AMERICAN HEALTH CONSULTANTS®

ALTERNATIVE MEDICINE ALERT™

The Clinician's Evidence-Based Guide to Complementary Therapies

American Health Consultants Home Page—http://www.ahcpub.com

CME for Physicians—http://www.cmeweb.com

Ginkgo for Intermittent Claudication

By Christine M. Stoltz, MD

SINCE THE EARLY DAYS OF MEDICINE, PHYSICIANS AND PATIENTS alike have appreciated the importance of "good" circulation. Nowadays, patients are familiar with the consequences of "bad" circulation, including coronary artery disease, cerebrovascular disease, and peripheral vascular disease.

An early symptom of peripheral vascular disease, intermittent claudication (IC) is associated with atherosclerosis of the aorta and arteries of the lower extremities. IC is characterized by muscular pain during exercise that can progress to pain at rest, ulcers, and gangrene. Traditional IC therapy has emphasized reducing the progression of atherosclerosis. Common interventions include exercise, smoking cessation, low-fat diets, and control of comorbid conditions such as diabetes, hypertension, and hyperlipidemia. Adjunct pharmacologic therapy for mild-to-moderate IC may include antiplatelet therapy with aspirin, but pentoxifylline and cilostazol also are used.

Ginkgo biloba, which has received attention as an antioxidant and memory enhancer, has been used for a variety of medical conditions characterized by impaired circulation. Several studies have shown that it may be useful in the management of IC.

Historical Perspective

The ginkgo or maidenhair tree is estimated to be about 200 million years old, and was brought to the United States from China in the late 1700s.[1] Derived from dried leaves, *Ginkgo biloba* extract has been used in traditional Chinese medicine to improve brain and respiratory function. Over the past decade, ginkgo has become increasingly popular for treatment of dementia, cognitive insufficiency, and IC. In 1998, ginkgo was the top-selling medicinal herb in the United States.[2]

Pharmacokinetics/Composition

The major constituents of *Ginkgo biloba* extracts are flavone glycosides (specifically quercetin, kaempferol, and isorhamnetin) and

Volume 4 • Number 8 • August 2001 • Pages 85-96

INSIDE

Acupuncture for post-operative dental pain **page 89**

Yarrow as a poultice **page 91**

Curanderismo use by Hispanic patients **page 94**

Fish consumption and depression **page 95**

Acupuncture and massage therapies for low back pain **page 96**

terpene lactones (ginkgolides A, B, and C; and bilobalide). Most studies use standardized extracts of EGb 761, which contains 24% ginkgo flavone glycosides and 6% terpene lactones. Gastrointestinal absorption in rats appears to be about 60%. Bioavailability following an oral dose of EGb 761 in humans is 98-100% for ginkgolide A, 79-93% for ginkgolide B, and 70% or more for bilobalide.[3]

Mechanism of Action

The flavone glycoside components of EGb 761 are believed to act as antioxidants and mild inhibitors of platelet aggregation. Terpene lactones are thought to be neuroprotective because they increase glucose and oxygen utilization, improve perfusion, and generally stimulate cognitive function.

In Vitro and Animal Studies

Several lines of evidence have suggested that ginkgo may modulate the endothelial microenvironment. It has been implicated as a free-radical scavenger, inhibitor of platelet-activating factor, and mediator of nitric oxide metabolism, erythrocyte aggregation, and nuclear transcription factors. Using a bovine endothelial cell model, Wei and colleagues showed ginkgo's free-radical scavenging capability,[4] which was consistent with other studies of its antioxidant activity.[5,6] Wei et al also found that ginkgo inhibited nuclear factor kappa-B, which is thought to be an important regulator of vascular pathophysiology.[4]

Other groups have focused on alterations in nitric oxide production. Although generally regarded as a vasodilator, both high and low levels of nitric oxide have been observed in atherosclerosis. Using a human endothelial cell line, Cheung et al found dose-dependent attenuation of nitric oxide production following treatment with EGb 761.[7] This appeared to be caused by a decrease in an inducible isoform of nitric oxide synthetase.[7]

Additional areas of research have explored ginkgo's antiplatelet effects. Using a rabbit model, Akiba et al showed that EGb 761 inhibited platelet aggregation in response to oxidative stress,[8] which may be relevant at the endothelial level in preventing thrombus formation. In addition, although some groups have proposed that ginkgolide B inhibits platelet-activating factor,[9] others have challenged this notion.[10]

Despite their biologic plausibility, the clinical importance of these in vitro effects is unknown.

