

# The Herbal Medicine Pharmacy Update

By Philip J Tuso, MD, FACP

## Introduction

The continued use of herbal medicine in the United States and among members of Kaiser Permanente (KP) makes an updated review of this topic timely and important. Many pharmacies at KP facilities in Southern California now carry traditional herbal preparations. These

“dietary supplements” are over-the-counter therapy that is not routinely screened for drug interaction by the pharmacy team.

This article discusses herbal medicine with the interests of the physician in mind by emphasizing the importance of understanding the risks and benefits of herbal treatment. We use the skills taught to us by Eddy<sup>1-4</sup> to determine if selected herbal medicines pass the evidence-based-medicine test. We discuss selected ex-

amples of herbal medicine that have the potential to harm patients. The discussion is not intended to be a complete review of all aspects of herbal remedies.

## Use of Herbal Therapy in the United States

Alternative forms of therapy are defined as intervention neither taught widely in US medical schools nor widely available in US hospitals.<sup>5,6</sup> A 1997 national survey showed that 42% of Americans used some form of alternative medicine,<sup>5,6</sup> but that figure may be higher for young, affluent, educated populations.<sup>7</sup>

Eisenberg<sup>5</sup> reported that in the US general population, use of over-the-counter herbal medicine increased from 2.5% in 1990 to 12.1% in 1997, and consultation with alternative medicine providers increased from 10.2% in 1990 to 15.1% in 1997. The estimated total retail cost of herbal medicine in the United States is about \$4 to \$5 billion per year<sup>8</sup> and is primarily paid by the people seeking herbal medicine treatment.<sup>5</sup>

Little was known about prevalence of the use of alternative and herbal medicine by older adults—the largest consumers of health care—until survey results were published by Foster in 2000.<sup>9</sup> Thirty percent of the people surveyed who were aged 65 years or more reported using alternative medicine, usually chiropractic services and herbs. By extrapolation, about three million people aged 65 or more used herbal therapy in 1997, and two million used herbal therapy and prescription medication at the same time.<sup>9</sup>

Physicians are becoming aware of the potential benefit of some herbal medicines and are using them to treat conditions common in our elderly population. Fifty-five percent of Alzheimer patient caregivers reported that they had tried at least one alternative therapy to improve the patient's memory,<sup>10</sup> and 29% of older patients with arthritis reported seeing an alternative medicine provider for their arthritis.<sup>11</sup> However, In 1997, Eisenberg reported that 57% of those aged 65 years or more did not disclose use of any alternative medicine to their physician.<sup>6</sup> These

data suggest that physicians should ask all patients, including high-risk patients such as the elderly, about their use of herbal medicine.

## Adverse Effects and Drug-Herb Interaction

Patients taking prescription drugs and therapeutic herbs may be at risk for adverse drug-herb interactions, including interaction that alters bioavailability and efficacy of the prescription drugs.<sup>12</sup> Drug interaction and adverse effects from herbal medicines are more likely to occur among patients who have chronic medical conditions, such as liver, heart, or kidney disease. Older patients have more comorbid illnesses and may be more susceptible to complications caused by herbal medicines.<sup>9,12,13</sup> KP pharmacists routinely report potential drug interaction and adverse affects to patients and physicians. However, herbal medicine is not routinely included in these reports, because this information is not routinely programmed into our computer data systems.

## Tenuous Position of Herbal Medicines in Evidence-Based Medicine

That we practice evidence-based medicine means that we base our decisions on evidence of benefit. If a therapy has sufficient evidence of benefit, we should recommend it to our members; if insufficient evidence of benefit exists or if evidence indicates that the therapy will harm patients, we should not recommend the

**Fifty-five percent of Alzheimer patient caregivers reported that they had tried at least one alternative therapy to improve the patient's memory ...**



**Philip J Tuso, MD, FACP**, has been with the Southern California Medical Group since 1993. In 2001, he was appointed Physician Director for the Kaiser Permanente Fresenius Medical Care Unit in Lancaster, California. E-mail: philip.j.tuso@kp.org.

treatment. Our goals as physicians are to provide treatment that makes our patients better and to protect our patients from treatment that may cause harm. In addition, we do not want to waste members' money.

