Pharmacognosy Magazine
ISSN: 0973-1296

PHCOG MAG.
An official Publication of Phcog.Net

PHCOG MAG.: General Article
Herbal Supplements: Regulation and Safety Aspects

Sunil Kumar*, Dinesh Kumar and Om Prakash

Department of Pharmaceutical Sciences, Kurukshetra University, Kurukshetra-136119
**Corresponding Author: Ph. 09416581005 ; E-mail: sunilmadhuban@yahoo.com*

ABSTRACT - Many people all over the world use herbal supplements but there is no strict regulation on these products. Before 1994, these were regulated as food and were evaluated for safety before being launched into the market for consumer purchase. In 1994, Dietary Supplement Health and Education Act (DSHEA) was passed which weakened the FDA and allowed the distribution herbal supplements without testing their efficacy and toxicity. Currently, there are many agencies, which are working on the regulation of these products. Herbal supplements may also cause toxic reactions. So, people should be aware about the safety and adverse effects of these products.
KEYWORDS: Herbal Supplements, FDA, DSHEA, GMP, German Commission E, WHO.

INTRODUCTION

Herbal supplements (a type of dietary supplement) are simple or multicomponent herb mixture used to supplement the traditional medical treatment. Dietary supplement is a product other than tobacco intended to enrich the diet containing one or more of vitamins; minerals; herbs or other botanicals; amino acids; or any combination of the above ingredients and is not used as a conventional food or as a sole item of a meal or the diet (1).

Regulation of herbal supplements

In the early 20th century, fraud was rampant among the producers of both food and drugs in the United States(2). There was no regulating body or committee to check fraudulent practices such as misbranding and adulteration of drugs, so in order to ensure the identity, purity, quality, strength, composition, safety and effectiveness of dietary supplements, the following organizations came into existence for their regulation:

Food and Drug Administration (FDA)

The act to create this agency was passed in 1906 by efforts of Harvey W. Wiley, then chief of the Bureau of Chemistry of the U.S. department of agriculture (2). The job of the FDA is to regulate the drugs, food, and cosmetics in several countries, which assures the public that drugs are safe and effective and have been subject to scientific scrutiny. In 1962, the FDA required that all drugs be evaluated for safety and efficacy (3). It is estimated that more than 1400 herbs are commonly sold and promoted for medicinal uses worldwide (4,5). The FDA maintains a list of products "Generally Recognized as Safe" (GRAS). Approximately 250 herbs appear on this list, but these are herbs used for food flavoring and not for medicinal purposes. Currently, only a handful of herbs have been shown safe and effective based on a 1990 FDA review of over-the-counter drugs (6).

In 1993, the FDA distributed an advance notice of a proposed rule that addressed the concerns regarding the herbal and supplement industry. The report discussed instances of herb-related deaths and concerns about toxicities. But the manufacturers had little incentive to seek FDA approval due to the costs associated with drug research and to avoid the burden of proof associated with FDA approval, herbal manufacturers began to label herbs as "foods" and sell them in health food stores. Due to public and supplement industries concerns, DSHEA was constituted, which limits the FDA's influence on herbal products (5). Now FDA can only take action if a product is found to present a significant or unreasonable risk of illness or injury (7).

Dietary Supplement Health and Education Act (DSHEA)

The act to create this agency was passed in 1994 and it supported the fact that dietary supplements (which include herbal medicines) can play an important role in health promotion and the prevention of chronic disease (8,9). This legislation allows herbal products to be sold without testing for efficacy. The herbal supplements manufacturing companies cannot make claims on an herb's ability to cure a disease, but they may claim about how a supplement affects the structure and function of the body (10). Under this act, herbs can be sold without FDA approval (4-5,10-12). The only way a dietary supplement can be withdrawn from the consumer market is if the FDA can prove that the

product is unsafe (1,7,13).

This legislation defined the dietary supplements, addressed safety issues and provided a mechanism for monitoring safety. DSHEA also called for good manufacturing practices to be used in producing dietary supplements.

