AACT Herbal Dietary Supplements SIG Abstracts Nov. 2016

1. Trends in Dietary Supplement Use Among US Adults From 1999-2012. Kantor ED, Rehm CD, Du M, White E, Giovannucci EL.

JAMA. 2016 Oct 11;316(14):1464-1474. doi: 10.1001/jama.2016.14403.

Abstract
IMPORTANCE: Dietary supplements are commonly used by US adults; yet, little is known about recent trends in supplement use. OBJECTIVE: To report trends in dietary supplement use among US adults. DESIGN, SETTING, AND PARTICIPANTS: Serial cross-sectional study using nationally representative data from the National Health and Nutrition Examination Survey (NHANES) collected between 1999 and 2012. Participants include noninstitutionalized adults residing in the United States, surveyed over 7 continuous 2-year cycles (sample size per cycle, 4863 to 6213). EXPOSURES: Calendar time, as represented by NHANES cycle. MAIN OUTCOMES AND MEASURES: In an in-home interview, participants were queried on use of supplements in the preceding 30 days to estimate the prevalence of use within each NHANES cycle, and trends were evaluated across cycles. Outcomes included use of any supplements; use of multivitamins/multiminerals (MVMM; defined as a product containing ≥10 vitamins and/or minerals); and use of individual vitamins, minerals, and nonvitamin, nonmineral supplements. Data were analyzed overall and by population subgroup (including age, sex, race/ethnicity, and educational status), and were weighted to be nationally representative. RESULTS: A total of 37 958 adults were included in the study (weighted mean age, 46.4 years; women, 52.0%), with an overall response rate of 74%. Overall, the use of supplements remained stable between 1999 and 2012, with 52% of US adults reporting use of any supplements in 2011-2012 (P for trend = .19). This trend varied by population subgroup. Use of MVMM decreased, with 37% reporting use of MVMM in 1999-2000 and 31% reporting use in 2011-2012 (difference, -5.7% [95% CI, -8.6% to -2.7%], P for trend < .001). Vitamin D supplementation from sources other than MVMM increased from 5.1% to 19% (difference, 14% [95% CI, 12% to 17%], P for trend < .001) and use of fish oil supplements increased from 1.3% to 12% (difference, 11% [95% CI, 9.1% to 12%], P for trend < .001) over the study period, whereas use of a number of other supplements decreased. CONCLUSIONS AND RELEVANCE: Among adults in the United States, overall use of dietary supplements remained stable from 1999-2012, use of MVMM decreased, and trends in use of individual supplements varied and were heterogeneous by population subgroups.

2. Finding Potentially unsafe nutritional supplements from user reviews with topic modeling. Sullivan R, Sarker A, O'Connor K, Goodin A, Karlsrud M, Gonzalez G.

Pac Symp Biocomput. 2016;21:528-39.

Although dietary supplements are widely used and generally are considered safe, some supplements have been identified as causative agents for adverse reactions, some of which may even be fatal. The Food and Drug Administration (FDA) is responsible for monitoring supplements and ensuring that supplements are safe. However, current surveillance protocols are not always effective. Leveraging user-generated textual data, in the form of Amazon.com reviews for nutritional supplements, we use natural language processing techniques to develop a system for the monitoring of dietary supplements. We use topic modeling techniques, specifically a variation of Latent Dirichlet Allocation (LDA), and background knowledge in the form of an adverse reaction dictionary to score products based on their potential danger to the public. Our approach generates topics that semantically capture adverse reactions from a document set consisting of reviews posted by users of specific products, and based on these topics, we propose a scoring mechanism to categorize products as "high potential danger", “average potential danger" and "low potential danger." We evaluate our system by comparing the system categorization with human annotators, and we find that the our system agrees with the annotators 69.4% of the time. With these results, we demonstrate that our methods show promise and that our system represents a proof of concept as a viable low-cost, active approach for dietary supplement monitoring.

PMID: 26776215 [PubMed - indexed for MEDLINE]
DOI: 10.1111/bcpt.12437
PMID: 26119520 [PubMed - indexed for MEDLINE]

3. Methods for estimating causal relationships of adverse events with dietary supplements. Ide K, Yamada H, Kitagawa M, Kawasaki Y, Buno Y, Matsushita K, Kaji M, Fujimoto K, Waki M, Nakashima M, Umegaki K.

BMJ Open. 2015 Nov 25;5(11):e009038. doi: 10.1136/bmjopen-2015-009038.

