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Kava: Curing or Causing Anxiety?

By Melinda Ring, MD, and Marjorie Alschuler, PhD

RECENT REPORTS TYING SERIOUS LIVER DAMAGE WITH THE HERBAL sedative kava (*Piper methysticum*) have created anxiety for consumers, practitioners, and federal regulators. Although the possible connection was strong enough for the Food and Drug Administration (FDA) to issue an advisory, the proof of risk to American consumers was not sufficient for an enforced withdrawal of kava products.[1] So the question becomes: Are these adverse reactions significant in light of thousands of years of kava ingestion?

Historical Perspective

The fascinating legends of kava's use and discovery provide insight into how it became one of today's most popular herbal remedies.

In the 18th century, Capt. James Cook reported to the Western world of an intoxicating substance encountered on his voyages to the South Seas. Islanders of Oceania (Micronesia, Melanesia, and Polynesia) imbibed a "magical drink" called kava for informal social occasions and ritualistic ceremonies.[2] Tribal members prepared the drink first by chewing the root, and then spitting the macerated pieces into a bowl to be pressed and strained with coconut milk. The kava was drunk from the coconut shell, purportedly inducing feelings of harmony and sociability.

The kava ceremony still is performed in some Pacific islands, although more sanitary methods of preparation generally are employed.

Pharmacology

P. methysticum is a slow-growing perennial member of the pepper family.[2] The plant may grow to heights of 9 feet or taller, and has sparse heart-shaped leaves. The active ingredients are located in the root/rhizome. The pharmacological activity of kava has been attributed to lipid-soluble compounds known as kavalactones, or kava alpha-pyrones. Of the 15 known kavalactones, kavain, methysticin, and dihydrokavain are considered major components. The root's kavalactone content varies between 3% and 20%, depending on the plant lineage, age, and cultivation conditions.[3]

INSIDE

Plasma levels of kavalactones peak 1.8 hours after dosing, and the elimination half-life is nine hours.[4] Kavalactones and their metabolites are excreted in urine and feces. Human and animal studies suggest that kavalactones given as part of a crude extract (i.e., with other naturally occurring substances in the root) are more rapidly absorbed, have greater bioavailability, and achieve higher brain concentrations than the isolated compounds.[2]

Bioactivity of Kavalactones

Although kava is most widely recognized for its psychoactive/anxiolytic effects, it also has sedative, analgesic, anticonvulsant, and neuroprotective properties.

Analgesic/anesthetic. Four of the kavalactones have exhibited analgesic effects in animal studies.[5] Kavalactones, particularly kavain, also exert local anesthetic properties similar to cocaine when applied topically or by subcutaneous injection.

Anticonvulsant/neuroprotective. The infarct area from ischemia induced in rats was significantly reduced by kava extract and isolated methysticin and dihydromethysticum, comparable to that provided by the anticonvulsant memantine.[6] Kava extracts also halted induced seizures in animal models.

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Mechanism of Action

Anxiolytic. Several mechanisms of action for these CNS effects have been postulated, based on results of animal studies and in vitro assays.[3,7] Reduced excitability of the limbic system, particularly the amygdala complex, appears responsible at least in part for emotion modulation by kavalactones. In contrast to most hypnotic-sedatives, such as benzodiazepines, kavalactones inconsistently bind GABA or benzodiazepine receptors. Potentiation of GABA neurotransmission could occur by other means such as altering receptor domains. Inhibition of monoamine oxidase and noradrenaline uptake also may contribute to kava's psychoactivity.

Other effects. Analgesia does not appear to operate by opiate pathways, since opiate-receptor binding was not found, and naloxone is ineffective in reversing the effect.

The anticonvulsant and neuroprotective actions may result from inhibition of voltage-dependent sodium channels, similar to several traditional anti-epileptics. Antithrombotic effects may assist in cerebrovascular protection. COX-I and COX-II inhibition by six compounds from kava extract was demonstrated; the kavalactones dihydrokavain and yangonin were the most potent in this assay.[8] Kavain also has been found to reduce platelet aggregation, presumably from reversible inhibition of cyclooxygenase, and thence thromboxane A2 production.[9] Antioxidant activity of some kavalactones also was demonstrated in a free radical scavenging assay.[8]

Clinical Evidence of Efficacy in Anxiety

Ernst et al published a systematic literature review and meta-analysis of randomized controlled trials culled from MEDLINE, EMBASE, Biosis, AMED, CISCOM and the Cochrane Library.[10,11] Only studies on kava as a singular extract, not as part of an herbal combination product, were included. The authors identified seven double-blind placebo-controlled studies, six of which met criteria for methodological quality. Three trials that used the Hamilton Rating Scale for Anxiety (HAM-A) as the main outcome measure *(see Table 1)*, and employed the same dose kava extract WS1490, were suitable for inclusion in a meta-analysis *(see Table 2)*.

The results of the meta-analysis showed a significant reduction in baseline HAM-A scores (9.69 out of possible total score of 56, 95% confidence interval 3.54-15.83) after treatment for 4-24 weeks. The number needed to treat ranged from six to 21. The remaining four studies also demonstrated superiority of kava extract over placebo using varied anxiety measurements and dosages of 60-240 mg kavalactones daily.

