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INSIDE

Coming Clean on Supplements Designated the 'Dirty Dozen'

PART I OF A SERIES ON POTENTIALLY HAZARDOUS SUPPLEMENTS

By Francis Brinker, ND

THE MAY 2004 ISSUE OF *CONSUMER REPORTS* (*CR*) GENERATED national controversy with publication of a list of products regulated in the United States as dietary supplements that it described as "12 supplements you should avoid." The list (also referred to by *CR* as the "Dirty Dozen") accompanied an article[1] that focused on documented and theoretical safety concerns about products readily available through Internet sales and often through retail stores. The article focuses on regulatory issues regarding the implementation of features of the 1994 Dietary Supplement Health and Education Act and the FDA's enforcement of its provisions.

The discussion emphasized safety concerns as they apply to product testing, labeling, and reporting. The prolonged effort to ban ephedra as a thermogenic weight loss agent associated with numerous adverse effects was used to illustrate the need for greater enforcement. The call for greater regulation to reduce dietary supplement accessibility and improve public safety was balanced by recognition of the need for greater FDA funding for enforcement of

Editor's Note—*From time to time,* Alternative Medicine Alert *breaks from its typical format to present unique information requiring significant space. Such is the case this month, as one of the world's foremost experts on herbal dietary supplements addresses issues of safety in the now infamous* Consumer Reports *"Dirty Dozen." While many, if not most,* Alternative Medicine Alert *readers do not routinely use the agents mentioned by* Consumer Reports*, it is nonetheless important to understand the distinctions between preparations and patterns of use. This is what most determines safe use versus risk. In this regard, what is necessary in most cases is education and information involving appropriate label warning requirements (as opposed to universal bans). It is especially important to recognize the degree of scientific support, or lack thereof, behind such classifications of safe and unsafe.*

—Russell H. Greenfield, MD

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current provisions that are viewed as adequate by the supplement industry.

The range of toxicity evidence and differences in the relative risk for the designated supplements led the list of the dozen supplements to be divided into three separate categories: definitely hazardous, very likely hazardous, and likely hazardous. This report fails, as do most media reports on products involving botanicals, to distinguish between the effects produced by different types of products made from the same herbal source. The article does point out the reality that many supplement makers concentrate extracts of botanicals to increase content of pharmacologically active components in products that are then marketed as "natural" in spite of their enhanced drug-like effects.

The *CR* article also does not differentiate appropriate applications from inappropriate or abusive use that often is associated with adverse event reports. The failure to recognize and acknowledge the features that separate safe and beneficial utilization from inappropriate and risky use demonizes a number of products that are neither inherently safe or unsafe. With regard to consumer safety, this failure largely rests with inadequate label instructions and warnings that need to be addressed as a central feature of regulatory controls. To its credit, *CR* identifies proper identification and labeling as key issues that must be addressed.

The discussion that follows of the 12 supplements ear-marked by *CR* for greater scrutiny addresses pertinent aspects as it considers the evidence for the relative safety and toxicity of the different products. Classifications determined by the American Herbal Products Association (AHPA), as published in its *Botanical Safety Handbook* (*BSH*),[2] will be used as another expert perspective on the these concerns. The AHPA serves as a trade association that provides guidance to assure its members manufacture preparations that provide both quality and safety for the public good. The *BSH* contains contributions and reviews by panels of expert herbalists and naturopathic physicians. It was edited by four respected herbal practitioners and scholars who used their extensive experience and more than 300 citations from the scientific and medical literature to reach a consensus on relative risks for herbs available in American commerce. Attention will be paid to both traditional and modern botanical products that represent these complex and at times confusing issues, as four categories are employed to revise the *CR* assessments. The proposed categories covered in Part 1 are: 1) hazardous and 2) potentially hazardous with prolonged internal use. Covered in Part 2 will be: 3) hazardous with acute excessive dosage and 4) unlikely hazardous.

Although potential risks of health products and practices need to be weighed against potential benefits, it is not possible to address the wide range of applications for the multiple products of each supplements addressed here. Except for concentrated extracts of kava for the treatment of anxiety, preparations of the herbs have not been therapeutically validated by controlled clinical trials. Their usefulness is based on knowledge from traditional empirical applications supported by pharmacological studies of a few extracts, fractions, and/or major active constituents. To elaborate on the evidence that supports the specific clinical utility of the different types of preparations would require a separate major article for each herb. Instead, the major therapeutic properties will be mentioned for each.

Category 1: Definitely Hazardous

1. Aristolochic acid (from *Aristolochia* spp. all parts/*Asarum canadense* rhizome)

CR lists only one "product" as definitely hazardous: aristolochic acid. This is confusing, since aristolochic acid is not sold as a supplement. Rather, it is a component of plants in the genera Aristolochia, sold under Chinese names such as fang ji, mu tong, ma dou ling, and mu xiang and American names like birthwort and

