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# Risks of Herbal Remedies: More of the Bad and the Ugly

Richard B. Philp, *University of Western Ontario*

## Introduction

Previously (Philp, 2004a) the subject of adverse effects and drug interactions of herbal remedies was discussed. Clinical reports and results of trials continue to emerge, often casting doubt on the efficacy and/or safety of some herbal remedies. New risks for old herbs also have been reported. The present work attempts to update this subject by reviewing the some of recent scientific literature.

## Effects of Herbs on Laboratory Diagnostic Tests

An area of increasing concern is the potential for herbal agents to disrupt laboratory diagnostic procedures, causing false positive or false negative results. This is especially problematic as patients often fail to report their herbal consumption to medical personnel. Dasgupta and Bernard (2006) reported on some of these problems. The Chinese medicine *Chan Su* or *Dan Shen* can interfere with the antibody used in the immunoassay of serum levels of digoxin, leading to falsely low or high results. Chinese herbal products are sometimes contaminated with prescription medications leading to confusing findings in laboratory assays. Since the liver is the site of metabolism for many drugs, herbal remedies that can cause liver damage (kava-kava, germander, chapparral etc.) can interfere with that metabolism and cause elevated blood levels of the drugs.

## Effects on Drug Metabolism

Obviously laboratory tests measuring the plasma levels of drugs would be affected if their rate of metabolism is accelerated. The ability of the herbal antidepressant St. John's wort to increase the clearance of drugs by up-regulating the CYP450 drug metabolizing enzymes was discussed previously (Philp, 2004a). The list of interactions with this herbal agent keeps growing. Huang et al. (2004) reported the findings of a conference supported by the American Society for Clinical Pharmacology and the US Food and Drug Administration. It was noted that St. John's wort reduced the plasma levels of numerous drugs including the antiviral indinavir, the immunosuppressive agent cyclosporine and the cardiac drug digoxin. Interactions with oral contraceptives have also been reported (breakthrough bleeding and pregnancy) as well as with sildenafil (Viagra<sup>®</sup>, loss of efficacy) and other drugs. Grapefruit juice and echinacea have the opposite effect by inhibiting the CYP3A isozyme leading to reduced metabolism of calcium channel blockers and other drugs (components of grapefruit juice) and tolbutamide (echinacea). Many drugs are metabolized by CYP450 isozymes and echinacea and grapefruit juice should be avoided when prescription drugs are being taken. Tirona and Bailey (2006) recently reviewed herb-induced accelerated drug metabolism and

discussed the mechanisms whereby levels of drug metabolizing enzyme proteins can be increased. Experimental evidence that herbal agents can induce these enzymes has now been shown for American ginseng, ginkgo biloba, garlic, devil's claw and the Chinese herbal remedies Wu Wei Zi and Gan Cao (Mu et al, 2006). Tirona and Bailey (2006) point out that health care professionals may still neglect to recognize the potential for adverse effects resulting from herbal-drug interactions.

### Herbals and Diabetes

Johnson et al. (2006) studied the use of anti-diabetic herbal remedies by Hispanic women with type II diabetes. Twenty-three subjects were interviewed and the charts of 81 others were reviewed but they were not interviewed. Of the interviewed patients 21/23 (91%) reported using at least one herbal remedy. Among the charts reviewed, 6.7% contained reports of use of diabetes-specific herbs and 15.4% documented general herb use. Seventy-seven different herbs were identified, most as part of mixtures or supplements. The authors concluded that while some herbs may have potential for benefit or for adverse effects or interactions in diabetic patients, they did not see evidence of either positive or negative effects in the study group. Thus although there was no evidence of additional benefit over conventional therapy alone, neither was there evidence that they interfered with it.

### Glycyrrhizin-Containing Herbals and Pseudoaldosteronism

The possibility that licorice could interfere with hormonal function due to its glycyrrhizin content was discussed in Philp (2004a). Glycyrrhizin, however, can appear in other products, often without the knowledge of the consumer. Iida et al. (2006) described a case of a 77-year old man with a history of hypertension and hyperuricemia being treated with the angiotensin converting enzyme (ACE-I) inhibitor enalapril. He was also taking a Chinese herbal remedy for allergic rhinitis and, about six months before admission to hospital he had begun taking another Chinese herbal for chronic constipation. He was admitted to hospital with limb weakness, persistent constipation and worsening hypertension. Laboratory blood and urine tests revealed marked hypokalemia (low blood potassium) and metabolic alkalosis both associated with excessive urinary loss of potassium and chloride. A diagnosis of pseudoaldosteronism was made and it was assumed that the Chinese herbal remedies contained enough glycyrrhizin to produce aldosterone-like effects. The Chinese herbals were discontinued and potassium supplementation normalized the electrolyte imbalance and relieved all the symptoms in a short time. The authors also concluded that the ACE-I inhibitor retarded the development of pseudoaldosteronism as the problem only emerged after the dose of enalapril was reduced from 20

mg to 10 mg. Thus another possible drug interaction has been identified. Several Chinese herbals contain glycyrrhizin (Philp, 2004b).

