

AMERICAN ACADEMY OF CLINICAL TOXICOLOGY
Herbs & Dietary Supplements Special Interest Group
Abstracting Service
December, 2008

1. Amara S. Oral glutamine for the prevention of chemotherapy-induced peripheral neuropathy. *Ann Pharmacother.* 2008;42(10):1481-5.
OBJECTIVE: To evaluate the role of glutamine in the reduction of peripheral neuropathy associated with neurotoxic chemotherapy. DATA SOURCES: Relevant literature was accessed through PubMed (1990-May 2008), using the search terms glutamine, chemotherapy, peripheral neuropathy, neurotoxicity, safety, paclitaxel, platinum compounds, and vinca alkaloids. References in the identified articles were also reviewed for pertinent information. STUDY SELECTION AND DATA EXTRACTION: Studies evaluating the role of oral glutamine for prevention and treatment of chemotherapy-induced peripheral neuropathy (CIPN) were included. Studies regarding the role of glutamine in the reduction of other radiation- and chemotherapy-related toxicities, such as mucositis, cardiotoxicity, diarrhea, and cachexia, were excluded. DATA SYNTHESIS: CIPN is a significant adverse effect associated with neurotoxic chemotherapy, particularly with taxanes, platinum compounds, and vinca alkaloids. There is no standard therapy for the treatment of this dose-limiting reaction. Glutamine is a nonessential amino acid that is thought to have a neuroprotective role, possibly due to the upregulation of nerve growth factor. Two studies revealed that oral glutamine was effective in reducing peripheral neuropathy associated with high-dose paclitaxel, as evidenced by a reduction in numbness, dysesthesias, and motor weakness, as well as a smaller loss of vibratory sensation. Another study found that glutamine effectively reduced peripheral neuropathy in patients with colorectal cancer being treated with oxaliplatin, thereby decreasing the need for an oxaliplatin dose reduction. However, data are limited by small sample sizes in these studies and the lack of placebo-controlled, randomized clinical trials. CONCLUSIONS: Larger, well-designed, placebo-controlled trials assessing both safety and efficacy of oral glutamine are warranted before this agent can be definitively recommended for the prevention of CIPN in patients treated with high-dose paclitaxel or oxaliplatin.
2. Bostanci MO, Bagirici F. Neuroprotective effect of aminoguanidine on iron-induced neurotoxicity. *Brain Res Bull.* 2008;76(1-2):57-62.
Iron is a commonly used metal to induce neuronal hyperactivity and oxidative stress. Iron levels rise in the brain in some neurodegenerative disorders such as Parkinson's and Alzheimer's diseases. A body of evidence indicates a link between neuronal death and nitric oxide. The present study was performed to investigate whether nitric oxide produced by inducible nitric oxide synthase is involved in iron-induced neuron death. For this purpose rats were divided into four groups: control, iron, aminoguanidine and iron+aminoguanidine. Animals in iron and iron+aminoguanidine groups received intracerebroventricular FeCl₃ injection (200 mM, 2.5 microl). Rats belonging to control and aminoguanidine groups received the same amount of saline into the cerebral ventricles. All animals were kept alive for 10 days following the operation and animals in aminoguanidine and iron+aminoguanidine groups received intraperitoneal aminoguanidine injections once a day (100mg/kg day) during this period. After 10 days, rats were perfused intracardially under deep urethane anesthesia. Removed brains were processed using the standard histological techniques. The total numbers of neurons in hippocampus of all rats were estimated with the unbiased stereological techniques. It was found that aminoguanidine decreased mean neuron loss from 43.4% to 20.3%. Results of the present study suggest that aminoguanidine may attenuate the neurotoxic effects of iron by inhibiting inducible nitric oxide synthase.
3. Rosa RM, Roesler R, Braga AL, Saffi J, Henriques JA. Pharmacology and toxicology of diphenyl diselenide in several biological models. *Braz J Med Biol Res.* 2007;40(10):1287-304.
The pharmacology of synthetic organoselenium compounds indicates that they can be used as antioxidants, enzyme inhibitors, neuroprotectors, anti-tumor and anti-infectious agents, and immunomodulators. In this review, we focus on the effects of diphenyl diselenide (DPDS) in various biological model organisms. DPDS possesses antioxidant activity, confirmed in several in vitro and in vivo systems, and thus has a protective effect against hepatic, renal and