Because herbal products in the United States are not approved by the US Food and Drug Administration (FDA) as drugs used to help treat diseases, these products do not undergo premarketing safety and efficacy studies and are not manufactured in a standard way. Herbal medicines are defined by the Dietary Health and Education Act of 1994 as dietary supplements,<sup>14</sup> and they are presumed safe until new information shows otherwise. Companies manufacturing herbal medicine can make structure and function claims without support of scientific research, although the claims must be truthful and not misleading. Because herbs cannot be patented, no incentive exists for pharmaceutical companies to invest in research. The FDA would have to prove that an herb was harmful before taking it off the market; however, the FDA has no authority to test herbs.

From a quality control perspective, many are concerned about reported observations that herbal preparations are contaminated with pesticides,<sup>15</sup> heavy metals,<sup>16</sup> microorganisms,<sup>17</sup> and conventional medication (acetaminophen, hydrochlorothiazide, indomethacin, phenobarbital, theophylline, and corticosteroids).<sup>18</sup> This is just one of the reasons that pregnant women should not use herbal medicines. In addition, many herbal products do not contain what is written on the label.

The reference standard for testing efficacy of any therapy is the randomized clinical trial (RCT). Since *The Permanente Journal* last published a review of herbal medicine,<sup>19</sup> more RCTs and meta-analyses of RCTs on herbal medicine have been published. We used these data to

help determine whether or not selected categories of herbal medicine constitute evidence-based therapy.

Tables 1 and 2 show the results of RCTs, meta-analyses of RCTs, and case reports for a variety of herbal medicines. For a more complete review of this topic, please see the Ernst and Pittler article titled "Herbal Medicine."<sup>15</sup> Table 1 lists herbal medicine that passes the evidence-based-medicine test. Systematic reviews and meta-analyses of RCTs show that some

herbs may be efficacious for treating symptoms of certain diseases, such as ginkgo for dementia<sup>20</sup> and intermittent claudication,<sup>21</sup> horse chestnut extract for chronic venous insufficiency,<sup>22</sup> kava for anxiety,<sup>23</sup> and St John's wort for depression.<sup>24</sup> However, before starting these forms of herbal medicine, consumers and their physicians should review the consumer report on the herb posted on the Internet at [consumerlab.com](http://consumerlab.com)<sup>25</sup> and other resources for information. For example, a recent study published in the *Journal of the American Medical Association (JAMA)* suggests that St John's wort may lack efficacy for treatment of moderately severe depression.<sup>26</sup>

Table 2 lists herbal medicine forms that are not supported by RCTs, systematic reviews, or meta-analyses of RCTs as efficacious treatment for certain diseases. These medications should not be part of our treatment regimens.

### Herbs That May Harm Patients

Table 3 lists types of herbal medicine that may be harmful as de-

scribed in RCTs, meta-analyses of RCTs, and case reports. These herbs should not be used or should be used only with extreme caution. For instance, licorice has mineralocorticoid properties and has been reported to cause hypokalemia in some patients.<sup>44</sup> Hepatitis has been reported in patients taking comfrey, chaparral, or celandine and should not be used by patients with liver disease or who are taking medication that may affect liver function.<sup>36,37</sup>

Other herbal medicine forms, such as ginger, ginseng, feverfew, devil's claw, and donq quai, can interact with warfarin sodium and may affect platelet function and bleeding times. This type of herbal medication should not be taken by patients already taking anticoagulant medication such as aspirin, warfarin sodium, or nonsteroidal anti-inflammatory agents. Patients scheduled to receive any procedure that may cause bleeding should be asked if they are taking herbal medicine and should be instructed to stop taking herbs which have anticoagulant