World Health Organization (WHO)

World Health Organization's Guidelines for the Assessment of Herbal Medicines, which state that a substance's historical use is a valid way to document safety and efficacy in the absence of scientific evidence to the contrary (14). A long history of use may allow for safety information to be gathered; however, it may do little to assess efficacy.

German Commission E

German Commission E was established in 1978. It is the interdisciplinary commission of scientists and health professionals, which is responsible for reviewing herbal medicines. In its review, the commission considers traditional use; chemical data; clinical, experimental, pharmacological, toxicological and epidemiological studies; patient case records from physicians' files; and unpublished proprietary data from manufacturers to determine the safety and effectiveness of each herbal medicine. It then develops monographs for informing the public of its findings. These monographs have recently been translated into English and are useful tools for other countries attempting to establish high standards for herbal medicines (7,15).

This Commission E has reviewed clinical literature (including clinical trials and case studies) on more than 1400 herbal drugs (4,5). The commission has produced more than 300 monographs on common herbal remedies. However, these monographs must be used with caution given their reliance on historical bibliographic information that may or may not include data gathered from clinical trials (16).

Labeling Requirements[4]

FDA requires that certain general information must appear on the dietary supplement label:

- Name of product (including the word "supplement" or a statement that the product is a supplement)
- Net quantity of contents
- Name and place of business of manufacturer, packer, or distributor
- Directions for use

The label of a dietary/herbal supplement product is required to be truthful and not misleading. If the label does not meet this requirement, FDA may remove the product from the marketplace or take other appropriate actions.

A label may not claim that a product can be used to diagnose, treat, cure, or relieve a specific disease. For example, it cannot include the claim "treats arthritis." Regulations apply only to product labels. However, unapproved health claims can appear in places other than the label, such as magazines, websites, and signs in stores.

Good manufacturing practices (GMP) Regulation

FDA is authorized to issue Good Manufacturing Practice (GMP) regulations describing conditions under which dietary supplements must be prepared, packed, and stored. DSHEA also maintains the FDA's right to establish good manufacturing practices (GMPs), which are standard for the pharmaceutical industry and felt to be a key to product purity and safety (10). FDA published a proposed rule in March 2003 that is intended to ensure that manufacturing practices will result in an unadulterated dietary supplement and that dietary supplements are accurately labeled. Until this proposed rule is finalized, dietary supplements must comply with food GMPs, which are primarily concerned with safety and sanitation rather than dietary supplement quality. Some manufacturers voluntarily follow drug GMPs, which are more rigorous, and some organizations that represent the dietary supplement industry have developed unofficial GMPs.

These regulations would govern the preparation, packing, and holding of dietary supplements under conditions that assure their safety. These regulations are to be modeled under guidelines currently in effect for the food industry. To date, the FDA has not fully implemented manufacturing guidelines for the herbal industry (17). The herbal industry has taken strides to police itself with regard to product quality. The National Nutritional Foods Association randomly tests products produced by its members. The Association also plans to begin certification of factories every three years using the same good manufacturing processes proposed by the FDA, although manufacturers are not obligated to belong to this organization. In addition to the National Nutritional Foods Association, the United States Pharmacopoeia (USP) sets standards for pharmaceuticals, vitamins, and minerals. The USP, a private, nonprofit organization, has begun to produce monographs about herbs that sum up evidence of effectiveness and detail standards for quality, strength, and purity of the final product (17). Adoption of these standards is voluntary,

and manufacturers claiming to meet them are not checked except in response to complaints.

Safety and Purity

The prevalence of herbal use is largely unstudied (4,5,18). Also, the lack of scientific research on herbs, combined with the lack of FDA regulation of herbal preparations, can give consumers a false sense of security about the safety of herbal supplements (11,19,20). Both consumers and health care professionals are concerned about whether herbal products are safe. Sometimes, even if you take an herb or supplement for one certain reason, there can be other unintended reactions. Herbal and dietary products have chemical properties just like manufactured drugs. So, these may also have side effects. One of the major problems with many of the products on the market today is that the amount and the purity of their active ingredients vary so greatly from product to product. In many cases, we do not always know how much of the natural substance we are really getting in each dose or if other ingredients have been added. Another problem is determining how much of each active ingredient is really safe, particularly over long-term use. There are even case reports of contaminated herbs causing death. Also, studies are being done to see how herbals and supplements react with other medications.

