AMERICAN HEALTH CONSULTANTS®

THE PHARMACIST'S DIETARY SUPPLEMENT ALERT™

An Evidence-Based Medicine Newsletter

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Lemon Balm (*Melissa officinalis*) for Treatment of Herpes Labialis

By Cydney E. McQueen, PharmD

LEMON BALM (*MELISSA OFFICINALIS*) TRADITIONALLY HAS BEEN USED as a carminative for gastrointestinal distress 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 conducted, two of which are available in English.[7,10,11] (*For a review of clinical studies, see Table 1.*)

Koytchev's study[7] was a randomized, double-blinded controlled trial (RDBCT) of Lomaherpan™, a proprietary 1% cream of a lyophilized aqueous extract.[3] The cream was applied qd for five days and compared to a placebo of identical vehicle. A priori calculations indicated 33 patients per group were needed for 80% power.

INSIDE

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 prodrome 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 prodrome 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 presentations of herpes labialis symptoms 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 actually clinically significant. Other questions involve the lack of reporting of side effects, if any occurred, and use of concomitant medications. *Level II, major limitations* (*See Figure 1 for an explanation of the evaluation standards and scales used in rating clinical studies.*)

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. *Level V*

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 was also found in planar area on day 2. Melissa was also favored in GAE ratings

The Pharmacist's Dietary Supplement Alert, ISSN 1527-7348, is published monthly by American Health Consultants, 3525 Piedmont Rd., NE, Bldg. 6, Suite 400, Atlanta, GA 30305.

PUBLISHER: Brenda L. Mooney.

EDITORIAL GROUP HEAD: Leslie G. Coplin.

ASSOCIATE MANAGING EDITOR: Paula L. Cousins.

GST Registration Number: R128870672

Periodical postage pending at Atlanta, GA.

POSTMASTER: Send address changes to ***The Pharmacist's Dietary Supplement Alert***, P.O. Box 740059, Atlanta, GA 30374.

Subscriber Information

Customer Service: 1-800-688-2421.

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World-Wide Web: http://www.ahcpub.com

Subscription Prices

United States

$229 per year (Student/Resident rate: $120).

Outside the United States

$259 per year plus GST (Student/Resident rate: $135 plus GST).

Back Issues

$38 per issue. Missing issues will be fulfilled by Customer Service free of charge when contacted within one month of the missing issue's date.

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Table 1

Clinical trials of melissa extract for herpes simplex infections

Trial	Subjects	Infection Site	Results	LOE*	Limitations
Koytchev[7]	66	Labialis	↓ Symptom severity	II	Major
Wölbling[11]	115	All locations	↓ Symptom severity	V	Major
Wölbling[11]	116	All locations	↓ Symptom severity	II	Major
Vogt[10]	116	All locations	↓ Symptom severity	Unknown	Unknown
Wölbling[9]	Unknown	All locations	↓ Relapse frequency	Unknown	Unknown

* LOE = Level of evidence

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 prodrome symptom durations were the same in both groups. A primary trial limitation is the variable dosing; there was no explanation of why this was permitted, especially considering results of the open-label study. Another primary 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. *Level II, major limitations*

Adverse Events

Used topically for herpes labialis, adverse events are limited to irritation. There has been one report of exacerbation of symptoms.[11,12]

Contraindications

Patients with hypersensitivity to *Melissa officinalis* or preparation components should be counseled against use.

Pregnancy and Lactation

There are no known concerns or documented warnings against the use of topical preparations.

Interactions

No interactions are known for topical administration.[12]

Formulation and Dosage

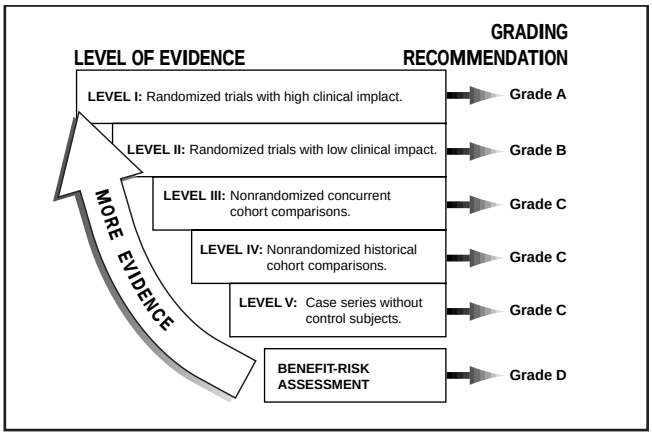
The proprietary concentrated preparation used in the trials is made with a 1% lyophilized aqueous extract that is applied two to five times daily. Melissa brews or teas used as poultices, although recommended in some references, are unlikely to be effective.[13]