Clinical Studies

The most recent meta-analysis of randomized, double-blind, placebo-controlled trials (RDBCTs) of IC was conducted by Pittler and Ernst.[11] Using systematic literature searches and unpublished data solicited from manufacturers, they identified eight RDBCTs that evaluated the effects of ginkgo, using pain-free walking distance as a primary outcome measure. In these trials, a total of 415 patients with IC (as defined by the Fontaine criteria) received 120-160 mg/d of *Ginkgo biloba* extract or placebo for 6-24 weeks. Three of the trials used the standardized extract, EGb 761.

Studies were analyzed independently by two reviewers and were given a quality score based on study design, description of withdrawals and dropouts, and randomization strategy (maximum score = 5). Of the eight studies used in the analysis, one had a perfect quality score (5),[12] five studies scored 4,[13-17] and two studies scored 3.[18,19] (*See Table 1.*) Seven studies showed that *Ginkgo biloba* was more effective than placebo, though only four of these achieved statistical significance.

When subject to statistical pooling, an increase in pain-free walking distance was noted in subjects treated with ginkgo as compared to placebo. The difference was approximately 34 m (95% confidence interval: 24-43 m). This improvement is of unclear clinical relevance. This result was consistent with the findings from

Alternative Medicine Alert, ISSN 1096-942X, is published monthly by American Health Consultants, 3525 Piedmont Rd., NE, Bldg. 6, Suite 400, Atlanta, GA 30305.

VICE PRESIDENT/PUBLISHER: Brenda L. Mooney.
EDITORIAL GROUP HEAD: Leslie G. Coplin.
MANAGING EDITOR: Paula L. Cousins.
GST Registration Number: R128870672.

Periodical postage paid at Atlanta, GA.
POSTMASTER: Send address changes to ***Alternative Medicine Alert***, P.O. Box 740059, Atlanta, GA 30374.

Back Issues: $42 per issue. Missing issues will be fulfilled by Customer Service free of charge when contacted within one month of the missing issue's date.

AMERICAN HEALTH CONSULTANTS™
THOMSON HEALTHCARE

Subscriber Information

Customer Service: 1-800-688-2421.
Customer Service E-Mail: customerservice@ahcpub.com
Editorial E-Mail: paula.cousins@ahcpub.com
World-Wide Web: http://www.ahcpub.com

Subscription Prices

United States
$299 per year (Student/Resident rate: $125).
Multiple Copies
1-9 additional copies: $224 each; 10 or more copies: $199 each
Outside the United States
$329 per year plus GST (Student/Resident rate: $140 plus GST).

Accreditation

American Health Consultants (AHC) is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

American Health Consultants designates this continuing medical education activity for up to 24 hours in category 1 credit toward the AMA Physician's Recognition Award. Each physician should claim only those hours of credit that he/she actually spent in the educational activity.

This CME activity was planned and produced in accordance with the ACCME Essentials.

Alternative Medicine Alert has been approved by the American Academy of Family Physicians as having educational content acceptable for Prescribed credit hours. Term of approval covers issues published within one year from the beginning distribution date of July 1, 2001. This volume has been approved for up to 24 Prescribed credit hours. Credit may be claimed for one year from the date of this issue.
For CME credit, add $50.

Questions & Comments

Please call **Paula Cousins,** Managing Editor, at (816) 960-3730 between 8:30 a.m. and 4:30 p.m. ET, Monday-Friday.

Statement of Financial Disclosure

In order to reveal any potential bias in this publication, and in accordance with Accreditation Council for Continuing Education guidelines, physicians have reported the following relationships with companies related to the field of study covered by this CME program. Dr. Balk, Dr. Barrette, Dr. Cirigliano, Dr. deLeon, Dr. Gaster, Dr. La Puma, Dr. Marcolina, Dr. Schiedermayer, Dr. Sorrentino, and Dr. Stoltz have no relationships with companies related to the field of study covered by this CME program.