**Table 1. Herbal medicine forms that have studies supporting their use as evidence-based medicine**

Herb	Condition treated	Reference
Ginkgo ( <i>Ginkgo biloba</i> )	Dementia	20
	Intermittent claudication	21
Horse chestnut seed extract	Chronic venous insufficiency	22
Kava ( <i>Piper methysticum</i> )	Anxiety	23
St John's wort ( <i>Hypericum perforatum</i> )	Depression	24

**Table 2. Herbal medicine forms that do not have studies supporting their use as evidence-based medicine**

Herb	Condition treated	Reference
Asian ginseng ( <i>Panax ginseng</i> )	Decreased mental performance	27
Evening primrose ( <i>Oenothera biennis</i> )	Premenstrual syndrome	28
Feverfew ( <i>Tanacetum parthenium</i> )	Prevent migraine	29
		30
Garlic ( <i>Allium sativum</i> )	High blood cholesterol levels	31
Ginkgo ( <i>Ginkgo biloba</i> )	Tinnitus	32
Valerian ( <i>Valeriana officinalis</i> )	Insomnia	33

... these products do not undergo premarketing safety and efficacy studies and are not manufactured in a standard way.

properties for two weeks before receiving the procedure.<sup>38-43</sup>

Several recent publications report on renal failure caused by Chinese herbs.<sup>44-53</sup> Other recent reports indicate that taking St John's wort can result in lower cyclosporin levels, which have been associated with transplant rejection.<sup>54-59</sup> Both of these findings are explained in more detail in the following sections.

taking Chinese herbs, urinary tract carcinomas have developed.<sup>50-53</sup>

### St John's Wort and Acute Organ Transplant Rejection

St John's wort (*Hypericum perforatum*), an herb extract, is an over-the-counter remedy for treating depression.<sup>54,55</sup> Moschella<sup>56</sup> published a case study describing a renal transplant recipient who self-prescribed

any herbal medicine to patients.

To keep the FDA apprised of the real risks of using herbs, physicians can report adverse effects of any herbal medicine to FDA MedWatch on the Internet at [www.fda.gov/medwatch](http://www.fda.gov/medwatch).<sup>14</sup>

### Conclusions

This article describes selected forms of herbal medication that have some evidence that they help to treat certain disease conditions, some herbs that have no evidence of benefit, and some herbs that are known to cause harm. Most of these conditions can also be treated with conventional medication.

As a result of the Dietary Supplement Health and Education Act of 1994,<sup>14</sup> manufacturing of herbal extracts is not submitted to the type of quality control used for manufacturing conventional medication; nor is premarketing safety and efficacy research required. Not all herbal preparations are safe, not all herbal products are standardized to particular levels of the active ingredient, and herbal products may contain contaminants such as pesticides and heavy metals.

St John's wort, an action which resulted in marked reduction in cyclosporin levels. Acute transplant rejection after ingestion of St John's wort has been described in heart,<sup>57</sup> kidney,<sup>58</sup> and liver<sup>59</sup> transplant recipients. Transplant rejection episodes did not recur when patients stopped taking St John's wort.

### Herb Information Resources

ConsumerLab.com, LLC ([www.consumerlab.com](http://www.consumerlab.com)) provides independent test results to help consumers and

health care providers evaluate nutrition products.<sup>25</sup> This resource should be reviewed by physicians as well as by consumers, although the Web site may not be free and may require subscription for some users. For example, a search of the ConsumerLab.com Web site in preparation for this article yielded a report on ginseng<sup>19</sup> which showed that of the 21 ginseng products tested, seven contained less than the acceptable amounts of ginsenoside (active ingredient for ginseng), two had levels of pesticides 20 times more than allowed levels, and two contained more than the acceptable level of lead.

