

American Academy of Clinical Toxicology  
Herbs & Dietary Supplements Special Interest Group

Abstracting Service  
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1. Xu H, Xu HE. Analysis of trace elements in Chinese therapeutic foods and herbs. *Am J Chin Med.* 2009;37(4):625-38.

The bioactive elements in Chinese therapeutic foods and herbs that are frequently consumed by people in both the East and West are analyzed. These elements in their appropriate dosage range are considered to be beneficial to health. Inductively Coupled Plasma Mass Spectrometry (ICP-MS) and Atomic Absorption Spectrometry (AAS) were applied to determine the concentrations of various elements. Twenty-two Chinese therapeutic foods and herbs, resourced from the traditional high therapeutic quality areas or provinces were selected. Bioactive analysis focused on Lanthanum (La), Strontium (Sr), Zinc (Zn) and Selenium (Se), especially in the prevention and treatment of hyperlipidemia and its associate disorders. The higher elemental concentration herbs, La in: *Rhizoma Gastrodiae Elatae*, *Fructus Crataegi* and *Herba Hedyotidis Diffusae*. Sr in: *Radix Puerariae* and *Folium Ginkgo Biloba*. Zn in: *Flos Carthami Tinctorii* and *Fructus Crataegi*. Se in: *Flos Lonicerae Japonicae* and *Portulaca Oleracea*. The results mainly showed that Chinese herbs which are also therapeutic foods may be used as nutritional supplements for preventing and treating elemental deficiency, e.g., hyperlipidemia. More attention in this regard should be paid to herbs that contain La and are traditionally used for regulating cardiovascular disorders. The knowledge of the effects and concentrations of bioactive elements in foods and herbs could guide the selection of Chinese herbs in clinical practice in conjunction with traditional Chinese medicine theories. Further studies should also be considered in relation to Sr, Zn and blood regulating herbs, which could prove to be beneficial.
2. Chau FT, Chan HY, Cheung CY, Xu CJ, Liang Y, Kvalheim OM. Recipe for uncovering the bioactive components in herbal medicine. *Anal Chem.* 2009;81(17):7217-25.

Using whole chromatographic profiles and measurements of total bioactivity as input, a quantitative pattern-activity relationship (QPAR) approach is proposed as a general method for providing two pieces of crucial information about complex bioactive mixtures available: (i) a model for predicting total bioactivity from the chromatographic fingerprint and (ii) the features in the chromatographic profile responsible for the bioactivity. While the first piece of information is already available through existing approaches, the second one results from our ability to remove dominant features in the chromatographic fingerprints which mask the components specifically related to pharmacological activity. Our targeted approach makes information about bioactivity available at the molecular level and provides possibilities for assessment of herbal medicine (HM) possible beyond just authentication and total bioactivity. As an example, the antioxidant property of the HM *Radix Puerariae lobatae* is measured through its reducing power toward a ferric ion complex. A partial least-squares (PLS) model is created to predict the antioxidant activity from the chromatographic fingerprint. Using the antioxidant activity as a target, the most discriminatory projection in the multivariate space

spanned by the chromatographic profiles is revealed. From this target-projected component, the chromatographic regions most strongly connected to antioxidant activity are identified using the so-called selectivity ratio (SR) plot. The results are validated by prediction of samples not included in the modeling step.