Table 1

Hamilton Rating Scale for Anxiety (HAM-A)

I. Symptoms

A. *Anxious mood*
   1. worries
   2. anticipates worst

B. *Tension*
   1. startles
   2. cries easily
   3. restless
   4. trembling

C. *Fears*
   1. fear of the dark
   2. fear of strangers
   3. fear of being alone
   4. fear of animals

D. *Insomnia*
   1. difficulty falling asleep or staying asleep
   2. difficulty with nightmares

E. *Intellectual*
   1. poor concentration
   2. memory impairment

F. *Depressed mood*
   1. decreased interest in activities
   2. anhedonia
   3. insomnia

G. *Somatic complaints: muscular*
   1. muscle aches and pains
   2. bruxism

H. *Somatic complaints: sensory*
   1. tinnitus
   2. blurred vision

I. *Cardiovascular symptoms*
   1. tachycardia
   2. palpitations
   3. chest pain
   4. sensation of feeling faint

J. *Respiratory symptoms*
   1. chest pressure
   2. choking sensation
   3. shortness of breath

K. *Gastrointestinal symptoms*
   1. dysphagia
   2. nausea or vomiting
   3. constipation
   4. weight loss
   5. abdominal fullness

L. *Genitourinary symptoms*
   1. urinary frequency or urgency
   2. dysmenorrhea
   3. impotence

M. *Autonomic symptoms*
   1. dry mouth
   2. flushing
   3. pallor
   4. sweating

N. *Behavior at interview*
   1. fidgets
   2. tremor
   3. paces

II. Interpretation

A. Symptoms above are graded on scale:
   1. 0 = Not present
   2. 4 = Very severe

B. Criteria
   1. 18-24 = Mild anxiety
   2. 25-29 = Moderate anxiety
   3. 30+ = Severe anxiety

Acceptance of these positive findings has been cautious due to criticisms about the small sample sizes, brief treatment duration, and ill-defined patient populations.[12]

Preparation/Dosage

Commercial kava supplements usually are standardized to either 30% or 70% kavalactone content (e.g., 30 mg or 70 mg kavalactones per 100 mg total). These formulations are prepared by extraction from dried kava root with ethanol-water (30%) and acetone-water (70%) mixtures.

Many clinical studies involve 70 mg kavalactones given in three doses daily (known as WS1490). Recommended daily dosages for the treatment of anxiety disorders range from 120 mg to 225 mg kavalactones in divided doses, with maximum limits of 120 mg recommended by the German Commission E and 300 mg by an herbal product trade group.[13]

A tea prepared from 2-4 g of rootstock simmered for 5-10 minutes in 150 mL water also may be imbibed three times a day, although the kavalactone content will be more variable.

Safety: Drug and Disease Interactions

Hepatic. The greatest concern regarding adverse effects is whether kava causes liver toxicity. In Germany and Switzerland, 25 cases of serious conditions have been reported including hepatitis, cirrhosis, and liver failure.[1] The sale of the kava extract associated with these problems has been prohibited in Switzerland, and German authorities have proposed a similar ban. One report of hepatotoxicity identified the patient as having decreased metabolism by cytochrome P450 secondary to CYP2D6 deficiency, and proposed this as a risk factor for liver damage.[14] In susceptible patients, symptoms and abnormal labs suggestive of hepatotoxicity may appear as soon as one month after regular use.

Neurologic. There are several reports of extra-pyramidal-like dystonic reactions (oral/lingual dyskinesia, torticollis, oculogyric crisis, painful twisting movements of the trunk) as well as exacerbation of Parkinson's disease.[15]

The use of kava with CNS depressants (e.g., sedatives, alcohol, and antipsychotics) is discouraged. One report attributed a coma, reversed after cessation of all medications, to kava-benzodiazepine drug interaction.[16]

Table 2

Trials included in the meta-analysis of kava extract WS1490 for treatment of anxiety

Study	Patient Profile	Duration	HAM-A Score-Kava Baseline/final (reduction)	HAM-A Score-Placebo Baseline/final (reduction)
Kinzler et al	Outpatients with anxiety syndrome of non-psychotic origin; HAM-A ≥ 19; n = 58	4 weeks	25.3/12.6 (-12.7)	24.3/21.0 (-3.3)
Warnecke et al	Postmenopausal female patients with anxiety syndrome; HAM-A ≥ 19; n = 40	8 weeks	31.1/5.5 (-25.6)	30.2/22.5 (-7.7)
Volz et al	DSM-IIIr-diagnosed anxiety syndromes of non-psychotic origin;* HAM-A ≥ 19; n = 101	24 weeks	30.7/9.7 (-21.0)	31.4/15.2 (-16.2)

* Includes generalized anxiety disorder, adjustment disorder with anxiety, agoraphobia, and specific phobia.

Adapted from: Pittler MH, Ernst E. Efficacy of kava extract for treating anxiety: Systematic review and meta-analysis. *J Clin Psychopharmacol* 2000;20:84-89.

Current recommendations suggest cessation of kava use at least 24 hours before surgery to avoid potentiation of the sedative effects of anesthetics.[4] A double-blind crossover study of oxazepam and kava extract showed that, unlike benzodiazepines, kava did not impair cognitive performance and vigilance.[17]

Dermatologic. Kava dermopathy is a well-defined entity associated with prolonged intake of high-doses (> 400 mg kavalactones daily), although there have been several reports of onset after only 2-3 weeks at recommended doses. It manifests as dry, scaling areas with yellow pigmentation most prominent on the palms, soles, forearms, shins, and torso.[18] Dermopathy usually reverses after cessation of kava use.