OBJECTIVE: Dietary supplement use has increased over past decades, resulting in reports of potentially serious adverse events. The aim of this study was to develop optimised methods to evaluate the causal relationships between adverse events and dietary supplements, and to test these methods using case reports. DESIGN: Causal relationship assessment using prospectively collected data. SETTING AND PARTICIPANTS: 4 dietary supplement experts, 4 pharmacists and 11 registered dietitians (5 men and 14 women) examined 200 case reports of suspected adverse events using the modified Naranjo scale and the modified Food and Drug Administration (FDA) algorithm. PRIMARY OUTCOME MEASURES: The distribution of evaluation results was analysed and inter-rater reliability was evaluated for the two modified methods employed using intraclass correlation coefficients (ICC) and Fleiss' κ. RESULTS: Using these two methods, most of the 200 case reports were categorised as 'lack of information' or 'possible' adverse events. Inter-rater reliability among entire assessors ratings for the two modified methods, based on ICC and Fleiss' κ, were classified as more than substantial (modified Naranjo scale: ICC (95% CI) 0.873 (0.850 to 0.895); Fleiss' κ (95% CI) 0.615 (0.615 to 0.615). Modified FDA algorithm: Fleiss' κ (95% CI) 0.622 (0.622 to 0.622). CONCLUSIONS: These methods may help to assess the causal relationships between adverse events and dietary supplements. By conducting additional studies of these methods in different populations, researchers can expand the possibilities for the application of our methods.

DOI: 10.1136/bmjopen-2015-009038
PMCID: PMC4663420
PMID: 26608636 [PubMed - indexed for MEDLINE]

4. Combined DNA, toxicological and heavy metal analyses provides an auditing toolkit to improve pharmacovigilance of traditional Chinese medicine (TCM). Coghlan ML, Maker G, Crighton E, Haile J, Murray DC, White NE, Byard RW, Bellgard MI, Mullaney I, Trengove R, Allcock RJ, Nash C, Hoban C, Jarrett K, Edwards R, Musgrave IF, Bunce M.

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

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

DOI: 10.1038/srep17475
PMCID: PMC4675079
PMID: 26658160 [PubMed - indexed for MEDLINE]

5. The effects of dietary and herbal phytochemicals on drug transporters. Li Y, Revalde J, Paxton JW.

Adv Drug Deliv Rev. 2016 Sep 13. pii: S0169-409X(16)30259-9. doi: 10.1016/j.addr.2016.09.004. [Epub ahead of print]

Membrane transporter proteins (the ABC transporters and SLC transporters) play pivotal roles in drug absorption and disposition, and thus determine their efficacy and safety. Accumulating evidence suggests that the expression and activity of these transporters may be modulated by various phytochemicals (PCs)

found in diets rich in plants and herbs. PC absorption and disposition are also subject to the function of membrane transporter and drug metabolizing enzymes. PC-drug interactions may involve multiple major drug transporters (and metabolizing enzymes) in the body, leading to alterations in the pharmacokinetics of substrate drugs, and thus their efficacy and toxicity. This review summarizes the reported in vitro and in vivo interactions between common dietary PCs and the major drug transporters. The oral absorption, distribution into pharmacological sanctuaries and excretion of substrate drugs and PCs are considered, along with their possible interactions with the ABC and SLC transporters which influence these processes.

DOI: 10.1016/j.addr.2016.09.004
PMID: 27637455 [PubMed - as supplied by publisher]

6. The non-competitive blockade of GABAA receptors by an aqueous extract of water hemlock (Cicuta douglasii) tubers. Green BT, Goulart C, Welch KD, Pfister JA, McCollum I, Gardner DR.

Toxicon. 2015 Dec 15;108:11-4. doi: 10.1016/j.toxicon.2015.09.015. Epub 2015 Sep 28.

Water hemlocks (Cicuta spp.) are acutely toxic members of the Umbellierae family; the toxicity is due to the presence of C17-polyacetylenes such as cicutoxin. There is only limited evidence of noncompetitive antagonism by C17-polyacetylenes at GABAA receptors. In this work with WSS-1 cells, we documented the noncompetitive blockade of GABAA receptors by an aqueous extract of water hemlock (Cicuta douglasii) and modulated the actions of the extract with a pretreatment of 10 μM midazolam.

DOI: 10.1016/j.toxicon.2015.09.015
PMID: 26415905 [PubMed - indexed for MEDLINE]

7. 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 [PubMed - in process]

8. Pharmacokinetic Interactions between Drugs and Botanical Dietary Supplements. Sprouse AA, van Breemen RB.

Drug Metab Dispos. 2016 Feb;44(2):162-71. doi: 10.1124/dmd.115.066902. Epub 2015 Oct 5.

