcp.13639
PMID: 29768673

14. Severe postoperative hemorrhage in a patient on dietary and herbal supplements. Wang L, Lanka L, Chen D, Pruthi RK.

J Perioper Pract. 2018 Jan 1;1750458918780112. doi: 10.1177/1750458918780112. [Epub ahead of print]

We report a case of a patient with severe postoperative bleeding complication, secondary to dietary and herbal supplements induced platelet dysfunction. This case demonstrates the importance of preoperative assessment which includes questioning the patient with regards to their dietary and herbal supplements and of stressing the importance of discontinuing them prior to surgery.

DOI: 10.1177/1750458918780112
PMID: 29888990

15. Elevated International Normalized Ratio in a Patient Taking Warfarin and Mauby: A Case Report. Sorbera M, Joseph T, DiGregorio RV.

J Pharm Pract. 2017 Oct;30(5):567-570. doi: 10.1177/0897190016663435. Epub 2016 Aug 19.

We describe a 70-year-old Haitian man who had been taking warfarin for 5 years for atrial fibrillation and pulmonary hypertension. This patient had his international normalized ratio (INR) checked in the pharmacist-run anticoagulation clinic and was followed monthly. Prior to the interaction, his INR was therapeutic for 5 months while taking warfarin 10.5 mg/d. The patient presented with an INR > 8.0. Patient held 4 days of warfarin and restarted on warfarin 8.5 mg/d. Two weeks later, his INR was 2.5. After continuing dose, patient presented 2 weeks later and INR was 4.8. Upon further questioning, the patient stated he recently began ingesting mauby. Mauby is a bitter dark liquid extracted from the bark of the mauby tree that is commonly used in the Caribbean population as a folk remedy with many health benefits. This case report illustrates that mauby may have a probable drug-herb interaction (Naranjo Algorithm Score of 6) when given with warfarin. There is a lack of published literature and unclear information on the Internet describing the interaction of mauby and warfarin. Health professionals should be cautious regarding interactions between warfarin and mauby until the interaction is fully elucidated.

DOI: 10.1177/0897190016663435
PMID: 27543375 [Indexed for MEDLINE]