Addiction. Abuse potential does exist; however, issues such as whether it can result in withdrawal syndromes, addiction, and tolerance still need clarification. In the seven clinical trials analyzed by Ernst, no reports of withdrawal after cessation of the extract were reported.

Other. Use of kava with antiplatelet agents is discouraged to prevent bleeding complications due to COX inhibition. Avoidance is recommended in pregnancy/lactation. Chronic heavy use (mean 440 g/wk) among Pacific Islanders was found to result in elevated liver enzymes, hematuria, macrocytic anemia, lymphopenia, increased patellar reflexes, significant weight loss, hypoalbuminemia, rash, and social problems similar to alcoholism.[19,20]

Conclusion

Despite some problems with methodology, the recent meta-analysis and literature review support the efficacy of kava in treating a variety of anxiety disorders. Insufficient proof exists for the use of kava for other indications. Unfortunately, the escalating reports of serious hepatotoxicity abroad warrant close examination of whether the evidence for benefit is strong enough to outweigh potential risks.

Recommendation

The FDA is investigating whether U.S. formulations carry the same risks of liver damage as their European counterparts. Until this question is answered, or predictive risk factors for susceptibility are identified, it would be prudent to suggest that patients avoid products containing kava extracts. Patients should be warned to check the labels of combination products, such as "Herbal Ecstacy," which often contain kava. For those patients who choose to use kava, emphasize the need to limit use to one month, since most hepatic damage does not occur before that time. Avoid herb-drug interactions and monitor closely for problems. ❖

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Correction

In the July issue of *Alternative Medicine Alert*, Table 1: Causes of Secondary Insomnia (page 79) should have been divided into two columns: 1) medical causes (delirium [e.g., sepsis or medication-induced], pain syndromes, endocrinopathies [e.g., hyperthyroidism], cardiac dysfunction [CHF, angina], sleep apnea syndrome [central, obstructive], side effects of medications [e.g., theophylline, nicotine, caffeine, steroids], chronic obstructive lung disease, restless leg syndrome/periodic limb movements in sleep, and gastroesophageal reflux); 2) and psychiatric causes (mood disorders, anxiety disorders, schizophrenias, substance dependence/abuse, and dementia). ❖

Role of Osteopathic Manipulation in the Treatment of Back Pain

By Georges Ramalanjaona, MD, DSc, FACEP, MBA, and Joseph J. Calabro, DO, FACOEP, FACEP

ACUTE LOW BACK PAIN IS THE MOST PREVALENT AILment and most frequent cause of disability for persons younger than age 45 in the United States: Back pain injuries comprise 33% of all national disability costs and 21% of all compensable work injuries.[1] Eighty percent of people in developed Western societies suffer from one or more episodes of low back pain during their lifetime.

The current evidence for the effectiveness of osteopathic manipulation (OM) in the management of back pain is compelling and deserves a careful review.

Pathophysiology of Back Pain

Multiple theories have been advanced to explain the pathophysiology of back pain. Knowledge of four basic possible mechanisms involved in the production of back pain is important in understanding the role of OM in its treatment.[2] They include:

- disc protrusion after injury of the annulus and stretching of the nerve root;
- scar tissue formation (or adhesion) between lamellae of the disc and capsule;
- muscle contractures controlling the joints; and
- deformation of the articular surfaces with restriction of movements.

Mechanism of Action

The accepted rationale usually given for the benefits of OM in the management of back pain includes:[3]

- correction of internal displacement of the disc

Table

Recent clinical trials of osteopathic manipulation (OM) in treatment of low back pain

Study	Condition	N	Treatment	Results
Hadler et al[5]	acute	54	OM vs. mobilization	OM group improved short-term ($P < 0.02$)
MacDonald et al[6]	acute	95	OM vs. education	OM group improved short term
Koes et al[7]	sub-acute	256	OM vs. physiotherapy (PT) vs. drug therapy	OM and PT groups improved short term
Koes et al[8]	sub-acute	256	OM vs. PT vs. drug therapy	OM group significantly improved vs. PT group in long term
Andersson et al[9]	sub-acute	178	OM vs. standard therapy	No difference between the two groups

fragments and reduction of a bulging disc (controversial);
- freeing of adhesions around a prolapsed disc;
- inhibition of transmission of nociceptive impulses;
- relaxation of tense muscle by sudden stretching; unbuckling motion segments that have undergone disproportionate displacements; and
- relaxation of entrapped synovial folds.

Osteopathic Techniques

OM manipulates muscles, tendons, and bones to promote blood flow through tissues. It consists of manual application of forces to the spinal structure to restore normal vertebral biomechanics and relieve pain. It utilizes a variety of techniques to alleviate back pain. A single OM session usually requires 2-6 minutes to perform.

The principal goal of OM is to relieve pain and improve function by normalizing movement and position. All osteopathic physicians are trained in OM during their residency program and are required to pass written examinations in OM before graduation from a college of osteopathic medicine, though the intensity and depth of training varies from one college to the next. OM is classified into soft-tissue techniques, articulation, and mobilization.[4]

Soft-tissue techniques stretch the skin and muscle tissues to promote their motion and elasticity, either as a specific therapeutic goal or in preparation for other procedures (e.g., strain-counter strain and the myofascial release).