gastric injuries, in addition to its neuroprotective activity. The activity of the compound on the central nervous system has been studied since DPDS has lipophilic characteristics, increasing adenylyl cyclase activity and inhibiting glutamate and MK-801 binding to rat synaptic membranes. Systemic administration facilitates the formation of long-term object recognition memory in mice and has a protective effect against brain ischemia and on reserpine-induced orofacial dyskinesia in rats. On the other hand, DPDS may be toxic, mainly because of its interaction with thiol groups. In the yeast *Saccharomyces cerevisiae*, the molecule acts as a pro-oxidant by depleting free glutathione. Administration to mice during cadmium intoxication has the opposite effect, reducing oxidative stress in various tissues. DPDS is a potent inhibitor of delta-aminolevulinatase and chronic exposure to high doses of this compound has central effects on mouse brain, as well as liver and renal toxicity. Genotoxicity of this compound has been assessed in bacteria, haploid and diploid yeast and in a tumor cell line.

4. Koren G. Mycophenolate mofetil: emerging as a potential human teratogen. *Can Fam Physician*. 2008;54(8):1112-3.
5. Mazzoleni R, Kreisler A, Lucas C, Kwiatkowski A, Gautier S, Destee A, Defebvre L. Seizure after use of almotriptan. *Clin Neurol Neurosurg*. 2008;110(8):850-1.
We report the case of a young woman who suffered from a seizure after use of almotriptan. There was a recurrence with ergotamine. We discuss possible link with susceptibility genes.
6. Dietert RR. Developmental immunotoxicity (DIT) in drug safety testing: matching DIT testing to adverse outcomes and childhood disease risk. *Curr Drug Saf*. 2008;3(3):216-26.
Developmental immunotoxicity (DIT) recently emerged as a significant concern for drug safety and was the topic of several recent scientific forums in Europe, North America and Asia. The heightened concern is based on several observations: 1) many childhood diseases with recent increases in prevalence, such as asthma, allergic disease, leukemia and certain infections, have clear linkages to the immune system and immune dysfunction, 2) the developing immune system has been shown to be a particularly sensitive target for xenobiotic-induced adverse outcomes, 3) immunotoxicity assessment following adult exposure to xenobiotics is ineffective for predicting immunotoxic risk in the non-adult and 4) in several cases developmental immunotoxicity to low-level xenobiotic exposure can take the form of immune dysfunction in the absence of readily detected morphometric/histological alterations. The present review examines harmonized preclinical drug safety guidelines for immunotoxicity in light of environmentally-mediated childhood disease trends as well as research-based mechanisms for DIT. Because none of the guidelines was designed to address risk of DIT, suggestions are offered for closing the early-life immune dysfunction data gap. A longer-term goal is to help narrow the difference between current guideline expectations and the known sensitivity of the developing immune system for potential adverse outcomes.
7. Levin R, Brown MJ, Kashtock ME, Jacobs DE, Whelan EA, Rodman J, Schock MR, et al. Lead exposures in U.S. Children, 2008: implications for prevention. *Environ Health Perspect*. 2008;116(10):1285-93.
OBJECTIVE: We reviewed the sources of lead in the environments of U.S. children, contributions to children's blood lead levels, source elimination and control efforts, and existing federal authorities. Our context is the U.S. public health goal to eliminate pediatric elevated blood lead levels (EBLs) by 2010. DATA SOURCES: National, state, and local exposure assessments over the past half century have identified risk factors for EBLs among U.S. children, including age, race, income, age and location of housing, parental occupation, and season. DATA EXTRACTION AND SYNTHESIS: Recent national policies have greatly reduced lead exposure among U.S. children, but even very low exposure levels compromise children's later intellectual development and lifetime achievement. No threshold for these effects has been demonstrated. Although lead paint and dust may still account for up to 70% of EBLs in U.S. children, the U.S. Centers for Disease Control and Prevention estimates that >or=30% of current EBLs do not have an immediate lead paint source, and numerous studies indicate that lead exposures result from multiple sources. EBLs and even deaths have been

associated with inadequately controlled sources including ethnic remedies and goods, consumer products, and food-related items such as ceramics. Lead in public drinking water and in older urban centers remain exposure sources in many areas. CONCLUSIONS: Achieving the 2010 goal requires maintaining current efforts, especially programs addressing lead paint, while developing interventions that prevent exposure before children are poisoned. It also requires active collaboration across all levels of government to identify and control all potential sources of lead exposure, as well as primary prevention.

