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Herb-Drug Interactions

By Dónal P. O'Mathúna, PhD

THE USE OF HERBAL REMEDIES HAS EXPANDED WIDELY IN THE LAST decade. Sales of dietary supplements in the United States doubled every two years between 1991 and 1999.[1] According to the Natural Marketing Institute, a consulting group that monitors consumer trends, nearly $17 billion was spent on dietary supplements in 2001 in the United States—with herbal remedies estimated to generate $4 billion.[2] Izzo and Ernst have estimated that Europe spends nearly $7 billion on herbal therapies.[3]

Along with this sustained growth in usage has come increasing scrutiny into the safety of herbal remedies. On the one hand, some studies find evidence that certain herbs may be effective for specific conditions. But on the other hand, there is growing evidence that many products available on the U.S. market are of poor quality.[4] In addition, several studies have found herbal products that are contaminated with prescription drugs, pesticides, or heavy metals.[5] As is the case with pharmaceuticals, even the highest quality herbal remedies have dangers inherent to their use; dangers of which consumers often are unaware. A National Consumers League survey released in 2002 found that 86% of Americans believe that products labeled "natural" are safe.[6] Yet if herbal remedies are effective, they must contain biologically active chemicals, which increases the possible risk of side effects and interaction with other drugs.

This article will focus on the interactions between herbal remedies and pharmaceutical drugs. Research in this area has been slow to develop, in part because of a failure to recognize the significance of the problem.

Systematic reviews of the medical literature reveal relatively few case reports.[7] Some take this to mean that the risks of herbal remedies are being blown out of proper proportion as a way to distract public attention from the risks of pharmaceuticals.[8] Yet there also are many reasons to believe that herb-drug interactions have been under-reported. As one reviewer commented, "Lack of evidence of risks is clearly not the same as evidence of lack of risks."[9] However, a number of unexpected bleeding episodes during and after surgery have been linked to interactions between herbal remedies and drugs used during and after surgery, leading the American Society of

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INSIDE

Anesthesiologists to suggest that patients discontinue all dietary supplements at least two weeks prior to surgery.[10]

All herbal remedies are complex mixtures of compounds, any number of which might interact with drugs taken at the same time. However, often there is little information on the active ingredient in the remedy, and even less on which ingredient(s) might interact with drugs or other herbs. People taking herbs often are treating themselves for chronic ailments for which they likely are taking prescribed pharmaceutical drugs. Because many patients take herbal remedies without telling their conventional practitioners, the chances are increased that adverse symptoms may not be viewed as interactions between herbs and drugs.

As more case reports become available involving herbal remedies, it will be important to evaluate the quality of reports. Fugh-Berman and Ernst have developed a 10-point scale that allows ready evaluation of the quality of a case report.[7]

Each case is given one point for each criterion satisfied *(see Table 1)*, and then scored according to the following scale:

0-3 points: unevaluable—report contains insufficient information to determine the likelihood of an interaction;

Table 1

10-point scoring system[8]

- Adequate patient history given
- Concurrent diseases, conditions, or medications associated with the adverse event
- Concomitant medications documented
- Adequate description of interactors
- Obvious alternative explanations have been excluded
- Chronology complete
- Time between taking herb and adverse event manifesting itself is reasonable
- Adverse event is adequately described
- Event ceases when herb stopped
- Event recurs upon rechallenge

4-7 points: possible interaction—evidence points to an interaction, but other causes may be involved;

8-10 points: likely interaction—report provides reliable evidence for an interaction.[7]

As additional cases of interactions between herbs and drugs are reported, this scoring system gives providers a handy checklist for evaluating the quality of each report. These same authors went on to review the medical literature and identified 108 case reports of adverse events alleged to involve interactions between herbal remedies and drugs.[7] Using the above system, 74 were classified as unevaluable, 20 were possible interactions, and 14 were likely interactions. Warfarin was the drug most commonly involved in adverse event reports, while St. John's wort was the herb most commonly implicated.

The case of St. John's wort is a good example of the importance of conducting rigorous research on herbal remedies. Clinical studies have demonstrated that St. John's wort is as effective as sertraline and imipramine in the treatment of mild depression, but is no more effective than placebo in treating major depression.[11] Increased medical attention and widespread popular use of St. John's wort also has led to it being the herb with the largest number of case reports of herb-drug interactions (85 cases). Of these, 54 involved cyclosporin, 12 involved oral contraceptives, seven involved warfarin, nine with antidepressants, and one each with phenprocoumon, theophylline, and loperamide.[7] In addition, four clinical studies have provided more rigorous data about the nature of the interactions.[12]

Patients taking St. John's wort also may be taking pharmaceutical antidepressants. Nine case reports have documented symptoms of serotonin syndrome that may have been the result of each substance potentiating the

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other. A variety of antidepressants were involved, most commonly sertraline, but also including nefazodone and trazodone.[12] Some may assume that treating their conditions with both herbal remedies and pharmaceutical drugs will bring added benefits; however, this may increase the likelihood of adverse effects.