Conclusion

Results of the two Level II trials available for analysis demonstrated statistically significant differences in

Figure 1

Level of evidence and grading recommendation



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 affecting clinical applicability. 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 Level II 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. *Grade B* ❖

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DSHEA: Implications for the Pharmacy

By Gerry Gianutsos, PhD, JD

This statement has not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure or prevent any disease.

PHARMACISTS AND CONSUMERS ALIKE ARE FAMILIAR with this statement, found on the labels of dietary supplements marketed in the United States. However, pharmacists need to recognize the significance of this disclaimer, particularly how it impacts product selection and the use of dietary supplements.

Not Evaluated by the FDA

The first part of the statement describes one of the major differences between the regulation of dietary supplements and pharmaceutical drugs. Under the Food, Drug, and Cosmetic (FDC) Act of 1938, the Food and Drug Administration (FDA) regulates the marketing and sale of drugs, foods, and supplements. Simply stated, this act, and its later amendments, set up a rigorous, lengthy, and costly procedure for the premarket testing of drugs to ensure that they are both safe and effective. Food additive manufacturers are also required to demonstrate safety before the FDA will permit them into the marketplace. However, when the FDA attempted to regulate dietary supplements using the same criteria,

their efforts were challenged. Since dietary supplements do not fit neatly into the drug or food additive categories, courts often sided with dietary supplement manufacturers. An early response to the FDA's efforts to regulate supplements, the Proxmire Amendment of 1976 prohibited the FDA from setting maximum limits on vitamin and mineral contents in foods and from classifying a vitamin or mineral as a drug solely because the potency exceeded the amount deemed nutritionally sound.

Dietary Supplement Health and Education Act

To address the issues raised by the proliferation of supplement products, Congress passed the Dietary Supplement Health and Education Act (DSHEA) in 1994.[1] This act broadened the definition of dietary supplements beyond vitamins, minerals, and amino acids to include herbs and botanicals. DSHEA also defined the limits of the FDA's regulatory authority of dietary supplements.

As a result of these changes, dietary supplement manufacturers are not required to prove that a product is safe and effective; a manufacturer only needs to give the FDA notice of its intent to market a product. This is similar to the exemption for homeopathic remedies that has been in effect since 1938. Only claims on product labels are reviewed or restricted by the FDA. Thus, unlike pharmaceutical drugs, marketing of dietary supplements is not subjected to an independent or governmental review. This, of course, does not mean that herbal remedies are inherently unsafe or ineffective. It does mean, however, that safety and efficacy have not been independently verified, and pharmacists should consult objective sources of information when counseling patients or making recommendation regarding use of dietary supplements. (*See Table 1 for information about DSHEA.*)

As required by DSHEA, the Office of Dietary Supplements of the National Institutes of Health provides fact sheets and a database of bibliographic information on its website (http://dietary-supplements.info.nih.gov). Product literature and other written information are available in most pharmacies where supplements are sold. However, DSHEA exempts such publications from FDA review even though they may contain therapeutic information. These publications cannot accompany the product (i.e., they must be displayed separately from the product) or be part of an integrated plan to promote the product.

Pharmacists also should be familiar with the process by which the FDA responds when there are concerns about post-marketing adverse events caused by a dietary supplement. Under DSHEA, the FDA is obligated to demonstrate that a product is unsafe before it can take an enforcement action to remove it from commerce. This is unlike the situation with pharmaceutical drugs where the manufacturer has the burden of demonstrating safety.