3. Musallam KM, Baydoun EA, Uthman I. Clinical images: severe photosensitive skin reaction secondary to an herbal treatment in a patient with systemic lupus erythematosus. *Arthritis Rheum.* 2009;60(9):2854.
4. Boldyrev AA. Molecular mechanisms of homocysteine toxicity. *Biochemistry (Mosc).* 2009;74(6):589-98.  
Hyperhomocysteinemia is a risk factor for a number of cardiovascular and neurodegenerative processes as well as a complicating factor in normal pregnancy. Toxic effects of homocysteine and the product of its spontaneous oxidation, homocysteic acid, are based on their ability to activate NMDA receptors, increasing intracellular levels of ionized calcium and reactive oxygen species. Even a short-term exposure of cells to homocysteic acid at concentrations characteristic of hyperhomocysteinemia induces their apoptotic transformation. The discovery of NMDA receptors both in neuronal tissue and in several other tissues and organs (including immunocompetent cells) makes them a target for toxic action of homocysteine. The neuropeptide carnosine was found to protect the organism from homocysteine toxicity. Treatment of pregnant rats with carnosine under conditions of alimentary hyperhomocysteinemia increases viability and functional activity of their progeny.
5. Aliyev F, Turkoglu C, Celiker C. Nodal Rhythm and Ventricular Parasystole: An Unusual Electrocardiographic Presentation of Mad Honey Poisoning. *Clin Cardiol.* 2009.  
Mad honey poisoning syndrome has been reported in the Eastern Black Sea region and Southeastern regions of Turkey. Herein we report a case of 70-y-old man presented with syncope and severe hemodynamic instability following ingestion of one teaspoon of honey and his unusual electrocardiographic manifestations: nodal rhythm alternating with sinus bradycardia and intermittent ventricular parasystole. In this report, we also tried to explain the possible mechanism responsible for these electrocardiographic findings. Copyright (c) 2009 Wiley Periodicals, Inc.
6. Bradberry S, Vale A. A comparison of sodium calcium edetate (edetate calcium disodium) and succimer (DMSA) in the treatment of inorganic lead poisoning. *Clin Toxicol (Phila).* 2009;47(9):841-58.  
INTRODUCTION: This article reviews the experimental and clinical studies that have compared the efficacy (impact on urine lead excretion, blood and tissue lead concentrations, resolution of features and survival) of sodium calcium edetate (edetate calcium disodium) and succimer (DMSA) in the treatment of inorganic lead poisoning. It also summarizes the pharmacokinetic and pharmacodynamic aspects and the adverse effects of treatment. METHODS: Medline, Toxline, and Embase were searched for all available years to June 2009. PHARMACOKINETICS AND PHARMACODYNAMICS: The absorption of oral DMSA is more complete than sodium calcium edetate; the latter has to be administered parenterally. Both antidotes are distributed predominantly extracellularly. Sodium calcium edetate is

not metabolized, whereas DMSA is extensively metabolized to mixed disulfides of cysteine. The two antidotes have elimination half-lives of less than 60 min. There is no evidence that either antidote crosses the blood-brain barrier to any major extent. Sodium calcium edetate chelates lead by displacement of the central  $\text{Ca}^{2+}$  ion with  $\text{Pb}^{2+}$ . The nature of the DMSA-lead chelate is less clearly defined. There is evidence that the mixed disulfides of cysteine are the active chelating moiety in humans. If this is the case, this suggests that chelation occurs principally, if not exclusively, in the kidney. The primary source of lead mobilized by sodium calcium edetate is bone with an additional contribution from kidney and liver.

**EFFICACY:** Comparison of the experimental studies is complicated by substantial variations in study design, particularly the antidote dose, the route and duration of treatment, the amount and duration of lead dosing, and lack of direct comparison between antidotes (comparison was usually made with control). In experimental studies that used equimolar and clinically relevant antidote doses and assessed the impact of DMSA and sodium calcium edetate on urine lead excretion and/or blood lead concentrations, similar results were found, though no direct comparison between antidotes was undertaken. DMSA was more effective than sodium calcium edetate in reducing the kidney lead concentration, sodium calcium edetate was more effective than DMSA in reducing bone lead concentrations, and there was no consistently observed effect of chelation therapy on brain lead concentrations in these experimental studies. Only two clinical studies have compared equimolar or similar antidote doses in enhancing urine lead excretion; there was no statistical difference between the antidotes, though both studies had limitations. DMSA and sodium calcium edetate had a comparable impact on lowering blood lead concentrations in a clinical study using similar molar antidote doses.

**ADVERSE EFFECTS:** Sodium calcium edetate causes dose-related nephrotoxicity. Both agents deplete zinc and copper, the effect on zinc being significantly greater with sodium calcium edetate. A transient increase in hepatic transaminase activity has been reported with both antidotes but appears to be more common with DMSA and neither has been associated with clinically significant hepatic toxicity. Skin lesions during treatment with sodium calcium edetate are unusual and have been attributed to zinc deficiency. DMSA has occasionally been associated with a severe mucocutaneous reaction necessitating discontinuation of therapy.

**CONCLUSIONS:** Oral DMSA and parenteral sodium calcium edetate are both effective chelators of lead. There are currently insufficient data, however, to conclude that either antidote is superior in enhancing lead excretion. Both antidotes resolve the symptoms of moderate and severe lead toxicity rapidly. Although there is greater clinical experience with sodium calcium edetate, particularly in the treatment of lead encephalopathy, oral DMSA may now be considered as an alternative in circumstances where oral therapy is preferable.