Several studies (though not every study) have found evidence that St. John's wort induces one of the cytochrome P450 enzymes, thus providing a mechanism of action to explain the reports of interactions.[13] Yet St. John's wort contains several biologically active ingredients, and the extent of the reported herb-drug interactions could not be explained by induction of P450 enzymes alone. A recent clinical study demonstrated that after taking St. John's wort for 32 days, patients had a four-fold increase in the expression of P-glycoprotein.[14] This molecular complex functions as a pump to actively eliminate drugs from cells and facilitates the development of resistance to those drugs, which include methotrexate, protease inhibitors, and steroids. Research is ongoing in developing inhibitors of P-glycoprotein that might serve to enhance the effectiveness of other drugs, particularly chemotherapy agents. Clearly, the effectiveness of those drugs would be counteracted by St. John's wort.

Consumer interest in St. John's wort has led to research into its effectiveness and safety. This has revealed evidence of both efficacy and drug-herb interactions. As a result, patients can be better advised about the conditions for which St. John's wort may be most beneficial, and about the drugs that should be avoided or carefully monitored if taken concomitantly.

Table 2

Herb-drug interactions

Herb Name(s)	Drug Name	Type of Interaction	Signs and Symptoms	Type of Evidence
Aloe gel Aloe vera *Aloe barbadensis*	Diuretics	Potentiation due to potassium-depleting effects	Confusion, weakness, irregular heartbeat	Case reports
	Hypoglycemic agents	Potentiation		Traditional
	All drugs	Reduced effectiveness due to binding with drug		Traditional
Bilberry *Vaccinium myrtillus*	Anticoagulants	Potentiation at high doses	Increased bleeding time	Case reports
Cascara sagrada *Rhamnus purshianus*	Diuretics	Potentiation due to potassium-depleting effects	Confusion, weakness, irregular heartbeat	Case reports
Chamomile, German *Matricaria recutita*	Sedatives (e.g., chlorpheniramine, trazodone, diazepam)	Potentiation	Excessive drowsiness, loss of coordination, trouble driving	Theoretical
	Anticoagulants	Potentiation	Increased bleeding time	Theoretical
Chaparral *Larrea tridentata*	Phenobarbital	Potentiation of liver toxicity	Liver toxicity	Theoretical
Chasteberry, Chaste tree *Vitex agnus-castus*	Oral contraceptives and hormone replacement	Reduced effectiveness due to herb's effect on progesterone		Theoretical
	Anticancer agents for hormone-sensitive cancers	Reduced effectiveness due to herb's estrogenic activity		Theoretical

Table 2

Herb-drug interactions, cont'd

Herb Name(s)	Drug Name	Type of Interaction	Signs and Symptoms	Type of Evidence
Comfrey *Symphytum officinale*	Phenobarbital	Potentiation of liver toxicity	Liver toxicity	Case reports
Danshen *Salvia miltiorrhiza*	Warfarin	Potentiation due to presence of coumarins in herb	Increased bleeding	Case reports
Dong quai *Angelica sinensis*	Anticoagulants	Potentiation due to presence of coumarins in herb	Increased bleeding	Case reports
Echinacea *Echinacea purpurea*, *E. angustifolia*, *E. pallida*	Immunosuppressive agents (e.g., cyclosporin)	Reduced effectiveness	Shivering, fever, muscle weakness	Theoretical
	Drugs metabolized by cytochrome P450 3A4 enzyme (e.g., lovastatin, fexofenadine, triazolam)	Potentiation due to inhibition of metabolizing enzyme		In vitro studies
Ephedra Ma huang *Ephedra sinica*	MAO inhibitors	Potentiation due to sympathomimetic action	Excitability, restlessness, hypertension	Case reports
	Caffeine and other stimulants	Potentiation	Excitability, hypertension, stroke, death	Case reports
	Antihypertensive agents	Reduced effectiveness due to herb's sympathomimetic actions	Hypertension	Case reports
	Theophylliine	Potentiation due to sympathomimetic action	Rapid heart rate, anxiety, hypertension	Theoretical
	Cardiac glycosides	Reduced effectiveness	Cardiac arrhythmia	Theoretical
Evening primrose oil (EPO) *Oenothera biennis*	Phenothiazines, anesthetics	Increased risk of seizures as drug and herb lower the seizure threshold level	Epileptic events	Case reports
Feverfew *Tanacetum parthenium*	Anticoagulants	Potentiation due to inhibition of platelet aggregation	Increased bleeding	Case reports
Garlic *Allium sativa*	Anticoagulants	Potentiation due to inhibition of platelet aggregation	Increased bleeding	Case reports
Ginger *Zingiber officinalis*	Anticoagulants	Potentiation due to inhibition of platelet aggregation	Increased bleeding	Case reports
	Antacids	Reduced effectiveness due to increased gastric secretion	Heart burn	Case reports