With expanded use and misuse of supplements, there is an increased incidence of reported adverse effects. Examples include γ-butyrolactone (GBL) and its metabolite, γ-hydroxybutyrate (GHB), marketed as sleep aid and bodybuilding supplements, and ephedrine, most often marketed inappropriately as a stimulant and weight reduction product. GHB is reported to induce seizures[2] while ephedrine has been associated with at least 15 deaths.[3] The FDA has issued warnings about these products, but pharmacists also need to be aware of possible sales restrictions on products since individual states can regulate the sale of supplements under state law. For example, Texas and Ohio restrict sales of ephedrine. State Boards of Pharmacy will be able to supply this information.

These issues also demonstrate the critical need for post-marketing surveillance to monitor the incidence of adverse effects. Pharmacists are in a unique position to provide valuable information protective of public health, since they will often be the first to recognize adverse events associated with dietary supplement use. Health professionals can report adverse events to the FDA's Special Nutritionals Adverse Event Monitoring System (http://vm.cfsan.fda.gov/~dms/aems.html) or the MedWatch program (http://www.fda.gov/medwatch/report).

Product Claims

The second part of the familiar disclaimer refers to the claims a dietary supplement manufacturer may make regarding a product.[4] A substance that is intended for use to diagnose, cure, mitigate, treat, or prevent a disease

Table 1

Recommendations for the pharmacist

- Be familiar with product labeling and know how to properly evaluate product claims.
- Know that promotional literature may contain claims, but must be physically separated from product displays in retail locations.
- Be familiar with information sources on product quality and standards in order to help patients choose products wisely.
- Recognize the consumer who relies on misleading information and be able to educate that consumer.
- Be familiar with state regulations on particular supplements.

falls under the FDA definition of a drug and would be subjected to the normal regulatory standards required for drug approval. Consequently, dietary supplement health claims are essentially limited to: (1) a benefit related to a classical nutritional deficiency; (2) a claim that the product can promote general well-being, or (3) a "structure-function" claim. The subtle distinction between a structure-function claim made for a dietary supplement and a disease claim made for a drug may easily confuse the consumer. For example, a claim that a product "promotes cardiovascular function" or "maintains a healthy circulatory system" (both related to physiologic functioning) would be permissible on a supplement label. A claim that a product "prevents atherosclerosis" (related to a disease) would not be permissible. The average consumer, however, may have difficulty discriminating between these distinctions and might conclude that the product will prevent heart disease, which is often the very intent of the manufacturer. Pharmacists should be able to correctly evaluate label claims in order to counsel consumers appropriately. (*To test your knowledge of product labeling claims, see below.*) Many consumers fail to notify their physicians that they are taking herbal or supplement products and some may self-medicate to avoid conventional therapy. In these instances, it is especially important to recognize consumers who rely on misleading information.

A manufacturer can use a structure-function claim without prior FDA approval, but the claim must be based on the manufacturer's review and interpretation of the scientific literature. The FDA's ability to regulate claims made by dietary supplement manufacturers continues to evolve and has been at least partially eroded by a recent legal challenge (*Pearson v. Shalala*, 164 F3d 650 [D.C. Cir. 1999]).

How well do you know DSHEA?

TAKE A MOMENT TO READ THE FOLLOWING PRODUCT labeling claims and decide whether each statement is a permissible claim under the Dietary Supplement Health and Education Act.

1. "improves absentmindedness and forgetfulness"
2. "reduces joint pain"
3. "helps to maintain cholesterol levels already within normal range"
4. "maintains normal bone density in postmenopausal women"
5. "restores normal blood pressure"
6. "helps maintain normal urine flow in men over 50 years old"
7. "supports a normal, healthy attitude during PMS"
8. "promotes cholesterol clearance"
9. "maintains healthy lung function in smokers"
10. "relieves stress and frustration"

Answer key: 1. yes, 2. no, 3. yes, 4. no, 5. no, 6. no, 7. yes, 8. no, 9. no, 10. yes.

