

AACT Herbal Dietary Supplement Section

Abstracts November 2022

1. Dietary supplements and bleeding. Hatfield J, Saad S, Housewright C.

Proc (Bayl Univ Med Cent). 2022 Sep 15;35(6):802-807. doi: 10.1080/08998280.2022.2121575. eCollection 2022.

An estimated one-third of US adults use herbal supplements, often without reporting that use to their physicians. These supplements can potentially alter bleeding and coagulation during surgery and when used concomitantly with anticoagulants. Our objective was to provide a comprehensive review of the evidence of bleeding risks of the most popular herbal and dietary supplements. A PubMed search and review of the literature was performed. We found that garlic and hawthorn supplementation is strongly associated with surgical bleeding independent of anticoagulants. Cordyceps sinensis, echinacea, and aloe vera are loosely associated with surgical bleeding independent of anticoagulants. In patients on anticoagulants, ginkgo biloba, chondroitin-glucosamine, melatonin, turmeric, bilberry, chamomile, fenugreek, milk thistle, and peppermint are associated with bleeding risk. No evidence was found for bleeding with these supplements independent of anticoagulants. Fish oil, ginseng, and saw palmetto are not associated with bleeding. Evidence for overall bleeding risk associated with St. John's wort, ginger, ginkgo biloba, or cranberry supplementation is conflicting. In conclusion, physicians must be aware of the potential anticoagulant effects of these supplements. It is imperative to report dietary and herbal supplement usage to physicians and is best to discontinue nonessential supplement use 2 weeks prior to surgery.

DOI: 10.1080/08998280.2022.2121575

PMCID: PMC9586694

PMID: 36304597

2. Controversial Interactions of Tacrolimus with Dietary Supplements, Herbs and Food. Miedziaszczyk M, Bajon A, Jakielska E, Primke M, Sikora J, Skowrońska D, Idasiak-Piechocka I.

Pharmaceutics. 2022 Oct 10;14(10):2154. doi: 10.3390/pharmaceutics14102154.

Tacrolimus is an immunosuppressive calcineurin inhibitor used to prevent rejection in allogeneic organ transplant recipients, such as kidney, liver, heart or lung. It is metabolized in the liver, involving the cytochrome P450 (CYP3A4) isoform CYP3A4, and is characterized by a narrow therapeutic window, dose-dependent toxicity and high inter-individual and intra-individual variability. In view of the above mentioned facts, the aim of the study is to present selected interactions between tacrolimus and the commonly used dietary supplements, herbs and food. The review was based on the available scientific literature found in the PubMed, Scopus and Cochrane databases. An increase in the serum concentration of tacrolimus can be caused by CYP3A4 inhibitors, such as grapefruit, pomelo, clementine, pomegranate, ginger and turmeric, revealing the side effects of this drug, particularly nephrotoxicity. In contrast, CYP3A4 inducers, such as St. John's Wort, may result in a lack of therapeutic effect by reducing the drug concentration. Additionally, the use of Panax ginseng, green tea, Schisandra sphenanthera and melatonin in patients receiving tacrolimus is highly controversial. Therefore, since alternative medicine constitutes an attractive treatment option for patients, modern healthcare should emphasize the potential interactions between herbal medicines and synthetic drugs. In fact, each drug or herbal supplement should be reported by the patient to the physician (concordance) if it is taken in the course of immunosuppressive therapy, since it may affect the pharmacokinetic and pharmacodynamic parameters of other preparations.

DOI: 10.3390/pharmaceutics14102154

PMCID: PMC9611668

PMID: 36297591

3. Review article: clinical assessment of suspected drug-induced liver injury and its management. Vuppalachchi R, Ghabril M.

Aliment Pharmacol Ther. 2022 Dec;56(11-12):1516-1531. doi: 10.1111/apt.17246. Epub 2022 Oct 25.

BACKGROUND: Idiosyncratic drug-induced liver injury (DILI) is a rare instance of liver injury after exposure to an otherwise safe drug or herbal or dietary supplement. DILI can be associated with significant morbidity and mortality. Furthermore, it is an important consideration in drug development due to safety concerns. **AIMS AND METHODS:** To highlight pearls and pitfalls to aid clinicians in diagnosing DILI and surmising the management options. We also share the best practices from personal insights developed from decades long participation in the causality assessment committee meetings of the DILI Network. **RESULTS:** DILI lacks a diagnostic test and is currently diagnosed through a process of exclusion of competing aetiologies of liver injury. This requires a high degree of suspicion to consider the possibility of DILI, skill in ruling out the obvious and less obvious competing liver insults, and an understanding of the expected phenotypes of DILI. The facets of DILI cover multiple aspects, including the latency, liver injury pattern, course of injury, and associated autoimmune or immuno-allergic features. Care for patients with DILI is geared towards stopping the offending drug and symptom management that include the use of corticosteroids in select cases. **CONCLUSION:** The diagnosis of DILI is challenging and is primarily made through a carefully crafted patient interview, temporal relationship with the implicated drug or supplement, and exclusion of competing aetiology. LiverTox is a useful resource for clinicians to review the literature and recognise the likelihood of the implicated agent in causing DILI.