The dose and form of a botanical preparation also play important roles in its safety. Teas, tinctures, and extracts have different strengths. The same amount of a botanical may be contained in a cup of tea, a few teaspoons of tincture, or an even smaller quantity of an extract. Also, different preparations vary in the relative amounts and concentrations of chemical removed from the whole botanical. The safety of herbal products may be related to the mixtures of active chemicals that they contain; their interactions with other herbs and drugs, contaminants, or adulterants; or their inherent toxicity. Active ingredients in herbs and dietary supplements can cause unexpected reactions when used with other herbs or medications. Effects on the distribution, metabolism, or excretion of drugs may be pronounced and may lead to drug toxicity. Contaminants and adulterants of herbal products can be pharmacologically active and responsible for unexpected toxicity. Because of the variability in herbal product ingredients, the actual dose of active ingredients being consumed is often variable, unpredictable, or simply unknown. When compared with adults, children may be particularly susceptible to the effects of such dosage variations by virtue of their smaller size and different capacity for detoxifying chemicals.

Nearly 16% to 18% of adults in the United States regularly use herbal supplements (21). Sales of herbal products in the United States doubled to $16 billion between 1994 and 2002 and 23% of those >50 years use herbal products (22). There are about 15 million adults at risk of experiencing adverse interactions from prescription medication, herbs, and/or vitamin supplements, including nearly three million adults age 65 or older (19,23,24). Given the misconception that herbal supplements have benign side effects, it is not surprising that one study found that almost two thirds of patients do not tell their physicians that they are taking supplements (25,26).

Therefore it is imperative to ask each patient to tell his health care provider every medication (prescribed and over-the-counter) as well as every vitamin and supplement that they are taking or have been taking recently. The physician should warn patients that such supplements may interfere with prescribed medications or that they may have side effects.

Numerous cases of toxicity have been linked to the use of herbal products (Table 1). The resulting problems range from minor adverse reactions to serious physical disabilities and death. The herb ma huang and all ephedrine alkaloids have received considerable attention from the FDA. More than 15 deaths have been attributed to the use of ephedrine alkaloid products (27). In 1996, the FDA issued a warning to consumers to avoid nutritional supplements containing ephedrine (28). In 1997, the FDA proposed the use of warning labels addressing the adverse effects of ephedrine, banning products containing more than 8 mg per serving, and eliminating products containing combinations of ephedrine and caffeine (29). A recent FDA report identified 76 botanicals known or suspected of containing aristolochic acid and 92 botanicals believed adulterated with aristolochic acid. Products containing a large amount of this substance may produce rapid-onset toxicity. However, the effects of long-term use are unknown. The first indication of adverse effects may be irreversible, such as renal failure (30).

Despite safety claims, patients and health care providers should be aware that abuse of dosages and problems with adulteration may render an otherwise safe herbal product dangerous. Ginseng, although considered by many sources to be relatively safe, had a

high incidence of adverse effects in a 2-year study by Siegel. The long-term use of ginseng has been associated with central nervous system excitation and arousal. The long-term effects have been labeled ginseng abuse syndrome (31,32).

In June 2000, the New England Journal of Medicine published a report by Nortier and others of an outbreak of urinary tract cancers in Belgium among users of a Chinese herbal product that contained aristolochic acid -- a known carcinogen found in an herb called *Aristolochia fangi* (33).