Recent Developments

In January 2000, the FDA issued new rules for claims on dietary supplements in an effort to clarify the distinction between disease and structure-function claims.[5] The rule prohibits both express claims ("prevents osteoporosis") and implied disease claims ("prevents bone fragility in postmenopausal women"). It also prohibits claims made through product name (e.g., "CardioCure"); the use of pictures or symbols on the label (e.g., EKG tracings); or product formulation statements (e.g., contains aspirin). Claims for common, minor symptoms associated with life stages of aging (e.g., absentmindedness), menopause (e.g., hot flashes), and adolescence (e.g., noncystic acne) are permitted, but not claims for serious conditions such as osteoporosis. Pregnancy was originally included as a life stage, but the FDA has since advised that no claims for symptoms associated with pregnancy should be made until a further ruling is completed.[6]

Quality and GMPs

In evaluating the validity of any research on the use of supplements, pharmacists also need to be aware of the effects of different product formulations. For example, a product that may be used as a tea in folk medicine, may be available commercially only as a capsule containing the ground leaf; components, and therefore results, may not be identical. Conversely, there may be evidence that a particular active principle may exert pharmacological activity, but the dose available in a crude commercial preparation may be inappropriate for optimal therapeutic activity.

In 1999, the FDA modified its rules for supplement packaging. A supplement facts panel is now required to appear on all product labeling and includes: the product name, quantity, serving size, and total weight of each

ingredient; directions for use; a list of other ingredients; and the identity of any plant part from which a botanical ingredient is derived. Unfortunately, the label does not always reflect the contents of the package, so pharmacists who counsel on the use of supplements must consider quality control.[7] For example, a recent analysis of marketed ginseng products showed a tenfold variation in the amount of active ingredient among different brands that were labeled to contain the same amount; some brands contained no active ingredient at all.[8] Similar problems have been observed with other products.[7] Variability and lack of standardization can lead to significant under- or over-dosing.

In a recent study of Asian medicines available in California retail stores, almost 15% of the products examined had significant concerns, including the presence of adulterants, high levels of lead, and the presence of drugs not noted on the label.[8] Clearly, it is important for pharmacists to rely on reputable manufacturers.

The United States Pharmacopeia (USP) is developing standards for selected products; manufacturers who follow these standards are permitted to use USP or NF (National Formulary) on the label (more information can be found at http://www.usp.org).

The Institute for Nutraceutical Advancement Methods Validation Program is an industry-sponsored international project designed to select, validate, and publish scientific methods for use in analyzing raw botanical materials (http://www.nutraceuticalinstitute.com). Other potential sources of information on product quality include the Consumer Lab, an independent laboratory that tests dietary supplement quality and posts the results on their website, http://www.consumerlab.com (four product categories have been tested so far; more are forthcoming), and the Dietary Supplement Quality Initiative (http://www.dsqi.org).

If these sources do not provide information on a particular product that a patient is interested in using, a pharmacist may request a certificate of analysis from a manufacturer that indicates product ingredients and any known impurities. Pharmacists may also want to request proof that the product is not adulterated with pesticides, herbicides, heavy metals, or other harmful contaminants. Reputable manufacturers will be willing to supply such information.

DSHEA also gave the FDA authority to establish good manufacturing practices (GMPs) for dietary supplements. These regulations establish minimum requirements for methods and facilities used in the manufacture, processing, and packaging of dietary supplements and permits the FDA to inspect facilities for compliance. The FDA has been reviewing these proposed GMPs for several years, but has yet to issue new regulations.

DSHEA continues to evolve; the FDA recently announced a comprehensive 10-year strategy for achieving effective regulation of supplement products that includes issues of safety, labeling enforcement activities, and outreach. The strategy is available on the FDA website.[9]

Conclusion

DSHEA has ushered in a new era of consumer autonomy in selecting medicinal products. Along with this increase in consumer choice, there are concerns about product safety, efficacy, and purity. The pharmacist who recognizes both the benefits and shortcomings of DSHEA will be in a unique position to provide appropriate recommendations and advice to the public. ❖

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With Analysis by Cydney E. McQueen, PharmD

Kudzu Root for Chronic Alcoholism

Source: Shebek J, Rindone JP. A pilot study exploring the effect of kudzu root on the drinking habits of patients with chronic alcoholism. *J Altern Compl Med* 2000;6:45-48.

Objective: To assess the effects of kudzu root on sobriety alcohol craving in patients enrolled in a 12-step recovery program.