DOI: 10.1111/apt.17246

PMID: 36282208 [Indexed for MEDLINE]

4. Liver Injury Associated with Turmeric-A Growing Problem: Ten Cases from the Drug-Induced Liver Injury Network [DILIN]. Halegoua-DeMarzio D, Navarro V, Ahmad J, Avula B, Barnhart H, Barritt AS, Bonkovsky HL, Fontana RJ, Ghabril MS, Hoofnagle JH, Khan IA, Kleiner DE, Phillips E, Stolz A, Vuppalanchi R.

Am J Med. 2022 Oct 14:S0002-9343(22)00740-9. doi: 10.1016/j.amjmed.2022.09.026. Online ahead of print.

BACKGROUND: Turmeric is a commonly used herbal product that has been implicated in causing liver injury. The aim of this case series is to describe the clinical, histologic, and human leukocyte antigen (HLA) associations of turmeric-associated liver injury cases enrolled in the US Drug-Induced Liver Injury Network (DILIN). **METHODS:** All adjudicated cases enrolled in DILIN between 2004 and 2022 in which turmeric was an implicated product were reviewed. Causality was assessed using a 5-point expert opinion score. Available products were analyzed for the presence of turmeric using ultra-high-performance liquid chromatography. Genetic analyses included HLA sequencing. **RESULTS:** Ten cases of turmeric-associated liver injury were found, all enrolled since 2011, and 6 since 2017. Of the 10 cases, 8 were women, 9 were White, and median age was 56 years (range 35-71). Liver injury was hepatocellular in 9 patients and mixed in 1. Liver biopsies in 4 patients showed acute hepatitis or mixed cholestatic-hepatic injury with eosinophils. Five patients were hospitalized, and 1 patient died of acute liver failure. Chemical analysis confirmed the presence of turmeric in all 7 products tested; 3 also contained piperine (black pepper). HLA typing demonstrated that 7 patients carried HLA-B*35:01, 2 of whom were homozygous, yielding an allele frequency of 0.450 compared with population controls of 0.056-0.069. **CONCLUSION:** Liver injury due to turmeric appears to be increasing in the United States, perhaps reflecting usage patterns or increased combination with black pepper. Turmeric causes potentially severe liver injury that is typically hepatocellular, with a latency of 1 to 4 months and strong linkage to HLA-B*35:01.

DOI: 10.1016/j.amjmed.2022.09.026

PMID: 36252717

5. Hepatotoxicity due to herbal dietary supplements: Past, present and the future. Gurley BJ, McGill MR, Koturbash I.

Food Chem Toxicol. 2022 Nov;169:113445. doi: 10.1016/j.fct.2022.113445. Epub 2022 Sep 29.

Dietary supplements (DS) constitute a widely used group of products comprising vitamin, mineral, and botanical extract formulations. DS of botanical or herbal origins (HDS) comprise nearly 30% of all DS and are presented on the market either as single plant extracts or multi-extract-containing products. Despite generally safe toxicological profiles of most products currently present on the market, rising cases of liver

injury caused by HDS - mostly by multi-ingredient and adulterated products - are of particular concern. Here we discuss the most prominent historical cases of HDS-induced hepatotoxicity - from Ephedra to Hydroxycut and OxyELITE Pro-NF, as well as products with suspected hepatotoxicity that are either currently on or are entering the market. We further provide discussion on overcoming the existing challenges with HDS-linked hepatotoxicity by introduction of advanced in silico, in vitro, in vivo, and microphysiological system approaches to address the matter of safety of those products before they reach the market.

DOI: 10.1016/j.fct.2022.113445

PMID: 36183923 [Indexed for MEDLINE]

6. Evaluation of Concomitant Use of Anticancer Drugs and Herbal Products: From Interactions to Synergic Activity. Berretta M, Dal Lago L, Tinazzi M, Ronchi A, La Rocca G, Montella L, Di Francia R, Facchini BA, Bignucolo A, Montopoli M.