Table I: Side effects of some most commonly used herbal supplements

Common Name/ Source	Use	Possible Side effect
Ginkgo *(Ginkgo biloba)*	Dementia, memory improvement, SSRI-related impotence, antioxidant, inhibit platelet aggregation[34]	GI upset, headache, Nausea, Vomiting[35]
Kava *(Piper methysticum)*	Anxiolytic, sedative, muscle relaxant, anti-convulsant	Rare skin rash, sedation, Sedatives, hepatotoxicity[36, 37]
St. John's Wort *(Hypericum perforatum)*	Antidepressant, MAO inhibitor[38]	Photodermatitis, GI upset, sedation, Restlessness, fatigue, phototoxicity[39] constipation, dizziness, dry mouth, confusion[37, 40, 41]
Ephedra *(Ephedra spp.)*	Stimulant, nasal Decongestant, Bronchodilatior, appetite suppressant[42]	Death in overdose, cardiovascular Complications, Seizures, high blood pressure, cardiac arrhythmia and infarction, insomnia, psychosis, stroke, urine retention, uterine contractions[42]
Ginseng *(Panax ginseng)*	CNS stimulation and suppression, hypertensive, hypoglycemic, antioxidant, anti-inflammatory, anticancer, platelet inhibition, immune stimulant, antifatigue, improve sexual functions[43]	Diarrhea, euphoria, headache, hypertension, hypotension, insomnia (relatively common), mastalgia, nausea, vaginal bleeding, Sleeplessness, nervousness, hypertension, euphoria (GAS); hypertension together with nervousness, sleeplessness, skin eruptions, edema, morning diarrhea[32, 37, 44, 45]
Echinacea *(Echinacea spp.)*	Immune system stimulant, antifungal, anti-inflammatory	Anaphylaxis (rare) [37]
Kava *(Piper methysticum)*	Anxiolytic, muscle relaxant, mood enhancer, analgesic, sedative, antibacterial, platelet inhibitor, sedative	Reversible discoloration of skin, nails and hair[46] (chronic abuse); visual disturbances; dizziness; stupor; gastrointestinal discomfort; extrapyramidal effects[47] (rare); hepatotoxic[37]
Saw palmetto *(Serenoa repens)*	Treat benign prostatic hyperplasia, Improve overall prostate health, Enhance sexual vigor, enhance breast size.	GI disturbances, headaches, Large amounts may cause diarrhoea[37]

Aloe (Aloe barbadensis)	Laxative	Loss of electrolytes with chronic use[48]
Cascara (Rhamnus purshiana)	Topical analgesic/counter irritant Laxative	Loss of electrolytes with chronic use[48]
Senna *(Cassia spp.)*	Laxative	Diarrhea, nausea; avoid chronic use.[48]
Witch hazel *(Hamamelis virginiana)*	Astringent	Stomach irritation, liver damage if taken internally (rare).[48]
Valerian root *(Valeriana officinalis)*	Sleep aid[49]	Decreases blood pressure, heart palpitations, upset stomach[50]
Feverfew *(Crysanthemum parthenium)*	Treatment of migraine headaches, anti-inflammatory[51]	Increases heart rate, allergic reactions, mouth ulcers, headaches, gastric disturbances, post feverfew syndrome (withdrawal symptoms of aches, pains, and joint and muscle stiffness)[52]
Evening primrose oil *(Oenothera spp.)*	Anti-inflammatory, sedative, anticoagulant, astringent	Gastrointestinal disturbances[53]