Table 1

Summary of double-blind, placebo-controlled, randomized trials of *Ginkgo biloba* extract for intermittent claudication

Trial	Patients Entered (Analyzed)	Daily Dose of *Ginkgo biloba* Extract	Mean Baseline Pain-Free Walking Distance (m)		Mean Increase in Pain-Free Walking Distance (m)		Mean Increase in Maximal Walking Distance (m)		Ergometer Test Speed km/hr (Grade, %)
			Ginkgo	Placebo	Ginkgo	Placebo	Ginkgo	Placebo	
Blume[12]	60 (58)	120 mg for 24 weeks*	100	110	47	11	51	16	3 (12)
Natali[13]	25 (18)	160 mg for 24 weeks	78	100	61	16	188	-1	3 (5)
Bauer[14]	80 (79)	120 mg for 24 weeks†	59	79	64	28	112	29	3 (10)
Thomson[15]	49 (37)	120 mg for 24 weeks	81	101	38	33	—	—	4 (10)
Salz[16]	29 (26)	160 mg for 6 weeks	258	194	113	4	124	-35	120 steps/min on flat ground
Draboek[17]	20 (18)	120 mg for 12 weeks§	96	96	21	22	-1	3	2.5-4 (8-16)
Blume[18]	41 (40)	160 mg for 24 weeks*	81	74	38	4	46	5	3 (12)
Peters[19]	111 (109)	120 mg for 24 weeks*†	108	104	45	21	61	25	3 (12)

**Ginkgo biloba* extract EGb 761

§Crossover study

†Advised to exercise

Reprinted with permission from Excerpta Medica Inc.: Pittler MH, Ernst E. *Ginkgo biloba* extract for the treatment of intermittent claudication: A meta-analysis of randomized trials. *Am J Med* 2000;108:276-281.

the largest trial[19] and was consistent across studies in subgroup analysis.

In comparison, separate studies have shown that an exercise program can increase pain-free walking distances by 88-190% (i.e., up to 139 m).[11] Nonetheless, until larger RDBCTs are performed, this meta-analysis probably is the best available evidence of ginkgo's efficacy in the treatment of IC.

Adverse Effects and Drug Interactions

When used in standard doses, ginkgo generally is well tolerated. However, its use should be avoided in persons with known hypersensitivity to ginkgo preparations. Occasional rash, minor gastrointestinal disturbances, and headache have been described.[3]

The greatest concern, however, is the potential for bleeding, especially when ginkgo is coadministered with anticoagulants or antiplatelet agents. Several case reports have documented this untoward effect. For example, a spontaneous hyphema occurred in a patient using *Ginkgo biloba* 40 mg bid and aspirin 325 mg/d.[20] Intracerebral bleeding was reported in an elderly woman taking both warfarin and ginkgo.[21] In addition, bilateral subdural hematomas occurred in a young woman who had taken *Ginkgo biloba* 60 mg bid. This was associated with a prolonged bleeding time, which normalized upon discontinuation of the herb.[22] A spontaneous intracerebral hemorrhage also was reported in an elderly woman taking *Ginkgo biloba* 50 mg bid for approximately six months.[23] Subarachnoid hemorrhage occurred in a 61-year-old male taking *Ginkgo biloba* 40 mg 3-4 times daily.[24]

Concurrent use of ginkgo with other anticoagulants (e.g., heparins and heparinoids), antiplatelet agents, and nonsteroidal anti-inflammatory drugs should be avoided because coadministration may increase the risk of bleeding. Use with other herbs and supplements that can increase the risk of bleeding (e.g., garlic, ginseng, and

vitamin E) also should be avoided. Like other antiplatelet agents, ginkgo use should be discontinued prior to surgical procedures. Although the exact lead time for stopping *Ginkgo biloba* before surgery is unknown, 10-14 days probably is appropriate in most cases.

In addition, ginkgo's reversible inhibition of monoamine oxidase (MAO) in rat models has led to concern about potential interactions with antidepressants, but this has not been evidenced. Using positron emission tomography, a small study of 10 healthy humans failed to demonstrate alterations in MAO A and MAO B.[23] Insufficient data are available on ginkgo's safety in children and pregnant or lactating women.