Table 2

Herb-drug interactions, cont'd

Herb Name(s)	Drug Name	Type of Interaction	Signs and Symptoms	Type of Evidence
Ginkgo *Ginkgo biloba*	Anticoagulants	Potentiation due to inhibition of platelet aggregation factor	Increased bleeding, spontaneous bleeding	Case reports, animal study
	Trazodone	Potentiation due to inhibition of drug metabolism	Sedation, coma	Case report
	Thiazide diuretics	Unclear interaction	Hypertension	Case report
Ginseng (Asian) *Panax ginseng*	Hypoglycemic agents	Potentiation	Hypoglycemia	Case reports, clinical studies
	MAO inhibitors	Potentiation	Insomnia, headache, tremors	Case reports
	Digoxin	Elevated digoxin levels	Risk of digitalis toxicity, tachycardia	Case reports
	Anticoagulants	Potentiation due to inhibition of platelet aggregation and reduced effectiveness reported	Changed bleeding time	Conflicting case reports
	Sildenafil	Potentiation due to herb's stimulation of nitric oxide release		Theoretical
	Anti-estrogens	Reduced effectiveness due to estrogen-like activity of herb		Theoretical
Ginseng (Siberian) *Eleutherococcus senticosus*	Digoxin	Elevated digoxin levels, probably due to interference with digoxin assay	None	Case reports
Guarana *Paullinia cupana*	Antihypertensives	Reduced effectiveness due to herb's CNS stimulant effects	Increased blood pressure	Case report
	Halothane	Interaction	Dysrhythmias	Case reports
	Cardiac glycosides	Increased sensitivity to drug due to increased potassium secretion		Case reports
	Diuretics	Increased sensitivity to drug due to increased potassium secretion	Diuresis	Case reports
	CNS stimulants	Potentiation due to herb's caffeine content (up to 5%)	Restlessness, insomnia, excitability	Theoretical
Hawthorn *Crataegus laevigata*	Cardiac glycosides	Potentiation due to similar mechanism of action	Cardiac glycoside toxicity	Theoretical
	CNS depressant	Potentiation due to similar activities	CNS depression	Theoretical

Table 2

Herb-drug interactions, cont'd

Herb Name(s)	Drug Name	Type of Interaction	Signs and Symptoms	Type of Evidence
Kava *Piper methysticum*	Anxiolytics	Potentiation	Tremors, somnolence	Case reports
	Alcohol	Potentiation	Increased impairment, hypnotic effects	Clinical study
	Anticoagulants	Potentiation	Increased bleeding	Theoretical
	MAO inhibitors	Potentiation	Hypertension	Theoretical
Kelp, Bladderwrack *Fucus vesiculosus*	Thyroid-hormone replacement therapy	Interference as the herb contains iodine		Theoretical
Licorice *Glycyrrhiza glabra*	Prednisolone, hydrocortisone	Potentiation due to reduced plasma clearance	Hypertension, edema	Case reports, clinical studies
	Thiazide diuretics	Increased risk of hypokalemia due to increased urinary excretion of potassium		Case reports
	Antihypertensives	Reduced effectiveness after 4 weeks of herb due to inhibition of rennin-angiotensin system	Hypertension	Case reports, in vitro studies
	Cardiac glycosides	Increased sensitivity to drugs after 4 weeks due to hypokalemic effect of herb	Dysrhythmias, hypertension	Theoretical
Psyllium *Plantago ovata*	Lithium	Reduced effectiveness due to interference with lithium ionization		Case reports
Red yeast rice *Monascus purpureus*	Statin drugs	Potentiation as both contain the same class of drugs	Liver damage	Theoretical
Saw palmetto *Serenoa repens*	Hormone replacement therapy and oral contraceptives	Potentiation due to herb's steroidal content		Theoretical
	Anticoagulants	Potentiation	Bleeding risk	Theoretical
Senna *Senna alexandrina, Cassia angustifolia*	Diuretics	Potentiation due to potassium-depleting effects	Confusion, weakness, irregular heartbeat	Case reports
Stinging nettle *Urtica dioica*	Hypoglycemic agents	Reduced effectiveness	Hyperglycemia	Clinical study
	NSAIDs	Potentiation		Theoretical