The use of botanical dietary supplements has grown steadily over the last 20 years despite incomplete information regarding active constituents, mechanisms of action, efficacy, and safety. An important but underinvestigated safety concern is the potential for popular botanical dietary supplements to interfere with the absorption, transport, and/or metabolism of pharmaceutical agents. Clinical trials of drug-botanical interactions are the gold standard and are usually carried out only when indicated by unexpected consumer side effects or, preferably, by predictive preclinical studies. For example, phase 1 clinical trials have confirmed preclinical studies and clinical case reports that St. John's wort (Hypericum perforatum) induces CYP3A4/CYP3A5. However, clinical studies of most botanicals that were predicted to interact with drugs

have shown no clinically significant effects. For example, clinical trials did not substantiate preclinical predictions that milk thistle (Silybum marianum) would inhibit CYP1A2, CYP2C9, CYP2D6, CYP2E1, and/or CYP3A4. Here, we highlight discrepancies between preclinical and clinical data concerning drug-botanical interactions and critically evaluate why some preclinical models perform better than others in predicting the potential for drug-botanical interactions. Gaps in knowledge are also highlighted for the potential of some popular botanical dietary supplements to interact with therapeutic agents with respect to absorption, transport, and metabolism.

DOI: 10.1124/dmd.115.066902
PMCID: PMC4727115 [Available on 2017-02-01]
PMID: 26438626 [PubMed - indexed for MEDLINE]

9. Amygdalin, quackery or cure? Blaheta RA, Nelson K, Haferkamp A, Juengel E.

Phytomedicine. 2016 Apr 15;23(4):367-76. doi: 10.1016/j.phymed.2016.02.004. Epub 2016 Feb 17.

BACKGROUND: The cyanogenic diglucoside, amygdalin, has gained high popularity among cancer patients together with, or in place of, conventional therapy. Still, evidence based research on amygdalin is sparse and its benefit controversial. PURPOSE: Since so many cancer patients consume amygdalin, and many clinicians administer it without clear knowledge of its mode of action, current knowledge has been summarized and the pros and cons of its use weighed. METHODS: A retrospective analysis was conducted for amygdalin relevant reports using the PubMed database with the main search term "Amygdalin" or "laetrile", at times combined with "cancer", "patient", "cyanide" or "toxic". We did not exclude any "unwanted" articles. Additionally, internet sources authorized by governmental or national institutions have also been included. SECTIONS: Individual chapters summarize pharmacokinetics, preclinical and clinical studies and toxicity. CONCLUSION: No convincing evidence showing that amygdalin induces rapid, distinct tumor regression in cancer patients, particularly in those with late-stage disease, is apparent. However, there is also no evidence that purified amygdalin, administered in "therapeutic" dosage, causes toxicity. Multiple aspects of amygdalin administration have not yet been adequately explored, making further investigation necessary to evaluate its actual therapeutic potential.

DOI: 10.1016/j.phymed.2016.02.004
PMID: 27002407 [PubMed - indexed for MEDLINE]

10. Hypericum perforatum use during pregnancy and pregnancy outcome. Kolding L, Pedersen LH, Henriksen TB, Olsen J, Grzeskowiak LE.

Reprod Toxicol. 2015 Dec;58:234-7. doi: 10.1016/j.reprotox.2015.10.003. Epub 2015 Nov 1.

Erratum in
    Reprod Toxicol. 2016 Jan;59:183.

Hypericum perforatum (HP; also known as St. John's Wort) is one of the most commonly used herbal therapies in the management of depressive illness. The aim of this study was to evaluate the potential side effects of HP during pregnancy on pregnancy outcome. Using data from the Danish National Birth Cohort (DNBC), we investigated outcomes among 38 HP exposed pregnancies compared to a group of 90,128 women. Associations between HP use and gestational age, preterm birth, birth weight, malformations and Apgar scores were investigated. Preterm birth did not differ across the groups. While the prevalence of malformations in the HP exposed group was slightly higher (8.1%) than observed in the control groups (3.3%; p=0.13), this was based on only three cases and was not of any specific pattern.

DOI: 10.1016/j.reprotox.2015.10.003
PMID: 26536653 [PubMed - indexed for MEDLINE]

11. Liver Injury from Herbal and Dietary Supplements. Navarro V, Khan I, Björnsson E, Seeff LB, Serrano J, Hoofnagle JH.

Hepatology. 2016 Sep 27. doi: 10.1002/hep.28813. [Epub ahead of print]