Physicians need to be aware of potential risks of using herbal medicine and are encouraged to visit [www.consumerlab.com](http://www.consumerlab.com) and review the information on herbal products before recommending

Adverse effect	Herb
Renal failure	Chinese herbs ( <i>Aristolochia sp</i> )
Transplant rejection	St John's wort ( <i>Hypericum perforatum</i> )
Heart failure	Aconite ( <i>Aconitum napellus</i> )
Hypertension	<i>Ephedra sp</i>
Hypertension and hypokalemia <sup>35</sup>	Licorice ( <i>Glycyrrhiza glabra</i> )
Hyperthyroidism	Kelp ( <i>Fucus pyriferus</i> )
Hepatitis <sup>36,37</sup>	Comfrey ( <i>Symphytum officinale</i> ), Chaparral ( <i>Larrea tridentata</i> ), Celandine ( <i>Chelidonium majus</i> )
Bleeding disorders <sup>38-43</sup>	Ginger ( <i>Zingiber officinalis</i> ), ginkgo ( <i>Ginkgo biloba</i> ), ginseng ( <i>Panax ginseng</i> ), feverfew ( <i>Tanacetum parthenium</i> ), devil's claw ( <i>Harpagophytum procumbens</i> ), dong quai ( <i>Angelica sinensis</i> )
Seizures	Evening primrose oil ( <i>Oenothera biennis</i> )

For a more complete list of herbs that may have serious adverse effects, please refer to the complete *German Commission E Monographs, Therapeutic Guide to Herbal Medicines* (English translation) published in 1998.<sup>34</sup>

### Chinese Herbs Nephropathy

Chinese herbs nephropathy is characterized by rapidly progressive fibrosing interstitial nephritis without glomerular lesions.<sup>44,45</sup> Patients in whom this disease develops are seen initially for subacute renal failure that progresses rapidly to end-stage renal disease, even though the patient stops taking the herbs immediately upon diagnosis; ultimately, the patient requires dialysis and a renal transplant.<sup>46,47</sup> Aristolochic acid contained in these Chinese herbal preparations is suspected to be the nephrotoxic agent.<sup>48,49</sup> In other patients

**ConsumerLab.com, LLC ([www.consumerlab.com](http://www.consumerlab.com)) provides independent test results to help consumers and health care providers evaluate nutrition products.**

Because of the possibility of adverse effects from herbal medication and of drug-herb interaction, physicians need to obtain a detailed history about the use of over-the-counter medication in all patients. Herbs should not be used by pregnant women and may be harmful to high-risk groups, particularly the elderly. Herbal medication can cause severe adverse effects, such as bleeding complications,

nephropathy, and transplant rejection. The use of most herbal medicine is not evidence-based, and the risk clearly outweighs the benefit.

Consumers and clinicians need to become familiar with the potential risk and benefit of herbal medication,<sup>60</sup> and one good information resource is on the Internet at [www.consumerlab.com](http://www.consumerlab.com).<sup>25</sup> As health care providers, we should be leaders in asking our patients about herbal medicine use and counseling patients about any interaction herbal medicine may have with prescribed medication.<sup>61</sup> In addition, physicians are encouraged to report adverse reactions to herbal medicine to the FDA MedWatch on the Internet at [www.fda.gov/medwatch](http://www.fda.gov/medwatch).<sup>14</sup>

Sponsoring legislation should be considered in order to require that herbal medicine be subjected to the same stringent premarketing scrutiny and controls as conventional drugs. Pharmacist should be aware of herb-drug interaction, and our pharmacy and clinical information systems should be programmed to include information about herbal medicine and interaction profile screening. ❖