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Table 1

Toxicity, effects, and precautions

Agent	*Consumer Reports* Ratings	Potential Toxicity	Major Effects/Uses	Precautions
Aristolochia (all species/ all parts)	Definitely hazardous	Nephrotoxic and carcinogenic (aristolochic acid); death possible.	Internal: tonic for digestion Local: poultice for snakebites	Avoid use.
Wild ginger (*Asarum canadense*) rhizome	Definitely hazardous	Contains aristolochic acid (see above); death possible.	Carminative for flatulence and dyspepsia	Avoid use.
Germander (*Teucrium chamaedrys*) aerial plant	Very likely	Hepatotoxic (furano diterpenoids); death possible.	Diuretic for gout	Avoid use.
Comfrey (*Symphytum officinale*) root or leaves	Very likely hazardous	Hepatotoxic (pyrrolizidine alkaloids); rarely, death possible. Root has double alkaloids/toxicity of leaves. (Water extracts reduce toxin exposure.)	Cell proliferant (allantoin) and demulcent (mucilage) for local injuries	Avoid in pregnancy and nursing. Short-term external or local use on unbroken surfaces only.
Chaparral (*Larrea tridentata*) leaves	Very likely hazardous	Idiosyncratic hepatotoxicity, contact allergy; rarely, death possible. (Liquid extracts appear less toxic than leaf powder.)	Anti-inflammatory and anti-microbial for local skin and mucosal conditions	Avoid in liver and kidney disease. Stop if jaundice develops. Limit to topical use or short-term internal use.
Kava (*Piper methysticum*) roots/rhizomes	Very likely hazardous	Hepatotoxic predisposition, interactions, or stem alkaloid adulterants; rarely, death possible.	Anxiolytic for occasional symptomatic relief of anxiety attacks	Avoid in pregnancy and nursing, in children, if history of liver disease, in combinations with drugs/ alcohol, and long-term use of non-water extracts concentrates.
Androstenedione	Very likely hazardous	Reduced HDL, increased risk of some cancers, and gyneco-mastia or virilization.	Increases sex hormone production for body building	For non-pregnant adults only. Avoid long-term use of large doses.

snakeroot, as well as the rhizome of *Asarum canadense* sold as wild ginger.

In April 2001, the FDA issued an import alert and warning to consumers and industry regarding aristolochic acid.[1] It was brought to international attention in 1993 due to the tragedy of at least 30 cases of kidney failure in 70 cases of rapidly progressive interstitial renal fibrosis among Belgian women who were using a product supposedly providing about 450 mg daily each of the powdered Chinese herbs *Magnolia officinalis* and *Stephania tetrandra* for weight control. While its content of phytochemical markers for magnolia was confirmed, the marker tetrandrine for stephania was absent. The substitution of a Chinese species, *Aristolochia fangchi*, for stephania (having the same Chinese common name: fangji) was suspected and later confirmed by the content of aristolochic acid and lack of tetrandrine in 10 of 12 supplies of stephania from Belgium. One sample had both markers.[3,4] This illustrates the danger of relying on common names that can be shared by unrelated plants and may result in mistaken substitution.

By 2002, aristolochic acid (including *Aristolochia manshuriensis*) had been detected in herbal preparations—identified in adverse event reports—throughout the world: one case documented in the United States, at least 237 cases of Chinese herbal nephropathy in eastern Asia and Europe following prolonged use, and one case in Spain from *Aristolochia pistolochia* tea.[5] Tragically, a report in 2000 documented that among 39 of the Belgian patients who had been treated with

transplantation or dialysis for their aristolochic acid exposure, 18 had developed urothelial carcinoma, 19 had mild-to-moderate urothelial dysplasia, and only two had normal urothelium.[6] The aristolochic acid was found to be metabolically activated to carcinogens by cytochrome P450 (CYP) isozymes 1A1 and 1A2.[7] These isozymes are further activated by a number of drugs and commonly consumed items including tobacco smoke, char-grilled meat, and cruciferous vegetables.[8]

All *Aristolochia* species are suspected of containing aristolochic acid. The *BSH* discusses aristolochic acid and its toxicity and identifies as available commercial sources the Chinese *Aristolochia* species *A. contorta* and *A. debilis*, the American *A. clematitis* and *A. serpentaria*, and *Asarum canadense*. Warnings for aristolochia include avoiding use during pregnancy and recommending use "only under the supervision of an expert qualified in the appropriate use." *BSH* warns that wild ginger should not to be used during pregnancy nor for long-term use, and the recommended dose should not be exceeded.[2] *A. clematitis* (long birthwort), *A. serpentaria* (Virginia snakeroot), and wild ginger have been used in traditional American herbalism as digestive tonics or locally for treating snakebites. However, the *Aristolochia* species were noted for their toxic potential if taken internally even in small doses of tincture. Relatively old data show no apparent toxicity associated with small doses of wild ginger orally.[9] That stated, supplements containing aristolochic acid should be avoided.

2. Germander (*Teucrium chamaedrys*) aerial plant

Listed under the *CR* category of "very likely hazardous," germander is an herb with hepatic toxicity documented by positive rechallenge in numerous cases. In the early 1990s in France, 26 cases were reported after an average of nine weeks of ingestion for reduction of weight and/or cholesterol. These appeared clinically as weakness accompanied by jaundice with elevated transaminases and on pathology slides as periportal inflammation and centrilobular necrosis.[10] Of seven cases of acute hepatitis published in 1992, signs and symptoms developed 3-18 weeks after ingestion. Doses ranged from the median 600 mg up to 1,620 mg daily taken as powdered encapsulated herb or in one case as a tea. Jaundice disappeared within eight weeks after discontinuation, but complete recovery took 1.5-6 months. Hepatitis returned promptly after re-administration in three cases.[11] Two similar cases in Canada were reported in 1996 following consumption of 260 mg or 1,600 mg daily for six months. One of these recurred only a week after resuming consumption.[12]

Re-introduction appears to be most harmful. Another French case proved fatal in a 68-year-old woman after she took 450 mg daily for two courses, separated by six months, of about two weeks each. Massive hepatic necrosis was found on necropsy.[13] The hepatotoxic agents in germander are furano diterpenoids that are activated by CYP3A to decrease glutathione, as shown in rat hepatocytes. Hepatocyte death was prevented by CYP3A inhibitor troleandomycin or by preventing glutathione depletion with cystine, while apoptosis was increased by CYP3A inducer dexamethasone and a diet deficient in sulfur amino acids.[14]

The *BSH* warns that *T. chamaedrys* herb "be used only under the supervision of an expert qualified in the appropriate use of this substance."[2] This and other *Teucrium* species have not been commonly used in American herbal practice.[9] It is native to Great Britain with a tradition of medical use there as a diuretic and a specific for gout. Another British species, *T. scorodonia* or wood sage, was applied topically to skin sores.[15] According to *BSH*, *T. scorodonia* is designated as one of the "herbs for which insufficient data are available for classification." *BSH* notes that the species *T. stocksianum* has even demonstrated hepatoprotective effects in mice.[2] Nonetheless, *T. chamaedrys* products intended for long-term consumption are clearly responsible for consistently inducing hepatotoxicity with prolonged or repeated use by known mechanisms due to its diterpenoid components. Teucrium products that contain these toxic diterpenoids should be avoided.