Herbal and dietary supplements (HDS) are used increasingly both in the United States and worldwide and HDS induced liver injury in the U.S. has increased proportionally. Current challenges in the diagnosis and management of HDS-induced liver injury were the focus of a 2-day research symposium sponsored by the American Association for the Study of Liver Disease and the National Institutes of Health. HDS-induced liver injury now accounts for 20% of cases of hepatotoxicity in the United States based on research data. The major implicated agents include anabolic steroids, green tea extract, and multi-ingredient nutritional supplements (MINS). Anabolic steroids marketed as bodybuilding supplements typically induce a prolonged cholestatic, but ultimately self-limiting liver injury that has a distinctive serum biochemical as well as histological phenotype. Green tea extract and many other products, in contrast, tend to cause an acute hepatitis like injury. Currently, however, the majority of cases of HDS-associated liver injury are due to MINS, and the component responsible for the toxicity is usually unknown or can only be suspected. HDS-induced liver injury presents many clinical and research challenges, in diagnosis, identification of the responsible constituents, treatment and prevention. Also important are improvements in regulatory oversight of non-prescription products to guarantee their constituents and insure purity and safety. The confident identification of injurious ingredients within HDS will require strategic alignments among clinicians, chemists, and toxicologists. The ultimate goal should be to prohibit or more closely regulate potentially injurious ingredients and thus promote public safety.

DOI: 10.1002/hep.28813
PMID: 27677775 [PubMed - as supplied by publisher]

12. The mystery of the Hawaii liver disease cluster in summer 2013: A pragmatic and clinical approach to solve the problem. Teschke R, Schwarzenboeck A, Frenzel C, Schulze J, Eickhoff A, Wolff A.

Ann Hepatol. 2016 Jan-Feb;15(1):91-109.

BACKGROUND AND AIM: In the fall of 2013, the US Centers for Disease Control and Prevention (CDC) published a preliminary report on a cluster of liver disease cases that emerged in Hawaii in the summer 2013. This report claimed a temporal association as sufficient evidence that OxyELITE Pro (OEP), a dietary supplement (DS) mainly for weight loss, was the cause of this mysterious cluster. However, the presented data were inconsistent and required a thorough reanalysis. MATERIAL AND METHODS: To further investigate the cause(s) of this cluster, we critically evaluated redacted raw clinical data of the cluster patients, as the CDC report received tremendous publicity in local and nationwide newspapers and television. This attention put regulators and physicians from the medical center in Honolulu that reported the cluster, under enormous pressure to succeed, risking biased evaluations and hasty conclusions. RESULTS: We noted pervasive bias in the documentation, conclusions, and public statements, also poor quality of case management. Among the cases we reviewed, many causes unrelated to any DS were evident, including decompensated liver cirrhosis, acute liver failure by acetaminophen overdose, acute cholecystitis with gallstones, resolving acute hepatitis B, acute HSV and VZV hepatitis, hepatitis E suspected after consumption of wild hog meat, and hepatotoxicity by acetaminophen or ibuprofen. Causality assessments based on the updated CIOMS scale confirmed the lack of evidence for any DS including OEP as culprit for the cluster. CONCLUSIONS: Thus, the Hawaii liver disease cluster is now best explained by various liver diseases rather than any DS, including OEP.

PMID: 26626645 [PubMed - indexed for MEDLINE]

13. Systematic Review on Chinese Herbal Medicine Induced Liver Injury. Zhang P, Ye Y, Yang X, Jiao Y.

Evid Based Complement Alternat Med. 2016;2016:3560812. doi: 10.1155/2016/3560812. Epub 2016 Aug 29.

Background. In recent years, with the popularity of CHM, its hepatotoxicity has also been increasingly noticed. However, there are still veils on causative herbs and clinical characteristics. Aim. To systematically review data on CHM induced liver injury with particular focus on causative herbs and clinical characteristics. Methods. Using terms related to CHM and liver injury, PubMed and three Chinese electronic databases were searched, which was limited to the past 5 years. Publications meeting our eligibility criteria were included and further analyzed. Results. In total, 4 single herbs, 21 patent drugs, and 4 decoctions were reported to be of hepatotoxicity, with He-Shou-Wu being the most common one (65/114). Dang-Gui and other 5 herbs were the most common ingredients of patent drugs and decoctions. All patients were assessed using the RUCAM scale, with 26 being highly probable and 28 being probable. For these 54 cases, the latent period was 30 (47) days, and 81.48% were labeled as hepatocellular injuries. Most patients (96.3%) recovered, apart from

the fact that one died and one is receiving liver transplantation. Conclusions. CHM should be used carefully for hepatotoxicity. Liver injury from CHM is similar to that from conventional medicines in clinical characteristics. Details about causative herbs should be illustrated, and more RUCAM should be used in future.