Cancers (Basel). 2022 Oct 23;14(21):5203. doi: 10.3390/cancers14215203

CAM is used by about 40% of cancer patients in Western Countries, with peaks of 80% for breast cancer patients. Cancer patients use CAM to boost immune function, to control cancer symptoms and treatment-related side effects, and to improve health-related quality of life (HR-QoL) and survival. Unfortunately, self-prescription of natural remedies in cancer patients can lead to unexpected toxicities and can reduce the effectiveness of cancer therapy. Although CAM usually refers to all the "natural or organic" products/methods that are generally considered less toxic, there are concerns about drug interactions, especially in patients participating in clinical trials with experimental agents. Despite the claims of the promising and potential benefits made by prescribers, many CAMs lack clear scientific evidence of their safety and efficacy. Given the widespread use of CAM-both clearly declared and overt-in this review, we focused on the most important known data on the risk of interactions between biologics and oncology drugs with the goal of opening up CAM in accordance with the meaning of integrative medicine.

DOI: 10.3390/cancers14215203

PMID: 36358622

7. Plant vs. Kidney: Evaluating Nephrotoxicity of Botanicals with the Latest Toxicological Tools.

Pearson A, Gafner S, Rider CV, Embry M, Ferguson SS, Mitchell CA.

Curr Opin Toxicol. 2022 Dec;32:100371. doi: 10.1016/j.cotox.2022.100371. Epub 2022 Aug 31.

Botanicals can cause nephrotoxicity via numerous mechanisms, including disrupting renal blood flow, damaging compartments along the nephron, and obstructing urinary flow. While uncommon, there are various reports of botanical-induced nephrotoxicity in the literature, such as from aristolochia (*Aristolochia* spp.) and rhubarb (*Rheum* spp.). However, at present, it is a challenge to assess the toxic potential of botanicals because their chemical composition is variable due to factors such as growing conditions and extraction techniques. Therefore, selecting a single representative sample for an in vivo study is difficult. Given the increasing use of botanicals as dietary supplements and herbal medicine, new approach methodologies (NAMs) are needed to evaluate the potential for renal toxicity to ensure public safety. Such approaches include in vitro models that use layers of physiological complexity to emulate the in vivo microenvironment, enhance the functional viability and differentiation of cell cultures, and improve sensitivity to nephrotoxic insults. Furthermore, computational tools such as physiologically based pharmacokinetic (PBPK) modeling can add confidence to these tools by simulating absorption, distribution, metabolism, and excretion. The development and implementation of NAMs for renal toxicity testing will allow specific mechanistic data to be generated, leading to a better understanding of the nephrotoxic potential of botanicals.

DOI: 10.1016/j.cotox.2022.100371

PMCID: PMC9601601

PMID: 36311298

8. Acute kidney injury in the tropics. Kusirisin P, da Silva Junior GB, Sitprija V, Srisawat N.

Nephrology (Carlton). 2022 Oct 7. doi: 10.1111/nep.14118. Online ahead of print.

The tropics are a region consisting of more than 125 countries, accounting for 40% of the world's population. The region's population is expected to increase up to 60% in the coming decades. Many tropical countries continue to experience public health problems such as high rates of infectious diseases, lack of sanitation, climate change impacts, poor regulation of herbal medicines and low access to healthcare. These conditions produce the unique problem of tropical acute kidney injury (AKI), which is associated with high morbidity and mortality. Tropical infections such as leptospirosis, dengue and malaria have varied mechanisms of AKI, including both direct kidney invasion and indirect effects, depending on the disease characteristics. Animal toxins from snakebites and arthropods along with plant toxins, such as djenkol beans, starfruit and herbal medicine, are characterized by a harmful renal effect from each toxic substance. Environmental factors such as heat stress, natural disasters and chemical compounds also lead to AKI and have a systemic effect from their own pathogenesis. The long-term kidney prognosis varies among these etiologies depending on the cause and severity of disease. However, all these conditions are potentially preventable and treatable. Prompt management and good preventive approaches are needed. This article will focus on the epidemiology, pathogenesis and management of AKI associated with tropical infections, toxins and environment impacts.

DOI: 10.1111/nep.14118

PMID: 36207807

9. Aristolochic acid-associated cancers: a public health risk in need of global action. Das S, Thakur S, Korenjak M, Sidorenko VS, Chung FF, Zavadil J.

Nat Rev Cancer. 2022 Oct;22(10):576-591. doi: 10.1038/s41568-022-00494-x. Epub 2022 Jul 19.