Category 2: Potentially Hazardous with Prolonged Internal Use

1. Comfrey (*Symphytum officinale*) roots and leaves

Designated by *CR* as very likely hazardous, the FDA issued an advisory to industry for voluntary market removal of comfrey in July 2001.[1] Comfrey's reputation as a hepatotoxin comes from a few nonfatal human cases, but often is associated with many fatal animal and human cases arising from ingestion of other herbs, notably those of the genera Heliotropium, Senecio, and Crotalaris. These plants all contain pyrrolizidine alkaloids (PAs) and their less toxic water-soluble N-oxides. The extent of the hepatotoxicity from PAs depends upon total content and particular molecular structures that include an unsaturated 1,2-double bond.[16,17] Relative toxicity from these PAs can vary greatly from one genera, species, and plant part to another. PAs are metabolized in the liver to form the toxic pyrroles that result in acute hepatic veno-occlusive disease in humans. In animals the PA lasiocarpine also has been shown to produce fibrotic lung disease. PAs cross the placenta in animals causing teratogenic and fetotoxic abnormalities, and lasiocarpine in the milk of animals has caused liver

damage in their young. Another concern is that PA mutagenic effects may result in carcinogenesis.[17]

Incidences of poisoning from Russian comfrey (*S.* x *uplandicum*, a hybrid of *S. officinale* and *S. asperum*) and other *Symphytum* species must be distinguished because of their different PA profiles and high levels of the very toxic PA echimidine. Substitution of other *Symphytum* species for *S. officinale* is an appropriate concern.[18] Although comfrey roots contain little (0.0058%) of the mutagenic and carcinogenic lasiocarpine, they do have significant amounts (0.23-0.38%) of the similar PA symphytine.[17] The PA content of comfrey based on analysis of 300 samples ranged from 0.045% to 0.599%. Concentrations in the root are about 100 times greater than in the aerial parts.[16] The larger leaves have much lower concentrations than young, small leaves.[17] When several groups of rats were fed diets containing different percentages of comfrey roots or leaves for varying lengths of time, hepatocellular adenomas developed at varying rates. Rats fed the root diets first developed liver tumors after seven months with 8% and 2% roots, at eight months with 4% roots, and at 10 months with 1% roots. The rats fed leaf diets began having liver tumors after nine or 14 months with 33% leaves, at 18 months after 16% leaves, and at 20 months after 8% leaves.[19]

Several nonfatal cases of PA poisoning from comfrey have been documented. A 49-year-old woman developed hepatic veno-occlusive disease after she consumed an uncharacterized herbal tea for six months and took six comfrey root-pepsin tablets daily with meals for four months. The tea and tablets were analyzed and each was found to contain PAs that would have provided more than 85 mg PA total over six months.[20] A 13-year-old boy developed veno-occlusive disease after consuming comfrey root and a tea made from comfrey leaf over a two- to three-year period for Crohn's disease.[21] A 47-year-old woman with abdominal pain took up to 10 cups daily of comfrey tea as well as comfrey pills "by the handful" for over a year. Four years later she had elevated serum transaminases and after another four years developed clinical hepatic veno-occlusive disease.[22] A 77-year-old woman took a combination herbal remedy containing comfrey three times daily six days each week for six months. She became tired, anorexic, and moderately jaundiced and had dark urine with elevated transaminases. A cough accompanied reticulonodular shadowing on chest X-ray. Four months after stopping comfrey her liver function tests and chest X-ray were normal and two months later her symptoms had disappeared.[23]

One report documented a number of asymptomatic people who used dried comfrey leaves for years. These included 21 subjects who had consumed on average 3 g/d for 1-10 years, five people using 2.6 g/d for 11-20 years, and three others taking 11 g/d (ranging from 2 g to 25 g) for 21-30 years. Normal bilirubin, AST, and GGT levels were found except for two with slightly elevated bilirubin and one increased AST.[24] The FDA found in their analysis of different comfrey preparations that combination products had the lowest PA levels, whereas bulk comfrey root followed by bulk comfrey leaf had the highest. Tea made from the root had less than half the PA of bulk leaf, and tea from the leaf contained very few PAs. The PAs in the teas are mostly the water-soluble N-oxides.[25] However, PA N-oxides are largely metabolized by gut flora to free PAs.[18] Comfrey root extract applied to the skin in rats resulted in the urinary excretion of N-oxides in small amounts, whereas oral consumption resulted in 20-50 times higher urinary content of N-oxides and free PAs.[26] A recent review acknowledged the low PA content in comfrey leaves, their relatively low toxicity compared to PAs in other *Symphytum* species or other genera, and the safety of N-oxide forms extracted in water and applied topically. It concluded that a re-examination of comfrey's benefits versus risks was deserved.[27] The *BSH* classified *S. officinale* root and leaf for external use only, but warned that it not be applied to broken or abraded skin nor used during pregnancy or while nursing.[2] Traditionally, the powdered root has been used as a poultice on bruises, sores, strains/sprains, inflammations, and insect bites.[9]

Besides the much greater PA content, the higher yield of mucilage and allantoin (which stimulates cell proliferation) from comfrey root than from leaves[17] make short-term local use of root preparations preferable. People should be provided proper label warnings about the risks of using comfrey products internally. The selective use of a water extract of the official medicinal species for local applications in small amounts for short durations should be beneficial and safe rather than potentially dangerous. In this way it can continue to be used to promote healing and relieve pain as a demulcent, hemostatic, and/or emollient agent.[9]