Table 2

Herb-drug interactions, cont'd

Herb Name(s)	Drug Name	Type of Interaction	Signs and Symptoms	Type of Evidence
St. John's wort *Hypericum perforatum*	Other antidepressants	Potentiation due to increased serotonin levels	Euphoria, drowsiness, muscle twitching, sweating, diarrhea, loss of consciousness	Case studies
	Various drugs metabolized via cytochrome P450 (e.g., cyclosporin, oral contraceptives, theophylline, HIV protease inhibitors)	Reduced plasma levels of drugs due to induction of cytochrome P450 metabolizing enzymes	Reduced effectiveness of drugs taken concomitantly	Case reports, clinical studies
	Anticoagulants	Reduced effectiveness	Loss of anticoagulant effect	Case reports
	Digoxin	Reduced effectiveness	Loss of cardioprotective effect	Clinical study
	MAO inhibitors	Potentiation	Elevated blood pressure	In vitro studies
	Photosensitizing agents (e.g., chlorpromazine, tetracyclines, interferons, isotretinoin)	Potentiation of photosensitivity	Rash, sunburn	Animal studies
Valerian *Valeriana officinalis*	Barbiturates and other CNS depressants	Potentiation	Prolonged sleep and drowsiness, increased risk of falls	Case reports
Yohimbine *Pausinystalia yohimbe, Corynanthe yohimbe*	Tricyclic antidepressants	Potentiation of hypertension by drug	Hypertension, especially in hypertensive patients	Case reports
	Spironolactone	Reduced effectiveness due to potassium-depleting effects	Hypertension	Theoretical

For most herbs, however, the evidence for herb-drug interactions is of lesser quality. Even with the St. John's wort case reports, only seven (8%) satisfied enough of Fugh-Berman and Ernst's criteria to be classified as "likely interactions."[7] Given these limitations, Table 2 has been compiled from many sources to give guidance on the types of interactions most likely to occur with commonly used herbs. Many interactions are supported only by a theoretical connection with the herb's mechanism of action, or a concern based on traditional use.

Unfortunately, due to lack of uniform reporting requirements, the incidence of each interaction is not known.

For these reasons, clinicians merely can alert patients to the fact that herbs may interact with other medications and dietary supplements. Patients should be encouraged to be open about all the substances they are consuming, regardless of whether they view them as drugs. Such openness can be encouraged if clinicians know about the risks and benefits of herbal medicines, including some of the most common herb-drug interactions presented in this article.

Increased surveillance of patients for herb-drug interactions is another important way to develop accurate knowledge in this area. If an interaction between an herb and a drug is suspected, it should be reported to the Food and Drug Administration's MedWatch program in the

same way as drug-drug interactions are reported (1-800-FDA-1088 or www.fda.gov/medwatch).

Table 2 is not exhaustive and will need to be updated as new reports and studies are published. Those seeking more detailed information or information on herbs not mentioned in Table 2 are encouraged to consult the articles and general resources listed in the reference below. ❖

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Melissa officinalis (Lemon Balm) to Treat Herpes Labialis

By Cydney E. McQueen, PharmD

MELISSA OFFICINALIS (LEMON BALM) TRADITIONALLY has been used as a carminative for gastrointestinal distress, including flatulence and colic, or as a mild sedative.[1,2] The Greeks and Romans used lemon balm for wound dressings and to treat bites and stings. Investigations of its chemical constituents in various in vitro and animal studies reveal antibacterial, antiviral, anti-inflammatory, astringent, and sedative properties.[2]

Pharmacology

Melissa officinalis leaves have a range of chemical constituents; of primary importance are the tannins, polyphenols, glycosides, and rosmarinic acid.[2-4] Early

work with tannin and polyphenol components demonstrated activity against numerous viruses, including herpes simplex.[3,5,6] Later investigations attribute antiviral effects more specifically to phenolcarboxylic acid.[7] Two non-tannin components inhibit protein biosynthesis by blocking leucine incorporation and ribosomal activity.[8]

Mechanism of Action

Blockade of receptors used by the herpes virus for cell adsorption prevents viral entry into the cell, thereby interfering with viral replication.[7]

Clinical Trials

The earliest clinical trial examining topical melissa for herpes simplex infection was published in 1984.[9] Only three other trials have been published, two of which are available in English.[7,10,11]

Koytchev's study[7] was a randomized, double-blind controlled trial (RDBCT) of Lomaherpan™, a proprietary 1% cream of a lyophilized aqueous extract.[3] The cream was applied daily for five days and compared to a placebo of identical vehicle. A priori calculations indicated 33 patients per group were needed for 80% power. Because of the irregularly recurring nature of herpes outbreaks, 120 patients who met inclusion criteria were given either melissa or placebo cream with instructions to begin treatment within four hours of prodromal symptoms and to return for a physician visit within 24 hours. Sixty-six patients (34 treatment, 32 placebo) complied and constituted the enrolled subjects. Patients must have had at least four episodes per year of clinically diagnosed herpes labialis with typical blister presentation and experienced prodromal complaints of itching, tingling, and burning. Physician visits occurred at days 1, 2, 3, and 5 after symptom onset. Complaints, number of blisters, and size of affected area were scored on a scale developed for acyclovir trials.