Articulation consists of repetitive, oscillatory movements to break a restrictive barrier (capsule, ligaments, and paravertebral muscles). The goal is to improve range of movement by stretching connective tissue around a restricted joint (e.g., using high-velocity, low-amplitude [HVLA] manipulation).

Mobilization engages the restrictive barrier of the involved joint, followed by a HVLA manipulation. HVLA manipulation is the most frequently used OM technique and has the greatest potential for significant complications. The therapist, after identifying the dysfunctional segment, locks the inferior facets, thus eliminating spinal segmental motion except at the involved vertebrae. A sharp thrust is directed to the involved vertebrae in the direction of the limitation of movement. When the thrust is directed through the locked vertebral column, it is called indirect technique. If it is delivered directly to the spinal or transverse process of the involved vertebrae, it is called short-lever technique.

Although direct techniques provide significant pain relief compared to indirect manipulations, their use increases potential complications due to the high forces applied directly to the affected region. Thus, it is important to rule out any areas of fracture/dislocation prior to their use.

Clinical Studies

Controlled clinical trials comparing studies have been performed in an outpatient setting. Here, we summarize the most relevant and significant trials that provide level of evidence I on a scale of I to III for OM effectiveness in the treatment of back pain *(see Table)*.

In a prospective, stratified controlled trial, Hadler et al studied the effect of OM vs. mobilization on 57 patients suffering from acute low back pain.[5] Randomization was stratified into those who suffered back pain for less than two weeks (S1) and those who suffered back pain for 2-4 weeks (S2). Outcome was monitored by a self-administered survey questionnaire assessing functional impairment. The OM group in S2 showed statistically significant improvement ($P < 0.02$) in pain during the first two weeks (50% first week, 80% second week) compared to the mobilization group. The same finding was replicated in an open controlled trial assessing the effect of OM vs. back pain education in 95 patients with nonspecific back pain.[6]

In another randomized clinical trial of 256 patients with sub-acute neck/back pain (six weeks or more), Koes et al found no difference in effectiveness between OM and physiotherapy for the principal outcome

measurement (severity of complaints, global perceived effects, and physical functioning) during a three-, six-, and 12-week short-term follow-up.[7] However, the results of one-year follow-up of the same cohort of patients showed that OM produced a significant improvement in the main complaint (difference 0.9, 95% confidence interval [CI] 0.1-1.7) and in physical functioning (difference 0.9, 95% CI -0.1 to -1.3) vs. physiotherapy.[8] Both OM and physiotherapy were clearly more significantly effective than placebo and general practitioner treatment after 12 months.

A recent landmark article by Andersson et al reported a 12-week randomized, double-blind, controlled trial of 178 patients from two outpatient clinics who suffered back pain for at least three weeks but less than six months.[9] These patients were treated either with OM (n = 83) or with one or more standard medical therapies (n = 72). The authors found no statistically significant differences between the two groups in any primary outcome measure, including scores on the Roland Morris and Oswestry questionnaires (assessing loss of function due to back pain), visual analogue pain scale, range of motion, and straight leg raising. Furthermore, the OM group required significantly less medication ($P < 0.001$) and less physical therapy ($P < 0.05$) than the standard therapy group.

A recent meta-analysis of 23 randomized, controlled clinical trials showed stronger and more consistent effectiveness of OM in the treatment of low back pain than any other alternative treatment, including drugs, mobilization, and physiotherapy.[10] OM displayed a significant overall effect size for 86% of outcome variables compared to alternative treatments. However, these findings were based on a limited number of true controls (or on placebo) and variable outcome measurements, so the usefulness of the meta-analysis is modest.

Adverse Effects

The most frequently reported complications of OM are vertebrobasilar accidents (one per 20,000 patients after cervical manipulation), followed by cauda equina syndrome and disc herniation.[11] These same complications are seen in both OM and chiropractic manipulation (CM), with a slightly higher proportion of complications in CM. In general, these rare but serious adverse effects can be prevented by pre-manipulative evaluation and adherence to recognized techniques.

Contraindications and Precautions

Standard radiologic studies should be obtained in patients with a history of trauma to rule out fracture and dislocation. Absolute contraindications to OM include vertebral fractures/dislocation, infections, malignancy, spondylolisthesis, spondyloarthropathies (psoriasis, Reiter's Syndrome), myelopathy, cauda equina syndrome, vertebral hypermobility (Marfan's and Ehlers-Danlos syndrome), and anticoagulation therapy.[12] Relative contraindications are pregnancy, radiculopathy, and vertebrobasilar artery insufficiency. The role of OM in the pediatric population has not been extensively studied; thus, the risk:benefit ratio cannot be determined.

Regulation and Reimbursement

Recent guidelines published by the Agency for Healthcare Research and Quality recommend the use of spinal manipulation (including OM) for the treatment of low back pain.[13] OM can be used either as primary therapy or as an adjunct to other interventions.[14] It usually is practiced by osteopathic physicians, and recently has obtained its own reimbursement rates.

Conclusion

OM is a safe and effective intervention for short-term pain relief and functional improvement of acute/sub-acute back pain in outpatient clinics.

