

Herbal medicines: Poisons or potions?

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Plants have played a significant role in maintaining human health and improving the quality of human life for thousands of years. In botany, herbs refer to seed-producing plants with nonwoody stems that die at the end of growing season. In herbal medicine, the term herb is used loosely to refer not only to seed-producing plants but also bark, roots, leaves, seeds, flowers, and fruits of trees. Herbs have been used as food and for medicinal purposes for centuries. According to the World Health Organization, about 80% of world's population relies on traditional medicine for their primary health care needs, and most of this therapy involves the use of plant extracts or their active components.

There has been a tremendous resurgence in the interest and use of herbal products, especially in the United States. Surveys of plant and medicinal usage by the American public have shown an increase from 3% of the population in 1990 to over 12% in 1997.¹ Herbal products, in the past available only at health food stores and gyms, are now sold by popular retailers such as Wal-Mart and supermarkets. An estimated \$2 billion was spent in 1996 for herbs in bulk, as well as capsules, tablets, extracts, and teas.² The sale of herbal products reached over \$3.5 billion in 1999.

REASONS FOR USE OF HERBS

There are many reasons why people use herbs and other alternative therapies. Often cited is a "sense of control," a mental comfort for taking action. Natural products are also perceived to be healthier than manufactured drugs. In addition, there is dissatisfaction with conventional medicine. Patients feel that their doctors 1) do not listen to or respect cultural beliefs or traditions, 2) are not knowledgeable or willing to discuss

alternative therapies, and 3) focus on curing the disease or condition more than patient. Traditional medicine is a johnny-come-lately approach that focuses on treating or curing the disease after it has occurred. Many patients who have chronic or incurable diseases such as diabetes, arthritis, or depression often believe that conventional medicine has failed them.

SAFETY ISSUES

Before 1994, marketing of herbal medicines and other dietary supplements had been subject to approval by the US Food and Drug Administration (FDA). In 1993, the FDA began scrutinizing the herbal and dietary supplement industry. This triggered a massive letter-writing campaign organized by the multi-billion dollar dietary supplement industry. Consumers were urged to "write to your congressman to exempt herbs and other supplements from FDA regulation or kiss your supplement goodbye." Public response was overwhelming. Congress reportedly received more mail on this subject than any other issue since the Vietnam War.³ It led to the passage of Dietary Supplement Health and Education Act (DSHEA) in 1994 which severely limited the FDA's ability to regulate the dietary supplement industry.⁴ It classified herbal medicines (along with vitamins, minerals, amino acids, etc) as dietary supplements. Since then these products have flooded the market.

The DSHEA requires no proof of efficacy, no proof of safety, and sets no standards for quality control for products labeled as dietary supplements. If the question arises, the burden of proof lies with the FDA, rather than the manufacturer, to prove that a product is unsafe. In contrast, regulatory agencies in Germany, France, the United Kingdom, and Canada enforce safety assessment and standards of herb quality on manufacturers.

Using herbs may be chancey. Just because herbs are labeled "natural" does not necessarily mean they are without risks. They do not undergo the same rigorous testing demanded by FDA for other drugs. Little is known about their effectiveness, optimum dosage, side effects, or interaction with other medications. And they are subject to few controls on quality and purity. Unlike foods and drugs, herbal products do not require good manufacturing practices (GMP). These ensure that

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products meet specific quality standards, are not adulterated and misbranded, and contain the ingredients at doses stated on the label.⁵ The only real determinant of whether or not the specified concentration on the label is accurate is often the label itself. Because it is costly and there is no quality control pressure from the government, herbal manufacturers have little incentive to do so. For example, analysis of 54 ginseng products revealed that 25% contained no ginseng at all, while 60% of these had 50% or less of the amount stated in the label.⁶ Without GMP, herbal products also run the risk of adulteration and contamination.

Most herbal medicines are probably harmless. In addition, they seem to be used primarily by people who are healthy and who believe that the remedies will help them stay that way, or by people who have common relatively minor problems such as backache or fatigue. Most such people would probably seek conventional doctors if they have indications of serious diseases such as cancer, etc. However, some people may depend on herbs and other alternative therapies exclusively, putting themselves in greater danger.