Primary endpoint was symptom score on day 2 (DS2), with a secondary endpoint of total scores (TS) of symptoms over five days of treatment. Both groups were similar in regard to demographics and baseline characteristics of time, duration, and severity of last episode, as well as time between current and last episodes. There was a significant difference ($P = 0.042$) between treatment and placebo groups for mean DS2 (4.03 and 4.94, respectively). The small difference between groups for symptom scores over the five-day treatment period was not significant ($P = 0.16$) and the physician assessment showed a trend toward improvement, but this also was not statistically significant ($P = 0.083$). Difference in number of blisters present was significant in favor of treatment when ratings were grouped (0 or 1 blister, and > 2 blisters, $P = 0.047$), but not when each rating was considered separately (0, 1, 2-3, > 3 blisters, $P = 0.15$). Investigators concluded that results for primary and secondary endpoints were "coherent" and demonstrated efficacy and "a significant reduction in each of the components" of the total score.

This well-designed study had validated primary endpoints; all statistical tests were used appropriately. Using DS2 as the primary endpoint is appropriate because symptoms of herpes labialis are typically the worst on day 2 of an outbreak. Investigators did compare results to previous trials and discussed confounding factors. Major trial limitations include inadequate enrollment to meet power and overstated conclusions given the results presented. There is question as to whether the statistically significant difference between groups on day 2 is clinically significant. Other questions involve the lack of reporting of side effects, if any occurred, and use of concomitant medications.

Wölbling's 1994 publication described two studies, both using the same 1% extract cream.[11] The first was an open-label pilot with 115 patients who had skin and transitional mucosa herpes simplex infections. The subjects were directed to use the cream five times daily until lesions were healed, but for no more than 14 days. Symptoms were assessed at days 0, 4, 6, and 8. On day 8, 96% of patients had completed the healing process, which the authors note, has a normal range of 10-14 days.

The second study in Wölbling's article was a RDBCT using the same melissa cream against placebo in 116 patients. Patients must have had prodrome symptoms for no more than 72 hours, could have either skin or transitional mucosa infections, and could not be on any antiviral treatment. Patients were to apply cream two to four times daily for at least five but no more than 10 days. Patients were assessed on a 1-4 symptom scale for redness, swelling, vesicles, scabs, pain, and healing; lesion size was measured; and a global assessment of efficacy (GAE, 1-5 scale) was carried out by the patient and physician at trial end. Groups were similar after randomization for all characteristics (duration of prodrome, prestudy treatments, and sites of infection) and demographics except for age, because of the inclusion of three children in the placebo group. At day 2, there was significantly greater improvement in the melissa group for redness ($P < 0.01$) and swelling ($P < 0.05$), but not other symptoms. Melissa patients had less scabbing, but this did not reach significance. A significant difference ($P = 0.037$) favoring melissa also was found in the planar area on day 2. Melissa also was favored in GAE ratings by both physicians and patients ($P = 0.031$,

P = 0.022, respectively). Reported side effects included irritation (two in the placebo group, one in the melissa group) and burning (in two placebo patients). Of three dropouts, one melissa patient withdrew because of symptom exacerbation and one did not follow up; the placebo patient withdrew secondary to persistent itching. A subgroup analysis performed on the herpes labialis patients (n = 67) showed a faster decrease in lesion area in the treatment group that was significant on day 5 (P = 0.012), but not on day 2.

Outcome measures were appropriate. Investigators discussed a possible bias against the treatment group; patients had a longer duration of symptoms (4.5 hours on average) before beginning treatment than the placebo patients. This explanation is not clear and conflicts with earlier text stating mean prodromal symptom durations were the same in both groups. A significant trial limitation is the variable dosing; there was no explanation of why this was permitted, especially considering results of the open-label study. Another limitation is inclusion of various types of herpes infections, leading to difficulties in comparing characteristics such as lesion size and area. The authors concluded that treatment must be "started in the very early stages of the infection" in order to be effective, yet there are no conclusive data regarding differences in outcome compared to timing of treatment start to support this statement.

Adverse Events

Used topically for herpes labialis, adverse events are limited to irritation. There has been one report of exacerbation of symptoms.[11] Patients with hypersensitivity to *Melissa officinalis* or preparation components should be counseled against use. No interactions are known for topical administration.[12]

There are no known concerns or documented warnings against the use of topical preparations in pregnant or lactating women.