Recommendation

Based on current data, OM is recommended as a reasonable adjunctive maneuver for the short-term symptomatic pain relief and functional improvement of musculoskeletal acute/sub-acute back pain in an outpatient clinic. Further clinical trials are needed to assess long-term effectiveness of OM (more than 24 weeks with at least eight sessions) in patients with back pain. ❖

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Saw Palmetto for Benign Prostatic Hyperplasia: An Update

By E-P. Barrette, MD, FACP

WITH THE GRAYING OF AMERICA, MEN ARE PAYING more attention to their health. When bothersome urinary symptoms disrupt a night's sleep, they seek remedies. Saw palmetto extract (SPE) remains one of the top-selling herbal therapies in the United States for benign prostatic hyperplasia (BPH). In many European countries it is the therapy of first choice for BPH. In spite of its popularity, many U.S. physicians remain skeptical.

Since last reviewed in these pages,[1] further trials of SPE have been published. Overall, studies suggest that SPE appears to have a modest effect on the symptoms of BPH without changing the prostate specific antigen (PSA). Currently, the National Center for Complementary and Alternative Medicine (NCCAM) is funding a randomized trial of SPE in the United States and planning a much larger trial.

History

Native Americans used the extract of the fruit of the dwarf palm tree (*Serenoa repens*, or alt. *Sabal serrulata*), indigenous to the southeastern United States, for urinary complaints. In the 19th century, naturopathic physicians treated various ailments with SPE. The National Formulary listed SPE but eventually dropped it.

Current Use

In Germany, Italy, and France, herbal therapy is the preferred initial therapy for BPH. Although several agents often are used, including African plum tree (*Pygeum africanum*), stinging nettle (*Urtica dioica*), South African star grass (*Hypoxis rooperi*), and pumpkin seeds (*Cucurbita pepo*), saw palmetto is the most popular. Ironically, Florida provides saw palmetto for herbal pharmaceuticals sold in Europe, continent-wide. The commercial harvest of saw palmetto berries in Florida yielded $50 million in 1998.[2] Since the passage of Dietary Supplement Health and Education Act in 1994, SPE has become one of the top 10 herbal agents sold in the United States.

Mechanism of Action

SPE is a complex mixture of fatty acids, long-chain alcohols, and plant sterols including β-sitosterol, stigmasterol, cycloartenol, lupeol, lupenone, and methylcycloartenol. The precise active agent in SPE is unknown, although several studies of β-sitosterol alone have shown significant improvement in men with BPH.[3,4] Several mechanisms have been proposed:[5] inhibition of 5-alpha-reductase, anti-inflammatory effects, alpha-adrenergic receptor blockade, and growth factor alteration. Most research has focused on inhibition of 5-alpha-reductase, which is the mechanism of action of the pharmaceutical agent finasteride.[6] Conversion of testosterone to dihydrotestosterone by 5-alpha-reductase within the prostate is part of the pathology of BPH. Most studies, but not all, of SPE on 5-alpha-reductase activity have shown inhibition.

Clinical Studies

Well-documented improvement in both symptoms and urinary flow has been seen in men with BPH receiving placebo in large prospective trials.[7] This improvement can persist beyond six months. Consequently, all uncontrolled trials lacking a placebo arm and all positive trials of less than six months duration should be interpreted with caution.

An early review summarized the studies up to 1998.[8] This meta-analysis of all controlled trials of SPE in men with symptomatic BPH of at least 30 days published from 1966 through 1997 included 18 randomized controlled trials. Sixteen of 18 were double-blind trials; all 18 were conducted in Europe. The trials studied 2,939 men. Of the 18 trials, 10 studied SPE vs. placebo, two compared SPE to an active control (finasteride), four compared SPE compounded with a second agent vs. placebo, one compared SPE vs. pygeum vs. placebo, and one compared oral vs. rectal SPE. In 10 studies, nocturia was reduced by SPE, with a weighted mean difference of -0.76 times per night (95% confidence interval [CI] -1.22 to -0.32). Compared with placebo, SPE improved self-rating of urinary symptoms (six studies), risk ratio 1.72 (95% CI 1.21-2.44), and increased peak flow rates (eight studies), with a weighted mean difference of 1.93 mL/sec (95% CI 0.72-3.14). The peak flow improved 24% compared with placebo.

Weaknesses of these studies included the short duration of follow-up (four weeks in five trials, six weeks in two trials, and eight weeks in three trials) and small sample size (≤ 30 in five trials, ≤ 80 in 12 trials). Only nine of 18 studies had adequate blinding and only three trials used a standardized symptoms score.

In a second meta-analysis of 11 trials, Permixon (a European formulation of SPE) improved peak flow rates by 1.87 mL/sec ($P < 0.001$) and decreased nocturia by 0.55 episodes ($P < 0.001$) more than placebo.[9] Symptom score improvement was not analyzed.

A recent randomized double-blind controlled trial (RDBCT) that was conducted in the United States enrolled 85 men with moderate BPH.[10] Subjects received SPE 160 mg bid or placebo for six months. Greater improvement of symptom scores was seen with SPE (16.7 to 12.3, change = -4.4) when compared with placebo (15.8 to 13.6, change = -2.2). Although this difference was statistically significant ($P = 0.038$), the absolute difference between SPE and placebo was -2.2. It is generally accepted that the minimally perceptible change in symptom score is 3.[11] This degree of change was seen with SPE over six months, but not when compared with placebo. Peak flow rates improved in both arms ($P = 0.73$).