Table 2: Possible interaction between herbal supplements and prescribed drugs

Common name/ Source	Prescribed drugs	Possible interaction
Ginkgo *(Ginkgo biloba)*	Aspirin	Increased anti-coagulation[55]
	Warfarin	Haemorrhage[56]
Ginseng *(Panax ginseng)*	Warfarin	Potentiation[57]
	Phenelzine	Headache, tremor, mania[54]
	Antidepressants	Induces mania in depressed patients[54]
	Benzodiazapines	Possible additive effects[54]
	MAOI'S	Possible additive effects[46]
	SSRI's (Antidepressant)	Additive serotonin-like effects[51]
St. John' s Wort *(Hypericum perforatum)*	Theophylline	Decreased theophylline concentration[54]
	Serotonin-reuptake inhibitors	Mild serotonin syndrome, decreased bioavailability of digoxin, theophylline, cyclosporin, phenprocoumon[54]
	Paroxetine	Lethargy, incoherence[54] Nausea, Fatigue[58]
	Oral contraceptive	Breakthrough bleeding[54]
Liquorice *(Glycyrrhiza glabra)*	Hydrocortisone	Glycyrrhetinic acid (an acid in topical anti-inflammatories) potentiates cutaneous vasoconstrictor response[54]
	Oral and topical corticosteroids	Potentiates corticosteroids[54]
	Oral contraceptives	Hypertension, edema, hypokalemia[54]

Interaction between herbal supplements and prescribed drugs:

Patients often neglect to mention herbal supplements when asked by their health care providers about medications taken on a regular basis because they assume that herbs are natural[18] and also feel their physician will not approve of their herbal use.(49, 53) However, not informing health care providers about herbal supplements use places patients at risk because of the possible interactions between drugs and herbs (Table 2). The known effects of using prescription drugs and herbs in combination are that herbs can mimic, magnify, or oppose the effect of the drugs. (53-54)

CONCLUSION

Many people use herbal supplements because they believe natural means safer and fewer side effects. The truth is, many herbs are dangerous and can interact with your prescription and over-the-counter drugs. Therefore the public need to be aware that "natural" does not mean "safe." Herbs should not be considered as miraculous cure-alls but rather compounds that work through simple biochemistry. Specific compounds trigger a specific physiologic effect-an effect that can be exacerbated if too much of a product is used or if it is used in combination with other medications. In addition, public should be aware that the hyperbolic advertising and advocacy literature surrounding herbal products often contains untested claims. If someone wishes to take an herbal supplement, he or she should use a standardized product. Products should have the scientific name and quantity of the botanical clearly identified on the label. The name and address of the manufacturer, lot number, and expiration date should be clearly marked. Inform the doctor, pharmacist and other health care professionals of any herbs we are considering or routinely use. People should be advised to stop taking the herb immediately if adverse effects occur.

REFERENCES

1. C. Brumley. Herbs and the perioperative patient. *AORN J.* **72:** 785-796 (2000).
2. J.E. Robbers, V.E. Tyler, Tyler's Herbs of Choice: The therapeutic use of Phytomedicinals, Vol I, New Delhi, CBS Publishers and Distributors; 23-39 (2002).
3. Washington, DC: US Food and Drug Administration; 1962. United States Code Title 21, Chapter 9, Section 360d Federal Food, Drug, and Cosmetic Act. Drug Amendments. (1962).
4. V.E. Tyler. What pharmacists should know about herbal remedies? *J. Am. Pharm. Assoc.* **36:** 29–37 (1996).
5. E.Q. Youngkin, D.S. Israel. A review and critique of common herbal alternative therapies. *Nurse Pract.* **21:** 39–52(1999).
6. V.E. Tyler, The Honest Herbal, 3rd ed. New York, Pharmaceutical Products Press; (1993).
7. M. D. Rotblatt. Herbal medicine: A practical guide to safety and quality assurance. *Western J. Med.* **171:** 172-175 (1999).
8. M. Blumenthal. HerbalGram No.32. 18-20 (1999).
9. L.D. Israelsen. *J. Altern. Complem. Med.* 245-248 (1995).
10. Public Law 103-418 (S. 798) Dietary Supplement Health and Education Act of 1994. pp. 1–47. 103rd Cong, 2nd Sess. (1994).
11. C. Mar, S. Bent. An evidenced based review of the 10 most commonly used herbs. *Western J. Med.* **171:** 168-171. (1999).
12. Washington, DC: US Food and Drug Administration. Dietary Supplement Stakeholder Meeting. (1999).
13. K. Flanagan. Preoperative assessment: Safety considerations for patients taking herbal products. *J. Perianesth. Nurs.* **16:** 19-26 (2001).
14. G. Benzi, A. Ceci. Herbal medicines in European regulation. *Pharmacol. Res.* **35:** 355–362 (1997).
15. B. Barrett, D. Kiefer, D. Rabago. Assessing the risks and benefits of herbal medicine: An overview of scientific evidence. *Altern. Ther.* **5:** 40-49 (1999).
16. M. Blumenthal, German Commission E Monographs: Therapeutic Monographs on Medicinal Plants (Austin, Tex: American Botanical Council, 1998).
17. M. S. Nelson, J. Novack, K. Puntam. Safety of herbal supplements. *Top. Clin. Nutr.* **14:** 42–51 (1998).
18. D.M. Eisenberg, R.C. Kessler, C. Foster, F.E. Norlock, D.R. Calkins, T.L. Delbanco. Unconventional medicine in the United States: prevalence, costs, and patterns of use. *N. Engl .J. Med.* **328:** 246–252 (1993).
19. D. M. Eisenberg. Trends in alternative use in the United States, 1990-1997: Results of a follow-up national survey. *J. Am. Med. Assoc.* **286:** 1569-1575 (1998).
20. M. K. Ang-Lee, J. Moss, C. Yuan. Herbal medicines and perioperative care. *J. Am. Med. Assoc.* **286:** 208-216 (2001).
21. K.B. Keller, L. Lemberg. Herbal or complementary medicine: Fact or fiction? *Am. J. Crit. Care.* **10(6):** 438-43 (2001).