2. Chaparral (*Larrea tridentata*) leaves

Designated as very likely hazardous by *CR*, the FDA issued a warning to consumers in December 1992.[1] The warning was based on a *Morbidity and Mortality Weekly Report* (*MMWR*) article of two cases of toxic hepatitis. One involved a man who developed scleral icterus and jaundice with elevated bilirubin, GGT, AST, and LDH after consuming 1.5 g of chaparral daily for six weeks. Three weeks after discontinuation he was asymptomatic and in another three weeks his liver enzymes were normal. The other was a woman with right upper-quadrant pain and jaundice who consumed 150 uncharacterized

chaparral tablets over an 11-week period. Her total bilirubin, transaminases, GGT, and LDH were greatly elevated. After two months her enzymes were nearly normal and several weeks later she was asymptomatic.[28] Prior to this there had been only one reported case of hepatitis associated with chaparral leaf use, a Canadian woman who had taken 15 uncharacterized tablets per day. Her anorexia, nausea, and dark urine disappeared when she reduced the dose to one tablet each day. She experienced a severe relapse when, several weeks later, she increased the dose to seven tablets daily. Upon stopping chaparral her serum chemistries steadily improved over the next four months, though fatigue persisted for one year. After 2.5 years her condition had normalized.[29] Another toxic hepatitis case from using tablets with 160 mg/d for two months was published in 1994.[30]

So few adverse case reports made up to that the time was surprising, since hundreds of tons of this popular herbal remedy had been consumed following a report in 1969 of remission of a melanoma in conjunction with the use of chaparral tea. Research with 59 cancer patients revealed neither anticancer nor hepatotoxic effects from chaparral.[31] Nonetheless, the AHPA recommended that members voluntarily suspend sales of chaparral while commissioning an expert review of the four known hepatic toxicity cases. The panel concluded in 1994 that these were idiosyncratic reactions associated with pre-existing liver conditions. The panel and AHPA recommended the following label warning: "Seek advice from a health care practitioner before use if you have any history of liver disease. Discontinue use if nausea, fever, fatigue, or jaundice occur (e.g., dark urine or yellow discoloration of the eyes)." It also established a reporting mechanism to track problems or concerns.

The *BSH* warns that chaparral should not to be used in large amounts by persons with pre-existing kidney disease and liver conditions such as hepatitis and cirrhosis.[2] A case report of chaparral-associated hepatitis in Australia in 1993 after using two capsules twice daily for eight weeks also was assessed by its authors as idiosyncratic.[32] Part of the rationale for the idiosyncratic explanation comes from a lack of documented hepatotoxic effects in animals.[2] Exhaustive solvent extraction to test chemical fractions of chaparral leaves and twigs on rat hepatocytes in vitro found the phenolic subfraction of the methanolic extract had the lowest observed-effect level, whereas the water extract produced effects only at highly concentrated levels of reconstituted freeze-dried tea.[33] Later, significant inhibition of microsomal phase I and phase II enzymes from rat hepatocytes was shown with high concentrations of the methanol extract.[34]

From the mid- to late-1990s more case reports of hepatotoxicity were attributed to chaparral. By 1997 there had been a total of 13 cases of hepatotoxicity associated with chaparral use in the United States. Five were using other potentially hepatotoxic substances. Chaparral consumption ranged from three weeks to over a year, and all involved ingesting capsules (400-480 mg 1-3 times/d) except the one *MMWR* case with tablets and one case of tea (four tea bags daily for 78 weeks). Signs and symptoms resolved from one to 17 weeks after discontinuation, and a liver transplantation was required in one case after many years of use.[35] In another, a 60-year-old woman taking two capsules daily for 10 months eventually required a liver transplant.[36] Several retrospective cases from 1989 in Canada were published in 1995. A 71-year-old man who consumed nearly a pint of wine daily for years had taken two chaparral capsules daily for three months. Upon developing jaundice, he stopped both, but began the chaparral again five months later. Hepatitis recurred within a month but resolved three months after stopping the chaparral. A woman taking chaparral leaf tablets several times daily developed nausea and jaundice after six and eight weeks, respectively. Stopping the chaparral, she gradually improved and had normal liver enzymes four months later.[37] In 1998 another case of chaparral-induced hepatotoxicity was documented in a young man after 10-12 months of consuming from three to seven 500 mg capsules daily. Liver function stabilized six weeks after the hepatitis was recognized and chaparral use stopped.[38]

While hepatotoxicity is the primary serious adverse effect following prolonged ingestion of chaparral, a case of cystic renal disease and cystic adenocarcinoma also was associated with prolonged consumption of chaparral tea.[39] This is likely due to its component nordihydroguaretic acid (NDGA), which makes up 1.6-8% of the resinous leaves. NDGA was at one time used as an antioxidant food additive. However, the FDA removed it from the list of Generally Recognized As Safe substances following a study with rats in which 1% NDGA in the diet produced cysts in paracecal lymph nodes and kidneys through which it is excreted.[31] Five other non-hepatotoxic cases involving chaparral tea or capsule consumption have been documented, but many complicating factors were involved. The reasons for liver and other toxic effects seem to be related largely to host factors and possibly product form, i.e., encapsulated powdered leaf.[37] Allergic contact dermatitis has been associated with exposure to the chaparral plant.[40]

