

American Academy of Clinical Toxicology
Special Interest Group: Herbs & Dietary Supplements
Abstracting Service
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1. Huang CF, Lin SS, Liao PH, Young SC, Yang CC. The immunopharmaceutical effects and mechanisms of herb medicine. *Cell Mol Immunol.* 2008;5(1):23-31. PMID: 18318991
In recent years, studies on evaluation of the therapeutic and toxic activity of herbal medicinal products became available and popular. The advances in modern biotechnology have led to discovery of many new active constituents. However, it is a constant challenge to establish the pharmacological basis for efficacy and safety of herbal medicinal products. A better understanding of the effects and bioavailability of phytopharmaceuticals can help in discovering suitable and rational therapies. In this review, we present the bioavailability studies in immune system that has been conducted for some of the more important or widely used phytopharmaceuticals. Furthermore, various new drug targets worthy of using for drug development in immunomodulating herbal medicine area and their regulatory mechanisms are also discussed. Adverse effects, drug interactions, and contraindications are also discussed which show that caution should be exercised when combining phytopharmaceuticals with chemically derived pharmaceutical components.

2. Gorospe EC, Gerstenberger SL. Atypical sources of childhood lead poisoning in the United States: A systematic review from 1966-2006. *Clin Toxicol (Phila).* 2008;1-10. PMID: 18608287
Background. Lead poisoning from atypical sources, which excludes the well-established lead-based paint ingestions and exposure in occupational settings, are increasingly reported in medical literature. Our objective is to increase awareness on atypical sources of lead exposure and to formulate recommendations for their detection based on actual reported cases. Methods. We systematically retrieved and reviewed reports on pediatric lead poisoning in the U.S. from atypical sources by searching Medline, Embase, CINAHL, Academic Search Premier, AltHealth, websites of state lead poisoning prevention programs, and the U.S. Consumer Product Safety Commission database for reports published from January 1966 to December 2006. Results. We retrieved 28 published reports that met our inclusion criteria. Of these reports, 20 are case reports and 8 case series, documenting a total of 82 incidents of lead poisoning in children from atypical sources. Conclusion. There are varied sources of atypical lead exposure among U.S. children. The sources were grouped in the following categories based on their utility: fashion accessories, folk remedies, imported condiments & candies, pellets & bullets, and lastly, recreational & domestic items. Based on these findings, we have formulated a questionnaire that may assist in the identification of atypical lead sources in the home.

3. Gunduz A, Turedi S, Russell RM, Ayaz FA. Clinical review of grayanotoxin/mad honey poisoning past and present. *Clin Toxicol (Phila).* 2008;46(5):437-42. PMID: 18568799
Grayanotoxin is a naturally occurring sodium channel toxin which enters the human food supply by honey made from the pollen and nectar of the plant family Ericaceae in which rhododendron is a genus. Grayanotoxin/mad honey poisoning is a little known, but well studied, cholinergic toxidrome resulting in incapacitating and, sometimes, life-threatening bradycardia, hypotension, and altered mental status. Complete heart blocks occur in a significant fraction of patients. Asystole has been reported. Treatment with saline infusion and atropine alone is almost always successful. A pooled analysis of the dysrhythmias occurring in 69 patients from 11 different studies and reports is presented. The pathophysiology, signs, symptoms, clinical course, and treatment of grayanotoxin/mad honey poisoning are discussed. In the nineteenth century grayanotoxin/mad honey poisoning was reported in Europe and North America. Currently, documented poisoning from locally produced honey in Europe or North America would be reportable. Possible reasons for this epidemiologic change are discussed.

4. Woolf AD, Hussain J, McCullough L, Petranovic M, Chomchai C. Infantile lead poisoning from an Asian tongue powder: A case report & subsequent public health inquiry. *Clin Toxicol (Phila)*. 2008;1-4. PMID: 18608276