Formulation and Dosage

Depending on the manufacturing process used, there may be variation in the composition of ginkgo preparations. The average oral dose is 120 mg of dried extract in 2-3 divided doses daily.[26] Although more expensive than exercise or aspirin, ginkgo generally is less costly than pentoxifylline or cilostazol. (*See Table 2.*)

The formulation most commonly used in the United States and in many clinical trials is EGb 761. As with any herbal supplement, there may be batch-to-batch variation in product, although most manufacturers standardize their extract to 24% ginkgo flavone glycosides and 6% terpene lactones.

Conclusion

At this time, there is tentative evidence to suggest that *Ginkgo biloba* may be a useful adjunct to exercise and lifestyle modification in the treatment of mild-to-moderate IC. Data are lacking about its efficacy compared to other commonly used therapies and about the safety of long-term use. Further randomized, controlled studies are needed to evaluate its effectiveness and how it may compare with other lifestyle and pharmacologic therapies for peripheral vascular disease.

Table 2

Approximate costs of medical therapies used for intermittent claudication

Therapy	Dose	Cost per Day
Ginkgo biloba	120 mg	$0.36-0.84
Aspirin	325 mg qd	$0.08
Pentoxifylline (generic)	400 mg tid	$1.87
Cilostazol	100 mg bid	$3.83

Source: Pharmacy and on-line mail-order firms

Recommendation

Patients who are interested in using *Ginkgo biloba* should consider using the standardized extract, EGb 761. Because of potential for bleeding, patients should avoid taking ginkgo in combination with anticoagulants, antiplatelet agents, nonsteroidal anti-inflammatory drugs, and herbs that increase bleeding risk. Like other antiplatelet agents, it should be discontinued prior to surgical procedures. Until larger studies are available, coadministration with MAO inhibitors also should be avoided. At this time, the use of *Ginkgo biloba* for IC should be combined with other effective therapeutic modalities such as exercise and smoking cessation. ❖

Dr. Stoltz is Instructor of Medicine, Division of General Internal Medicine, Presbyterian Medical Center, University of Pennsylvania Health System in Philadelphia.

References

1. Hadley SK, Petry JJ. Medicinal herbs: A primer for primary care. *Hosp Pract* 1999;34:105-106, 109-112, 115-116, 121-123.
2. Brevoort P. The booming US botanical market: A new overview. *HerbalGram* 1998;44:33-46.
3. Blumenthal M, ed. *The Complete German Commission E Monographs: Therapeutic Guide to Herbal Medicines*. Austin, TX: American Botanical Council; 1998:136-138.
4. Wei Z, et al. *Ginkgo biloba* inhibits hydrogen peroxide-induced activation of nuclear factor kappa B in vascular endothelial cells. *Gen Pharmacol* 1999;33:369-375.
5. Pincemail J, et al. Superoxide anion scavenging effect and superoxide dismutase activity of *Ginkgo biloba* extract. *Experientia* 1989;45:708-712.
6. Maitra L, et al. Peroxyl radical scavenging of *Ginkgo biloba* extract EGb 761. *Biochem Pharmacol* 1995;49: 1649-1655.
7. Cheung F, et al. Inhibitory effect of *Ginkgo biloba* extract on the expression of inducible nitric oxide synthase in endothelial cells. *Biochem Pharmacol* 1999; 58:1665-1673.
8. Akiba S, et al. Inhibitory effect of the leaf extract *Ginkgo biloba* L. on oxidative stress-induced platelet aggregation. *Biochem Mol Biol Int* 1998;46:1243-1248.
9. Smith PF, et al. The neuroprotective properties of the *Ginkgo biloba* leaf: A review of the possible relationship to platelet-activating factor (PAF). *J Ethnopharmacol* 1996;50:131-139.
10. Braquet P. Cedemin, a *Ginkgo biloba* extract, should not be considered as a PAF antagonist. *Am J*

Gastroenterol 1993;88:2138.