BENEFICIAL EFFECTS

About one-third of all FDA approved drugs used in conventional medicine have their origin from plants.⁷ Reserpine, used for treatment of high blood pressure, was originally extracted from *Rauwolfia serpentina*. Digitalis, used as a heart stimulant, was derived from the foxglove plant. Salicylic acid (a component of aspirin) was obtained from willow tree bark to help relieve fever. Ma huang, which contains ephedrine, was used for the treatment of asthma. Taxol, a new chemotherapeutic agent, was obtained from the bark of the Pacific yew (*Taxus brevifolia*) and the needles of other yew species. The active ingredients from plants known to offer health benefits were identified, synthesized, and their mechanisms of actions were studied. Safe, effective, and toxic doses of each of the active ingredients were established, and only then were they approved as drugs. Studies on the identification of active principles of several other medicinal plants are currently in progress. A few examples are given below.

Cranberry juice is known to help prevent urinary tract infections. At one time, it was thought to work by acidifying the urine or by the excretion of hippuric acid. Recently, researchers have identified condensed tannins in cranberries (as well as blueberries) that fight infections in the urinary tract by inhibiting the adherence of *Escherichia coli* to uroepithelial cells, a prerequisite for the development of infection.⁸ Cranberry products can now be considered safe prophylactic therapy that may help reduce the frequency of urinary tract infections in susceptible individuals. However, cranberry juice con-

tains traces of quinine, which is known to cause immune-mediated thrombocytopenia. Recently, a 68-year-old man was reported to have thrombocytopenia linked to cranberry juice.⁹

Moxibustion—a traditional Chinese practice that uses heat from burning herbs to stimulate acupuncture points—can help move a fetus into the proper position for head-first delivery. In a 1997 study of 260 Chinese women—all of whom were pregnant for the first time and whose fetuses were still in the breech or upright position after 33 weeks—half of the women received daily moxibustion treatment on their little toes for 1 to 2 weeks. The others did not receive the moxibustion. The fetuses in the treatment group became more active, and 75% of them (versus 48% of the controls) righted themselves in time for a normal delivery.¹⁰ If further studies confirm these findings, moxibustion could become a part of western obstetrics, helping to reduce our high rate of caesarian birth; this would be good for the mother, the baby, and insurance companies.

Chinese herbs may hold similar promise for treating irritable bowel syndrome, which affects 1 in 5 Americans. Researchers in Australia reported that patients who took cocktails of powdered herbs for 16 weeks enjoyed nearly 3 times more relief than those who took a placebo.¹¹

Echinacea, the top-selling herbal product in the United States, is at the forefront of the herbal revolution, with annual sales of more than \$300 million. Extracts, teas, tinctures, tablets, and ointments containing various parts of the plant have been used by Native Americans since the 1600s for a variety of medical problems, from sore gums and coughs to bowel troubles and snakebites. Recent clinical studies have focused on echinacea as a treatment for and prevention of upper respiratory infections. It has at least 6 different active ingredients, though there is controversy over which chemical is most effective. It does appear to exert its effect through immune system modulation, thus indirectly providing “anti-infective” effect.¹¹

Kava has gained widespread popularity as both an anxiolytic and sedative. Results from chemical trials suggest that Kava has a therapeutic potential in the symptomatic treatment of anxiety.¹² The active constituents, kava lactones, have experimentally been found to have skeletal muscle relaxant, anticonvulsant, and local anesthetic properties. Kava may be a beneficial herbal medicine for patients with mild stress or anxiety, and it carries minimal abuse potential. However, the potential for adverse effects from higher than recommended doses (140-250 mg/day) and drug interactions are of concern. Kava is contraindicated in Parkinson's disease. On rare occasions, kava may cause at least one side effect: liver inflammation or damage. Recently,

Britain has pulled kava from shelves, and, following 30 cases of serious liver damage attributed to kava, Germany and Switzerland are considering doing the same. In Germany alone, three people needed liver transplants and one person died of liver failure. There have been no reports of any problems in North America, but the FDA is investigating the supplement.¹³

Further work in the identification of active ingredients and the mechanisms of action of these ingredients need to be determined. Some of the other more commonly used herbs include garlic, ginkgo biloba, ginseng, ma huang, saw palmetto, and St. John's wort. Evidence on the safety and efficacy of these products has recently been reviewed.¹⁴⁻¹⁷ The proper use of herbal products may provide therapeutic benefits but indiscriminate or excessive use of herbs can be unsafe and even dangerous.