Comparisons to Finasteride

Two large double-blind studies compared SPE to finasteride. In the larger study, 1,098 men were randomized to 160 mg SPE twice daily or 5 mg finasteride daily for six months.[12] Both treatments improved the symptom score (37% vs. 39%, $P = 0.17$) and quality of life equally well. Peak urinary flow increased slightly more with finasteride (30% vs. 25%, $P = 0.035$).

The second trial followed 543 men with mild-to-moderate BPH for 48 weeks.[13] The SPE was compounded with 120 mg stinging nettle extract. The symptom score, quality of life, and peak urinary flow rates improved equally in both arms. Unfortunately, neither trial included a placebo arm.

Comparisons to Alpha-Adrenergic Antagonists

Very little is known regarding the comparative efficacy of SPE to the first-line agents most commonly used in the United States, alpha-adrenergic antagonists. No studies comparing SPE to doxazosin or terazosin have been published. A European multicenter double-blind trial compared SPE with tamsulosin (Flomax, 0.4 mg/d).[14] Seven hundred and four men with moderate BPH were followed for one year. Results, available only in abstract, showed equal improvement in symptom score (27% decrease) and peak flow. No placebo arm was included.

Two earlier studies suggested that alpha-adrenergic antagonists may be better than SPE. Prazosin appeared to be slightly better than SPE when studied for 12 weeks in 45 men;[15] however, non-standardized symptom scores were used. Alfuzosin, an alpha-adrenergic antagonist not available in the United States, also improved urinary symptoms and flow rates better than SPE.[16] Unfortunately, this trial was only three weeks in duration.

Adverse Effects and Drug Interactions

Mild side effects have been noted at rates similar to placebo. No interactions with drugs have been reported. However, many trials have excluded men on medications. One case report of a serious intra-operative hemorrhage is the only published serious adverse event occurring with SPE.[17] Bleeding time was prolonged and no other cause was found. Whether SPE was causally related is unknown. Follow-up bleeding time after restarting SPE was not reported.

Dosage and Formulation

The usual dose of SPE is 160 mg twice daily. A single report compared SPE 160 mg twice daily vs. 320 mg daily in a RDBCT with 100 men for three months and found them equivalent.[18] SPE often is sold compounded

Table

American Urological Association (AUA) Urinary Symptom Index for Prostatism

Symptom	Score: Not at All	< 1 in 5 Times	< ½ the Time	= ½ the Time	> ½ the Time	Almost Always
1. Over the past month or so, how often have you had a sensation of not emptying your bladder completely after you finished urinating?	0	1	2	3	4	5
2. Over the past month or so, how often have you had to urinate again less than two hours after you finished urinating?	0	1	2	3	4	5
3. Over the past month or so, how often have you found you stopped and started several times when you urinated?	0	1	2	3	4	5
4. Over the past month or so, how often have you found it difficult to postpone urination?	0	1	2	3	4	5
5. Over the past month or so, how often have you had a weak urinary stream?	0	1	2	3	4	5
6. Over the past month or so, how often have you had to push or strain to begin urination?	0	1	2	3	4	5
7. Over the past month or so, how many times did you most typically get up to urinate from the time you went to bed at night until the time you got up in the morning?	0 times	1 time	2 times	3 times	4 times	5 times

Interpretation of AUA Symptom Index

Mild prostatism ≤ 7

Moderate prostatism 8-18

Severe prostatism > 18

Highest possible score = 35

AUA Symptom Score = Sum of Questions 1-7 = _____

Adapted from: Barry M, et al. The American Urological Association symptom index for benign prostatic hyperplasia. *J Urol* 1992;148:1549-1557.

with many other herbal ingredients. In Europe, SPE frequently is compounded with stinging nettle (*U. dioica*) or pumpkin seeds (*C. pepo*). The most rigorous studies have used SPE alone (160 mg bid) or SPE with nettle (160/120 mg bid).

Future Studies

The NCCAM, the National Institute of Diabetes, Digestive, and Kidney Disorders (NIDDK), and the National Institutes of Health (NIH) are sponsoring a randomized placebo-controlled trial of SPE in 225 men with moderate-to-severe BPH followed for one year. Results are expected in late 2003.

The NCCAM, NDDK, NIH, and the Office of Dietary Supplements are planning a randomized placebo-controlled trial comparing SPE, *P. africanum*, and placebo.[19] The goal is to enroll 3,100 men with BPH and follow them for 4-6 years. This will be the largest SPE trial to date.

Conclusion

Two meta-analyses suggest that SPE has a modest benefit for BPH symptoms, with improved urine flow and decreased nocturia. All of these studies contain one or more deficiencies, i.e., short study period, non-validated symptom scores, small numbers of subjects, and inadequate blinding. Several new studies lend further support that SPE improves symptoms of BPH. However, no definitive trial has been published. Too little is known about the relative efficacy of SPE and alpha-adrenergic antagonist to make a fully informed decision. Moreover, most SPE products tested are manufactured in Europe and are not readily available in the United States. It is not certain whether SPE that is manufactured in the

United States is equivalent to SPE manufactured in Europe.