Design and Setting: Four-month, RDBCT against placebo at the Veteran Affairs Hospital in Prescott, AZ.

Subjects: Forty-nine (48 male) veterans entering a substance abuse treatment program with a DSM-IV diagnosis of chronic alcoholism.

Treatment: A 12-step recovery program, group therapy, and either kudzu or placebo.

Dose/Route/Duration: 1.2 g kudzu root or identical placebo capsules bid for four months.

Outcome Measures: Evaluation was by patient-completed questionnaire every 30 days. Primary outcome measures were sobriety and alcohol craving, each measured on a visual analogue scale (VAS).

Results: Thirty-eight patients completed the first month, but only 15 patients completed all four months. There was no difference between groups for sobriety or craving scores at months 1, 2, 3, or 4, although at month 2 in both groups and month 3 in the kudzu group, all patients had sobriety scores of 0 (no drinking at all). Side effects of headache, dry mouth, and anxiety were reported, but it is unclear whether these effects occurred in one or more individuals on kudzu; no placebo patients reported side effects.

Strengths/Limitations: Because of the large number of dropouts, only results from month 1 met power; the remaining numbers are so small as to render statistical analysis of extremely little value. The accuracy of self-completed questionnaires can be doubted and no information on concomitant medications or disease states was provided.

Level of Evidence: Negative results; study limitations prevent firm conclusions. *Level II, major limitations*

Comment: Investigators did recognize and discuss weaknesses of the trial and state that firm conclusions were not possible. Because alcoholism is a long-term disease and recovery programs traditionally have very high dropout rates, a larger and lengthier study is necessary to provide truly useful data. ❖

Andrographis for Cold Symptoms

Source: Caceres DD, et al. Use of visual analogue scale measurements (VAS) to assess the effectiveness of standardized *Andrographis paniculata* extract SHA-10 in reducing the symptoms of common cold. A randomized double-blind placebo study. *Phytomedicine* 1999;6:217-223.

Objective: To demonstrate that *A. paniculata* extract decreased the intensity of common cold symptoms compared to placebo.

Design and Setting: Randomized, double-blind, controlled trial (RDBCT) in Valdivia, Chile, in the winter of 1995.

Subjects: One hundred fifty-eight patients ages 25-50, with cold symptoms for less than two days, and not taking prescription or over-the-counter medications.

Treatment: 100 mg standardized *A. paniculata* extract SHA-10 tablets or placebo.

Dose/Route/Duration: 1,200 mg/d (4 tablets tid) for five days.

Outcome Measures: Patients were instructed to use a visual analog scale (VAS) to record symptoms of headache, fatigue, earache, sleep disturbance, sore throat, nasal secretions, expectoration, and cough frequency and severity at baseline, treatment day 2, and day 4 after treatment. (A VAS is a 10-cm line on which patients mark their level of discomfort—the left end is equivalent to absence of symptom; the right end indicates highest severity. A linear measurement was used in analysis.)

Results: Analysis was per protocol and on an intent-to-treat basis, in which dropouts had baseline scores carried through to days 2 and 4. At day 2, differences in VAS scores were statistically significant (P = 0.001-0.05) in favor of SHA-10 for fatigue, sleep disturbance, sore throat, and nasal secretions. At day 4, difference in severity was significant (P = 0.001-0.03) for SHA-10 in all assessment measures, but especially in earache, sleep disturbance, nasal secretions, and sore throat.

Strengths/Limitations: Power was calculated (n = 208) but not met (158 at end). Effect on duration of symptoms was not evaluated; side effects were not monitored. No objective outcome measures (e.g., labs, tissue counts) were included.

Level of Evidence: Treatment reduced severity of symptoms, but clinical significance is ill defined. *Level II, major limitations*

Comment: Investigators attributed the high dropout rate to scheduling conflicts (winter holiday). Lack of difference in improvement in all symptoms casts doubt on the clinical impact of the statistically significant changes. *A. paniculata*, or nees, is not widely sold in pharmacies, but more patients may be asking for information about products purchased at health food stores or on the Internet. Despite positive results, this study's usefulness lies primarily in pointing out potential for benefit and the need for further research. ❖