Aristolochic acids (AAs) are a group of naturally occurring compounds present in many plant species of the Aristolochiaceae family. Exposure to AA is a significant risk factor for severe nephropathy, and urological and hepatobiliary cancers (among others) that are often recurrent and characterized by the prominent mutational fingerprint of AA. However, herbal medicinal products that contain AA continue to be manufactured and marketed worldwide with inadequate regulation, and possible environmental exposure routes receive little attention. As the trade of food and dietary supplements becomes increasingly globalized, we propose that further inaction on curtailing AA exposure will have far-reaching negative effects on the disease trends of AA-associated cancers. Our Review aims to systematically present the historical and current evidence for the mutagenicity and carcinogenicity of AA, and the effect of removing sources of AA exposure on cancer incidence trends. We discuss the persisting challenges of assessing the scale of AA-related carcinogenicity, and the obstacles that must be overcome in curbing AA exposure and preventing associated cancers. Overall, this Review aims to strengthen the case for the implementation of prevention measures against AA's multifaceted, detrimental and potentially fully preventable effects on human cancer development.

DOI: 10.1038/s41568-022-00494-x

PMID: 35854147 [Indexed for MEDLINE]

10. A cross-sectional clinical study in women to investigate possible genotoxicity and hematological abnormalities related to the use of black cohosh botanical dietary supplements. Smith-Roe SL, Garantziotis S, Church RL, Bemis JC, Torous DK, Shepard KG, Hobbs CA, Waidyanatha S, Mutlu E, Shockley KR, Kissling GE, McBride SJ, Xie G, Cristy T, Pierfelice J, Witt KL.

Environ Mol Mutagen. 2022 Nov 2. doi: 10.1002/em.22516. Online ahead of print.

Black cohosh (BC; *Actaea racemosa* L.), a top-selling botanical dietary supplement, is marketed to women primarily to ameliorate a variety of gynecological symptoms. Due to widespread usage, limited safety information, and sporadic reports of hepatotoxicity, the Division of the National Toxicology Program (DNTP) initially evaluated BC extract in female rats and mice. Following administration of up to 1000 mg/kg/day BC extract by gavage for 90 days, dose-related increases in micronucleated peripheral blood erythrocytes were observed, along with a nonregenerative macrocytic anemia resembling megaloblastic anemia in humans. Because both micronuclei and megaloblastic anemia may signal disruption of folate metabolism, and inadequate folate levels in early pregnancy can adversely affect neurodevelopment, the DNTP conducted a pilot cross-sectional study comparing erythrocyte micronucleus frequencies, folate and B12 levels, and a variety of hematological and clinical chemistry parameters between women who used BC and BC-naïve women. Twenty-three women were enrolled in the BC-exposed group and 28 in the BC-naïve group. Use of any brand of BC-only supplement for at least three months was required for inclusion in the

BC-exposed group. Supplements were analyzed for chemical composition to allow cross-product comparisons. All participants were healthy, with no known exposures (e.g., x-rays, certain medications) that could influence study endpoints. Findings revealed no increased micronucleus frequencies and no hematological abnormalities in women who used BC supplements. Although reassuring, a larger, prospective study with fewer confounders (e.g., BC product diversity and duration of use) providing greater power to detect subtle effects would increase confidence in these findings.

DOI: 10.1002/em.22516

PMID: 36323641

11. Black Cohosh Herbal Extract and Hematologic Alterations in B6C3F1/N Mice. Cora M.

Toxicol Pathol. 2022 Oct;50(7):886-889. doi: 10.1177/01926233221133549. Epub 2022 Nov 14.

Black cohosh is a readily available dietary supplement currently marketed as a remedy for dysmenorrhea and menopausal symptoms and is one of the top-selling herbal supplements in the United States. Black cohosh extract (BCE) was nominated to the National Toxicology Program (NTP) by the National Cancer Institute and the National Institute of Environmental Health Sciences due to its widespread use and lack of animal toxicity studies. Results of the NTP BCE subchronic mouse toxicity study revealed a dose-dependent, non-regenerative decrease in the erythron with an increase in the mean corpuscular volume (macrocytosis). Howell-Jolly bodies, or micronuclei, were significantly increased. These particular changes indicated an ineffective erythropoiesis consistent with a condition known as megaloblastic anemia. Megaloblastic anemia is due to disruptions in DNA synthesis during hematopoiesis and can be a result of an inherited or drug-induced disorder or a consequence of folate or cobalamin deficiency. Subsequent mouse studies revealed hematological and biochemical changes that were consistent with a functional cobalamin deficiency. This article will review basic mechanisms and laboratory features of megaloblastic anemia. The results of our studies including morphological abnormalities of the erythron and biomarkers of folate and cobalamin deficiencies, as well as hepatic microarray gene changes, are also discussed.