11. Pittler MH, Ernst E. *Ginkgo biloba* extract for the treatment of intermittent claudication: A meta-analysis of randomized trials. *Am J Med* 2000;108:276-281.
12. Blume J, et al. Placebokontrollierte doppelblindstudie zur qirkamkeit von *Ginkgo-biloba*-spezialextrakt Egb 761 bein austrainierten patienten mit claudicatio intermittens. *VASA* 1996;25:265-274.
13. Natali J, Bossier P. Internal report. *Schwabe.* 1985.
14. Bauer U. Six-month double-blind randomised clinical trial of *Ginkgo biloba* extract versus placebo in two parallel groups in patients suffering from peripheral vascular disease. *Arzheim-Forsch/Drug Res* 1984; 34:716-720.
15. Thomson GIL, et al. A clinical trial of *Ginkgo biloba* extract in patients with intermittent claudication. *Int Angiol* 1990;9:75-78.
16. Salz H. Zur wirksamkeit eines *Ginkgo-biloba*-Präparats bei arteriellen Durchblutungstörungen der enteren Extremitäten. *Therapie Gegenwart* 1980; 119:1345-1356.
17. Draboek H, et al. Effekten af *Ginkgo biloba*-ekstrakt hos patienter med claudicatio intermittens. *Ugeskr Lager* 1996;158:3928-3931.
18. Blume J, et al. Ginkgo-Spezialextrakt EGb 761 bei peripherer arterieller Verschlußkrankheit. *Fortschr Med* 1998;116:137-143.
19. Peters H, et al. Demonstration of the efficacy of *Ginkgo biloba* special extract EGb 761 on intermittent claudication—A placebo-controlled, double-blind multicenter trial. *VASA* 1998;27:106-110.
20. Rosenblatt M, Mindel J. Spontaneous hyphema associated with the ingestion of *Ginkgo biloba* extract [letter]. *N Engl J Med* 1997;336:1108.
21. Matthews MK Jr. Association of *Ginkgo biloba* with intracerebral hemorrhage [letter]. *Neurology* 1998;50: 1933-1934.
22. Rowin J, Lewis SL. Spontaneous bilateral subdural hematomas associated with chronic *Ginkgo biloba* ingestion. *Neurology* 1996;46:1775-1776.
23. Gilbert GJ. *Ginkgo biloba* [letter]. *Neurology* 1997; 48:1137.
24. Vale S. Subarachnoid haemorrhage associated with *Ginkgo biloba* [letter]. *Lancet* 1998;352:36.
25. Fowler JS, et al. Evidence that *Ginkgo biloba* extract does not inhibit MAO A and B in living human brain. *Life Sci* 2000;66:141-146.
26. Gruenwald J, et al, eds. *PDR for Herbal Medicines*. Montvale, NJ: Medical Economics Company; 1998: 871-873.

Acupuncture for Postoperative Dental Pain

By Judith L. Balk, MD, FACOG

ACUPUNCTURE IS USED FOR A WIDE VARIETY OF painful conditions, including operative and postoperative analgesia, migraine headaches, dysmenorrhea, musculoskeletal pain, and osteoarthritis. Acupuncture's analgesic effects on dental pain were noted in mainland China in 1966.[1] Since then, multiple studies have evaluated various aspects of dental pain, including experimental and postoperative dental pain, and pain during dental procedures such as drilling into dentine, root canal, molar extraction, and tooth restoration. Ernst and Pittler have reviewed these studies.[2]

Acupuncture, like many pain medications, appears to be site-specific. In 1997, the NIH Consensus Development Panel on Acupuncture concluded, "Promising results have emerged, for example, efficacy of acupuncture . . . in postoperative dental pain."[3] Conventional treatment for postoperative dental pain includes narcotic analgesics and nonsteroidal anti-inflammatory drugs.[4] Alternatives to these agents may be preferable to some patients.

Mechanism of Action

How acupuncture achieves its analgesic effect is not well understood.