8. Palanza P, Gioiosa L, vom Saal FS, Parmigiani S. Effects of developmental exposure to bisphenol A on brain and behavior in mice. *Environ Res.* 2008;108(2):150-7. Bisphenol A (BPA) is a widespread estrogenic chemical used in the production of polycarbonate, and epoxy resins lining food and beverage cans and in dental sealants. During fetal life the intrauterine environment is critical for the normal development, and even small changes in the levels of hormones, such as estradiol or estrogen-mimicking chemicals, can lead to changes in brain function and consequently in behavior. We review here a series of ethological studies on the effects of maternal oral exposure during the last part of gestation (prenatal exposure) or from gestation day 11 to postnatal day 7 (perinatal exposure) to a low, environmentally relevant dose of BPA (10 microg/kg bw/day) on behavioral responses of CD-1 mouse offspring. We examined both male and female offspring and found that maternal exposure to BPA affected: (1) behavioral responses to novelty before puberty and, as adults; (2) exploration and activity in a free-exploratory open field; (3) exploration in the elevated plus maze and (4) sensitivity to amphetamine-induced reward in the conditioned place preference test. A consistent effect of the maternal exposure to BPA is that in all these different experimental settings, while a significant sex difference was observed in the control group, exposure to BPA decreased or eliminated the sex difference in behavior. In addition, exposure of female mice to BPA in both adulthood or during fetal life altered subsequent maternal behavior. These findings, together with those from other laboratories, are evidence of long-term consequences of maternal exposure to low-dose BPA at the level of neurobehavioral development.
9. Ajith TA, Aswathy MS, Hema U. Protective effect of *Zingiber officinale roscoe* against anticancer drug doxorubicin-induced acute nephrotoxicity. *Food Chem Toxicol.* 2008;46(9):3178-81. Oxidative stress due to abnormal production of reactive oxygen species has been implicated in the nephrotoxicity induced by a commonly used anticancer antibiotic doxorubicin (DXN). The nephroprotective effect of aqueous ethanol extract of *Zingiber officinale* (200 and 400mg/kg, p.o) was evaluated against doxorubicin-induced (15mg/kg, i.p) acute renal damage in rat. Serum urea and creatinine levels were evaluated as the markers of renal failure. Renal antioxidant status such as activities of superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx) and level of reduced glutathione (GSH) were determined. Level of lipid peroxidation as equivalents of malondialdehyde (MDA), and glutathione-S-transferase (GST) activity were determined in the kidneys. Serum urea and creatinine levels were reduced in the *Z. officinale* (200 and 400mg/kg, p.o) plus DXN treated groups. The renal antioxidant enzymes activities such as SOD, CAT GPx, levels of GSH and GST activity were restored and that of MDA declined significantly ($p < 0.001$) in the *Z. officinale* (400mg/kg) plus DXN treated group. The nephroprotection is mediated by preventing the DXN-induced decline of renal antioxidant status, and also by increasing the activity of GST.
10. Mazzanti G, Battinelli L, Daniele C, Costantini S, Ciaralli L, Evandri MG. Purity control of some Chinese crude herbal drugs marketed in Italy. *Food Chem Toxicol.* 2008;46(9):3043-7. The widespread use of herbal drugs, among which those coming from eastern Countries, has created a more compelling need for quality, a pre-requisite that can influence safety. In the present study, 10 Chinese crude herbal drugs marketed in Italy (*Radix Ginseng*, *Radix Astragali*, *Rhizoma Coptidis*, *Rhizoma Atractylodis Macrocephalae*, *Radix Bupleuri*, *Radix Rehmanniae*, *Radix Paeoniae Alba*, *Pericarpium Citri Reticulatae*, *Radix Polygalae*, *Radix Salviae Miltiorrhizae*) were analysed by the following purity assays: foreign matter, total ash, microbial and heavy metal contamination. Each herbal drug was purchased in Italy from three different sources: two Chinese firms and one Chinese herbal shop. Except for the heavy

metal content, the tests were performed according to the European Pharmacopoeia. The presence of parasites was shown in two samples; moreover, level of ash (in three samples), lead content (in one sample) and total viable aerobic count (in one sample), were higher than the limits set by the European or Italian Pharmacopoeias. Our results, even if obtained from a small number of herbal drugs, show some purity issues and underline the importance of the quality control, particularly for this kind of products whose therapeutic value is not always demonstrated.