Formulation and Dosage

The proprietary concentrated preparation used in the trials is made with a 1% lyophilized aqueous extract that is applied two to five times daily. A 1% *Melissa officinalis* 70:1 extract called "Cold Sore Relief" is available in the United States from Enzymatic Therapy.

Melissa brews or teas used as poultices, although recommended in some references, are unlikely to be effective.[13]

Conclusion

Results of the two Level II trials available for analysis demonstrated statistically significant differences in resolution of some herpes labialis symptoms in a comparison of *Melissa officinalis* extract cream and placebo. However, only one of these trials limited the herpes infections to labialis, and both have major limitations that affect assessment of clinical effectiveness. The extent to which melissa speeds healing of cold sores has not been well quantified and comparisons to antiviral treatments such as topical acyclovir are needed. Claims that melissa, when administered during the prodrome, will prevent full development of an outbreak also need to be tested.

Recommendation

Despite the positive results of these two trials, there is still not enough evidence to state with certainty that melissa extract is an efficacious treatment for herpes labialis. However, considering that herpes labialis is normally a self-limiting condition, that reported adverse events for melissa are minor, and that topical pharmaceutical preparations also are not highly effective, topical melissa extract can be considered an option for treatment. Patients should be counseled that although some controlled studies demonstrated benefit, the effects may be minor, are not known with certainty, and may vary according to product. ❖

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CME Questions

CME Instructions: Physicians participate in this continuing medical education program by reading the article, using the provided references for further research, and studying the CME questions. Participants should select what they believe to be the correct answers, then refer to the list of correct answers to test their knowledge. To clarify confusion surrounding any questions answered incorrectly, please consult the source material. After completing this activity, you must complete the evaluation form provided at the end of each semester (June and December) and return it in the reply envelope provided to receive a certificate of completion. When your evaluation is received, a certificate will be mailed to you.

21. Several studies of herbal products have found them to be contaminated with:
a. prescription drugs.
b. pesticides.
c. heavy metals.
d. All of the above

22. Unexpected bleeding episodes that have been linked to interactions between herbal products and drugs used during and after surgery prompted the American Society of Anesthesiologists to suggest that patients discontinue all dietary supplements:
a. at least two hours prior to surgery.
b. at least two days prior to surgery.
c. at least two weeks prior to surgery.
d. at least two months prior to surgery.

23. Concerns about many herb-drug interactions are supported by:
a. theoretical evidence.
b. a possible mechanism of action.
c. traditional usage.
d. All of the above

24. When *Melissa officinalis* is used topically for herpes labialis, adverse effects are limited to irritation.
a. True
b. False

25. Although not proven to be efficacious, *Melissa officinalis* may be considered an option for treating herpes labialis because:
a. herpes labialis normally is a self-limiting condition.
b. reported adverse events for melissa are minor.
c. topical pharmaceutical preparations are not highly effective.
d. All of the above

Answer key: 21. d, 22. c, 23. d, 24. a, 25. d.

Clinical Briefs

With Comments from Russell H. Greenfield, MD

PUFAs and Atherosclerotic Plaques

Source: Thies F, et al. Association of n-3 polyunsaturated fatty acids with stability of atherosclerotic plaques: A randomized controlled trial. *Lancet* 2003;361:477-485.

Goal: To ascertain whether incorporation of n-3 and n-6 polyunsaturated fatty acids (PUFAs) into advanced atherosclerotic plaques increases and decreases, respectively, plaque stability.

Design: Double-blind, randomized controlled study.

Subjects: One hundred eighty-eight patients awaiting carotid endarterectomy (total of 162 patients completed the study).

Methods: Patients were given either control oil (80:20 blend of palm and soybean oils); sunflower oil, or fish oil while continuing on their drug regimens and regular diet. Each patient took six capsules daily (two with each meal) until the date of surgery. Duration of treatment was 7-189 days (median of 42 days). Plaque morphology was evaluated for evidence of stability or instability. The researchers measured concentrations of eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), and linoleic acid in carotid plaques, and tested for the presence of macrophages in plaques via immunohistochemical staining.

Results: Concentrations of EPA and DHA in plaque were highest in patients receiving the fish oil capsules. Plaques from patients treated with fish oil had

fewer morphologic signs consistent with inflammation than plaques from those in the sunflower oil or control groups. The number of macrophages found within the plaques of subjects receiving fish oil was less than in the other two groups. Carotid plaque morphology, fatty-acid compositions of plaque lipid fractions, and macrophage infiltration did not differ between control and sunflower oil groups.

Conclusion: n-3 PUFAs from fish oil supplementation are rapidly incorporated into atherosclerotic plaques and limit inflammatory changes, thereby enhancing plaque stability.