ADVERSE EFFECTS

Current US regulations provide little assurance that commercial herbal preparations have predictable pharmacological effects or that product labels provide accurate information. The potency of herbal medications can vary from manufacturer to manufacturer and from batch to batch within a product run.¹⁸ Plants may be incorrectly identified or deliberately replaced with cheaper or more readily available alternatives. Herbal medications, especially those of Eastern origins, can be adulterated with heavy metals, pesticides, and even conventional drugs. Because there is no mechanism for post-marketing surveillance, the incidence and the exact nature of adverse events is unknown.

More than 5000 suspected herb-related adverse reactions were reported to the World Health Organization before 1996. Between January 1993 and October 1998, 2621 adverse events, including 101 deaths associated with dietary supplements, were reported to the FDA.¹⁹ For every adverse event in its files, the FDA estimates that 100 more go unreported because there are no central mechanisms for mandatory reporting as there are for conventional medications. Other factors that contribute to underreporting are that physicians do not always recognize adverse events associated with herbal medical use and that patients are reluctant to report and seek treatment for adverse reactions.

Ephedra (ma huang) products have been among the most controversial and lucrative of all supplements. More than 1200 complaints about the hundreds of ephedra products on the market fill FDA files, including reports of 70 deaths. Dietary supplements containing ma huang are widely consumed in the United States for purposes of weight reduction and energy enhancement. In response to growing concern about the safety of ephedra-containing supplements, the FDA requested an

independent review of 140 of its adverse event reports to assess causation and determine the level of risk these products pose to consumers. Among these 140 cases, the independent investigators found 104 descriptions of strokes, heart attacks, seizures, hypertension, and more that were likely or probably related to ephedra. There were 10 reports of cardiac arrest and sudden deaths. The review concluded that given these side effects, ma huang (ephedra) supplements should not be used without medical supervision.²⁰

Ephedra supplements are raising the greatest worry in the medical community at this time, but other herbal remedies are also of some concern. Recently, it has been reported²¹ that colchicine was present in placental blood from patients taking ginkgo supplements. Colchicine was found in these same ginkgo tablets. These supplements should be avoided by women who are pregnant and those who are trying to conceive because colchicine is an alkaloid with teratogenic activity. A few examples of adverse effects related to other herbs are described below.

Herbal ecstasy and Parkinson's syndrome. Ecstasy is a mixture of herbal stimulants including ma huang (which contains ephedrine), kola nuts, guarana, and green tea, all of which contain caffeine. It is advocated as a safe, all-natural energy source with no side effects, as well as being a safe alternative to illicit street drugs. Recently, a case of Parkinson's syndrome involving ecstasy was described.²² A 29-year-old male had taken ecstasy 10 times during the preceding year. He also admitted to taking creatine regularly and had been taking dehydroepiandrosterone for a week when he began to get lightheaded. He went to a medical center for treatment of slight clumsiness of his upper and lower extremities. During the next four weeks, he began to have difficulty walking and lost his ability to write and drive. Parkinsonism was diagnosed, as a result of a delayed neurotoxic effect of the ingredient(s) in ecstasy on the substantia nigra and striatum. Neurotoxicity to the serotonergic system in the brain can cause permanent physical and psychiatric problems. A detailed review of the literature has revealed over 87 ecstasy-related fatalities.²³

Chinese medications with undeclared prescription drugs. There are several documented cases of complications, some life-threatening, associated with the medication known as "Chinese Black Balls." This medication is marked for liver and kidney ailments, muscle aches, rheumatism, as well as several other conditions at dosages of 6 to 12 pills daily. The only ingredients listed on the bottle are 20 or more herbs.