## References

- Eddy D. Embedding Permanent medicine into the clinical information system. National Clinical Content Network, Evidence-based Medicine, March 2001. Available from: [http://pkc.kp.org/national/ikmr/nccn/powerpoint/NCCN%20Evidence-based%20Med%2003\\_01.ppt](http://pkc.kp.org/national/ikmr/nccn/powerpoint/NCCN%20Evidence-based%20Med%2003_01.ppt).
- Eddy DM. Clinical policies and the quality of clinical practice. *N Engl J Med* 1982 Aug 5;307(6):343-7.
- Eddy DM. Clinical decision making: from theory to practice. *Anatomy of a decision*. JAMA 1990 Jan 19;263(3):441-3.
- Eddy DM. Clinical decision making: from theory to practice: a collection of essays from JAMA. Boston: Jones and Bartlett Publishers; 1996.
- Eisenberg DM, David RB, Ettner SL, et al. Trends in alternative medicine use in the United States, 1990-97: results of a follow-up national survey. *JAMA* 1998 Nov 11;280(18):1569-75.
- Eisenberg DM. Advising patients who seek alternative medical therapies. *Ann Intern Med* 1997 Jul 1;127(1):61-9.
- Delbanco T. A piece of my mind. Leeches, spiders, and astrology: predilections and predictions. *JAMA* 1998 Nov 11;280(18):1560-2.
- Brevoort P. The booming US botanical market: a new overview. *HerbalGram* 1998;48:33-40.
- Foster DF, Phillips RS, Hamel MB, Eisenberg DM. Alternative medicine use in older Americans. *J Am Geriatr Soc* 2000 Dec;48(12):1560-5.
- Coleman LM, Fowler LL, Williams ME. Use of unproven therapies by people with Alzheimer's disease. *J Am Geriatr Soc* 1995 Jul;43(7):747-50.
- Kaboli PJ, Doebbeling BN, Saag KG, Rosenthal GE. Use of complementary and alternative medicine by older patients with arthritis: a population-based study. *Arthritis Rheum* 2001 Aug;45(4):398-403.
- Ernst E. Harmless herbs? A review of the recent literature. *Am J Med* 1998 Feb;104(2):170-8.
- Gurwitz JH, Avorn J. The ambiguous relation between aging and adverse drug reactions. *Ann Intern Med* 1991 Jun 1;114(11):956-66.
- United States. Food and Drug Administration. Dietary Supplement Health and Education Act of 1994, Public Law No. 103-417. Available at: [www.fda.gov/opacom/laws/dshea.html](http://www.fda.gov/opacom/laws/dshea.html) (Accessed October 10, 2002).
- Ernst E, Pittler MH. Herbal medicine. *Med Clin North Am* 2002 Jan;86(1):149-61.
- Cheng TJ, Wong RH, Lin YP, Hwang YH, Horng JJ, Wang JD. Chinese herbal medicine, sibship, and blood lead in children. *Occup Environ Med* 1998 Aug;55(8):573-6.
- Halt M. Moulds and mycotoxins in herb tea and medicinal plants. *Eur J Epidemiol* 1998 Apr;14(3):269-74.
- Huang WF, Wen KC, Hsiao ML. Adulteration by synthetic therapeutic substances of traditional Chinese medicines in Taiwan. *J Clin Pharmacol* 1997 Apr;37(4):344-50.
- Tuso PJ. The herbal medicine pharmacy: what Kaiser Permanente providers need to know. *Perm J* 1999 Winter;3(1):33-5.
- Ernst E, Pittler MH. Ginkgo biloba for dementia: a systematic review of double-blind, placebo-controlled trials. *Clin Drug Invest* 1999;17(4):301-8.
- Pittler MH, Ernst E. Ginkgo biloba extract for the treatment of intermittent claudication: a meta-analysis of randomized trials. *Am J Med* 2000 Mar;108(4):276-81.
- Pittler MH, Ernst E. Horse-chestnut seed extract for chronic venous insufficiency. A criteria-based systematic review. *Arch Dermatol* 1998 Nov;134(11):1356-60.
- Pittler MH, Ernst E. Efficacy of kava extract for treating anxiety: systematic review and meta-analysis. *J Clin Psychopharmacol* 2000 Feb;20(1):84-9.
- Williams JW Jr, Mulrow CD, Chiquette E, Noel PH, Aguilar C, Cornell J. A systematic review of newer pharmacotherapies for depression in adults: evidence report summary. *Ann Intern Med* 2000 May 2;132(9):743-56.
- ConsumerLab.com. [Web site] Available from: [www.consumerlab.com](http://www.consumerlab.com).
- Effect of *Hypericum perforatum* (St John's wort) in major depressive disorder: a randomized controlled trial. *JAMA* 2002 Apr 10;287(14):1807-14.
- Vogler BK, Pittler MH, Ernst E. The efficacy of ginseng. A systematic review of randomised clinical trials. *Eur J Clin Pharmacol* 1999 Oct;55(8):567-75.