DOI: 10.1155/2016/3560812
PMCID: PMC5019919
PMID: 27651817 [PubMed]

14. Clinical Features of Drug-induced Liver Injury According to Etiology. Lee BM, Lee WC, Jang JY, Ahn P, Kim JN, Jeong SW, Park EJ, Lee SH, Kim SG, Cha SW, Kim YS, Cho YD, Kim HS, Kim BS.

J Korean Med Sci. 2015 Dec;30(12):1815-20. doi: 10.3346/jkms.2015.30.12.1815. Epub 2015 Nov 30.

Drug-induced liver injury (DILI) is an increasingly common cause of acute hepatitis. We examined clinical features and types of liver injury of 65 affected patients who underwent liver biopsy according DILI etiology. The major causes of DILI were the use of herbal medications (43.2%), prescribed medications (21.6%), and traditional therapeutic preparations and dietary supplements (35%). DILI from herbal medications, traditional therapeutic preparations, and dietary supplements was associated with higher elevations in aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels than was DILI from prescription medications. The types of liver injury based on the R ratio were hepatocellular (67.7%), mixed (10.8%), and cholestatic (21.5%). Herbal medications and traditional therapeutic preparations were more commonly associated with hepatocellular liver injury than were prescription medications (P = 0.002). Herbal medications and traditional therapeutic preparations induce more hepatocellular DILI and increased elevations in AST and ALT than prescribed medications.

DOI: 10.3346/jkms.2015.30.12.1815
PMCID: PMC4689826
PMID: 26713057 [PubMed - indexed for MEDLINE]

15. The Diagnosis and Manifestations of Liver Injury Secondary to Off-Label Androgenic Anabolic Steroid Use. Cabb E, Baltar S, Powers DW, Mohan K, Martinez A, Pitts E.

Case Rep Gastroenterol. 2016 Sep 12;10(2):499-505.

Drug-induced liver injury (DILI) presents as a broad spectrum of adverse drug reactions which can range from a mild elevation in liver enzymes to fulminant liver failure. The primary goal is to identify DILI early when the patient's liver enzymes are elevated and to discontinue the offending agent as soon as possible to prevent further injury. Herbal, dietary supplements and anabolic steroids represent a significant component of the drugs thought to cause DILI in the United States. Unlike all other drugs known to cause DILI, these drugs fall into a category of injury that is neither intrinsic nor idiosyncratic due to overlapping characteristics between the two. Here, we present a case of the off-label use of androgenic anabolic steroids inducing liver injury. A combination of clinical, laboratory, and histologic workup eventually led to the diagnosis of DILI. This can be a diagnostic challenge for practitioners. The American College of Gastroenterology (ACG) published guidelines to aid the clinician in diagnosing DILI. Proving that an episode of liver injury is caused by a drug is difficult in many cases as it requires the exclusion of alternative etiologies. Some of the variables include temporal association, clinical-biochemical features, type of injury (hepatocellular and/or cholestatic), extrahepatic features, and the likelihood that a given agent is the culprit based on its known manifestations with prior cases. This case illustrates the utility of the diagnostic tools used for DILI as recommended by the ACG, along with a supplemental histopathologic diagnosis.

DOI: 10.1159/000448883
PMID: 27721739 [PubMed - in process]

16. An unexpected cause of acute kidney injury in a patient with ANCA associated vasculitis. Choudhry WM, Nori US, Nadasdy T, Satoskar AA.

Clin Nephrol. 2016 May;85(5):289-95. doi: 10.5414/CN108760.

Diagnostic kidney biopsies sometimes yield clinically unsuspected diagnoses. We present a case of a 69-year-old woman with established ANCA-associated vasculitis (AAV) of 4 years duration who was in clinical remission following cytotoxic therapy and was on maintenance immunosuppression. She presented to the hospital with acute kidney injury (AKI), symptoms suggestive of a systemic vasculitis, and in addition had hypercalcemia, metabolic alkalosis. A relapse in the AAV was suspected but a diagnostic kidney biopsy showed acute tubular necrosis, patchy interstitial inflammation, and calcium phosphate deposits. It was found that the patient recently started consuming large doses of over-the-counter calcium-containing antacids and vitamin Dcontaining multivitamin supplements. Cessation of these drugs led to improvement of renal function to baseline. This case highlights several teaching points: (1) the kidney biopsy can prove to be critically important even in cases where there appears to be a more obvious clinical diagnosis, (2) AK due to calcium-alkali syndrome has characteristic histopathological changes, and (3) that the triad of hypercalcemia, metabolic alkalosis, and AKI is exclusively associated with the ingestion of excessive quantities of calcium-containing antacids. The physician should keep this in mind, and pro-actively seek pertinent medication history from the patient. A brief review of calcium-alkali syndrome is given.