Some patients taking the medication had to be rushed to the emergency room because of complications. Laboratory data and examination of 5 patients demon-

strated ulcers and esophagitis. Several urine toxicology screens were positive for benzodiazepines. Analysis of Chinese medication revealed the presence of 1.3 mg of diazepam (a hypnotic sedative) and 93.4 mg of mefenamic acid (a non-steroidal anti-inflammatory agent) in each pill. It was determined that ingestion of 12 pills a day would exceed the recommended maximum dose of mefenamic acid. These cases illustrate the adverse effects associated with adulterated medications.²⁴

Indian herbal medication with lead contamination. A 43-year-old male taking 8 tablets daily of Indian herbal medications for type II diabetes had to be hospitalized due to a three-day stretch of epigastric pain and constipation. Among the laboratory findings were low hemoglobin (8.9 g/dl), a very high urinary coproporphyrin, and lead.²⁵ Toxicologic examination of the pills showed that each pill contained 10 mg of lead. Thus the patient's cumulative lead intake before hospitalization was approximately 4 grams. The patient did not tell the physician that he was taking these pills. The possibility that the pills contained lead was not considered. Had the physician known that the patient was taking an herbal preparation, the possibility of some kind of lead intoxication might have been considered earlier.

Valerian withdrawal syndrome. Valerian has been a popular calming and sleep-promoting agent for centuries. Its benefits are similar to the benzodiazepines. A 58-year-old North Carolina man went to hospital for biopsy of a lung nodule and suffered delirium and a racing heart, landing him in intensive care. A doctor's inquiry found that the patient had been taking megadoses (2 grams, 5 times daily) of valerian for several years. This practice ended abruptly in the hospital, which triggered symptoms of withdrawal.²⁶

St. John's wort and adverse reactions. St. John's wort is a perennial herb found in Europe and North America. Since the Middle Ages it has been used as a remedy for the treatment of depression and anxiety. One of the active ingredients, hypericin, appears to be a monoamine oxidase inhibitor. A number of clinical trials have reported efficacy in the short-term treatment of mild to moderate depression. However, a recent multi-center clinical trial concluded that this herb is not effective in the treatment of major depression.²⁷ St. John's wort can interact with sunlight producing oxygen free radicals that damage myelin around the nerves. This can produce electrical activity which feels like tingling, needles, or pain. Also, its safety has recently been questioned, especially when taken in the presence of certain prescribed drugs.

A 20-year-old New Yorker, under antidepressant treatment with a selective serotonin re-uptake inhibitor, became agitated and confused, shouting in the hospital. Psychiatrists later found that the patient had added St. John's wort (nicknamed "natural Prozac") to his pre-

scription regimen. This combination unleashed a "serotonin syndrome" due to an overload of the neurotransmitter.²⁸ If the patient had disclosed his self-treatment or if the doctor had been more probing, these complications could have been prevented. Several other cases have been reported involving "central serotonin excess syndrome" as a result of St. John's wort.

One other property of St. John's wort is that it is a potent inducer of some hepatic enzymes involved in drug metabolism. The metabolism of several drugs, given for treatment of certain conditions, have been shown to be increased as a result of consumption of this herb. They include indinavir (a protease inhibitor for the treatment of HIV patients), cyclosporin (given to prevent transplant rejection), some anesthetic drugs, and several other drugs. A recent study reported 2 cases of active heart transplant rejection associated with St. John's wort's effect on cyclosporin.²⁹ Thus discontinuation of this herb is especially important for patients waiting for organ transplant or surgery.