Recommendation

Until definitive trials are published, one must use the available evidence. Decisions to initiate referral to a urologist or start therapy with SPE, finasteride, or an alpha-adrenergic antagonist need to be negotiated with the patient. For patients wishing to try SPE for mild-to-moderate BPH, a trial of SPE alone (160 mg bid) or SPE with nettle (160/120 mg bid), for several months is not unreasonable. An attempt to monitor symptoms objectively with an easy and rapid questionnaire, e.g., the America Urological Association symptom index *(see Table)*, will help determine the benefits of treatment. Unlike finasteride, SPE will not affect the PSA. ❖

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CME Questions

8. The FDA issued a warning regarding kava use due to concerns about:

a. neurotoxicity.
b. hepatotoxicity.
c. drug addiction.
d. pulmonary fibrosis.

9. Kava extract is contraindicated in patients:

a. with Parkinson's disease.
b. taking a benzodiazepine.
c. who are pregnant or lactating.
d. All of the above

10. The most frequently used osteopathic manipulation technique to relieve back pain is:
a. soft-tissue technique.
b. articulation.
c. low-velocity, high-amplitude thrust.
d. high-velocity, low-amplitude thrust.

11. Absolute contraindications to osteopathic manipulation for back pain include all of the following *except*:
a. vertebral fracture.
b. infections.
c. pregnancy.
d. malignancy.
e. myelopathy.

12. In many European countries, saw palmetto extract (SPE) is first-line therapy for benign prostate hyperplasia (BPH).
a. True
b. False

13. Like finasteride, SPE has been shown to lower the prostate specific antigen (PSA) levels.
a. True
b. False

14. In large meta-analyses, SPE was noted to improve:
a. BPH symptoms and prostate size.
b. BPH symptoms and nocturia.
c. BPH symptoms , nocturia, and residual volume.
d. BPH symptoms, nocturia, and libido.

Clinical Briefs

With Comments from John La Puma, MD, FACP

Evaluating Supplements

Source: Petersen A. New Seals of Approval Certify Unregulated Herbs, Vitamins. *Wall Street Journal* July 10, 2002, D1.

"AT ONE BRANCH OF THE NATIONAL chain Vitamin Shoppe, there are 83 different types of calcium, 77 kinds of vitamin C and 22 distinct bottles of ginkgo biloba. Choosing between them could drive the savviest consumer to skip the herbs and go right for the Tylenol.

"Several new 'seals of approval' are vying to cut through the clutter of competing products in the largely unregulated $17 billion dietary-supplement industry. At least four outfits, from a nonprofit foundation to the venerable Good Housekeeping Institute, have begun or ramped up issuing official-looking stamps to herbs, vitamins and other supplements that meet certain standards.

"Generally, the programs test and certify that the ingredients listed on the label accurately reflect the makeup of the pills inside the bottle.

"Most also purport to ensure that a substance is free of common contaminants, including heavy metals and pesticides. Two require companies to follow good manufacturing practices.

"But while the seals give consumers some reassurance, they don't conclusively answer the most important questions on shoppers' minds: Is the product safe and does it work?"

COMMENT

What should we tell patients to look for when purchasing vitamins, minerals, and herbal supplements?

The best program is from the United States Pharmacopeia (USP)—I tell my patients to look for it on the label of all vitamins and minerals. Although it doesn't verify efficacy and safety—no group does, or can—its seal of approval does reflect tested contents; a lack of contaminants, including heavy metals and pesticides; and actual dissolution. Its Dietary Supplement Verification Program (DSVP) seal should be every bit as good. See www.usp-dsvp.org for more information on the DSVP program.

If the bottle says "NSF," on approximately 60 products by year's end, it's been manufactured using good manufacturing practices, contains what it says it does, and is free of "common contaminants." Dissolution apparently is not tested. See www.NSF.org for its certification list.

Consumerlab.com tests claimed ingredient profiles, and posts some results on its site.

Good Housekeeping says its label reflects the amount of active ingredient on the bottle, requiring clinical studies; however, this should be taken with several grains of salt because most active ingredients in herbal supplements are not yet identified. Good Housekeeping requires advertising in its magazine to test its product.

All of these groups charge manufacturers for testing, though Consumerlab.com tests some products for free, and charges all who want to use their seal. Interestingly, getting information about the products that Consumerlab.com tests for free requires a paid subscription from the consumer; the products posted are from companies that paid for the tests.

Recommendation

Look for USP on vitamin and mineral supplements, and USP, DSVP, or NSF on supplement bottles. A Consumerlab.com subscription will get you the longest list of evaluated products. Caveat emptor. ❖

In Future Issues:

Folate for the Prevention of Colon Cancer

Chelation Therapy for Atherosclerotic Disease

Role of Huperizine A in Alzheimer's Disease

Supplement to *Alternative Medicine Alert*
August 2002

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

Reading a Dietary Supplement Label

THE FOOD AND DRUG ADMINISTRATION (FDA), AS WELL AS HEALTH PROFESSIONALS AND THEIR organizations, receive many inquiries each year from consumers seeking health-related information about dietary supplements. Clearly, people choosing to supplement their diets with herbs, vitamins, minerals, or other substances want to know more about the products they choose so that they can make informed decisions.

In response to new legislation, dietary supplement labels have changed over the past several years.

Supplement Labeling

Ingredients. Like other foods, dietary supplement products must bear ingredient labeling. This information must include the name and quantity of each dietary ingredient, or for proprietary blends, the total quantity (by weight) of all dietary ingredients in the blend.