Study strength: Adherence to protocol was estimated to be 85-90% in each treatment group.

Study weakness: No group was randomized to a diet high in oily fish.

Of note: Study results suggest that atherosclerotic plaques are relatively dynamic; the fatty acid content of the 80:20 palm and soybean oil blend is stated to closely match that of the average British diet; increased intake of n-6 PUFAs from sunflower oil did not affect the fatty acid composition of plaque, nor plaque stability compared with controls.

Did you know? n-3 PUFAs lower triglyceride levels and have been shown to be very effective in reducing rates of sudden death; the amount of fish oil provided in the capsules can be obtained through regular dietary consumption of oily fish; macrophages contribute to plaque inflammation and instability; vulnerability of plaque to rupture is the primary determinant of acute thrombosis-mediated cardiovascular events.

Clinical import: Although no direct harm was identified with the use of n-6 PUFAs from sunflower oil, there was evidence of benefit from the use of fish oil supplementation. The n-3 PUFAs were incorporated into atherosclerotic plaques and helped stabilize them. This is yet another well-designed study singing the praises of fish oil, whether through dietary intake or supplementation.

What to do with this article: Keep a hard copy in your file and make copies for your peers. ❖

Homeopathic Arnica and Surgery

Source: Stevinson C, et al. Homeopathic arnica for prevention of pain and bruising: Randomized placebo-controlled trial in hand surgery. *J R Soc Med* 2003;96:60-65.

Goal: To determine whether homeopathic arnica can reduce post-operative complications and promote recovery.

Design: Double-blind, randomized, placebo-controlled trial with three parallel arms.

Subjects: Sixty-four adults (62 included in final analysis) ages 18-70 years undergoing elective surgery for carpal tunnel syndrome.

Methods: Patients were given placebo, arnica 6C, or arnica 30C to be taken three times daily for seven days preoperatively and 14 days postoperatively. Primary outcome measures were pain (questionnaire including a visual analogue scale) and bruising (digital evaluation of photographs); secondary measures were swelling (measurement of wrist circumference) and use of analgesics (tablet counts).

Results: No differences were found between any of the groups on the primary outcome measures of pain and bruising; swelling and use of analgesics also revealed no difference between the arnica groups and placebo.

Conclusion: Homeopathic arnica is no better than placebo in reducing postoperative complications such as pain, swelling, and bruising.

Study strengths: Trial design; manner in which outcome measures of pain and bruising were determined.

Study weaknesses: Minimal swelling or bruising was noted in any of the groups; unusually frequent administration and lengthy duration of use of homeopathic arnica; poor adherence to the trial regimen seen in more than one-third of the sample; the sample size is relatively small, although there presently exists insufficient literature to drive sample size calculations.

Of note: Compared with the placebo group, a greater proportion of participants in both arnica groups guessed what they had received.

Did you know? If taken orally at all, arnica should only be taken internally in the form of a homeopathic remedy.

Clinical import: The results of this small, but well-done, study support the majority of published data that suggest little or no benefit from the peri-operative use of homeopathic arnica; however, patients continue to use, and some practitioners regularly recommend, arnica in such a circumstance. The good news is that a container of homeopathic arnica costs approximately $7 in your neighborhood health food store, is typically taken once or twice daily for a short period of time, and does not appear to interfere with medications. Although available data point to a lack of benefit of homeopathic arnica in the peri-operative period, there seems little reason to actively recommend against its use for those patients so inclined.

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In Future Issues:

Biofeedback for Asthma

Acupuncture and Irritable Bowel Syndrome

Supplement to *Alternative Medicine Alert*
April 2003

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

FDA Proposes Labeling and Manufacturing Standards for All Dietary Supplements

THE FOOD AND DRUG ADMINISTRATION (FDA) RECENTLY TOOK ACTION TO HELP CONSUMERS get accurately labeled and unadulterated dietary supplements by proposing a new regulation to require current good manufacturing practices (GMPs) in their manufacturing, packing, and holding. The proposed rule, in development since the release of the Dietary Supplement Health and Education Act in 1994, would establish standards to ensure that dietary supplements and dietary ingredients are not adulterated with contaminants or impurities, and are labeled accurately to reflect the active ingredients and other ingredients in the product.

This proposed rule includes requirements for designing and constructing physical plants, establishing quality control procedures, and testing manufactured dietary ingredients and dietary supplements. It also includes proposed requirements for maintaining records and for handling consumer complaints related to GMPs.

In a press release posted on its web site, the American Botanical Council in Austin, TX, is among several organization to point out that "… many responsible manufacturers in the herb and DS [dietary supplement] industry have not waited for FDA's publication of GMPs and have voluntarily increased their GMPs to meet or exceed what the FDA is projected to be proposing. Also, some manufacturers, because they produce over-the-counter (OTC) drug products, already operate under high level GMPs.