Mu Tong and nephropathy. Mu Tong is the name of a Chinese plant derived either from *Aristolochia monchuriensis* (AM) or various species of *Akebia* or *Clematis*. The plant derived from AM is called Guam Mu Tong and contains aristolochic acid, a nephrotoxin. The other varieties do not contain this toxin. Mu Tong has been added in weight-reducing products because it is supposed to cause muscle relaxation and eliminate stress-related water retention. Between 1991 and 1992, 30 women who were using Mu Tong as part of their weight-reduction diets died of kidney failure.³⁰ Recently, 2 women in UK who were taking herbal tea containing Mu Tong had kidney failure requiring renal transplant.³¹ It has also been reported that some patients using Mu Tong containing products have high incidence of uroepithelial cancer.³² The probable reason for the presence of toxin is lack of verification of the type of Mu Tong used. Incidences of this kind highlight the importance of developing and enforcing appropriate quality assurance procedures for herbal medicines.

Saw Palmetto and liver disease. Saw Palmetto is widely used in Europe for the treatment of benign prostatic hyperplasia. It improves urine flow and symptoms. The active ingredient has antiandrogenic activity which is thought to help in the management of prostatic hyperplasia. A 65-year-old man with nocturia began taking prostata, a combination of saw palmetto, ginseng, and other ingredients. Two weeks later he developed jaundice.³³ The hepatotoxic effect apparently was due to estrogenic and antiandrogenic activity of the herb.

Dong Quai and hypertension. Dong Quai is a popular Chinese herbal medicine used for various gynecologic ailments. Its reputation in traditional Chinese medicine is second only to ginseng, and Dong Quai is considered

Table I. Some facts to share with patients

1. Not all that is natural is harmless.
2. If something is good for your health, it does not mean that more is necessarily better: it can be harmful. Medical herbs and supplements may not only have potential benefits, but also the potential to interact with other drugs and cause toxic reactions.
3. Manufacturers have no regulatory responsibility to ensure safety of their products. There are no requirements for FDA approval. Adulteration and misidentification of plant species may exist.
4. Use of supplements should be avoided during pregnancy and lactation because of possible adverse effects on the fetus and the newborn.
5. Children and the elderly may be more prone to adverse effects from herbal treatments because of their decreased metabolizing ability.

the ultimate all-purpose women's tonic. In the US it is among the 20 top-selling herbal medicines. A 32-year-old woman, three weeks post partum, had eaten soup prepared from Dong Quai. She had to be taken to the emergency room due to an acute onset of headache, weakness, and vomiting. Her blood pressure was 195/85mm Hg. She was normotensive during her uneventful pregnancy and improved within 12 hours. The next day, her 3-week-old breast-fed son was evaluated for possible hypertension. The infant's blood pressure was 115/69mm Hg. Breastfeeding was temporarily discontinued and his blood pressure normalized within 48 hours. A possible explanation for hypertension in this woman and her child is an adverse effect of the herb soup which then passed to the child via breast milk.³⁴

Kombucha mushroom and coagulation disorders. Kombucha mushroom is derived from fermentation of several species of yeast and bacteria with black tea, sugar, and other ingredients; the resulting liquid is called Kombucha tea. In the popular press, this tea is advertised as having several beneficial effects, such as prevention of cancer, relief of symptoms from arthritis, and stimulation of hair growth. In 1996, 2 women died as a result of disseminated intravascular coagulation.³⁵ In the same year, 20 patients in Iran who had applied the tea as a pain killer developed skin lesions.³⁶ Cultures from skin lesions confirmed the presence of *Bacillus anthracis*. If these patients had taken tea orally, they might have developed intestinal anthrax, which has a high mortality rate.

THE ROLE OF PHYSICIANS

The adverse effects described above illustrate the point that although many herbs may be safe and effective complements to conventional medical treatment, they also can be dangerous. Clinicians are being confronted on a daily basis with patients taking herbal and nonherbal supplements. Morbidity and mortality associated with herbal medications may be more likely in the perioperative period because of physiologic alterations that occur. Such complications include myocardial infarction, stroke, bleeding, prolonged or inadequate anesthesia, organ transplant rejection, and

interference with medications indispensable for patient care.³⁷ Herbal supplements can pose a greater health risk to seniors who are more likely to be on prescription drugs and have existing medical problems. These two factors can be adversely affected by supplements. Patients who use supplements are often misguided by misconceptions or inaccurate information. Frustrated patients who have chronic disease often seek herbal treatment. Manifestations of illness and organ dysfunction may result not only from disease or therapy that meets scientific protocols but from herbs as well.