A retrospective assessment was made that involved 13 patients using low doses of chaparral tincture taken internally, and 23 subjects using topical applications of

its extract in castor oil, as part of individualized naturopathic protocols. No evidence of organ damage was found. Herbal combinations that included 7-18% chaparral tincture were taken orally in significant amounts by five patients (about 1 oz chaparral tincture per month for 1, 3, 4, 5, or 14 months). Four of these patients had complete blood chemistry panels before and after chaparral use, and one was using other potentially hepatotoxic medication. The other eight patients consumed less than 30 mL (1 oz) of tincture over a period of weeks to months.[41] Its use as a tea and poultice by native Americans in the Southwest served as a panacea for infectious and inflammatory problems, respectively.[40,41] The NDGA component has broad-spectrum antimicrobial activity and is a powerful lipoxygenase inhibitor. In addition, other components are antiviral. Hydroalcoholic tinctures are more effective than traditional teas at extracting resin components, including phenolics and NDGA.[40] The unextracted leaves have been most commonly associated with adverse effects.[37] For short-term internal use, these liquid chaparral extracts should be safe to help reduce local inflammation and symptoms associated with colds, enteritis, diarrhea, and urinary tract infections.[40]

3. Kava (*Piper methysticum*) roots and rhizomes

CR designated kava as very likely hazardous, and the FDA issued a warning to customers in March 2002 about its association with severe liver toxicity.[1] In 2001, three such case reports in Europe followed use of kava extracts made with organic solvents. In Switzerland a man had used 3-4 capsules daily for two months of a concentrated acetone extract providing 210-280 mg kava lactones. He had a 60- to 70-fold increase in serum liver transaminases and elevated GGT, LDH, and bilirubin. After transplantation his excised liver appeared atrophic with severe necrosis.[42] Another case in Switzerland involved the same acetone extract taken by a woman with 210 mg lactones daily for three weeks, followed by intake of 60 g of alcohol in one day. Serum elevations of liver transaminases, bilirubin, and alkaline phosphates were 60-, 15- and three-fold, respectively. Biopsy identified bridging necrosis and other impairments, but enzyme levels returned to normal eight weeks after discontinuing the extract.[43] In Germany, a woman developed jaundice, fatigue, and weight loss over several months while using an alcoholic extract of kava. With elevated bilirubin and transaminases and extensive hepatic necrosis indicative of progressive liver failure, she was given a liver transplant.[44]

Following the FDA action in 2002, a summary of the 27 case reports made to authorities in Germany and Switzerland was published in America along with assessments of these made by the British Medicines Control Agency. According to the British agency, none of the reports could be correlated to kava with certainty, 12 were unlikely or unassessable, and 15 were probably or possibly due to kava products. Of the 15, 12 (including all four transplant cases) involved conventional medicines with hepatotoxic potential and another two were directly associated with high alcohol consumption. In all, there were six positive dechallenges and two positive rechallenges. According to Swiss health authority estimates, the incidence of reported kava hepatotoxicity cases is one per 170,000 30-day courses of treatment.

An expert toxicological review commissioned by the AHPA was submitted by Donald Waller, PhD, professor of pharmacology and toxicology at the University of Illinois-Chicago. He concluded that kava products taken in appropriate doses for a reasonable time had no scientifically established potential to cause liver damage. He did acknowledge that idiosyncratic reactions and drug interactions were possible. Consequently, AHPA advocated a kava label warning that reads in part: "U.S. FDA advises that a potential risk of rare, but severe, liver injury may be associated with kava-containing dietary supplements. Ask a health care professional before use if you have or have had liver problems ... or are taking any medication. Stop use and see a doctor if you develop symptoms that may signal liver problems ... . Not for use by persons under 18 years of age, or by pregnant or breastfeeding women. Not for use with alcoholic beverages."[45] In addition, the AHPA's *BSH* advises to not exceed the recommended dose.[2]

An independent 2003 review discussed the 19 hepatotoxicity cases that the German regulatory authority concluded were associated with the use of kava products and used as the basis for banning them. This assessment also considered the Medicines Control Agency report and indicated that there was only a single well-documented case report that showed a clear association with kava extract monotherapy and recurrent transaminase increases. Another case showed a possible causal relationship, 12 were not definitively assessable, and five were not probable. Most reports were based on evidence of a temporal, rather than causal, relationship between kava extract intake and toxic hepatitis.[46] A meta-analysis of seven randomized controlled trials (six German, one American) with concentrated kava acetone or alcoholic extracts (60-240 mg kava lactones daily) for anxiety found them superior to placebo for relief of symptoms. Among the 298 patients in five studies of four weeks or longer, the adverse events reported from the extracts were stomach complaints, restlessness, drowsiness, tremor, headache, and tiredness among 11 patients.[47] In

November 2002, *MMWR* described two people in the United States who underwent liver transplantation after using kava-containing products according to label directions for several months.[48] An Australian case reported in 2003 described one person's death after consumption of a kava extract combination product for three months.[49]

A study comparing relative usage of kava root water extracts among 73 Australian aboriginals, many of whom formerly abused alcohol, found that heavy and very heavy users (average consumption, 310 and 440 g/wk of extracted root, respectively) had greatly elevated GGT levels. There was also a high carriage rate of hepatitis B surface antigen.[50] A recent study of abusive consumption of water extracts by aboriginals (average consumption, 205 g of kava powder over 14.4 hours) leads to cognitive impairment and elevated GGT and alkaline phosphatase.[51] In one case, generalized choreoathetosis followed kava bingeing.[52] Only two cases of hepatitis following consumption of traditional water extracts of kava were reported with patients of Oceanian origin. One person used kava for four weeks, but also had a history of long-term use of other medications including phenobarbital. The other consumed about 18 g of kava lactones per week for five weeks. Both recovered and laboratory values were normal within three months. A survey of heavy kava drinkers in New Caledonia found 27 subjects who had drunk water extracts of kava for at least five years, averaging about 32 g of kava lactone intake per week (70 mg/kg daily). Three had elevated transaminases, and 23 showed increased GGT. None had overt symptoms of liver disease.[53] On the island of Pohnpei in Micronesia where ingestion of kava fresh root juice/water extract is common but hepatitis is not, the average estimated kava lactone consumption per sitting is 2.4 g.[54]

Studies using aqueous extracts in rats at kava lactones dosages of 200 or 500 mg/kg/d for two or four weeks found no liver enzyme elevations. In some cases they were significantly reduced.[55] Mice fed 100 mg/kg/d kava lactones for 11 days showed no signs of liver injury but had increased liver weight and cytochrome P450 content.[53] A study of piperine alkaloids from kava stem peelings showed structural features indicative of potential hepatotoxicity. Though these compounds were not found in commercial root powders from Hawaii, Fiji, or Tonga, the stem peelings have reportedly been sold as raw material for extraction to the pharmaceutical industry.[56]

Whether it is using organic solvents instead of water or stem components rather than pure root that is responsible for potential hepatotoxicity cases remains to be demonstrated. Idiosyncratic reactions or herb/drug pharmacokinetic interactions are other possible explanations. For short-term monotherapy to help manage acute situational anxiety or promote relaxation, kava seems to be a safe and appropriate intervention. Regular use with alcohol or other medications is not recommended.