7. Giampreti A, Lonati D, Locatelli C, Rocchi L, Campailla MT. Acute neurotoxicity after yohimbine ingestion by a body builder. *Clin Toxicol (Phila)*. 2009;47(8):827-9.  
Yohimbine is an alkaloid obtained from the *Corynanthe yohimbe* tree and other biological sources. Yohimbine is currently approved in the United States for erectile dysfunction and has undergone resurgence in street use as an aphrodisiac and mild hallucinogen. In recent years yohimbine use has become common in body-building communities for its presumed lipolytic and sympathomimetic

effects. We describe a 37-year-old bodybuilder in which severe acute neurotoxic effects occurred in 2 h after yohimbine ingestion. The patient presented with malaise, vomiting, loss of consciousness, and repeated seizures after ingestion of 5 g of yohimbine during a body-building competition in a gymnasium. His Glasgow Coma Score was 3, requiring orotracheal intubation. Two hours after admission, vital signs were blood pressure 259/107 mmHg and heart rate 140 beats/min. Treatment with furosemide, labetalol, clonidine, and urapidil and gastrointestinal decontamination were performed. Twelve hours later the patient was extubated with normal hemodynamic parameters and neurological examination. The yohimbine blood levels at 3, 6, 14, and 22 h after ingestion were 5,240; 2,250; 1,530; and 865 ng/mL, respectively, with a mean half-life of 2 h. Few data are available about yohimbine toxicity and the related blood levels. This is a case of a large ingestion of yohimbine in which severe hemodynamic and neurological manifestations occurred and elevated blood levels of yohimbine were detected.

8. Frazier TH, Krueger KJ. Hepatotoxic herbs: will injury mechanisms guide treatment strategies? *Curr Gastroenterol Rep.* 2009;11(4):317-24.  
Harmful and fatal outcomes related to specific herbal therapies are reported with increasing regularity. However, US physicians remain inadequately informed about potential toxicities. The purpose of this focused review is to highlight past and more recently recognized herbal therapies or complementary and alternative medicine (CAM) that are shown to cause hepatotoxicity. Where available, the proposed mechanisms for toxicity are discussed. An aggressive approach for more stringent regulation of CAM is needed, in addition to a systematic and scientific study of causality and underlying toxic mechanisms, to provide reliable information about the safety of CAM and enable practitioners to deliver effective remedies when toxicities occur.
9. Boas M, Main KM, Feldt-Rasmussen U. Environmental chemicals and thyroid function: an update. *Curr Opin Endocrinol Diabetes Obes.* 2009;16(5):385-91.  
PURPOSE OF REVIEW: To overview the effects of endocrine disrupters on thyroid function. RECENT FINDINGS: Studies in recent years have revealed thyroid-disrupting properties of many environmentally abundant chemicals. Of special concern is the exposure of pregnant women and infants, as thyroid disruption of the developing fetus may have deleterious effects on neurological outcome. Evidence is reviewed for the following groups of chemicals: polychlorinated biphenyls, dioxins, flame retardants, pesticides, perfluorinated chemicals, phthalates, bisphenol A and ultraviolet filters. Chemicals may exert thyroid effects through a variety of mechanisms of action, and some publications have focused on elucidating the mechanisms of specific (groups of) chemicals. SUMMARY: A large variety of ubiquitous chemicals have been shown to have thyroid-disrupting properties, and the combination of mechanistic, epidemiological and exposure studies indicates that the ubiquitous human and environmental exposure to industrial chemicals may impose a serious threat to human and wildlife thyroid homeostasis. Currently, available evidence suggests that authorities need to regulate exposure to thyroid-disrupting chemicals of pregnant women, neonates and small children in order to avoid potential impairment of brain development. Future studies will indicate whether adults also are at risk of thyroid damage due to these chemicals.

10. Koh MJ, Tay YK. An update on Stevens-Johnson syndrome and toxic epidermal necrolysis in children. *Curr Opin Pediatr.* 2009;21(4):505-10.  
PURPOSE OF REVIEW: This study summarizes current research and understanding of the pathogenesis of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) and provides an update on the treatment of these conditions in children. RECENT FINDINGS: The association of specific human leukocyte antigen subtypes with SJS and TEN occurring in certain racial groups to specific drugs has led to recommendations on pretreatment testing. Several pathways have been postulated to lead to keratinocyte apoptosis in SJS and TEN. These include Fas-Fas ligand interaction, cytotoxic T-cell and natural killer-cell damage via perforin/granzyme B/granulysin and tumor necrosis factor-alpha. The use of intravenous immunoglobulins and systemic corticosteroids in TEN is still controversial, and more trials are needed to prove the efficacy of these agents. Newer agents such as cyclosporin, infliximab and plasmapheresis have shown promise in the treatment of SJS and TEN. SUMMARY: As the pathogenesis of SJS and TEN is further unraveled, the emergence of newer therapeutic agents with more specific mechanisms of action may lead to improved survival in this oftentimes devastating disease.
  