Introduction. Lead poisoning from novel environmental sources continues to present a challenge to clinicians who treat infants and children. Case report. A 12 month old infant of Thai parents was found during well child care to have a venous blood lead concentration of 61 mcg/dL. He was hospitalized for parenteral chelation with CaNa₂EDTA and subsequently managed as an outpatient with oral succimer, with a reduction in blood lead concentration to 23 mcg/dL. Chronic lead poisoning was attributed to the use of a Thai tongue powder by the parents for the first seven months of the infant's life. This ethnic remedy was applied to the tongue to absorb toxins, reduce white patches present after milk feedings, and preserve the infant's health. Investigations. Lead contaminated the powder at 109,000 ppm as measured by x-ray fluorescence spectrometry. Two poison centers in Thailand were contacted and initiated a public health inquiry with the Thai Food & Drug Administration (Thai FDA) to remove contaminated products from the marketplace. Their investigation found six additional contaminated tongue powders (of 10 tested) in a Bangkok shop offering Chinese remedies, some with lead levels > 9000 ppm. These products, unregistered with the Thai FDA, were confiscated and the shop closed. Local media attention and case-finding activities of health officials identified one additional infant suffering from lead poisoning due to tongue powders. Conclusions. Asian tongue powders can be a source of lead poisoning. Medical toxicologists, poison centers, and public health agencies can work together internationally to accomplish effective post-marketing product surveillance.

5. Wolff MS, Britton JA, Boguski L, Hochman S, Maloney N, Serra N, Liu Z, Berkowitz G, Larson S, et al. Environmental exposures and puberty in inner-city girls. *Environ Res*. 2008;107(3):393-400. PMID: 18479682

BACKGROUND: Hormonally active environmental exposures are suspected to alter onset of puberty in girls, but research on this question has been very limited. OBJECTIVE: We investigated pubertal status in relation to hormonally active environmental exposures among a multiethnic group of 192 healthy 9-year-old girls residing in New York City. METHODS: Information was collected on breast and pubic hair stages, weight and height. Phytoestrogen intake was estimated from a food-frequency questionnaire. Three phytoestrogens and bis-phenolA (BPA) were measured in urine. In a subset, 1,1'-dichloro-2,2'-bis(4-chlorophenyl)ethylene (DDE), polychlorinated biphenyls (PCBs) were measured in blood plasma and lead (Pb) in blood. Associations of exposures with pubertal stages (present=stage 2+ vs absent=stage 1) were examined using t-tests and Poisson multivariate regression to derive prevalence ratios (PR, 95%-confidence limits [CI]). RESULTS: Breast development was present in 53% of girls. DDE, Pb, and dietary intakes of phytoestrogens were not significantly associated with breast stage. Urinary phytoestrogen biomarker concentrations were lower among girls with breast development compared with no development. In multivariate models, main effects were strongest for two urinary isoflavones, daidzein (PR 0.89 [0.83-0.96] per ln microg/g creatinine) and genistein (0.94 [0.88-1.01]). Body mass index (BMI) is a hormonally relevant, strong risk factor for breast development. Therefore, BMI-modification of exposure effects was examined, and associations became stronger. Delayed breast development was observed among girls with below-median BMI and third tertile (high exposure) of urinary daidzein (PR 0.46 [0.26-0.78]); a similar effect was seen with genistein, comparing to girls \geq median BMI and lowest two tertiles (combined) of these isoflavones. With urinary enterolactone a phytoestrogen effect was seen only among girls with high BMI, where breast development was delayed among those with high urinary enterolactone (PR 0.55 [0.32-0.96] for the upper tertile vs lower two combined). There was no main effect of PCBs on breast stage, but girls with below-median BMI and \geq median PCB levels had reduced risk for breast development (any vs none) compared with other BMI-PCB groups. No biomarkers were associated with hair development, which was present in 31% of girls. CONCLUSIONS: Phytoestrogens and PCBs are environmental exposures that may delay breast development, especially in conjunction with BMI, which governs the endogenous hormonal milieu.

Further research to confirm these findings may improve our understanding of the role of early life development in breast cancer risk and other chronic diseases related to obesity.