Labeling of products containing herbal and botanical ingredients must state the part of the plant from which the ingredient is derived (i.e., root, stem, leaves). Although many herbal products list the binomial name of the herb, herbal supplements are not required to do so. Because it is important to use the same products that have been tested and shown effective in clinical trials, this information can be very important in distinguishing between similarly named products that may have very different effects. Ginseng products offer a good example of this possible confusion: Which ginseng product should you purchase: *Panax ginseng* (Asian ginseng) or *Panax quinquefolius* (American ginseng)?

Supplement Facts. Dietary supplements also are required to include facts about the nutritional content of the product. This information can be found in the "Supplement Facts" box on the label. All ingredients that are present (except inert ingredients) in the product must be listed in this box; ingredients for which the FDA has established a daily consumption recommendation must include the percent daily value they provide.

Claims and Disclaimers. Under the Dietary Supplement and Health Education Act of 1994 (DSHEA) dietary supplement manufacturers can make three types of claims about their products: health claims, structure/function claims, and nutrient content claims.

Health claims describe a relationship between a food substance and a disease or health-related condition. "Diets high in calcium may reduce the risk of osteoporosis" is an example of a health claim. Examples of authorized health claim statements can be found at: www.cfsan.fda.gov/~dms/flg-6c.html.

DSHEA created the structure/function category of claims. These statements may claim a benefit related to a nutrient deficiency disease (e.g., vitamin C and scurvy), as long as the statement also tells how widespread such a disease is in the United States. Structure/function claims also may describe the role of a nutrient or dietary ingredient intended to affect a structure or function in humans (e.g., "calcium builds strong bones"). In addition, they may characterize the means by which a nutrient or dietary ingredient acts to maintain such structure or function (e.g., "fiber maintains bowel regularity" or "antioxidants maintain cell integrity") or they may describe general well-being from consumption of a nutrient or dietary ingredient.

The manufacturer is responsible for ensuring the accuracy and truthfulness of these claims; they are not approved by the FDA. For this reason, dietary supplement labels that include such a claim must state in a disclaimer that the FDA has not evaluated the claim. The disclaimer also must state that the dietary supplement product is not intended to "diagnose, treat, cure, or prevent any disease"; only a drug can legally make such a claim.

Foods and dietary supplements also can use nutrient content claims. These claims describe the level of a nutrient or dietary substance in the product, using terms such as "good source," "high," or "free." Nutrient content claims may only be made if the FDA has a regulation specifying the criteria that a food must meet in order to use the claim. With few exceptions, nutrient content claims can be made only for nutrients or dietary substances that have an established daily value. The requirements that govern the use of nutrient content claims help ensure that descriptive terms, such as "high" or "low," are used consistently for all types of food products and are meaningful to consumers.

For more information about structure/function and nutrient content claims, go to www.cfsan.fda.gov/~dms/ds-labl.html.

Manufacturer's Information. Manufacturers of dietary supplements are required to include their address and telephone number in the labeling. If you cannot tell whether the product you are purchasing meets the same standards as those used in research studies you read about, contact the manufacturer. It is the manufacturer's responsibility to determine that the supplement it produces or distributes is safe and that there is substantiated evidence that the label claims are truthful and not misleading.

Source: Food and Drug Administration. Available at: www.cfsan.fda.gov/~dms/supplmnt.html.

How to Identify a Problem and What to Do

Dietary supplements may not be risk-free under certain circumstances. If you are pregnant, nursing a baby, or have a chronic medical condition, such as diabetes, hypertension, or heart disease, be sure to consult your doctor or pharmacist before purchasing or taking any supplement. Although vitamin and mineral supplements are widely used and generally considered safe for children, you may wish to check with your doctor or pharmacist before giving these or any other dietary supplements to your child.

If you plan to use a dietary supplement in place of drugs or in combination with any drug, tell your health care provider first. Many supplements contain active ingredients that have strong biological effects and their safety is not always assured in all users. If you have certain health conditions and take these products, you may be placing yourself at risk.

Under certain circumstances, taking a combination of supplements or using these products together with medications (whether prescription or over-the-counter [OTC] drugs) could produce adverse effects, some of which could be life-threatening.

Be alert to advisories about these products, whether taken alone or in combination. For example: Coumadin (a prescription medicine), *Ginkgo biloba* (an herbal supplement), aspirin (an OTC drug) and vitamin E (a vitamin supplement) can each thin the blood, and taking any of these products together can increase the potential for internal bleeding. Combining St. John's wort with certain HIV drugs significantly reduces their effectiveness. St. John's wort also may reduce the effectiveness of prescription drugs for heart disease, depression, seizures, and certain cancers, and oral contraceptives.

It is important to fully inform your doctor about the vitamins, minerals, herbs, or any other supplements you are taking, especially before elective surgery. You may be asked to stop taking these products at least 2-3 weeks ahead of the procedure to avoid potentially dangerous supplement/drug interactions—such as changes in heart rate, blood pressure, and increased bleeding—that could adversely affect the outcome of your surgery.

You, your health care provider, or anyone may report a serious adverse event or illness directly to the FDA if you believe it is related to the use of any dietary supplement product, by phone (800) FDA-1088, fax at (800) FDA-0178, or on-line at: www.fda.gov/medwatch/how.htm.

FDA would like to know whenever you think a product caused serious problem, even if you are not sure that the product was the cause, and even if you did not visit a doctor or clinic.

Source: Food and Drug Administration. Available at: www.cfsan.fda.gov/~dms/ds-savvy.html.