22. S. B. Eskin, Dietary supplements and older consumers. *Data Digest*. Washington, DC: 1-8. (2001).
23. S.S. Handa, V.K. Kapoor, Text Book of Pharmacognosy, 2nd ed., Delhi, Vallabh Prakashan, 312-324 9 (2005).
24. D.M. Studdert. Medical malpractice implications of alternative medicine. *J. Am. Med. Assoc*. **280(18):** 1610-5 (1998).
25. D. M. Eisenberg, Advising patients who seek alternative medical therapies. *Ann. Intern. Med*. **127(1):** 61–9 (1997).
26. A.H. Wong, M. Smith, H.S. Boon. Herbal remedies in psychiatric practice. *Arch. Gen. Psychiatry*. **55(11):** 1033–44 (1998).
27. J.B. Myers, K.M. Guskiewicz, B.L. Riemann. Syncope and atypical chest pain in an intercollegiate wrestler: a case report. *J. Athl. Train*. **34:** 263–266 (1999).
28. M.D. Rockville, US Food and Drug Administration: National Press Office. FDA statement on street drugs containing botanical ephedrine. (1996).
29. Dietary supplements containing ephedrine alkaloids: proposed rule. Federal Register. 30677-30724. (1997).
30. C.J. Lewis, M. D. Rockville. FDA Center for Food Safety and Applied Nutrition; Letter to industry: FDA concerned about botanical products, including dietary supplements containing aristolochic acid. (2000).
31. Siegel, R. K. Ginseng abuse syndrome: problems with the panacea. *J. Am. Med. Assoc*. **241:** 1614-1615 (1979).
32. R. Siegel. Ginseng and high blood pressure. *J. Am. Med. Assoc*. **243:** 32 (1980).
33. J.L. Nortier. Urothelial carcinoma associated with the use of a Chinese herb *(Aristolochia fangchi)*. *N. Engl .J. Med*. **342:** 1686-1692 (2000).
34. S. Foster, Herbal medicine: an introduction for pharmacists. *NARD J*. **10:** 127-44. (1996).
35. N. C. Brazier, M. A. Levine. Drug-herb interaction among commonly used conventional medicines: A compendium for health care professionals. *Am. J. Ther*. **10(3):** 163–9 (2003).
36. E.M. Williamson. Drug interactions between herbal and prescription medicines. *Drug Saf*. **26(15):** 1075–92 (2003).
37. F. Ernst. The risk-benefit profile of commonly used herbal therapies: Ginkgo, St. John's wort, ginseng, echinacea, saw palmetto and kava. *Ann. Intern. Med*. **136:** 42-53 (2002).
38. J. M. Cott. In vitro receptor binding and enzyme inhibition by *Hypericum perforatum* extract. *Pharmacopsychiatry*. **30(2):** 108-12 (1997).
39. S. Golsch, E. Vocks, J. Rakoski, K. Brockow, J. Ring. Reversible increase in photosensitivity to UV-B caused by St. John's wort extract. *Hautarzt*. **48:** 249-52 (1997).
40. M. Blumenthal, A. Goldberg, J. Brinckman, Herbal Medicine: Expanded Commission E Monographs. Newton, MA: Lippincott Williams & Wilkins; 359-366 (2000).