11. Jeschke E, Ostermann T, Luke C, Tabali M, Kroz M, Bockelbrink A, Witt CM, Willich SN, Matthes H. Remedies containing Asteraceae extracts: a prospective observational study of prescribing patterns and adverse drug reactions in German primary care. *Drug Saf.* 2009;32(8):691-706.  
BACKGROUND: The use of complementary therapies by patients has increased over the past 20 years, both in terms of self-medication and physician prescriptions. Among herbal medicines, those containing extracts of Asteraceae (Compositae), such as Echinacea spp., Arnica montana, Matricaria recutita and Calendula officinalis, are especially popular in the primary-care setting. However, there remains a gap between the growing acceptance of these remedies and the lack of data on their safety. OBJECTIVE: The aim of this study was to analyse prescribing patterns and adverse drug reactions (ADRs) for Asteraceae-containing remedies in Germany. METHODS: Primary-care physicians, all of whom were members of the German National Association of Anthroposophic Physicians were invited to participate in this prospective, multicentre, observational study. During the study period (September 2004 to September 2006), all prescriptions and suspected ADRs for both conventional and complementary therapies were documented using a web-based system. The study centre monitored all ADR reports and conducted a causality assessment according to Uppsala Monitoring Centre guidelines. Relative risks (RRs) and proportional reporting ratios (PRRs) were calculated. RESULTS: Thirty-eight physicians, 55% of whom were general practitioners and 45% were specialists, fulfilled the technical requirements and were included in the investigation. Because documenting all ADRs (i.e. serious and nonserious) was time consuming, only a subgroup consisting of seven physicians agreed to report nonserious in addition to serious ADRs. During the study period, a total of 50 115 patients were evaluated and 344 ADRs for conventional and complementary remedies were reported. Altogether, 18 830 patients (58.0% female, 60.3% children) received 42 378 Asteraceae-containing remedies. The most frequently prescribed Asteraceae was Matricaria recutita (23%), followed by

*Calendula officinalis* (20%) and *Arnica montana* (20%). No serious ADRs for Asteraceae-containing remedies were reported. In the analysis of the subgroup of seven physicians who also documented nonserious ADRs, 11 nonserious ADRs for Asteraceae-containing remedies occurred in 6961 patients, resulting in an RR of 0.13 (95% CI 0.07, 0.23). The majority of reported ADRs for Asteraceae-containing remedies were classified as uncommon. A subgroup analysis comparing phytotherapeutic and homoeopathic preparations did not reveal any relevant differences. The PRR for Asteraceae-containing remedies with respect to all other prescriptions was 1.7 (95% CI 1.0, 2.0) for the system organ class 'skin and subcutaneous tissue disorders' (six ADRs) and 1.0 (95% CI 0.3, 3.6) for 'gastrointestinal disorders' (three ADRs). Neither result was significant according to the PRR criteria developed by Evans et al. CONCLUSION: This is the first study to provide a systematic overview of prescribing patterns and ADRs for Asteraceae-containing remedies in the German primary-care sector. Asteraceae-containing remedies were used frequently in this context, especially among children. Our results indicate that treatment with Asteraceae-containing remedies is not associated with a high risk of ADRs.