DOI: 10.5414/CN108760
PMID: 26932179 [PubMed - indexed for MEDLINE]

17. Drug rash with eosinophilia and systemic symptoms caused by the dietary supplement diindolylmethane. Le TM, Sanders CJ, van de Corput L, van Erpecum KJ, Röckmann H.

J Allergy Clin Immunol Pract. 2016 Jan-Feb;4(1):175-6. doi: 10.1016/j.jaip.2015.07.007. Epub 2015 Aug 19.

Diindolylmethane, a dietary supplement and potential investigational drug, can cause drug rash with eosinophilia and systemic symptoms, a severe drug reaction. The drug patch test was safe and useful in the diagnosis. This case stresses the importance of obtaining a complete drug history, including use of dietary supplements.

DOI: 10.1016/j.jaip.2015.07.007
PMID: 26298826 [PubMed - indexed for MEDLINE]

18. Bullous drug eruption to Nigella sativa oil: Consideration of the use of an herbal medicine - clinical report and review of the literature. Bonhomme A, Poreaux C, Jouen F, Schmutz JL, Gillet P, Barbaud A.

J Eur Acad Dermatol Venereol. 2016 Sep 29. doi: 10.1111/jdv.13982. [Epub ahead of print]

Nigella sativa oil (NSO), extracted from the plant Nigella sativa, is traditionally used in Africa and Asia for many therapeutic properties. Thymoquinone, its main constituent, has cellular and molecular targets, with pharmacological activities proved against various diseases.(1) We report the succession of an atypical Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN) overlap to NSO and bullous pemphigoid (BP). Furthermore, we review the cases of bullous cutaneous adverse drug reactions (CADRs) with traditional herbal medicines (THM).

DOI: 10.1111/jdv.13982
PMID: 27684404 [PubMed - as supplied by publisher]

19. Progressive Organ Failure After Ingestion of Wild Garlic Juice. Galland-Decker C, Charmoy A, Jolliet P, Spertini O, Hugli O, Pantet O.

J Emerg Med. 2016 Jan;50(1):55-60. doi: 10.1016/j.jemermed.2015.06.034. Epub 2015 Aug 15.

BACKGROUND: Wild garlic and related plants are increasingly sought after by fans of natural products. They can be confused with other plants containing colchicine and cause potentially fatal intoxications. CASE REPORT: We report a case of accidental poisoning by Colchicum autumnale, which was mistaken for wild garlic (Allium ursinum). The patient initially presented with mild gastrointestinal symptoms, but progressed rapidly to agranulocytosis, paraparesis, and delirium before the causative agent was identified. The laboratory tests revealed rhabdomyolysis, coagulopathy, alteration of liver tests, and prerenal azotemia. Botanical examination confirmed the incriminated plant (Colchicum autumnale). Serum and urine analysis confirmed the presence of colchicine. The patient required intensive support therapy, and she fully

recovered within 8 weeks. WHY SHOULD AN EMERGENCY PHYSICIAN BE AWARE OF THIS?: Colchicine poisoning should be considered in the differential diagnosis of patients presenting with gastroenteritis after ingestion of wild garlic.

DOI: 10.1016/j.jemermed.2015.06.034
PMID: 26281812 [PubMed - indexed for MEDLINE]

20. Fat burn X: burning more than fat. Hannabass K, Olsen KR.

BMJ Case Rep. 2016 Jan 25;2016. pii: bcr2015213374. doi: 10.1136/bcr-2015-213374.

A 50-year-old man presented with a 2-day history of bilateral lower extremity cramping and dark urine. The patient was found to have a creatine phosphokinase (CPK) elevated of up to 2306 U/L, a serum uric acid of 9.7 mg/dL and 101 red blood cell's per high-powered field on urinalysis. On questioning, the patient endorsed daily exercise with free weights. There were no changes in his regular exercise and medication regimen, no muscle trauma, no recent drug use and no illness. The patient did mention using a new fat burner known as 'Fat Burn X', which he had begun taking 2 days prior to the onset of his muscle cramps. The patient was given normal saline intravenous fluid resuscitation for 48 h with resultant normalisation of his CPK and creatinine, and was discharged with primary care follow-up.

DOI: 10.1136/bcr-2015-213374
PMID: 26811412 [PubMed - indexed for MEDLINE]

21. Accidental overdose in the deep shade of night: a warning on the assumed safety of 'natural substances'. Chadwick A, Ash A, Day J, Borthwick M.

BMJ Case Rep. 2015 Nov 5;2015. pii: bcr2015209333. doi: 10.1136/bcr-2015-209333.