11. Venkataranganna MV, Gopumadhavan S, Sundaram R, Peer G, Mitra SK. Pharmacodynamics & toxicological profile of PartySmart, a herbal preparation for alcohol hangover in Wistar rats. *Indian J Med Res.* 2008;127(5):460-6.
BACKGROUND & OBJECTIVE: PartySmart is a herbal preparation intended for the management of alcohol hangover and other related toxic effects in clinical situation. The present study was designed to investigate the pharmacodynamics and oral toxicity of PartySmart, a herbal formulation in rats. METHODS: Effect of PartySmart on blood acetaldehyde and alcohol levels was evaluated at doses of 125, 250 and 500 mg/kg b.wt. in rats. Acute toxicity study was conducted with PartySmart at a limit test dose of 2000 mg/kg b.wt., p.o. In repeated dose 90 day study, PartySmart was administered at doses of 500 and 1000 mg/kg b.wt. once-a-day, orally throughout the study period. RESULTS: PartySmart dose-dependently decreased blood ethanol and acetaldehyde levels as compared to control. PartySmart at a dose of 500 mg/kg b.wt. significantly reduced the area under curve (AUC) of ethanol and acetaldehyde levels. It increased the hepatic alcohol dehydrogenase (ADH) at 500 mg/kg b.wt. and aldehyde dehydrogenase (ALDH) activities at doses of 250 and 500 mg/kg b.w. significantly. Acute toxicity study showed no clinical signs and pre-terminal deaths. The LD(50) of PartySmart was found to be greater than 2000 mg/kg b.wt. No significant differences in PartySmart-treated groups were observed on body weight, food intake, haematological and clinical chemistry, and organ weight ratios as compared to control group in the repeated dose study. Histopathological examination of all target organs showed no evidence of lesions attributing to drug toxicity. INTERPRETATION & CONCLUSION: PartySmart enhanced acetaldehyde metabolism by increasing ADH and ALDH activity without any side effects. These findings indicate that PartySmart may exert beneficial role in the management of alcohol hangover without any toxicity.
12. Rey JM, Walter G, Soh N. Complementary and Alternative Medicine (CAM) treatments and pediatric psychopharmacology. *J Am Acad Child Adolesc Psychiatry.* 2008;47(4):364-8.
13. Yin HQ, Wang B, Zhang JD, Lin HQ, Qiao Y, Wang R, Liu FY. Effect of traditional Chinese medicine Shu-Mai-Tang on attenuating TNFalpha-induced myocardial fibrosis in myocardial ischemia rats. *J Ethnopharmacol.* 2008;118(1):133-9.
Shu-Mai-Tang (SMT) is a traditional Chinese medicine for treatment of ischemic heart disease. The effect of SMT on inflammation-induced myocardial fibrosis, left ventricular (LV) remodeling, and the potential mechanism in myocardial ischemia (MI) rats were investigated. Rats with ligated left anterior descending coronary artery (MI model) were randomly divided into three groups (SMTL, SMTH, and MIR). A group undergoing Sham operation (Sham; n=16) was also included. SMT (342 or 1710 mg/kg for SMTL or SMTH groups, respectively) was orally administered daily for 1 and 6 weeks. Cardiac function, myocardial fibrosis, serum tumor necrosis factor-alpha (TNFalpha) concentration, the cardiac expressions of phosphorylated p38 MAPK and tissue inhibitor of matrix metalloproteinase (TIMP)-1 and TNFalpha were examined by echocardiography, histological staining, radioimmunoassay, western blot, respectively. In the present study, significant reduced myocardial fibrosis, as well as decreased phospho-p38 MAPK, TIMP-1, and TNFalpha proteins, and serum TNFalpha level, accompanied by improved cardiac function in the SMT-treated rats in a dose-dependent manner as compared with the MIR. These results suggested that SMT could anti-inflammation-induced myocardial fibrosis and reverse LV remodeling in MI rats, and the mechanism may be related to the effect of SMT on inhibiting p38 MAPK signaling pathway.
14. Rambold AS, Miesbauer M, Olschewski D, Seidel R, Riemer C, Smale L, Brumm L, et al.

Green tea extracts interfere with the stress-protective activity of PrP and the formation of PrP. *J Neurochem.* 2008;107(1):218-29.