12. Korkmaz A, Kolankaya D. Anzer honey prevents N-ethylmaleimide-induced liver damage in rats. *Exp Toxicol Pathol.* 2009;61(4):333-7.  
N-ethylmaleimide (NEM) is a sulphhydryl blocker which impairs the sulphhydryl dependent antioxidant system (mainly glutathione) in the body by alkylating endogenous sulphhydryls. This study was designed to investigate the effects of Anzer honey on NEM-induced liver injury in rats. Thirty female Wistar albino rats were divided equally into three groups. Group 1: control; Group 2: NEM; Group 3: Anzer honey+NEM. NEM (0.075mg kg<sup>-1</sup>) was given to both group 2 and 3 administered subcutaneously (s.c.) for 30 days. The animals in the Anzer honey+NEM group were treated with Anzer honey at a dose of 0.275g kg<sup>-1</sup>, (p.o.) at 1h prior to every NEM injection. At the end of the 30 day treatment period, liver samples were taken for determination of the glutathione levels and histological examination. NEM treatment alone caused a significant reduction of the liver glutathione levels in group 2. Furthermore, NEM treatment caused congestion and mononuclear cell infiltration in the liver when compared to the control group. In group 3, Anzer honey treatment reversed all the changes in glutathione level, as well as histopathological alterations, normally induced by NEM. The findings imply that depletion of glutathione concentration plays a causal role in NEM-induced liver injury, and that the hepatoprotective effect of Anzer honey may be mediated through sulphhydryl-sensitive processes. They further imply that it may also possess antioxidant properties.
13. Cederbaum A. Nrf2 and antioxidant defense against CYP2E1 toxicity. *Expert Opin Drug Metab Toxicol.* 2009;5(10):1223-44.  
The transcription factor Nrf2 regulates the expression of important cytoprotective enzymes. Induction of CYP2E1 is one of the central pathways by which ethanol generates oxidative stress. CYP2E1 can be induced by ethanol and several low molecular mass chemicals such as pyrazole. This review discusses biochemical and toxicological effects of CYP2E1 and the effects of Nrf2 in modulating these actions of CYP2E1. Besides ethanol, CYP2E1 metabolizes and activates many other toxicologic important compounds. One approach to try to understand the basic

effects and actions of CYP2E1 was to establish HepG2 cell lines that constitutively express human CYP2E1. Ethanol, polyunsaturated fatty acids and iron were toxic to the HepG2 cells, which express CYP2E1 (E47 cells) but not control C34HepG2 cells, which do not express CYP2E1. Toxicity was associated with enhanced oxidant stress and could be prevented by antioxidants and potentiated if glutathione was removed. The E47 cells had higher glutathione levels and a twofold increase in catalase, cytosolic and microsomal glutathione transferase, and heme oxygenase-1 than control HepG2 cells due to activation of their respective genes. These activations were prevented by antioxidants, suggesting that reactive oxygen species generated by CYP2E1 were responsible for the upregulation of these antioxidant genes. This upregulation may reflect an adaptive mechanism to remove CYP2E1-derived oxidants. Increases in Nrf2 protein and mRNA were observed in livers of chronic alcohol-fed mice or rats and of pyrazole-treated rats or mice, conditions known to elevate CYP2E1. E47 cells showed increased Nrf2 mRNA and protein expression compared with control HepG2 C34 cells. Upregulation of antioxidant genes in E47 cells is dependent on Nrf2 and is prevented by siRNA-Nrf2. Blocking Nrf2 by siRNA-Nrf2 decreases glutathione and increases reactive oxygen species and lipid peroxidation, resulting in decreased mitochondrial membrane potential and loss of cell viability of E47 cells, but not C34 cells. Nrf2 is activated and levels of Nrf2 protein and mRNA are increased when CYP2E1 is elevated. These results suggest that Nrf2 plays a key role in the adaptive response against increased oxidative stress caused by CYP2E1 in the HepG2 cells. However, it is not clear whether Nrf2 is protective against CYP2E1 toxicity in vivo as pyrazole which elevates CYP2E1 in wild-type mice did not elevate CYP2E1 in Nrf2 knockout mice, although pyrazole produced toxicity in the Nrf2 knockout mice.

14. Chan TY. Aconite poisoning presenting as hypotension and bradycardia. *Hum Exp Toxicol.* 2009.

The principal toxic ingredients of aconite roots include aconitine, mesaconitine and hypaconitine, which are known cardiotoxins and neurotoxins. A 58-year-old man took a decoction of 11 g each of processed 'chuanwu' (the main root of *Aconitum carmichaeli*) and processed 'caowu' (the root of *A. kusnezoffii*) as treatment for his neck pain. One hour later, he experienced numbness of tongue and the four limbs, generalized weakness, nausea, vomiting, diarrhoea and dizziness. Three hours after ingestion, he was admitted to hospital. His blood pressure was 106/53 mmHg and heart rate 65 beats/min. Six hours after ingestion, he became hypotensive (systolic blood pressure <100 mmHg) with bradycardia (heart rate <60 beats/min). As treatments for the hypotension, he was given intravenous infusions of 0.9% saline (125 mL/hour) for 15 hours (7-21 hours after ingestion) and dopamine (3 microg/kg/min) for 36 hours (10-45 hours after ingestion). He was given atropine 0.6 mg intravenously 7 and 24 hours after ingestion. He was hypotensive for 31 hours (6-36 hours after ingestion), with a systolic blood pressure of 84-106 mmHg (mean 93.5) and a diastolic blood pressure of 40-59 mmHg (mean 51.8). He had bradycardia for 36 hours (6-41 hours after ingestion), with a heart rate of 45-68 beats/min (mean 56.5). On discharge (48 hours after ingestion), his blood pressure was 117/82 mmHg and heart rate 70 beats/min. In patients with aconite poisoning, prolonged hypotension and sinus bradycardia may occur and supportive therapy with close monitoring of