DOI: 10.1177/01926233221133549

PMID: 36373576 [Indexed for MEDLINE]

12. Natural disasters: The toxicities of herbal abortifacient and contraceptive agents. Johnson-Arbor K.

Am J Emerg Med. 2022 Nov;61:217-218. doi: 10.1016/j.ajem.2022.07.033. Epub 2022 Jul 16.

DOI: 10.1016/j.ajem.2022.07.033

PMID: 35863978 [Indexed for MEDLINE]

13. The Prevalence of Dietary Supplements That Claim Estrogen-like Effects in Japanese Women.

Chiba T, Tousen Y, Nishijima C, Umegaki K.

Nutrients. 2022 Oct 26;14(21):4509. doi: 10.3390/nu14214509.

Recently, adverse events, such as irregular vaginal bleeding and menstrual disorders, associated with the use of dietary supplements containing *Pueraria mirifica*, have been reported in Japan. *P. mirifica* contains phytoestrogens, such as deoxymiroestrol and miroestrol. Therefore, we investigated the use of supplements that claim to have estrogen-like effects (i.e., estrogen-like supplements) in Japanese women aged from 15 to 69 years old in an online survey. The prevalence of estrogen-like supplement use was 5%, accounting for approximately 15% of the sample, including ex-users. The majority of the users were in their 40s and 50s, mainly using these supplements for the treatment of menopausal symptoms. In contrast, the younger generation mainly used them for beauty purposes, such as weight loss, mastogenic effects, and skin care. Many of them visited a clinic or took medicines for menstrual-related troubles. In all age groups, soybeans/isoflavones were the most commonly used, followed by equol and placenta. Participants in their teens and 20s also used *P. mirifica*. Among them, 16.2% had experienced adverse events, including irregular vaginal bleeding, breast swelling and pain, and heavy menstruation. In conclusion, estrogen-like supplement use is associated with adverse events; thus, it is necessary to pay attention to the use of these supplement. Furthermore, because the purpose of use differs depending on generation, caution according to each generation is necessary.

DOI: 10.3390/nu14214509
PMID: 36364772

14. Cannabidiol Safety Data: A Systematic Mapping Study. Henderson RG, Franke KS, Payne LE, Franzen A.

Cannabis Cannabinoid Res. 2022 Oct 14. doi: 10.1089/can.2022.0100. Online ahead of print.

Robust assessment of potential adverse outcomes is needed to determine a safe cannabidiol (CBD) intake level for consumer use. To assist in identifying knowledge gaps and inform future decision making regarding systematic development of health-based benchmarks, we have developed the first systematic map of the safety-related information available for CBD in the peer-reviewed literature. Literature searching conducted according to a published protocol yielded a total of 4186 unique titles and abstracts published through 2020. These were screened using DistillerSR for studies that evaluated at least one potential health outcome following exposure to CBD and/or other hemp-derived substances. Additional categorization was conducted for a subset of 1001 studies in which CBD was administered alone. Studies that investigated CBD most frequently reported on neurological outcomes (532), carcinogenic outcomes (129), and pharmacokinetics (118). Less frequently studied categories included developmental and reproductive, hepatic, and gastrointestinal outcomes. The primary outcomes associated with the most adverse events reported in the literature were neurological (13) and developmental and reproductive (12). Based on the studies identified, reproductive and developmental toxicity was identified as a data gap that warrants conducting a well-designed, guideline-compliant reproductive toxicity study on CBD. In addition, immune outcomes were noted as a potential emerging research area for CBD. This systematic map provides an important baseline from which to identify topics that may be suitable for further research related to the safe use of CBD. Implications for future potential work and limitations of the mapping exercise are discussed.

DOI: 10.1089/can.2022.0100
PMID: 36251454

15. A Case of Potential Pharmacokinetic Kratom-drug Interactions Resulting in Toxicity and Subsequent Treatment of Kratom Use Disorder With Buprenorphine/Naloxone. Brogdon HD, McPhee MM, Paine MF, Cox EJ, Burns AG.

J Addict Med. 2022 Sep-Oct 01;16(5):606-609. doi: 10.1097/ADM.0000000000000968. Epub 2022 Feb 14.