### Chinese Herbal Nephropathy

As previously discussed (Philp, 2004b) *Aristolochia* species are common world-wide and several members exist in North America. Snakeroot (*A. serpentaria*) is one of these and it has been used as a folk remedy for centuries. The ingredient aristolochic acid has been known for some time to cause a specific form of nephropathy and because it occurred most often in association with Chinese herbal remedies it became known as “Chinese herbal nephropathy”. Despite this knowledge, new cases continue to be reported. Yang et al. (2006) describe the case of a 49-year old man who developed subacute renal failure after ingesting the Chinese herbal remedy Xi Xin, which contains aristolochic acid. The authors point out that this is a common ingredient in traditional formulae and they recommend that it should be forbidden for use in such remedies to avoid its harmful effects.

### Misguided Overdose

Broom bush (*Retama raetsm*) is a plant indigenous to the arid dunes of the Middle East. It has been used by Bedouins and other local groups as a folk remedy, being applied as an ointment to wounds and inhaled for rheumatic problems and to induce abortion (Schmid et al. 2006). These authors describe a case of a seven day old baby boy who was brought to the emergency department of the Shaare-Zedek Medical Center in Jerusalem with a history of having been lethargic and cyanotic for one hour. Respiration was shallow and he was mildly jaundiced. A urine toxicology screen was negative for several central nervous depressants and stimulants. On questioning, the parents, who were orthodox Jews, revealed that they had given the infant 20 mL of a herbal preparation called “azfar” a few hours before admission. In Arabic, azfar means yellow and azfar, prepared as a tea from broom brush, is used as a treatment for neonatal jaundice. The parents wished to have the child jaundice-free so that ritual circumcision could take place on the eighth day of life as prescribed by Jewish tradition. Broom bush tea is normally given to the nursing mother to treat neonatal jaundice but the folk healer prescribed three drops of diluted tea to be given to the infant. Instead, the parents administered 20 mL, apparently thinking that more was better and would accelerate the cure. The infant thus received about 7000 times the dose recommended by the folk herbalist. Broom bush is rich in quinolizidine alkaloids, many of which are toxic, including ones that are cardiotoxic and that block autonomic ganglia. The infant responded to symptomatic treatment including assisted respiration via intubation and he was discharged after two days.

## Hypersensitivity Reactions

Any plant or plant product is capable of inducing an allergic reaction in a sensitive individual and herbal remedies are no exception. In a previous publication (Philp, 2004c) it was noted that members of the *Compositae* family, the source of many herbal agents, have a propensity to cause contact dermatitis. Hong and Chang (2006) described a case of localized, contact dermatitis following the use of an ointment containing *Alpinia galanga* (also known as spice ginger, not a *Compositae*) that progressed to generalized erythema multiforme-like eruptions. Skin patch tests confirmed that this popular Southeast Asian spice contained an allergen.

Allergic reactions may be more generalized and more serious. Berrin et al. (2006) described a case of a 28-year-old Turkish man who had consumed, in Swedish syrup, a mixture of herbs that included *Pimpinella anisum*, *Rosmarinus officinalis*, *Aloe ferox miller*, and *Matricaria chamomilla*. This mixture was purchased from an herb seller to treat dyspepsia. Thirty minutes after ingesting this mixture he developed severe cramps in the legs, dyspnea, diarrhea, vomiting and sore throat and he was admitted to an Istanbul hospital with signs of angioedema. Markedly elevated serum enzymes indicated breakdown of muscle tissue. Acute renal failure and cardiotoxicity developed about 12 h after admission. The complex clinical picture presented by this patient was in part a hypersensitivity reaction complicated by unrelated organ toxicity. The possibility that the renal failure was due to the presence of aristolochic acid was discussed but this could not be confirmed.

## Photosensitizing Herbs and PUVA

Many plants, some used as herbal remedies, contain psoralen and are thus capable of causing phytophotodermatitis (Philp, 2004d). Recently, however, a clinical study showed that St. John's wort (SJW), considered to be a photosensitizing plant due to its content of hypericin, was capable of increasing the sensitivity of patients to ultraviolet A1 during PUVA (psoralen-UVA) therapy. Eleven subjects took SJW for 10 days and erythema in response to high output UVA1 was compared before and after the course of SJW. Although the slope of the dose response curve to UVA1 was unchanged, the threshold was lowered. Herbal preparations capable of causing photosensitivity should be discontinued well before undertaking PUVA treatments (Beattie et al. 2005).

## Herbal Remedies in Pregnancy

There has been some debate over the safety of herbal remedies in pregnancy. Marcus and Snodgrass (2005a) review evidence that some

herbal remedies may be teratogenic. A case is discussed in which a mother was advised to drink blue cohosh to induce labor and the newborn developed seizures from an infarct of the middle cerebral artery. Blue cohosh has been associated with myocardial infarction in another neonate whose mother had also consumed blue cohosh tea prior to giving birth. The authors note that some botanicals (none herbal remedies) notably hemlock, hellebore and tragacanth, have been shown to be teratogenic in animals.