blood pressure and cardiac rhythm are essential.

15. Kales SN, Saper RB. Ayurvedic lead poisoning : An under-recognized, international problem. *Indian J Med Sci.* 2009;63(9):379-81.
16. Jose J, Rao PG, Kamath MS, Jimmy B. Drug safety reports on complementary and alternative medicines (ayurvedic and homeopathic medicines) by a spontaneous reporting program in a tertiary care hospital. *J Altern Complement Med.* 2009;15(7):793-7.  
OBJECTIVES: The objectives of this study were to initiate a pharmacist-coordinated program to improve the adverse drug reaction (ADR) reporting on complementary and alternative medicines (CAM) in a tertiary care hospital and to evaluate the pattern of the reported ADRs. DESIGN: A targeted approach was taken in increasing the ADR reporting to CAM in a tertiary care hospital in South India. Suspected ADRs to CAM spontaneously reported over a period of 24 months were selected for evaluation. Reported ADRs were evaluated for patient demographics, reaction and drug characteristics, causality, severity, and outcome. RESULTS: A total of 12 ADRs to CAM were reported, which included 9 to Ayurvedic and 3 to homeopathic medicines, which accounted for 1.5% of the ADRs reported to the ADR reporting unit. ADR resulted in hospitalization in 5 patients. The system organ class most commonly involved included skin and appendage disorders (58.3%). Only four of the reactions were previously reported in the literature. The mean time for onset of the ADR after the administration of the drug was 27.8 +/- 36.1 days. The suspected drug was withdrawn in all the reports that resulted in recovery, with mean time for recovery 5.9 +/- 3.6 days. The majority (66.6%) were moderate in severity and 2 were severe in nature. On causality assessment, 6 were probable in nature and the remaining were possible. CONCLUSIONS: Even though there were fewer ADRs reported by this spontaneous reporting system, it gave valuable information regarding the potential for adverse effects with these agents. The study has reinstated the potential role of spontaneous reporting in identifying lesser reported ADRs, including those to CAM. Such hospital-based programs can contribute much in increasing the safety-related data of these agents.
17. Teschke R, Genthner A, Wolff A. Kava hepatotoxicity: comparison of aqueous, ethanolic, acetonetic kava extracts and kava-herbs mixtures. *J Ethnopharmacol.* 2009;123(3):378-84.  
ETHNOPHARMACOLOGICAL RELEVANCE: Ethanolic and acetonetic kava extracts have previously been causally related to rare hepatotoxicity observed in patients from Germany and Switzerland, but causality assessment was not performed in cases of patients having taken the traditional aqueous kava extracts of South Pacific islands or kava-herbs mixtures. AIM OF THE STUDY: To study the possible hepatotoxicity of aqueous kava extracts of the South Pacific Islands. MATERIALS AND METHODS: Causality of hepatotoxicity by aqueous kava extracts and kava-herbs mixtures was assessed, using the updated score of the quantitative CIOMS (Council for the International Organizations of Medical Sciences). RESULTS: Causality was established in five patients from New Caledonia, Australia, the United States and Germany for aqueous kava extracts and kava-herbs mixtures. A comparison with 9 patients from Germany and Switzerland with established

causality of hepatotoxicity by ethanolic and acetonetic kava extracts reveals that the clinical picture in all 14 patients is similar, independently whether aqueous, ethanolic and acetonetic kava extracts or kava-herbs mixtures were used.

CONCLUSIONS: Kava hepatotoxicity occurs also with traditional aqueous kava extracts of the South Pacific islands and thereby independently from ethanol or acetone as chemical solvents, suggesting that the toxicity is linked to the kava plant itself with a possibly low quality of the used kava cultivar or kava plant part rather than to chemical solvents.