Researchers have proposed several mechanisms of action that have been reviewed extensively.[5] One theory proposes that effects may be mediated through stimulation of pain receptors, thereby leading to activation of the central nervous system and induction of circulating neurochemicals. Another mechanism may occur via gate control, where large nerve fibers cause inhibition of nociceptive impulses. Also, the participation of diffuse noxious inhibitory controls may provide some analgesic effects. Lastly, some consider acupuncture's effects to be a placebo effect. Given that acupuncture's analgesic effects on experimental dental pain are blocked partially by naloxone, the analgesic effects likely include some opioid type of effect.[6]

Clinical Studies

Most studies have found acupuncture to be beneficial in reducing postoperative dental pain. An excellent recent placebo-controlled clinical trial sought to evaluate the efficacy of Chinese acupuncture in treating postoperative oral surgery (removal of a partial bony impacted

third molar) pain, and the effects of psychological factors on outcomes.[7]

The true acupuncture procedure was manual manipulation of the acupuncture points LI-4, St-6, St-7, and SJ-17 on the tooth extraction side only. A pair of electrodes from a mock electrical stimulator was attached to the ends of the needles. For the placebo acupuncture, an empty plastic needle tube was tapped on the bony area next to each acupuncture point, and a needle with a piece of adhesive tape was then taped to the dermal surface. Again, a mock electrical stimulator was applied to the needles. "Manipulations" were created by palpating the surface of the skin with a blunt dental instrument. As explained in an earlier article, the mock electrical stimulator was used to confuse both the real and placebo acupuncture groups.[8] Patients' eyes were covered with patches so they could not view the treatment procedures.

Both the mean pain-free postoperative time and time until moderate pain were significantly longer in the acupuncture group compared with the placebo group. Also, mean time before requesting pain medication was longer in the treatment group. Average pain medication use also was significantly less in the treatment group, but total-pain-relief and pain-half-gone scores were the same in both groups.

Acupuncture seemed to be better at preventing pain rather than controlling existing pain, as acupuncture was the same as placebo in pain control after the patient reported "moderate" pain. Also, the placebo-control condition was assessed to be valid based on the high numbers of subjects who were uncertain of or incorrect about their group assignment. Lastly, outcomes did not differ based on psychological factors.

Another well-designed study was a randomized, double-blind, placebo-controlled trial of postoperative acupuncture after multiple tooth extractions.[9] Subjects were enrolled after recovery from local anesthesia and were randomized to one of four groups: placebo pill plus placebo acupuncture, codeine pill plus placebo acupuncture, placebo pill plus true acupuncture, or codeine pill plus true acupuncture. All needles were stimulated manually. Pain intensity scores were recorded every 30 minutes for three hours. The placebo acupuncture point used was on the midline of the thenar web, 5 mm above the edge. This point was selected because it is close to the LI-4 point (the true acupuncture point) but is not on the large intestine meridian. For the first 30 minutes, true acupuncture alone produced the most pain relief. However, for the other time periods, true acupuncture plus codeine produced the most pain relief. True acupuncture produced significantly more pain relief than placebo acupuncture. None of the groups had complete pain relief, and it appears that the combination of acupuncture and codeine gave both short- and long-term pain relief.

In a different study, 200 patients were randomly treated with either acupuncture at LI-4 bilaterally or at LI-4 and also at tooth-specific points on the affected side.[4] Pre- and post-acupuncture pain scores were compared. The median Visual Analogue Scale pain score after surgery but before acupuncture was statistically higher than after acupuncture. The tooth-specific acupuncture protocol provided more pain relief than using LI-4 alone. Plasma concentration of beta-endorphin significantly increased from baseline, but the investigators did not reveal if one acupuncture group was higher than the other. Patients were not compared to a usual care group.

A study with a different hypothesis also investigated the use of acupuncture for postoperative dental pain.[10] In this study, intraoperative (as opposed to postoperative) acupuncture was compared to traditional therapy—preoperative inhalation nitrous oxide and intramuscular meperidine. Tylenol 3 was prescribed for all patients to be used as needed for postoperative pain. No differences were seen between the two groups for pain intensity or medication consumption. Both groups experienced comparable intensities of postoperative pain.

In this study, acupuncture was as effective as the sedation technique of inhaling nitrous oxide and intramuscular meperidine for postoperative pain. The authors note that meperidine's half-life is 3.6 hours, so that no long-lasting pain relief would be expected from the traditional approach. No long-lasting effect is to be expected from intraoperative acupuncture either. The acupuncture group did not receive sedation, and the ability to perform dental procedures using only acupuncture would seem beneficial.