6. Antonio-Garcia MT, Masso-Gonzalez EL. Toxic effects of perinatal lead exposure on the brain of rats: involvement of oxidative stress and the beneficial role of antioxidants. *Food Chem Toxicol.* 2008;46(6):2089-95. PMID: 18417264
The aim of this study was to determine whether changes in the activities of antioxidant enzymes occur in the brain of lead-exposed rats (300mgPb/L in drinking water) and to investigate the potential benefit of the administration of some natural antioxidants (Zn 20mg/L+vitamins A 50.000U/L, C 2g/L, E 500mg/L and B6 500mg/L) during pregnancy and lactation. Lead exposure caused a significant increase in brain TBARS (23%) vs. control, whereas co-administration of antioxidants+lead was effective in reducing TBARS levels. The catalase activity in brain samples of the lead group was enhanced 99% vs. control, but no changes were found in the remainder of the groups. No statistically significant effect of lead and/or antioxidants in brain SOD activity was noted. Acid phosphatase activity was enhanced in both lead groups but no changes were found in alkaline phosphatase activity. Finally, a statistically significant decrease (-35%) of acetylcholinesterase activity was noted in the lead+antioxidants group. This study provides evidence of the beneficial role of antioxidants in early status of brain development in rats against lead exposure.
7. Wasfi IA, Zorob O, Al Katheeri NA, Al Awadhi AM. A fatal case of oleandrin poisoning. *Forensic Sci Int.* 2008. PMID: 18602779
The study presents a case of fatal poisoning with oleander leaves in an adult diabetic male. After repeated vomiting, and gastrointestinal distress the patient was admitted at the hospital with cardiac symptoms 1h after the ingestion. Urine samples were assayed immunochemically and by GC-MS for drugs of abuse and for general toxicological screen. Blood was analyzed for alcohol and volatiles by static head space GC-MS. Blood and oleander leaves were analyzed by LC-MS/MS for oleandrin and related compounds, the main cardiac glycosides of Nerium oleander. Oleandrin was detected by LC-MS/MS in the blood sample at a concentration of approximately 10ng/ml. Another cardiac glycoside with pseudo-molecular ion of m/z 577, a likely structural isomer of oleandrin, was also detected in the blood and oleander leaves. However, by using the response as a function of concentration for oleandrin, this cardiac glycoside was roughly estimated at a concentration of approximately 10ng/ml in the deceased blood. This would give a total fatal blood concentration of cardiac glycosides of about approximately 20ng/ml in the deceased blood.
8. Lu Y, Ma H, Liu D. Pharmacological investigations of the unique herbal formula Menoprogen in rats: estrogenic activity and mechanism. *Gynecol Endocrinol.* 2008;24(3):161-70. PMID: 18335332
The present study aimed to evaluate the pharmacological effects of Menoprogen in the management of menopausal symptoms for aged female rats. Menoprogen was supplemented to a group of elderly female rats for 8 weeks. Subsequently, histopathological examinations were conducted in the isolated uterine and ovary tissues and pituitary glands of the rats. Serum levels of estradiol (E(2)), progesterone (P), follicle-stimulating hormone (FSH) and luteinizing hormone (LH) were determined. The ultrastructure of the rat ovarian granulocytes was analyzed. The histopathological examinations revealed no statistical difference in the quantity of follicles in the ovary and of acidophil and basophil cells in the anterior pituitary gland of the Menoprogen-fed rats versus healthy normal rats. Moreover, the cellular morphogenesis was in a healthy state for the Menoprogen-fed rats. Menoprogen significantly increased the levels of serum E(2) and P but reduced FSH and LH levels. The electron microscopic analysis showed that Menoprogen significantly retarded apoptosis of the ovarian granulocytes of the rats. Further investigation of Menoprogen for the alternative treatment of menopausal symptoms is warranted.
9. Chen FP, Kung YY, Chen YC, Jong MS, Chen TJ, Chen FJ, Hwang SJ. Frequency and pattern of Chinese herbal medicine prescriptions for chronic hepatitis in Taiwan. *J Ethnopharmacol.*

2008;117(1):84-91. PMID: 18321671

ETHNOPHARMACOLOGICAL RELEVANCE: Chinese herbal medicine (CHM) has been commonly used in treating liver diseases in Asian countries. **AIM OF STUDY:** To conduct a large-scale pharmacoepidemiological study and evaluate the frequency and pattern of CHM prescriptions in treating chronic hepatitis. **MATERIALS AND METHODS:** We obtained the database of traditional Chinese medicine outpatient claims from the national health insurance in Taiwan for the whole 2002. Patients with chronic hepatitis were identified by the corresponding diagnosis of International Classification of Disease among claimed visiting files. Corresponding prescription files were analyzed, and association rule were applied to evaluate the co-prescription of CHM in treating chronic hepatitis. **RESULTS:** Among the 91,080 subjects treated by CHM for chronic hepatitis, the peak age was in the 40 s, followed by 30 s and 50 s. Male/female ratio was 2.07:1. Long-dan-xie-gan-tang and Saliva miltiorrhiza (Dan-shen) were the most commonly prescribed Chinese herbal formula and single herbal drug, respectively. The most common two-drug prescription was Jia-wei-xia-yao-san plus Saliva miltiorrhiza, and the most common three-drug prescription was Jia-wei-xia-yao-san plus Saliva miltiorrhiza and Artemisia capillaries (Yin-chen-hao). **CONCLUSIONS:** This study showed the utilization pattern of Chinese herbal drugs or formulae in treating chronic hepatitis. Further researches and clinical trials are needed to evaluate the efficacy of these Chinese herbs or its ingredients in treating chronic hepatitis.