Recent evidence suggests that patients often do not report the use of dietary supplements on written medication questionnaires.³⁸ It is imperative to ask patients about supplement use during medical history-taking. Physicians are ideally situated to help their patients in integrating alternative modalities with conventional care and to assist them in making informed treatment decisions.

Patients should be made to understand (Table 1) that 1) if something is "natural" it is not automatically safe, 2) if something is good for health it does not mean more of it is better, and in fact, it can be harmful, 3) important differences exist between approved drugs and supplements regarding safety issues, 4) the use of herbs should be avoided during pregnancy and lactation because of possible adverse effects on the fetus and the newborn, and that 5) children and elderly may be more prone to adverse effects because of their decreased metabolizing ability.

CONCLUSIONS

Popular demand for herbal products has increased considerably in recent years. These products are marketed as dietary supplements which, unlike pharmaceutical drugs, are exempt from FDA clinical scrutiny as a result of the DSHEA of 1994. Some herbs may have health benefits but many may be intrinsically dangerous when ingested alone or in combination with other supplements or drugs. Because of the lack of quality control, consumers cannot determine if 1) the herb's active ingredient is actually present in the product, 2) if the dosage is appropriate, and 3) what else is in the pill

besides the claimed ingredients. Adulteration, substitution, and contamination are possible. It is imperative for physicians to ask patients about supplement use. Physicians are ideally situated to help their patients in integrating herbal modalities with conventional care and to assist them in making informed treatment decisions.