4. Androstenedione

CR also designated androstenedione as very likely hazardous, and in March 2004 the FDA warned 23 companies to stop its manufacture, marketing, and distribution.[1] Unlike the herbal dietary supplements, this product is marketed as an isolated compound for use as a testosterone precursor. Normally produced in the adrenals and gonads, endogenous androstenedione is enzymatically converted into testosterone. The common rationale for use at doses of 100-300 mg/d is to enhance muscle development and strength for improved sports performance. As a result, it has been banned by many amateur and professional athletic organizations. The risk of adverse effects including gynecomastia is associated in part with its potential influence on sexual hormone production.[57] Increased risk of sex hormone-dependent cancers is another concern.[1]

A randomized controlled human trial with 20 normotestosterogenic young men examined the effects over time of androstenedione's ability to influence hormone levels and muscle development. A 300 mg daily dose was consumed while undergoing resistance training for eight weeks. Compared to baseline values, serum testosterone was not affected, but estradiol and estrone levels were higher after two, five, and eight weeks. Muscle strength and lean body mass were no better than with placebo, but serum HDL cholesterol was reduced over two, five, and eight weeks.[58]

A randomized, placebo-controlled double-blind study using 100 mg/d for 12 weeks in healthy weight-training men found no adverse effects on PSA, liver enzyme, or lipid levels, but neither did it increase strength, lean body mass, or testosterone levels.[59] An open-label seven-day trial compared the effects of 100 mg, 300 mg, or placebo on hormone levels in healthy men who were not engaged in bodybuilding. Testosterone levels 24 hours after the final dose were no different than baseline. However, 300 mg significantly increased serum testosterone area under the curve (AUC), whereas 100 mg and placebo did not. Both 100 mg and 300 mg doses increased estradiol AUC significantly, compared to placebo.[60] The peripheral conversion rate of androstenedione to testosterone is about 14% in both women and men, but for women the converted hormone accounts for about one-half of circulating androgens.

To study the testosterone effect in young women (ages 20-32 years) taking oral contraceptives, a double-blind crossover trial administered a single capsule of

100 mg androstenedione and placebo after a two-week washout. Testosterone increase from androstenedione was significant from 15 minutes to eight hours inclusive, compared to placebo. This suggests a high risk of virilization with prolonged use in healthy women.[61]

Since androstenedione is intended for long-term use, the adverse effects associated with its hormonal influence cannot be avoided by restricting its duration. The highly competitive nature of sports makes it a subject of potential abuse through excessive dosing. Due to concern over these issues, androstenedione and more potent anabolic steroids have come under recent Congressional scrutiny. On June 3, 2004, the U.S. House of Representatives overwhelmingly voted (408-3) to ban over-the-counter sales of steroidal precursors such as androstenedione. The bill would double penalties for manufacturing or distributing these products near a sports facility. Similar legislation is pending in the Senate. These bills are designed to help protect the integrity of competitive sports, but especially to stop children from imitating sports heroes and putting themselves at greater risk during their developing years.[62] Such legislation would mark the end of unlimited legal access to purified steroidal precursors in America and would abort speculation about the risk of androstenedione to public health in this country, much as the concern over ephedra has abated here.

Appropriate Limitations of Botanical Products of Risk

The items discussed here, described by *CR* as definitely hazardous or very likely hazardous, have greater or lesser risks based on the extant evidence. While some are best avoided altogether, others remain useful within the context of reasonable limitations. Herbs like *Aristolochia* species containing aristolochic acid are a proven liability to kidney function with associated carcinogenic effects for which safe levels of consumption or exposure have not been established. Likewise, germander contains identifiable diterpenoids that unequivocally produce hepatotoxicity with regular use. Even short-term or topical applications would seem unwise, there being little rationale for use of these herbs.

Comfrey seems, like any other PA-containing herb, worthy to be avoided, yet its short-term topical application to promote healing has a strong tradition. The water extract of comfrey leaf retains only a low level of these hepatotoxic PAs, such that its use has greatly reduced risk if applied to unbroken mucosal surfaces. Prolonged use of any form should be avoided. Chaparral has no identifiable component that has proven hepatotoxic, but ingestion of the whole leaf appears to present a risk with long-term use that is not documented with local use or short-term ingestion of the tincture or tea. Kava root and rhizome is another example where the traditional water extract appears to be the safest form. Whether the whole root or concentrated chemical solvent extracts are inherently hepatotoxic or potentiate drug adverse effects, or whether contamination with alkaloids from aboveground plant is responsible, remains to be discovered. For all kava and chaparral preparations, only short-term consumption is advisable. Requiring clear label instructions and warnings would provide a means for making use of these botanical products safer.

For androstenedione, the increase in circulating sex hormones presents potential risks to normal fetal and adolescent development, opposite gender effects in men and women, and a potential for promoting sex hormone-dependent cancers. Rather than requiring label warnings for this substance that is prone to widespread abuse, the government seems poised to reduce these risks by ending its legal marketing. ❖

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Clinical Briefs

With Comments from Russell H. Greenfield, MD

Antibiotics for Cardiovascular Disease Prevention?