41. S. Zhou, E. Chan, S.Q. Pan, M. Huang, E.J. Lee. Pharmacokinetic interactions of drugs with St John's wort. *J. Psychopharmacol*. **18(2):** 262–76 (2004).
42. Dietary supplements containing ephedrine alkaloids; proposed rule. 21 CFR Part 111. Fed Register. **62(107):** 30677-724 (1997).
43. K. Janetzky, A.P. Morreale. Probable interaction between warfarin and ginseng. *Am. J. Health/Syst. Pharm*. **54:** 692-3 (1997).
44. R. K. Siegel. Ginseng abuse syndrome: problems with the panacea. *J. Am. Med. Assoc*. **241:** 1614-1615 (1979).
45. J.T. Coon, E. Ernst. Panax ginseng: a systematic review of adverse effects and drug interactions. *Drug Saf*. **25:** 323-44 (2002).
46. U. Jappe, I. Franke, D. Reinhold, H.P. Gollnick, Sebotropic drug reaction resulting from kava-kava extract therapy: a new entity? *J. Am. Acad. Dermatol*. **38:** 104-6. (1998).
47. J.C. Almedia, E.W. Grimsley. Coma from the health food store: interaction between kava and alprazolam. *Ann. Intern. Med*. **125:** 940-1 (1996).
48. E.Q. Youngkin, D. S. Israel. A review and critique of common herbal alternative therapies. *Nurse Pract*. **21:** 39–52 (1999).
49. P.D. Leathwood, F. Chauffard, E. Heck, R. Munoz-Box. Aqueous extract of valerian root (*Valeriana officinalis* L.) improves sleep quality in man. *Pharmacol. Biochem. Behav*. **17:** 65-71 (1982).
50. M. Cropley, Z. Cave, J. Ellis, R.W. Middleton. Effect of kava and valerian on human physiological and psychological responses to mental stress assessed under laboratory conditions. *Phytother. Res*. **16:** 23-7 (2002).
51. C.K. O'Neil, J.R. Avila, C.W. Fetrow. Herbal medicines: getting beyond the hype. *Nursing*. 58-61 (1999).
52. P. Gardiner, K. J. Kemper. Herbs in pediatric and adolescent medicine. *Pediatr. Rev*. **21:** 44–57

(2000).

53. J. Fischman. Herbs and prescriptions can make a risky mixture. US News & World Report. **128:** 64–65 (2000).
54. A. Fugh-Bergman. Herb-drug interactions. *Lancet*. **355:** 134–138 (2000).
55. L. M. Gianni, W. B. Dreitlein. Some popular OTC herbals can interact with anticoagulant therapy. *US Pharmacist*. **80:** 83-4, 86 (1998).
56. M.K. Matthews. Jr. Association of Ginkgo biloba with intracerebral hemorrhage. *Neurology*. **50:** 1933-4 (1998).
57. L. Schelosky, C. Raffauf, K. Jendroska, W. Poewe. Kava and dopamine antagonism. *J. Neurol. Neurosurg. Psychiatry*. **58:** 639-40 (1995).
58. J. B.Gordon. SSRIs and St. John's wort: possible toxicity? *Am. Fam. Physician*. **57:** 950-953 (1998).