18. West P, Horowitz BZ. Zigadenus poisoning treated with atropine and dopamine. *J Med Toxicol.* 2009;5(4):214-7.

Introduction: Zigadenus (commonly known as "death camas" or "mountain camas") is a common plant in the lily family found throughout the United States. Its onion-like roots can be mistaken for an edible plant. Ingestion may cause hemodynamic instability which has successfully been treated with atropine. It has been suggested that vasopressors may be an effective therapy for this ingestion. We report the successful use of dopamine as therapy in Zigadenus ingestion. Case Report: A 45 year-old, previously healthy male presented to the ED with complaints of severe nausea and vomiting after ingesting two "wild onion" bulbs. He was noted to have marked hypotension and bradycardia in the ED, which initially responded to treatment with IV fluids and atropine. The plant was identified as a species of Zigadenus. After a second drop in heart rate and blood pressure in the ICU, hypotension and bradycardia were treated successfully with a dopamine infusion. Discussion: Zigadenus ingestion presents with vomiting, hypotension and bradycardia. The hemodynamic instability responded well to atropine for 1-2 hours. Dopamine infusion was used to stabilize both heart rate and blood pressure. With supportive care, poisoned individuals become relatively asymptomatic within 24 hours of their ingestion. Patients may be discharged once asymptomatic, typically the day after ingestion, and do not have any known long term sequelae. Conclusion: Zigadenus poisoning causes vomiting, hypotension and bradycardia. The hemodynamic instability may be treated with atropine administration and dopamine infusion.

19. Kumar P, Kalonia H, Kumar A. Lycopene modulates nitric oxide pathways against 3-nitropropionic acid-induced neurotoxicity. *Life Sci.* 2009;85(19-20):711-8.

AIM: The present study has been designed to investigate the involvement of the nitric oxide mechanism in the protective effect of lycopene against 3-nitropropionic acid-induced Huntington's disease-like symptoms in rats. MAIN METHODS: The present experimental protocol design includes systemic 3-nitropropionic acid (10mg/kg i.p) treatment for 14 days. Lycopene (2.5, 5 and 10mg/kg) was given orally, once a day, 1h before 3-nitropropionic acid treatment for 14 days. Body weight and behavioral parameters (locomotor and rotarod activity) were assessed on 1st, 5th, 10th and 15th day post-3-nitropropionic acid administration. Malondialdehyde, nitrite concentration, superoxide dismutase and catalase levels were measured on the 15th day in the striatum, cortex and hippocampus. Mitochondrial enzyme complexes were also assessed in these brain areas. Systemic 3-nitropropionic acid treatment significantly reduced body weight, locomotor activity and oxidative defense. The mitochondrial enzyme activities were also significantly impaired in the examined brain regions in 3-nitropropionic

acid-treated animals. KEY FINDINGS: Lycopene (2.5, 5 and 10mg/kg) treatment significantly attenuated the impairment in behavioral, biochemical and mitochondrial enzyme activities as compared to the 3-nitropropionic acid-treated group. L-arginine (50mg/kg) pretreatment with a sub-effective dose of lycopene (5mg/kg) significantly attenuated the protective effect of lycopene. Furthermore, L-NAME (10mg/kg) pretreatment with a sub-effective dose of lycopene (5mg/kg) for 14 days significantly potentiated the protective effect. SIGNIFICANCE: The results of the present study suggest that the nitric oxide modulation is involved in the protective effect of lycopene against 3-NP-induced behavioral, biochemical and cellular alterations in rats.

20. West PL, Horowitz BZ, Montanaro MT, Lindsay JN. Poison hemlock-induced respiratory failure in a toddler. *Pediatr Emerg Care*. 2009;25(11):761-3.  
The ingestion of poison hemlock, or Conium maculatum, is described in a 2-year-old boy. He had the onset of abdominal pain and weakness after being fed C. maculatum picked by his sister from the roadside 2 hours earlier. He had a rapidly progressive muscular weakness and was intubated for respiratory failure. His symptoms completely resolved within 24 hours of the ingestion. Conium maculatum is a common weed that causes toxicity by its primary toxin, coniine, which stimulates nicotinic receptors and causes a syndrome of rapidly progressive muscle weakness and paralysis. We describe the course of a benign-appearing plant ingestion resulting in respiratory failure.
  