Need for Manufacturing Standards

In recent years, analyses of dietary supplements by a private sector laboratory suggest that a substantial number of dietary supplement products analyzed may not contain the amounts of dietary ingredients that would be expected to be found based on their product labels. For example:

- Five of 18 soy and/or red clover-containing products were found to contain only 50-80% of the declared amounts of isoflavones.
- Of 25 probiotic products tested, eight contained less than 1% of the claimed number of live bacteria or the number of bacteria that would be expected to be found in such a product.

FDA also has encountered products being marketed that are not accurately labeled or contain contaminants that should not be present or may be harmful. For example:

- One firm recalled its dietary supplements that were contaminated with excessive amounts of lead, which may have posed a health risk to many consumers, especially children and women of childbearing age.
- Another firm recalled a niacin product after it received reports of nausea, vomiting, liver damage, and heart attack associated with the use of its product. A dietary ingredient manufacturing firm had mislabeled a bulk ingredient container that subsequently was used by another firm in making a product that contained almost 10 times more niacin than the amount that may be safe.

The Proposed Regulation

"This proposed regulation is another major step in our efforts to help Americans take more control over their own health. Too often, consumers purchase dietary supplements based on inaccurate or incomplete information on what they are getting. This proposed regulation would require that dietary supplements provide accurate information on the type and amount of ingredients they contain and that dietary supplements are produced using safe methods," said Mark B. McClellan, MD, PhD, Commissioner of Food and Drugs. "Consumers should have access to dietary supplements that are accurately labeled and are free from contaminants."

FDA's action also will permit more informative research on dietary supplements, to improve the science available on their safety and effectiveness. "We commend FDA for proposing good manufacturing practices that will help ensure that all dietary supplements are of the quality that the public deserves. Since credible research studies cannot be performed using many of the current, highly variable products, these practices will also speed our ability to provide the public with more definitive data about the safety and effectiveness of popular dietary supplements," said Stephen Straus, MD, Director, National Center for Complementary and Alternative Medicine at the National Institutes of Health.

This proposed regulation follows the agency's consumer initiative announced last December intended to improve FDA's policies on providing information about health consequences of food and dietary supplements and to increase enforcement efforts to prevent misleading health claims made by certain dietary supplement manufacturers. By putting in place requirements that will ensure universal good manufacturing practices, the proposed regulation should serve to eliminate the guesswork for consumers about which dietary supplements may or may not be of high quality. In turn, manufacturers of dietary supplements will have to compete based on the quality of their products, not through potentially misleading labels or inexpensive, but less safe, manufacturing processes.

Manufacturers' Obligations

Under the GMP proposal, manufacturers would be required to evaluate the identity, purity, quality, strength, and composition of their dietary ingredients and dietary supplements. In addition, manufacturers would be required to:

- Employ qualified employees and supervisors;
- Design and construct physical plants in a manner to protect dietary ingredients and dietary supplements from becoming adulterated during manufacturing, packaging, and holding;
- Use equipment and utensils that are of appropriate design, construction, and workmanship for the intended use;
- Establish and use a quality control unit and master manufacturing and batch production records;
- Hold and distribute materials used to manufacture, package, and label dietary ingredients, dietary supplements, and finished products under appropriate conditions of temperature, humidity, light, and sanitation so that their quality is not affected;
- Keep a written record of each consumer product quality complaint related to GMPs; and
- Retain records for three years beyond the date of manufacture of the last batch of dietary ingredients or dietary supplements.

If dietary supplements contain contaminants or do not contain the dietary ingredient they are represented to contain, FDA would consider those products to be adulterated. Some product quality problems the GMPs would help prevent include products that are superpotent or subpotent; that contain the wrong ingredient, a drug contaminant, or other contaminants (e.g., bacteria, pesticide, glass, lead); that contain foreign material; and that are improperly packaged and mislabeled.

This proposal is intended to cover all types of dietary supplements. However, to limit any disruption for dietary supplements produced by small businesses, FDA is proposing a three-year phase-in of a final rule for small businesses. The proposal includes flexible standards that can evolve with improvements in the state of science, such as in validating tests for identity, purity, quality, strength, and composition of dietary ingredients.

FDA is soliciting comments from the public and industry on how this proposed regulation can best achieve the goals of promoting accurate labeling information and preventing adulteration without imposing unnecessary regulatory burdens. Written comments will be received until 90 days after the date of publication in the *Federal Register* and may be addressed to Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Room 1061, Rockville, MD 20852.

Additional information, including the proposed rule, may be found on FDA's web site: www.fda.gov/bbs/topics/NEWS/2003/NEW00876.html.