Source: Brown DL, et al. Clinical and biochemical results of the metalloproteinase inhibition with subantimicrobial doses of doxycycline to prevent acute coronary syndromes (MIDAS) pilot trial. *Arterioscler Thromb Vasc Biol* 2004;24:733-738.

Goal: To determine whether low-dose doxycycline reduces vascular inflammation, matrix metalloproteinase (MMP) activity, and improves short-term clinical outcome.

Design: Prospective, randomized, double-blind, placebo-controlled pilot trial.

Subjects: Fifty patients admitted to a single center with symptomatic coronary artery disease, 24 randomized to placebo and 26 to subantimicrobial doses of doxycycline (SDD).

Methods: Patients randomized to receive SDD took 20 mg doxycycline orally twice daily for six months. Subjects were interviewed or examined at three months, then contacted at the end of six months regarding clinical events. Clinical endpoint was a composite of sudden death, fatal or nonfatal myocardial infarction, or troponin-positive unstable angina. Markers of inflammation, including CRP and various interleukins, were measured at study entry and completion for a subset of patients willing to return for phlebotomy.

Results: At six months, high-sensitivity CRP was reduced by 47% in the SDD group as compared to the placebo group, where there was little change from pretreatment values. Plasma levels of MMPs did not differ pre- and post-trial, but zymographic (in vitro) assessment of MMP activity revealed a 38% decrease from baseline values in the SDD group (no change noted in the placebo group), and a 55% reduction after six months of treatment as compared with placebo. Clinical endpoints were rare, and the composite endpoint did not differ significantly between groups.

Conclusion: Treatment with SDD in subjects with established coronary artery disease lessens markers of inflammation, and so may help stabilize atherosclerotic plaque.

Study strengths: Eager to avoid confounding factors such as the treatment of *Chlamydia pneumoniae*, the researchers used a subantimicrobial dose; no subject was lost to clinical follow-up.

Study weaknesses: Twenty out of the 50 subjects randomized did not return for biochemical analysis at the end of the trial; no assessment made of compliance with regimen; use of additional medication was at the discretion of the attending physician and could conceivably have included other anti-inflammatory agents; the authors readily point out that their study

was inadequately powered to detect differences in clinical outcomes associated with SDD therapy.

Of note: A total of 230 people were screened, but only 50 were randomized to participate in the trial (all of whom underwent angiography, and most of whom underwent angioplasty); IL-6 levels also were reduced compared with pretreatment levels in the SDD group, but levels were not significantly different between the two groups at trial's end; there were two clinical events in the SDD group and none in the placebo group; subantimicrobial doses of doxycycline can enter arterial walls and inhibit cytokine and protease mediators of inflammation, and directly inhibit MMP.

We knew that: Vulnerable atherosclerotic plaque shows signs of significant inflammation, including the buildup of macrophages that are capable of secreting MMPs that degrade collagenous components of the fibrous cap, leading to rupture and thrombosis; increased levels of MMP-9 have been correlated with plaque rupture; recent trials suggest that treatment against *C. pneumoniae* does not reduce the incidence of coronary events; doxycycline has been shown to lessen expansion of abdominal aortic aneurysms.

Clinical import: While many have considered participation of pathogens in the development and progression of coronary artery disease, in this intriguing study the authors explore the use of subantimicrobial doses of a widely available, affordable medication (doxycycline) to lessen vascular inflammation. Why discuss this paper in *Alternative Medicine Alert*? Because the implications are enormous. What if the same study were performed using an anti-inflammatory diet instead of an antibiotic? Is there cause to administer probiotic therapy along with SDD? Could herbal anti-inflammatory agents offer similar biochemical results? And with much of the excitement having died down about microbes potentially contributing to ischemic heart disease, would it not be remarkable if an antibiotic proved beneficial in preventing acute coronary events? Alas, this pilot trial does not answer that question, but it does inspire the larger trials to come that will focus primarily on clinical outcome.

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CME Questions

CME Instructions: Physicians participate in this continuing medical education program by reading the articles, using the provided references for further research, and studying the CME questions. Participants should select what they believe to be the correct answers, then refer to the list of correct answers to test their knowledge. To clarify confusion surrounding any questions answered incorrectly, please consult the source material.

After completing this activity, participants must complete the evaluation form provided at the end of each semester (June and December) and return it in the reply envelope provided to receive a certificate of completion. When an evaluation form is received, a certificate will be mailed to the participant.

35. The case of aristolochic acid illustrates the danger of relying on common names that can be shared by unrelated plants and may result in mistaken substitution.
a. True
b. False

36. The adverse effects associated with germander:
a. have been documented by positive rechallenge.
b. appeared clinically as weakness accompanied by jaundice.
c. may be most harmful upon re-introduction.
d. All of the above

37. With regard to comfrey, relative toxicity can vary greatly from one species and plant part to another.
a. True
b. False

38. The FDA recently warned companies to stop manufacturing, marketing, and distributing which of the following products?
a. Kava
b. Comfrey
c. Androstenedione
d. Chaparral

Answers: 35. a, 36. d, 37. a, 38. c.

In Future Issues:

Vitamin E and Cardiovascular Disease

Fenugreek for Hyperlipidemia

Probiotics to Treat Acute Diarrhea

Vitamin B and Magnesium for Migraine

Supplement to *Alternative Medicine Alert*
August 2004

ALTERNATIVE MEDICINE ALERT™
A Clinician's Evidence-Based Guide to Alternative Therapies

Did the Ephedra Ban Mark a New Era of Dietary Supplement Regulation at the FDA?

IN THE WEEKS SURROUNDING THE BAN OF EPHEDRA, WHICH TOOK EFFECT ON APRIL 12, IT appears that the Food and Drug Administration (FDA) has stepped up efforts to monitor the dietary supplement industry and enforce the Dietary Supplement Health and Education Act of 1994 (DSHEA). With the stated goals of making more and better information about foods and dietary supplements available to American consumers and protecting consumers from products bearing false or misleading claims, the FDA seems to be laying groundwork for the possibility of additional product bans and support for more restrictive legislation.