21. Mehta AK, Arora N, Gaur SN, Singh BP. Acute toxicity assessment of choline by inhalation, intraperitoneal and oral routes in Balb/c mice. *Regul Toxicol Pharmacol*. 2009;54(3):282-6.  
Studies suggest that choline has potential to be used as a dietary supplement and a drug for immune inflammatory diseases like asthma and rhinitis. But there are apprehensions regarding adverse effects of choline when given orally in high doses. To address this knowledge gap, toxicity assessment of choline chloride was carried out by intranasal (i.n.), oral and intraperitoneal (i.p.) routes in Balb/c mice for 28 days. Body weight, food and water consumption of mice were recorded daily. Hematology and clinical chemistry were assessed to check hepatocellular functions and morphological alterations of the cells. Splenocyte counts were analysed for evaluating cellular immunity. Liver function test was performed by assaying different enzyme systems in serum such as, urea, blood urea nitrogen (BUN), creatinine, alanine aminotransferase (ALT), and aspartate aminotransferase (AST). Body weight, food and water consumption did not differ between mice treated with choline and the saline control group. Hematologic and biochemical variables were not affected with any increase in serum toxicity marker enzymes indicating normal liver functioning. Choline administration did not affect total cholesterol and high density lipoprotein levels as compared to their respective controls. Urea and blood urea nitrogen levels in choline treated mice were not different than controls. Creatinine level was, however, higher than control in i.p. treatment group, but other parameters were normal. In conclusion, the repeated consumption of choline chloride via i.n. and oral or i.p. routes did not cause toxicity in mice in the toxicological endpoints examined.

22. Monzote L, Stamberg W, Staniek K, Gille L. Toxic effects of carvacrol, caryophyllene oxide, and ascaridole from essential oil of *Chenopodium ambrosioides* on mitochondria. *Toxicol Appl Pharmacol.* 2009;240(3):337-47. *Chenopodium ambrosioides* have been used for centuries in the Americas as a popular remedy for parasitic diseases. The essential oil of this plant possesses anthelmintic activity and is still used in some regions to treat parasitosis and leishmaniasis. However, the *Chenopodium* oil caused also some fatalities, leading to its commercial disuse. In this work, we studied the mechanism of toxicity of the essential oil and its major pure ingredients (carvacrol, caryophyllene oxide, and ascaridole, which was synthesized from alpha-terpinene) with respect to mammalian cells and mitochondria. We observed that all products, but especially caryophyllene oxide, inhibited the mitochondrial electron transport chain. This effect for carvacrol and caryophyllene oxide was mediated via direct complex I inhibition. Without Fe<sup>2+</sup>, ascaridole was less toxic to mammalian mitochondria than other major ingredients. However, evidence on the formation of carbon-centered radicals in the presence of Fe<sup>2+</sup> was obtained by ESR spin-trapping. Furthermore, it was shown that Fe<sup>2+</sup> potentiated the toxicity of ascaridole on oxidative phosphorylation of rat liver mitochondria. The increase of the alpha-tocopherol quinone/alpha-tocopherol ratio under these conditions indicated the initiation of lipid peroxidation by Fe<sup>2+</sup>-mediated ascaridole cleavage. Further ESR spin-trapping experiments demonstrated that in addition to Fe<sup>2+</sup>, reduced hemin, but not mitochondrial cytochrome c can activate ascaridole, explaining why ascaridole in peritoneal macrophages from BALB/c mice exhibited a higher toxicity than in isolated mitochondria.
23. Meggs WJ. Epidemics of mold poisoning past and present. *Toxicol Ind Health.* 2009;25(9-10):571-6. Molds are ubiquitous throughout the biosphere of planet earth and cause infectious, allergic, and toxic diseases. Toxic diseases arise from exposure to mycotoxins produced by molds. Throughout history, there have been a number of toxic epidemics associated with exposure to mycotoxins. Acute epidemics of ergotism are caused by consumption of grain infested by fungi of the genus *Claviceps*, which produce the bioactive amine ergotamine that mimics the neurotransmitters norepinephrine, serotonin, and dopamine. Acute aflatoxin outbreaks have occurred from ingestion of corn stored in damp conditions that potentiate growth of the molds of the species *Aspergillus*. Contemporary construction methods that use cellulose substrates such as fiber board and indoor moisture have caused an outbreak of contaminated buildings with *Stachybotrys chartarum*, with the extent of health effects still a subject of debate and ongoing research. This article reviews several of the more prominent epidemics and discusses the nature of the toxins. Two diseases that were leading causes of childhood mortality in England in the 1970s and vanished with changing dietary habits, putrid malignant fever, and slow nervous fever were most likely toxic mold epidemics.