## Practice Tips

Manufacturing of herb extracts is not submitted to the type of quality control used for manufacturing conventional medication; nor is premarketing safety and efficacy research required.

Not all herbal preparations are safe.

Not all herbal products are standardized to particular levels of the active ingredient.

Herbal products may contain contaminants such as pesticides and heavy metals.

Obtain a detailed history about the use of over-the-counter medication in all patients.

Herbs should not be used by pregnant women.

**As health care providers, we should be leaders in asking our patients about herbal medicine use and counseling patients about any interaction herbal medicine may have with prescribed medication.**

28. Budeiri D, Li Wan Po A, Dornan JC. Is evening primrose oil of value in the treatment of premenstrual syndrome? *Control Clin Trials* 1996 Feb;17(1):60-8.
29. Pittler MH, Vogler BK, Ernst E. Feverfew for preventing migraine. *Cochrane Database Syst Rev* 2000;(3):CD002286.
30. Vogler BK, Pittler MH, Ernst E. Feverfew as a preventive treatment for migraine: a systematic review. *Cephalalgia* 1998 Dec;18(10):704-8.
31. Stevinson C, Ernst E. Valerian for insomnia: a systematic review of randomized clinical trials. *Sleep Med* 2000 Apr 1;1(2):91-9.
32. Ernst E, Stevinson C. Ginkgo biloba for tinnitus: a review. *Clin Otolaryngol* 1999 Jun;24(3):164-7.
33. Stevinson C, Pittler MH, Ernst E. Garlic for treating hypercholesterolemia. A meta-analysis of randomized clinical trials. *Ann Intern Med* 2000 Sep 19;133(6):420-9.
34. Blumenthal M, Busse WR, Goldberg A, et al, editors. Klein S, Rister RS, translators. *The complete German Commission E monographs: therapeutic guide to herbal medicines: developed by a special expert committee of the German Federal Institute for Drugs and Medical Devices. Austin (TX): American Botanical Council; Boston: Integrative Medicine Communications; 1998.*
35. Cumming AM, Boddy K, Brown JJ, et al. Severe hypokalaemia with paralysis induced by small doses of liquorice. *Postgrad Med J* 1980 Jul;56(657):526-9.
36. Ernst E. Interactions between synthetic and herbal medicinal products: Part 2. A systematic review of the direct evidence. *Perfusion (Munich, Germany)* 2000;13:60-70.
37. Ernst E. Possible interactions between synthetic and herbal medicinal products: Part 1. A systematic review of the indirect evidence. *Perfusion (Munich, Germany)* 2000;13:4-15.
38. Argento A, Tiraferri E, Marzaloni M. [Oral anticoagulants and medicinal plants. An emerging interaction.] [Article in Italian]. *Ann Ital Med Int* 2000 Apr-Jun;15(2):139-43.
39. Boon HS, Smith M. *The botanical pharmacy: the pharmacology of 47 common herbs. Kingston (Ont.): Quarry Press; 1999.*
40. Bordia A, Verma SK, Srivastava KC. Effect of ginger (*Zingiber officinale* Rosc.) and fenugreek (*Trigonella foenumgraecum* L.) on blood lipids, blood sugar and platelet aggregation in patients with coronary artery disease. *Prostaglandins Leukot Essent Fatty Acids* 1997 May;56(5):379-84.
41. Fetrow CW, Avila JR. *Professional's handbook of complementary & alternative medicines. Springhouse (PA): Springhouse Corporation; 1999.*
42. Page RL 2nd, Lawrence JD. Potentiation of warfarin by dong quai. *Pharmacotherapy* 1999 July;19(7):870-6.