Below is a selection from recent FDA press releases, documenting the increased attention the dietary supplement industry is receiving. For more information on any of these releases, please visit the FDA web site at: www.cfsan.fda.gov/~lrd/press.html.

FDA outlines science-based plan for dietary supplement enforcement

Speaking before the American Society for Pharmacology and Experimental Therapeutics and the American Society for Nutritional Sciences, Lester M. Crawford, DVM, PhD, Acting Commissioner of the FDA, outlined on April 19, 2004, the agency's science-based approach to protecting American consumers from unsafe dietary supplements.

Crawford said the agency would soon provide further details about its plan to ensure that the consumer protection provisions of DSHEA are used effectively and appropriately. Through DSHEA, which sets up a distinct regulatory framework for dietary supplement products, Congress attempted to strike a balance between providing consumers access to dietary supplements and giving FDA regulatory authority to act against supplements or supplement ingredients that present safety problems, are marketed with false or misleading claims, or are otherwise adulterated or misbranded.

"FDA is absolutely committed to protecting consumers from misleading claims and unsafe products," said Crawford. "Unlike most foods, some dietary supplements are pharmacologically active. And we have seen over the last 10 years a huge growth in the dietary supplements industry, including the introduction of products that seem far removed from the vitamins and minerals of the pre-DSHEA days. We have become increasingly aware of the potential health problems some of these products pose."

Over a period of six months, FDA has inspected 180 domestic dietary supplement manufacturers; sent 119 warning letters to dietary supplement distributors; refused entry to 1,171 foreign shipments of dietary supplements; and seized or supervised voluntary destruction of almost $18 million worth of mislabeled or adulterated products. "We will continue to aggressively enforce DSHEA against unsafe or mislabeled products," Crawford said.

Over the next several months FDA will provide additional information to explain and implement the tools available to the agency under DSHEA to act against unsafe supplements and false or misleading supplement labeling claims.

FDA is also developing regulations for industry on good manufacturing practices. When finalized, this rule, proposed in the spring of 2003, will help protect consumers from dietary

supplements that contain impurities or contaminants as a result of how they are manufactured or handled.

In addition, FDA is more closely scrutinizing dietary supplement labeling. Dietary supplement labels cannot claim the supplement will treat or cure a disease, and since December 2002 FDA has worked with the Federal Trade Commission to challenge false claims of supplement effectiveness for treating a range of diseases.

To support its consumer protection actions, the agency is developing approaches to systematically review the evidence about the safety of individual dietary supplements. FDA expects to evaluate the available pharmacology, published literature (including animal, in vitro, epidemiological, and clinical trial data), evidence-based reviews, and adverse event information—the approach that formed the scientific foundation for FDA's recent rulemaking on ephedra.

FDA warns distributors of dietary supplements promoted on-line for weight loss

On April 1, 2004, the FDA sent warning letters to 16 dietary supplement distributors making false and misleading claims for weight loss products promoted over the internet.

"Obesity in America is at epidemic proportions, and we will not tolerate companies making false claims promising easy fixes," Health and Human Services (HHS) Secretary Tommy G. Thompson said.

Many of these products claim to block starch, carbohydrates, and fat calories, while allowing consumers to lose weight without any changes in lifestyle. "These products give unfounded hope to people who are attempting to lose weight. False and misleading claims have significant health consequences to individuals that may be overweight because these products do not produce the desired results," said Crawford. "FDA will continue to enforce the law and pursue products that lure consumers with unsubstantiated weight loss claims."

Although dietary supplement labeling may include claims about the supplement's effect on the structure or function of the human body, the law requires that structure/function claims must have substantiation and be truthful and not misleading. After reviewing the claims of the various products, FDA concluded that claims being made regarding these products are not supported by reliable scientific evidence.

FDA requested a response from the firms in writing within 15 days of receipt of the warning letters stating the action the firms will take to correct the noted violations and to ensure that similar violations do not occur in the future.

HHS launches crackdown on products containing androstenedione

On March 11, 2004, HHS Secretary Tommy G. Thompson announced a crackdown on companies that manufacture, market, and distribute products containing androstenedione ("andro"), which acts like a steroid once it is metabolized by the body and therefore can pose similar kinds of health risks as steroids. These products are generally advertised as dietary supplements that enhance athletic performance based on their claimed anabolic and androgenic properties to stimulate muscle growth and increase production of testosterone.

As part of the crackdown, the FDA sent warning letters to 23 companies asking them to cease distributing dietary supplements that contain androstenedione and warning them that they could face enforcement actions if they do not take appropriate actions.

"While andro products may seem to have short-term benefits, the science shows that these same properties create real and significant health risks," said FDA Commissioner Mark B. McClellan, PhD, MD. "While the products are advertised to athletes, they have the potential to get into the hands of our impressionable youth who may believe these products will help their development. Anyone who takes these products in sufficient quantities to build muscle or improve performance is putting himself or herself at risk for serious long-term and potentially irreversible health consequences. There is no proven safe substitute for hard work and training when it comes to improving athletic skill ... ."

Secretary Thompson also encouraged Congress to pass legislation sponsored by Senators Orrin Hatch and Joe Biden and Representatives James Sensenbrenner, John Sweeney, and John Conyers, Jr., that would classify andro-containing products as a controlled substance. Such legislation would enable the U.S. Drug Enforcement Agency (DEA) to regulate these types of products as anabolic steroids under the Controlled Substances Act. HHS and DEA are providing technical assistance to the Senators and Congressmen as they pursue such legislation.

FDA will determine whether further actions are necessary if firms refuse to cease distribution of these products. Such actions could include seizing violative product as well as pursuing injunctions or seeking criminal sanctions against persons who violate the law.