The botanical product kratom produces opioid-like effects at high doses and is sometimes used for opioid replacement by individuals with opioid use disorder. Mitragynine, a major alkaloid contained in kratom leaves, has been shown to inhibit multiple cytochromes P450 (CYPs) in vitro, including CYP2D6 and CYP3A. As such, kratom may precipitate pharmacokinetic drug interactions when co-consumed with certain medications. We present a case of a patient taking 150 mg venlafaxine (CYP2D6/3A substrate), 300 mg quetiapine (CYP3A substrate), and a high amount of kratom (~90 g) daily. The patient presented to the emergency department with serotonin syndrome and corrected electrocardiogram abnormalities that may have been secondary to supratherapeutic exposure to venlafaxine and/or quetiapine. The patient's symptoms resolved after discontinuation of venlafaxine and quetiapine. He was amenable to medication therapy for kratom discontinuation and successfully completed an at-home induction with buprenorphine/naloxone. This case report adds to the literature about potential pharmacokinetic kratom-drug interactions and suggests that buprenorphine/naloxone can facilitate recovery from kratom use disorder.

DOI: 10.1097/ADM.0000000000000968
PMCID: PMC9375773
PMID: 35165231 [Indexed for MEDLINE]

16. Silibinin: a toxicologist's herbal medicine? Horowitz BZ.

Clin Toxicol (Phila). 2022 Oct 12;1-4. doi: 10.1080/15563650.2022.2128815. Online ahead of print.

Silymarin is an herbal remedy, commonly called milk thistle, or St. Mary's Thistle, and has been used for over 2000 years. It has been available as a capsule of the plant extract in Europe since 1974 to treat hepatic disorders. To date toxicologists have relied on animal studies, human case series, or retrospective reviews to

decide on its use. In the U.S. the ability to use IV silibinin, its pharmacologically active purified flavonolignan, is hindered by its lack of availability as a Food and Drug Administration approved pharmaceutical preparation. This commentary reviews the in vitro studies, animal studies, and human retrospective analyses which form the basis for its clinical use. Despite the numerous publications, summarized in this issue in a systematic review, the mortality rate from *Amanita* mushroom ingestion remains stubbornly the same over four decades of use, and hovers around 10%. Although in the retrospective systematic review the use of silibinin, or penicillin, compared to routine care is statistically significantly superior when the primary outcome is fatality. Despite this there is no quality randomized trial to definitively demonstrate its utility. While, intravenous silibinin has a low toxicity, unanswered is whether it is useful in protecting the liver in cases of amanitin-containing mushrooms toxicity, and whether earlier administration would likely improve outcomes.

DOI: 10.1080/15563650.2022.2128815
PMID: 36222816

17. Botanical Briefs: Ginkgo (*Ginkgo biloba*). Barker CS, Elston DM.

Cutis. 2022 Jul;110(1):30-33. doi: 10.12788/cutis.0559.

Ginkgo biloba is an ancient tree that originated in China and is now cultivated worldwide for its ornamental foliage and resistance to disease and pollution. Direct or indirect interaction with the ginkgo tree can cause allergic contact dermatitis, with erythematous papules, vesicles, and edema on exposed areas due to ginkgolic acids. On the other hand, ginkgo extract, produced from the tree leaves, has long been used in Chinese traditional medicine and is now a popularly consumed herbal medicine. Components of the ginkgo tree can cause dermatitis, but active ingredients in ginkgo extract may be beneficial; research on its safety and potential uses is ongoing.

DOI: 10.12788/cutis.0559
PMID: 36179233 [Indexed for MEDLINE]

18. Toxicity of Usnic Acid: A Narrative Review. Croce N, Pitaro M, Gallo V, Antonini G.

J Toxicol. 2022 Oct 19;2022:8244340. doi: 10.1155/2022/8244340. eCollection 2022.

Usnic acid (UA) is a dibenzofuran derivative naturally present in lichens, organisms resulting from the symbiosis between a fungus and a cyanobacterium, or an alga. UA shows antimicrobial, antitumor, antioxidant, analgesic, anti-inflammatory as well as UV-protective activities. Its use as pharmacological agent is widely described in traditional medicine, and in the past few years, the product has been marketed as a food supplement for the induction of weight loss. However, the development of severe hepatotoxicity in a limited number of subjects prompted the FDA to issue a warning letter, which led to the withdrawal of the product from the market in November 2001. Data published in literature on UA toxicology, genotoxicity, mutagenesis, and teratogenicity have been reviewed, as well as the case reports of subjects who developed hepatotoxicity following oral administration of UA as a slimming agent. Finally, we reviewed the most recent studies on the topical use of UA, as well as studies aimed at improving UA pharmacologic activity and reducing toxicity. Indeed, advancements in this field of research could open the possibility to reintroduce the use of UA as therapeutic agent.