Ginger (*Zingiber officinale*) has been touted as a safer alternative to anti-emetic drugs for morning sickness. Marcus and Snodgrass (2005a) cite a recent clinical trial that showed ginger to be as effective as vitamin B6 in controlling morning sickness. The authors review substantial evidence that ginger has many pharmacological effects that would be undesirable in pregnant women. These include NSAID-like actions on cyclooxygenase and 5-lipoxygenase, inhibition of platelet function and blood coagulation, and possibly gastrointestinal ulceration. The authors quote a recommendation of the Teratology Society to the U.S. Food and Drug Administration that states “Dietary supplements cannot be considered safe for the embryo or fetus” and “---should not be labeled for use in pregnancy unless they have been shown to be safe by standard scientific methods”. Fugh-Berman et al. (2005) counter these arguments, essentially stating that ginger is as well-studied as most anti-nausea preparations and has been shown to be no more hazardous than them. They point out that the adulteration of some herbals mentioned by Marcus and Snodgrass does not mean all of them are so adulterated.

These arguments beg the question of risk vs. benefit although the authors concede that few herbal agents have been subjected to thorough testing for efficacy and safety. In their response, Marcus and Snodgrass (2005b) point out that “The need for greater oversight of the safety of herbal medicines has been noted by the Inspector General of the Department of Health and Human Services, the Institute of Medicine of the National Academies of Science and several organizations of health professionals”.

#### Adulterants in Herbal Remedies

Adulterants are generally added to herbal remedies for one of two reasons. A conventional, usually prescription, medication with the pharmacological properties claimed for the herbal remedy may be added to conceal its lack of efficacy. Thus Marcus and Snodgrass (2005a) document examples where sildenafil (Viagra®) or tadalafil (Cialis®) have been added to “natural” treatments for erectile dysfunction, diethylstilbestrol, indomethacin and warfarin were present in PC-SPEs, an “herbal” preparation for treating prostate cancer. The company that marketed this product sold eight others also shown to contain prescription medications. In 1988 the Texas Department of Health investigated

Chinese medicines manufactured in Hong Kong and sold (illegally) as “chuífong yokuwan”. They found that the tablets contained diazepam, indomethacin, hydrochlorothiazide, mefenamic acid, dexamethasone, as well as lead and cadmium (Philp, 2001).

Several authors have pointed out that folk remedies, especially from India and Africa, often contain heavy metals that are added deliberately in the mistaken belief that they possess healing powers. Lead, mercury and arsenic are added in large quantities to herbals, mainly Ayurvedic herbal medicines from India (Lynch and Braithwaite, 2005). Obi et al. (2006) purchased a random sample of ready-made herbal products from an open market in Nigeria and analyzed them for their content of copper, iron, nickel, selenium, zinc, lead and mercury and found that 100% of the samples had elevated amounts of heavy metals. Van Schalkwyk et al. (2006) reported eight cases of lead poisoning (plumbism) in the Auckland region of New Zealand. In all cases the poisoning resulted from the use of Ayurvedic medicines. Blood lead levels were 1.5-6.9 micromol/L. Six had symptomatic lead poisoning requiring chelation therapy.

Metals may find their way naturally into herbal agents. Steenkamp et al. (2005) analyzed 30 herbal remedies in South Africa for uranium content as that country has large mineral deposits and uranium is a byproduct of gold production. Eight samples had levels below the limit of detection but five had greatly elevated levels above 40,000 ppb. The mean content of the rest was about 15,000 ppb. Levels would obviously depend on the area from which the botanicals were harvested.

## Conclusions

Despite the increasing popularity of herbal medicines and the efforts of governments in developed countries to exert some control over their quality, unregulated mixtures of dubious purity continue to find their way onto the market. Adverse effects resulting from adulteration with potent prescription drugs or toxic metals are not restricted to emerging nations.

Another area of great concern is the possibility that an herbal remedy may alter the clearance of a prescription medication. The list of herbal agents capable of doing this is growing. People who are ill may be tempted to self-medicate with herbal remedies while taking their prescription medications with disastrous consequences.

It would seem prudent for pregnant women to avoid the use of herbal agents. Debate may continue regarding the relative safety of ginger versus conventional anti-nausea drugs but there seems little doubt that other herbal agents offer no significant benefits and considerable potential risks.

Herbal “prescriptions” by herbalists may be given verbally, possibly without any cautionary notes that would equate with the literature

usually handed out by pharmacists when a prescription is filled. This can lead to misunderstandings and overdosing with toxic consequences. Prescribing complex mixtures or several herbs to be taken by the individual appears to increase the risk of an adverse reaction.

Herbal remedies may interfere with laboratory tests, damage the kidneys, cause hypersensitivity reactions, produce pseudoaldosteronism, or interfere with phototherapy.

The frequency of adverse effects with herbal products may be quite low taken as a percentage of the total exposed population but the lack of convincing evidence of benefit in most cases suggests that the risk-benefit equation for them is not favorable.

One final note; it seems clear that millions, perhaps billions, of tax and research dollars will eventually be spent on researching the safety and efficacy of herbal remedies. Despite the likelihood that some useful medications will derive from this research, one cannot help but wonder if greater benefits to health care would have been generated if this money had been spent on conventional medical research.

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