There is an increasing use of herbal remedies and medicines, with a commonly held belief that natural substances are safe. We present the case of a 50-year-old woman who was a trained herbalist and had purchased an 'Atropa belladonna (deadly nightshade) preparation'. Attempting to combat her insomnia, late one evening she deliberately ingested a small portion of this, approximately 50 mL. Unintentionally, this was equivalent to a very large (15 mg) dose of atropine and she presented in an acute anticholinergic syndrome (confused, tachycardic and hypertensive) to our accident and emergency department. She received supportive management in our intensive treatment unit including mechanical ventilation. Fortunately, there were no long-term sequelae from this episode. However, this dramatic clinical presentation does highlight the potential danger posed by herbal remedies. Furthermore, this case provides clinicians with an important insight into potentially dangerous products available legally within the UK. To help clinicians' understanding of this our discussion explains the manufacture and 'dosing' of the A. belladonna preparation.

DOI: 10.1136/bcr-2015-209333
PMID: 26543025 [PubMed - indexed for MEDLINE]

22. Anticholinergic Accumulation: A Slumbering Interaction between Drugs and Food Supplements. Vrolijk MF, Opperhuizen A, Jansen EH, Bast A, Haenen GR.

Basic Clin Pharmacol Toxicol. 2015 Dec;117(6):427-32. doi: 10.1111/bcpt.12437. Epub 2015 Jul 24.

Many compounds display anticholinergic effects which might give rise to cognitive impairment and even delirium. These side effects are caused by their ability to bind to muscarinic receptors in our brain. Especially with combination of compounds, these serious effects are seen. This phenomenon, known as anticholinergic accumulation, is especially seen in the elderly. A classification of drugs for anticholinergic side effects has been made based on clinical observations, the ACB score. Here, we aimed to substantiate this classification by comparing the affinity of numerous drugs for the muscarinic receptors to the ACB score. Additionally, a number of supplements were screened. The affinity of the compounds was determined by their ability to displace the radioligand [(3)H]pirenzepine of the muscarinic receptor induced by these compounds. Our results show that the affinity of a compound for the muscarinic receptors correlated with its ACB score. Also food supplements appeared to bind to these muscarinic receptors. Moreover, several drug-drug, supplement-supplement and supplement-drug combinations had an affinity that is higher than the affinity of single compounds. This explains the phenomenon of anticholinergic accumulation. In conclusion, care

should be taken to drug-drug and supplement-drug combinations with respect to anticholinergic accumulation.

23. Licorice root components in dietary supplements are selective estrogen receptor modulators with a spectrum of estrogenic and anti-estrogenic activities. Boonmuen N, Gong P, Ali Z, Chittiboyina AG, Khan I, Doerge DR, Helferich WG, Carlson KE, Martin T, Piyachaturawat P, Katzenellenbogen JA, Katzenellenbogen BS.

Steroids. 2016 Jan;105:42-9. doi: 10.1016/j.steroids.2015.11.006. Epub 2015 Nov 26.

Licorice root extracts are often consumed as botanical dietary supplements by menopausal women as a natural alternative to pharmaceutical hormone replacement therapy. In addition to their components liquiritigenin (Liq) and isoliquiritigenin (Iso-Liq), known to have estrogenic activity, licorice root extracts also contain a number of other flavonoids, isoflavonoids, and chalcones. We have investigated the estrogenic activity of 7 of these components, obtained from an extract of Glycyrrhiza glabra powder, namely Glabridin (L1), Calycosin (L2), Methoxychalcone (L3), Vestitol (L4), Glyasperin C (L5), Glycycoumarin (L6), and Glicoricone (L7), and compared them with Liq, Iso-Liq, and estradiol (E2). All components, including Liq and Iso-Liq, have low binding affinity for estrogen receptors (ERs). Their potency and efficacy in stimulating the expression of estrogen-regulated genes reveal that Liq and Iso-Liq and L2, L3, L4, and L6 are estrogen agonists. Interestingly, L3 and L4 have an efficacy nearly equivalent to E2 but with a potency ca. 10,000-fold less. The other components, L1, L5 and L7, acted as partial estrogen antagonists. All agonist activities were reversed by the antiestrogen, ICI 182,780, or by knockdown of ERα with siRNA, indicating that they are ER dependent. In HepG2 hepatoma cells stably expressing ERα, only Liq, Iso-Liq, and L3 stimulated estrogen-regulated gene expression, and in all cases gene stimulation did not occur in HepG2 cells lacking ERα. Collectively, these findings classify the components of licorice root extracts as low potency, mixed ER agonists and antagonists, having a character akin to that of selective estrogen receptor modulators or SERMs.