10. Haller C, Kearney T, Bent S, Ko R, Benowitz N, Olson K. Dietary supplement adverse events: report of a one-year poison center surveillance project. *J Med Toxicol.* 2008;4(2):84-92. PMID: 18570167
Background: The safety and efficacy of dietary supplements is of growing concern to regulators, health-care providers and consumers. Few scientific data exist on clinical effects and potential toxicities of marketed products. Harmful supplements may not be identified for months or years with existing adverse event monitoring mechanisms. Retrospective review of poison center statistics to capture supplement-associated toxicity also has limitations. Methods: We collaborated with the FDA Center for Food Safety and Nutrition (CFSAN) to conduct a 1-year prospective surveillance study of dietary supplement-related poison control center calls in 2006. Prompt follow-up of symptomatic cases, laboratory analysis of implicated dietary supplements, and causality assessment by a case review expert panel were performed. Results: Of 275 dietary supplements calls, 41% involved symptomatic exposures; and two-thirds were rated as probably or possibly related to supplement use. Eight adverse events required hospital admission. Sympathomimetic toxicity was most common, with caffeine products accounting for 47%, and yohimbe products accounting for 18% of supplement-related symptomatic cases. Suspected drug-herb interactions occurred in 6 cases, including yohimbe co-ingested with bupropion (1) and methamphetamine (3), and additive anticoagulant/antiplatelet effects of NSAIDs taken with fish oils (1) and ginkgo (1). Laboratory analysis identified a pharmacologically active substance in 4 cases; supplement toxicity was ruled unlikely when analytical testing was negative in 5 cases. Conclusion: Most supplement-related adverse events were minor. Clinically significant toxic effects were most frequently reported with caffeine and yohimbe-containing products. Active surveillance of poison control center reports of dietary supplement adverse events enables rapid detection of potentially harmful products, which may facilitate regulatory oversight.
11. Sasser H, Nussbaum M, Beuhler M, Ford M. Classification tree methods for development of decision rules for botulism and cyanide poisoning. *J Med Toxicol.* 2008;4(2):77-83. PMID: 18570166
Introduction: Identification of predictors of potential mass poisonings may increase the speed and accuracy with which patients are recognized, potentially reducing the number ultimately exposed and the degree to which they are affected. This analysis used a decision-tree method to sort such potential predictors. Methods: Data from the Toxic Exposure Surveillance System were used to select cyanide and botulism cases from 1993 to 2005 for analysis. Cases of other poisonings from a single poison center were used as controls. After duplication was omitted and removal of cases from the control

sample was completed, there remained 1,122 cyanide cases, 262 botulism cases, and 70,804 controls available for both analyses. Classification trees for each poisoning type were constructed, using 131 standardized clinical effects. These decision rules were compared with the current case surveillance definitions of one active poison center and the American Association of Poison Control Centers (AAPCC). Results: The botulism analysis produced a 4-item decision rule with Sensitivity (Se) of 68% and Specificity (Sp) of 90%. Use of the single poison center and AAPCC definitions produced Se of 19.5% and 16.8%, and Sp of 99.5% and 83.2%, respectively. The cyanide analysis produced a 9-item decision rule with Se of 74% and Sp of 77%. The single poison center and AAPCC case definitions produced Se of 10.2% and 8.6%, and Sp of 99.8% and 99.8%, respectively. Conclusions: These results suggest the possibility of improved poisoning case surveillance sensitivity using classification trees. This method produced substantially higher sensitivities, but not specificities, for both cyanide and botulism. Despite limitations, these results show the potential of a classification-tree approach in the detection of poisoning events.

12. Ledford H. Irrawaddy may be poisoned by arsenic. *Nature*. 2008;454(7202):263. PMID: 18633380

13. Mukasa Y, Craven N. Management of toxic epidermal necrolysis and related syndromes. *Postgrad Med J*. 2008;84(988):60-5. PMID: 18322124

Toxic epidermal necrolysis and Stevens-Johnson syndrome are rare and life-threatening diseases that often configure as medical emergencies. The majority of cases are drug reactions. The clinical picture is one of widespread epidermal necrosis and mucosal erosions. Treatment is largely supportive and must be provided in an appropriate environment. The role of steroids and other potential disease-modifying therapies has yet to be fully established by controlled studies. The significant mortality associated with these conditions dictates that an understanding of these conditions is essential for all doctors.