REFERENCES

- Eisenberg DM, Davis RB, Ettner SL, Appel S, Wilkey S, Van Rompay M, et al. Trends in alternative medicine use in the United States, 1990-97. *JAMA* 1998;280:1569-75.
- Brevoort P. Overview of the U.S. botanical market. Presented at: Third Conference on Botanicals; January 27-28, 1999; Washington DC.
- Blumenthal M. Dietary Supplement Health Education Act of 1994. *Herbalgram* 1995;32:18-20.
- Dietary Supplement Health and Education Act of 1994. *Pub L No.* 103-417.
- US Food and Drug Administration. Current good manufacturing practice in manufacturing, packing or holding dietary supplements; proposed rule. *Federal Register*. February 6, 1997;62:5700-9.
- Liberti LE, DerMarderosian AD. Evaluation of commercial ginseng products. *J Pharm Sci* 1978;67:1487-9.
- Craig WJ. Health-promoting properties of common herbs. *Amer J Clin Nutr* 1999;70(suppl):491s-9.
- Howell AB, Vorsa N, Der Marderosian A, Foo LY. Inhibition of the adherence of P-fimbriated *Escherichia coli* to uroepithelial cell surfaces by proanthocyanidin extracts from cranberries. *N Engl J Med* 1998;339:1085-6.
- Davies JK, Ahktar N, Ranasinge E. A juicy problem. *Lancet* 2001;358:2126.
- Cardini F, Weixin H. Moxibustion for correction of breech presentation. A randomized controlled trial. *JAMA* 1998;280:1580-4.
- Bensoussan A, Talley NJ, Hing M, Menzies R, Guo A, Ngu M. Treatment of irritable bowel syndrome with Chinese herbal medicine. *JAMA* 1998;280:1585-9.
- O'Hara M, Kiefer D, Farrell K, Kemper K. A review of twelve commonly used medicinal herbs. *Arch Fam Med* 1998;7:523-36.
- CBC News Online staff. Britain pulls herbal drug kava kava. Available at: http://cbc.ca/cgi-bin/templates/view.cgi?category-Consumers&story-/news/2001/12/21/Consumers/kavakava_011221. Accessed December 24, 2001.
- Mar C, Bent S. An evidence-based review of the ten most commonly used herbs. *West J Med* 1999;171:168-71.
- Sardesai VM, Myers T. Nutrient supplements in clinical care. *Nutr Clin Pract* 2001;16:35-45.
- Miller LG. Herbal medicinals. Selected clinical considerations focusing on known or potential drug-herb interactions. *Arch Intern Med* 1998;158:2200-11.
- Ernst E. The risk-benefit profile of commonly used herbal therapies: Ginkgo, St. John's wort, ginseng, echinacea, saw palmetto, and kava. *Ann Intern Med* 2002;136:42-53.
- Herbal roulette. *Consumer Reports*, November 1995, 698-705.
- Herbal Rx: the promises and pitfalls. *Consumer Reports* March 1999:44-48.
- Haller CA, Benowitz NL. Adverse cardiovascular and central nervous system events associated with dietary supplements containing ephedra alkaloids. *New Engl J Med* 2000;343:1833-8.
- Borman S. Toxin reported in supplements. Colchicine in ginkgo and echinacea is cited as possible danger to pregnant women and fetuses. *Chem Eng News* 2001;Aug 13:33-34.
- Mintzer S, Hickenbottom S, Gilman S. Parkinsonism after taking ecstasy. *New Engl J Med* 1999;340:1443.
- Kalant H. The pharmacology and toxicology of 'ecstasy' (MDMA) and related drugs. *Can Med Ass J* 2001;165:917-28.
- Gertner E, Marshall PS, Filandrinos D, Potek AS, Smith TM. Complications resulting from the use of Chinese herbal medications containing undeclared prescription drug. *Arthritis Rheum* 1995;38:614-7.
- Beigel Y, Ostfeld I, Schoenfeld N. A leading question. *N Engl J Med* 1998;339:827-30.
- Garges HP, Varis I, Doraiswamy PM. Cardiac complications and delirium associated with valerian root withdrawal. *JAMA* 1998;280:1566-7.
- Shelton RC, Keller MB, Gellenberg A, Dunner DL, Hirschfeld R, Thase ME, et al. Effectiveness of St. John's wort in major depression. A randomized controlled trial. *JAMA* 2001;285:1978-85.
- Chase M. Patients need to keep their doctors informed about herbal therapies. *Wall Street Journal*. Nov 16, 1998.
- Ruschitzka F, Meier PJ, Turina M, Luscher TF, Noll G. Acute heart transplant rejection due to St. John's wort. *Lancet* 2000;355:548-9.
- VanHerweghem JL, Depierreux M, Tielemans C, Abramowicz D, Dratwa M, Jadoul M, et al. Rapidly progressive interstitial fibrosis in young women: Association with slimming regimen including Chinese herbs. *Lancet* 1993;341:387-91.
- Lord GM, Tagore R, Cook T, Gower P, Pusey CD. Nephropathy caused by Chinese herbs in the UK. *Lancet* 1999;354:481-2.
- Nortier JL, Martinez MC, Schmeiser HH, Arlt VM, Bieler CA, Petein M, et al. Urothelial carcinoma associated with the use of a Chinese herb (*Aristolochia fangchi*). *N Engl J Med* 2000;342:1686-92.
- Hamed S, Rojter S, Vierling J. Protracted cholestatic hepatitis after the use of Prostata. *Ann Intern Med* 1997;127:169-70.
- Nambiar S, Schwartz RH, Constantine A. Hypertension in mother and baby linked to ingestion of Chinese herbal medicine. *West J Med* 1999;171:152.
- Currier RW, Goddard J, Buechler K. Unexplained severe illness possibly associated with consumption of Kombucha tea--Iowa, 1995. *JAMA* 1996;275:96-8.
- Sadjadi J. Cutaneous anthrax associated with the Kombucha mushroom. *JAMA* 1998;280:1567-8.
- Ang-Lee MK, Moss J, Yuan C. Herbal medicines and perioperative care. *JAMA* 2001;286:208-16.
- Hensrud DD, Engle DD, Scheitel SM. Under-reporting the use of dietary supplements and non-prescription medications among patients undergoing a periodic health examination. *Mayo Clin Proc* 1999;74:443-7.