A hallmark in prion diseases is the conformational transition of the cellular prion protein (PrP(C)) into a pathogenic conformation, designated scrapie prion protein (PrP(Sc)), which is the essential constituent of infectious prions. Here, we show that epigallocatechin gallate (EGCG) and gallic acid, the main polyphenols in green tea, induce the transition of mature PrP(C) into a detergent-insoluble conformation distinct from PrP(Sc). The PrP conformer induced by EGCG was rapidly internalized from the plasma membrane and degraded in lysosomal compartments. Isothermal titration calorimetry studies revealed that EGCG directly interacts with PrP leading to the destabilizing of the native conformation and the formation of random coil structures. This activity was dependent on the gallate side chain and the three hydroxyl groups of the trihydroxyphenyl side chain. In scrapie-infected cells EGCG treatment was beneficial; formation of PrP(Sc) ceased. However, in uninfected cells EGCG interfered with the stress-protective activity of PrP(C). As a consequence, EGCG-treated cells showed enhanced vulnerability to stress conditions. Our study emphasizes the important role of PrP(C) to protect cells from stress and indicate efficient intracellular pathways to degrade non-native conformations of PrP(C).

15. Chan EY, Griffiths SM, Chan CW. Public-health risks of melamine in milk products. *Lancet.* 2008;372(9648):1444-5.
16. Teschke R, Schwarzenboeck A, Akinci A. Kava hepatotoxicity: a European view. *N Z Med J.* 2008;121(1283):90-8.

Kava was well tolerated and considered as devoid of major side effects only until 1998 when the first report of assumed kava hepatotoxicity appeared. Causality of hepatotoxicity for kava +/- comedicated drugs was evident after the use of predominantly ethanolic and acetic kava extracts in Germany (n=7), Switzerland (n=2), United States (n=1), and Australia (n=1) as well as after aqueous extracts in New Caledonia (n=2). Compliance regarding the recommendation for daily kava dose and duration was ascertained in only a few patients, including 2 from Germany and Switzerland. Since 450 millions of daily doses of kava extracts equating to 15 millions of monthly doses were sold in Germany and Switzerland, hepatotoxicity by kava appeared to be rare--similar to other herbal remedies, dietary supplements, and synthetic drugs. Risk factors were found in most patients and include daily kava overdose, prolonged therapy, and comedication with up to 5 other herbal remedies, dietary supplements, and synthetic drugs. Kava hepatotoxicity was not reported until 1998, thus raising the question of inferior quality of the kava raw material at times of the kava boom later on. Insufficiently defined regulatory guidelines to produce kava extracts are of some concern. Open questions refer not only to kava cultivars, but also to analytical methods and definitions of extract media and contents. Future strategies should therefore focus on the solution of a standard methodology of ascertaining quality that can assure a high degree of reliability in conjunction with actions by regulators, physicians, manufacturers, and producers. A medical advisory is also recommended as part of the labelling.
17. Cho HS, Kim S, Lee SY, Park JA, Kim SJ, Chun HS. Protective effect of the green tea component, L-theanine on environmental toxins-induced neuronal cell death. *Neurotoxicology.* 2008;29(4):656-62.

Several environmental neurotoxins and oxidative stress inducers are known to damage the nervous system and are considered major factors associated with the selective vulnerability of nigral dopaminergic neurons in Parkinson's disease (PD). Gamma-glutamylethylamide (L-theanine), a natural glutamate analog in green tea, has been shown to exert strong anti-ischemic effect. In this study, we investigated the protective effects of L-theanine on neurotoxicity induced by PD-related neurotoxicants, rotenone and dieldrin in cultured human dopaminergic cell line, SH-SY5Y. Our initial experiments revealed that L-theanine (500 microM) attenuated both rotenone- and dieldrin-induced DNA fragmentation and apoptotic death in SH-SY5Y cells. In addition, L-theanine partially prevented both rotenone- and dieldrin-induced heme oxygenase-1 (HO-1) up-regulation. Both rotenone- and dieldrin-induced down-regulation of extracellular signal-regulated kinase1/2 (ERK1/2) phosphorylation was significantly blocked by pretreatment with L-theanine. Furthermore,

pretreatment with L-theanine significantly attenuated the down-regulation of brain-derived neurotrophic factor (BDNF) and glial cell line-derived neurotrophic factor (GDNF) production in SH-SY5Y cells. These results suggest that L-theanine directly provide neuroprotection against PD-related neurotoxicants and may be clinically useful for preventing PD symptoms.