One opposing study, which was not placebo-controlled or blinded, found that postoperatively, patients receiving acupuncture reported greater pain intensity than a control group not receiving acupuncture.[11] Acupuncture was given to 25 patients before or after removal of impacted molars. The 60 control group patients did not receive acupuncture. Patients who received acupuncture only preoperatively consumed more analgesics than the control group. Furthermore, more patients in the acupuncture groups had dry socket, a wound healing complication. The lack of blinding and placebo control increases the bias in this study. The authors suggest the following possible reasons for their findings: personality characteristics, anxiety, patient expectation, vasodilatation from the acupuncture, and acupuncture technique. The authors conclude that acupuncture is not recommended as an adjuvant in oral surgery.

Adverse Effects

The only study to report any severe complications resulting from the acupuncture was the last article, in which subjects had a higher incidence of dry socket.[11] In the study utilizing a non-insertion placebo control, only the placebo group had systemic adverse effects such as dizziness, heaviness, nausea, and drowsiness.[7] These effects were attributed to the dental procedure. The acupuncture group had soreness at the acupuncture sites during and after the acupuncture treatment, which according to the investigators, is expected from eliciting the *de qi* sensation. The *de qi* sensation often is described as an ache or soreness at the needle site, and many traditional Chinese medicine practitioners believe obtaining this sore or achy sensation is necessary to obtain a good result with acupuncture.

Conclusion

Acupuncture appears to be useful for treatment and prevention of postoperative pain after dental surgery such as tooth extraction. It may work better at preventing pain rather than treating moderate-to-severe pain. When used intraoperatively, acupuncture does not appear to change pain intensity postoperatively, but it may allow for less intraoperative medication. The length of time needed to treat, the frequency of treatments, and whether acupuncture is synergistic with conventional medicine all currently are unknown.

Recommendation

Acupuncture can be used either alone or as an adjunct to conventional medical treatment for pain after dental surgery. When used in combination with conventional medicine, pain relief may be optimized. ❖

References

1. Lu DP, Lu GP. Acupuncture anesthesia/analgesia for pain and anxiety control in dental practice. Part I: Theory and application. *Compendium* 1993;14: 182-189.
2. Ernst E, Pittler MH. The effectiveness of acupuncture in treating acute dental pain: A systematic review. *Br Dent J* 1998;184:443-447.
3. NIH Consensus Conference. Acupuncture. *JAMA* 1998;280:1518-1524.
4. Scarsella S, et al. Electroacupuncture treatment of postoperative pain in oral surgery. *Acupunct Med* 1994;12:75-77.
5. Leong RJ, Chernow B. The effects of acupuncture on operative pain and the hormonal responses to stress. *Int Anesthesiol Clin* 1988;26:213-217.
6. Ernst M, Lee MH. Influence of naloxone on electro-acupuncture analgesia using an experimental dental pain test. Review of possible mechanisms of action. *Acupunct Electrother Res* 1987;12:5-22.
7. Lao L, et al. Evaluation of acupuncture for pain control after oral surgery: A placebo-controlled trial. *Arch Otolaryngol Head Neck Surg* 1999;125:567-572.
8. Lao L, et al. Efficacy of Chinese acupuncture on postoperative oral surgery pain. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1995;79:423-428.
9. Sung YF, et al. Comparison of the effects of acupuncture and codeine on postoperative dental pain. *Anesth Analg* 1977;56:473-478.
10. Lapeer GL, et al. Acupuncture analgesia for postoperative dental pain. *J Can Dent Assoc* 1987;53:479-480.
11. Ekblom A, et al. Increased postoperative pain and consumption of analgesics following acupuncture. *Pain* 1991;44:241-247.

Yarrow as a Poultice

By Susan T. Marcolina, MD

YARROW, OR *ACHILLEA MILLEFOLIUM*, IS A PERENNIAL herb in the Asteraceae (daisy) family. Native to Europe and western Asia, yarrow grows to approximately 3 feet in height during the summer months. It has dense clusters of white flower heads on flat-topped umbrella-like stalks with finely divided, fern-like leaves.[1]

Although yarrow has a hallowed medicinal history, there are very few scientific data to support more than its botanical use.

Historical Use

Yarrow has been used throughout history for its hemostatic, analgesic, and anti-inflammatory effects.