DOI: 10.1155/2022/8244340
PMCID: PMC9605823
PMID: 36310641

19. A Bitter Experience-A Bitter Apple (*Citrullus colocynthis*) Ingestion in a Child. Espinosa J, Lucerna A, Bassett R.

Am J Emerg Med. 2022 Oct;60:225.e5-225.e6. doi: 10.1016/j.ajem.2022.07.011. Epub 2022 Jul 6.

Here we present the case of a 4-year-old child who presented to the emergency department (ED) with bloody diarrhea. The causative agent was confirmed to be *Citrullus colocynthis* (bitter apple), which had been given to the patient by his grandmother for constipation. Hemorrhagic colitis can be induced by *Citrullus colocynthis*. Treatment is essentially support. Hypoglycemia and transaminitis have been associated with

Citrullus colocynthis ingestion. The case highlights that pediatric patients can be inadvertently exposed to herbal medications that can cause harm. It also highlights that certain herbal medications with toxic potential, such as Citrullus, can be seen in emergency departments that are geographically quite distant from the most common origins of the plant. To our knowledge, this is the first American pediatric case report of bitter apple induced hemorrhagic colitis.

DOI: 10.1016/j.ajem.2022.07.011

PMID: 35821084 [Indexed for MEDLINE]

20. Adverse Effects Associated with Multiple Categories of Dietary Supplements: The Military Dietary Supplement Use Study. Knapik JJ, Trone DW, Steelman RA, Farina EK, Lieberman HR.

J Acad Nutr Diet. 2022 Oct;122(10):1851-1863. doi: 10.1016/j.jand.2022.01.014. Epub 2022 Feb 2.

BACKGROUND: About 50% of Americans and 70% of US military service members (SMs) regularly use dietary supplements (DSs) and some are associated with adverse effects (AEs). SMs are more likely to use unsafe DSs than civilians. **OBJECTIVE:** The aim of this investigation was to examine the prevalence of, and factors associated with, AEs. **DESIGN:** Cross-sectional. **PARTICIPANTS:** A stratified random sample of 200,000 US SMs from the Air Force, Army, Marine Corps, and Navy were obtained from military workforce records. Eighteen percent (n = 26,681) of successfully contacted SMs (n = 146,365) volunteered to participate between December 2018 and August 2019. Participants completed a detailed online questionnaire on demographic characteristics, lifestyle factors, and AEs associated with DS use. **MAIN OUTCOME MEASURE:** Prevalence of, and factors associated with, AEs among DS users. **STATISTICAL ANALYSIS:** Prevalence of AEs was calculated by DS categories. Linear trends, χ^2 statistics, and multivariable logistic regression examined associations between AEs and demographic characteristics, lifestyle factors, and number DSs consumed. **RESULTS:** Proportion of DS users (≥ 1 time /week) reporting ≥ 1 AE was 18% overall, 20% for combination products (ie, weight loss, muscle building, and before/after workout supplements), 8% for purported prohormones, 6% for protein/amino acid products, 6% for multivitamin/multiminerals, 6% for individual vitamins/minerals, 4% for herbal products, and 2% for joint health products. Combination products are very popular in military personnel with nearly half of SMs regularly taking them. In multivariable analysis, reporting AEs were independently associated with female gender, younger age, higher body mass index, smoking, higher alcohol intake, service in the Army, Navy, or Marine Corps (compared with Air Force), and consumption of a greater number of DSs. **CONCLUSIONS:** A large proportion of SMs report experiencing AEs, especially users of combination products and purported prohormone supplements. This study presents contemporary data collected from a very large at-risk population on potentially hazardous categories of DSs.

DOI: 10.1016/j.jand.2022.01.014

PMID: 35123127 [Indexed for MEDLINE]

21. Complementary and alternative therapies in the palliative setting. Martin JH, Patel J.

Intern Med J. 2022 Oct;52(10):1677-1684. doi: 10.1111/imj.15922.

Complementary and alternative medicine (CAM) encompasses a wide range of medication, herbal, dietary and physical therapies that are not usually considered within the realm of conventional therapeutics. Approximately two thirds of the Australian population use CAMs and only around half of this number will discuss their use of these products with their doctor. Clinical use is commonly seen in patients with life-limiting illness, often because they experience a high burden of symptoms. However, it is also the case that many of these therapies do not have demonstrated efficacy, particularly for the often broad list of conditions and symptoms for which they are chosen to be used. Further, depending on whether they are sold as medications, sold as food supplements or imported illegally and distributed via nonstandard therapeutic channels, several products have had reports of toxicity, severe adverse effects, batch irregularities and drug interactions with other therapies. This awareness, together with lack of standardisation of products and lack of interchangeability between brands has made prescribers unwilling to put patients at risk of harm by supporting their use. In this article, we cover general pharmacological principles around use of a small selection of chemicals used in a medical setting to enable some guidance for use.