43. Heck AM, DeWitt BA, Lukes AL. Potential interactions between alternative therapies and warfarin. *Am J Health Syst Pharm* 2000 Jul 1;57(13):1221-7; quiz 1228-30.
44. Vanherweghem JL, Depierreux M, Tielemans C, et al. Rapidly progressive interstitial renal fibrosis in young women: association with slimming regimen including Chinese herbs. *Lancet* 1993 Feb 13;341(8842):387-91.
45. Depierreux M, Van Damme B, Vanden Houte K, Vanherweghem JL. Pathologic aspects of a newly described nephropathy related to the prolonged use of Chinese herbs. *Am J Kidney Dis* 1994 Aug;24(2):172-80.
46. Yang CS, Lin CH, Chang SH, Hsu HC. Rapidly progressive fibrosing interstitial nephritis associated with Chinese herbal drugs. *Am J Kidney Dis* 2000 Feb;35(2):313-8.
47. Vanherweghem JL. Nephropathy and herbal medicine. *Am J Kidney Dis* 2000 Feb;35(2):330-2.
48. Vanhaelen M, Vanhaelen-Fastre R, But P, Vanherweghem JL. Identification of aristolochic acid in Chinese herbs. *Lancet* 1994 Jan 15;343(8890):174.
49. Schmeiser HH, Bieler CA, Wiessler M, Van Ypersele de Strihou C, Cosyns JP. Detection of DNA adducts formed by aristolochic acid in renal tissue from patients with Chinese herbs nephropathy. *Cancer Res* 1996 May 1;56(9):2025-8.
50. Vanherweghem JL, Tielemans C, Simon J, Depierreux M. Chinese herbs nephropathy and renal pelvic carcinoma. *Nephrol Dial Transplant* 1995;10(2):270-3.
51. Nortier J, Simon J, Petein M, et al. Chinese herbs nephropathy and urinary tract carcinoma [abstract]. *J Am Soc Nephrol* 1998 Sep;9 Spec No:164A.
52. Nortier JL, Martinez MC, Schmeiser HH, et al. Urothelial carcinoma associated with the use of a Chinese herb (*Aristolochia fangchi*). *N Engl J Med* 2000 Jun 8;342(23):1686-92.
53. Cosyns JP, Jadoul M, Squifflet JP, Wese FX, Van Ypersele de Strihou C. Urothelial lesions in Chinese-herb nephropathy. *Am J Kidney Dis* 1999 Jun;33(6):1011-7.
54. Bisset NG. *Hyperici herba (St John's wort)*. In: Bisset NG (translator): *Herbal drugs and phytopharmaceuticals*. 2nd ed. Stuttgart: Medpharm Scientific GmbH Publishers. 1994, p 273-5.
55. Kessler RC, McGonagle KA, Zhao S, et al. Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States. Results from the National Comorbidity Survey. *Arch Gen Psychiatry* 1994 Jan;51(1):8-19.
56. Moschella C, Jaber BL. Interaction between cyclosporine and *Hypericum perforatum* (St John's wort) after organ transplantation. *Am J Kidney Dis* 2001 Nov;38(5):1105-7.
57. Ruschitzka F, Meier PJ, Turina M, Luscher TF, Noll G. Acute heart transplant rejection due to St John's wort [letter]. *Lancet* 2000 Feb 12;355(9203):548-9.
58. Breidenbach T, Hoffmann MW, Becker T, Schlitt H, Klempnauer J. Drug interaction of St John's wort with cyclosporin [letter]. *Lancet* 2000 May 27;355(9218):1912.
59. Breidenbach T, Kliem V, Burg M, Radermacher J, Hoffmann MW, Klempnauer J. Profound drop of cyclosporin A whole blood trough levels caused by St John's wort (*Hypericum perforatum*) [letter]. *Transplantation* 2000 May 27;69(10):2229-30.
60. Angell M, Kassirer JP. Alternative medicine—the risks of untested and unregulated remedies. *N Engl J Med* 1998 Sep 17;339(12):839-41.
61. Bauer BA. Herbal therapy: what a clinician needs to know to counsel patients effectively. *Mayo Clin Proc* 2000 Aug;75(8):835-41.