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PMID: 26631549 [PubMed - indexed for MEDLINE]

24. Herbal Highs: Review on psychoactive effects and neuropharmacology. Graziano S, Orsolini L, Rotolo MC, Tittarellie R, Schifano F, Pichini S.

Curr Neuropharmacol. 2016 Oct 31. [Epub ahead of print]

BACKGROUND: A new trend among users of new psychoactive substances' the consumption of "herbal highs": plant parts containing psychoactive substances. Most of the substances extracted from herbs, in old centuries were at the centre of religious ceremonies of ancient civilizations. Currently, these herbal products are mainly sold by internet web sites and easily obtained since some of them have no legal restriction. OBJECTIVE: We reviewed psychoactive effects and neuropharmacology of the most used "herbal highs" with characterized active principles, with studies reporting mechanisms of action, pharmacological and subjective effects, eventual secondary effects including intoxications and/or fatalities Method: The PubMed database was searched using the following key.words: herbal highs, Ayahuasca; Argyreia Nervosa, Ipomea Violacea and Rivea Corymbosa; Catha edulis; Datura stramonium; Piper Methysticum; Mitragina Speciosa; Trichocereus cacti; Salvia divinorum and Tabernanthe iboga. RESULTS: Psychoactive plants here reviewed have been known and used from ancient times, even if for some of them limited information still exist regarding subjective and neuropharmacological effects and consequent eventual toxicity when plants are used alone or in combination with "classical" drugs of abuse. CONCLUSION: Some "herbal highs" should be classified as harmful drugs since chronic administration has been linked with addiction and cognitive impairment; for some others taking into consideration only the recent trends of abuse, studies investigating these aspects are lacking.

PMID: 27799032 [PubMed - as supplied by publisher]

25. Renal toxic ingredients and their toxicology from traditional Chinese medicine. Xu XL, Yang LJ, Jiang JG.

Expert Opin Drug Metab Toxicol. 2016;12(2):149-59. doi: 10.1517/17425255.2016.1132306. Epub 2016 Jan 6.

INTRODUCTION: There have been increasing concerns regarding adverse reactions and toxicity incidents caused by traditional Chinese medicines (TCMs), among which the nephrotoxicity is particularly worrying. AREAS COVERED: This review summarizes the ingredients with renal toxicity from some TCMs through searching the relevant literature published over the past two decades. Renal toxicity components from TCMs include aristolochic acids (AAS), alkaloids, anthraquinones and others. TCM renal toxicity is most commonly caused by AAS and some alkaloids. AAS mainly come from Aristolochia contorta Bunge, Aristolochia manshuriensis Kom, Clematis Chinensis Osbeck, Aristolochia cathcartii Hook. Some renal toxic alkaloids are derived from Tripterygium regelii Sprague et Takeda, Stephania tetrandra S. Moore, Strychnos nux-vomica Linn. and Aconitum carmichaeli Debx. A few kinds of anthraquinones, flavonoids, and glycosides from TCMs also cause renal toxicity. All of these renal toxicity components and their associated renal toxicity, structures and toxic mechanism are introduced in detail in this review. EXPERT OPINION: Given the complexity of the toxic components, a lot of work needs to be done to analyze the specific modes of action of toxic components in vivo and in vitro, in particular, to elucidate the molecular mechanism of toxicity, in order to reduce the occurrence of renal toxicity of TCM.

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PMID: 26670420 [PubMed - indexed for MEDLINE]

26. Herbal medicines: challenges in the modern world. Part 4. Canada and United States. Job KM, Kiang TK, Constance JE, Sherwin CM, Enioutina EY.

Expert Rev Clin Pharmacol. 2016 Oct 3:1-13. [Epub ahead of print]

INTRODUCTION: Similar to other nations North American people used herbs for thousands of years to treat diseases and purify their spirits. By the middle of the 1900s, evidence-based conventional medicine received wide acceptance in Canada and the United States (US). Nowadays, people are going back to their roots and actively using herbal medicines (HMs) and natural health products (NHPs). Areas covered: This article is focusing on use and regulation of the HMs and NHPs in Canada and the US, raises concerns regarding HM and NHP safety and efficacy, offers suggestions on how to overcome these problems. Materials available from legislative and governmental websites, PubMed and news media were used. Expert commentary: Use of HMs, especially dietary supplements is widespread among adults in Canada and US. HMs and NHPs are regulated in both countries, but minimum criteria for product approval and post-market surveillance have been set. Concerns of quality, contamination, adulteration, and efficacy in are of central importance in the discussion of HMs and NHPs. Detailed product description and research are of vital importance to ensure safety and efficacy of these products. Additionally, 'herbal' education of healthcare providers and patients is needed to guarantee further successful integration of HM and conventional medicines.

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