DOI: 10.1111/imj.15922

PMID: 36266062 [Indexed for MEDLINE]

21. Veratrum parviflorum poisoning: identification of steroidal alkaloids in patient blood and breast milk. Seale JT, Carpenter JE, Eisenstat MD, Kiernan EA, Morgan BW, Noguee DP, Pu X, Therriault CA, Yeh M, McDougal OM.

J Toxicol. 2022 Oct 19;2022:8244340. doi: 10.1155/2022/8244340. eCollection 2022.

INTRODUCTION: The *Veratrum* genus is composed of plants containing a diverse set of steroidal alkaloids. *Veratrum* plant material has been utilized for centuries as herbal medicines, however the alkaloids have such a low therapeutic index that they are not used in modern medicine. Here we report an incident of inadvertent ingestion of *V. parviflorum* by hikers in Georgia that allowed detection, and in several instances identification of alkaloids from the plant, and correlated their presence within patient blood and breast milk specimens. **CASE HISTORY:** Eight patients, three male and five female, presented in the spring of 2020 and 2021 with symptoms requiring emergent medical attention after ingestion of *Veratrum parviflorum*. All patients believed the plants to be a local native species of wild leek, *Allium tricoccum*, locally known as ramps. Plants were identified using photographs as well as fresh and cooked plant material provided by patients, in consultation with botanists at the University of Georgia Herbarium. Written consent was obtained from all patients for collection of blood and breast milk specimens for laboratory identification of *Veratrum* alkaloids. **METHODS:** *V. parviflorum* plant material, and patient serum and breast milk were analyzed by high performance liquid chromatography-quadrupole time-of-flight mass spectrometry (HPLC-QTOF) to identify steroidal alkaloids. **RESULTS:** The *V. parviflorum* extract was confirmed to contain cyclopamine, veratramine, jervine, and muldamine. Two out of the eight patients had detectable concentrations of *Veratrum* alkaloids. Of the alkaloids identified in the plant, cyclopamine and jervine were detected within patient serum, and cyclopamine and veratramine were observed to be present in breast milk. **DISCUSSION:** Toxicity resulting from *Veratrum* steroidal alkaloids has primarily been reported from *V. album* and *V. viride*. This is the second report of *V. parviflorum* poisoning. The present work reports for the first time the presence of muldamine and jervine within *V. parviflorum*. This work provides the first instance of identification of *Veratrum* alkaloids in breast milk. Thus, the findings presented herein add to literature record causative agents contributing to the toxicity of *V. parviflorum* when ingested and potential for secondary poisoning through breastfeeding. **CONCLUSION:** *V. parviflorum* toxicity was observed to cause nausea, vomiting, hypotension, bradycardia, abdominal pain, light-headedness, blurred vision, and tingling in the arms. Patients experiencing mild symptoms improved with supportive care, IV fluids, and antiemetics, but hemodynamically unstable patients required atropine and vasopressors. This study demonstrated that more lipophilic *Veratrum* alkaloids can be passed along in breast milk, which suggests additional precautions may be critical to limit further poisonings.

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22. Ayurvedic treatment induced severe alcoholic hepatitis and non-cirrhotic portal hypertension in a 14-year-old girl. Philips CA, Ahamed R, Abduljaleel JK, Rajesh S, Theruvath AH, Raveendran R, Augustine P.

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We report a novel and as yet undescribed clinical scenario in a young girl with liver failure, in whom, the liver histopathology was suggestive of alcoholic hepatitis in the background of hepatoportal sclerosis and incomplete septal cirrhosis. An extensive clinical and investigational evaluation revealed chronic consumption of multiple Ayurvedic herbal medications for seizure disease. Six months after stopping herbal medicines, the repeat liver biopsy demonstrated resolution of alcohol-related changes but persistence of classical features of non-cirrhotic portal hypertension. Analysis of the retrieved agents, including state of the art chemical and toxicology analysis, using gas chromatography and mass spectroscopy methods demonstrated multiple organic and inorganic toxins associated with acute alcohol and arsenic poisoning related hepatoportal sclerosis/incomplete septal cirrhosis in the young girl.

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