More than 2,500 years ago, Chinese physicians used Asian yarrow to treat inflammation, bleeding, and menstrual disorders, as well as dog and snake bites. According to legend, the Greek warrior Achilles used the herb to staunch the bleeding of battle wounds.[2] Dioscorides, a Roman physician, also used the crushed plant on wounds, and its popular nicknames—herbe militaire, Soldier's woundwort, and bloodwort—arose from this use. More recently, the colonists introduced yarrow to North America and the native Indians adopted it as an external treatment for wounds, burns, and sprains, as

Table 1

***Achillea* species**

Species Name	Chromosome Number & Ploidy	Characteristics of Essential Oils	Location
A. millefolium	Hexaploid 2n = 54	Low to zero proazulene content; contains thujone	Central and northern Europe (native), North America (introduced)
A. lanulosa	Tetraploid 2n = 36	Up to 50% proazulene	Eastern Canada, New England (native)
A. collina	Tetraploid 2n = 36	Up to 50% proazulene	Europe, western Asia
A. pannonica	Octaploid 2n = 72	Low to zero proazulenes; contains thujone	Europe, western Asia
A. borealis	Hexaploid 2n = 54	Low to zero proazulenes; contains thujone	West coast North America from California to Alaska, Arctic, Subarctic
A. setacea, *A. aspleniifolia*	Diploid 2n = 18	Low to zero proazulenes; contains thujone	Europe, western Asia
A. distans, *A. stricta*	Hexaploid 2n = 54	Low to zero proazulenes; contains thujone	Europe, western Asia

Adapted from: Biste C. Cytotaxonomic studies of the group *Achillea millefolium* in East Germany. *Feddes Repert* 1977;88:53-61.

well as an internal treatment for arthritis, colds, and indigestion. Today, yarrow is used primarily as an ornamental plant and a mosquito repellent in flower gardens.[3]

Taxonomy

There has been considerable confusion about the taxonomic classification of yarrow and its chromosomal characteristics, which are associated with differences in the chemical composition of its flowers and leaves.[4] There are several *Achillea* species, which differ in their ploidy (chromosome numbers) and cannot be distinguished morphologically. The normal chromosome number for achillea is 9. Therefore, the diploid number is 18. There also are tetraploid (2n = 36), hexaploid (2n = 54) and octaploid species (2n = 72). Table 1 summarizes the most commonly recognized species and their general properties.

Other factors that influence the chemical composition of yarrow include climate, soil conditions, stage of flower development at harvest, and the time during the growing season at which the plant material is collected.[5] Further complicating matters, polymorphisms occur within a particular species that change the chemical composition. The species most often referenced in the clinical literature is *Achillea millefolium*, and subsequent references to yarrow indicate this species.

Since these taxonomic categories of yarrow were not fully acknowledged by researchers until the mid 1970s, the literature available on yarrow is confusing and has conflicting findings, probably because investigators were working with different plant species. Because of these nosological problems, clinical studies refer to a voucher specimen to confirm the genetic identity of the plant used.[3,6]

Chemical Constituents

The crushed leaves and flowers of yarrow contain several biologically active compounds that would support its use in the healing of wounds. Chemists have studied the volatile essential oil of yarrow, obtained by steam distillation of the flower heads and leaves, for more than 250 years. The oil is complex and varies in composition, as noted above, and depends upon growing conditions, season, soil mineral content, and developmental stage of part collected.[5,6]

Some of the essential oil components, the chamazulenes and other compounds called proazulenes, have potent anti-inflammatory effects. A correlation between the ploidy level and the ability of *Achillea* species to synthesize proazulenes has been shown.[7]

Preitschopf et al found a correlation between the frequency of proazulene-containing yarrows and increased concentrations of available phosphate, magnesium, and manganese in the soil in which the plants are grown.[8] The volatile oil of a tetraploid species of *Achillea* can contain up to 50% chamazulenes.[9] Diploid, hexaploid, and octaploid species, however, contain little to no chamazulenes, but can contain alpha-thujone, which has a stimulant effect on uterine musculature and has been used as an emmenagogue in some cultures.[4]

Other components of the essential oil—menthol and camphor—have bactericidal activity. Salicylic acid has both anti-inflammatory and analgesic activities. Yarrow also contains flavonoids such as rutin and quercetin, which have anti-inflammatory and antispasmodic activity.[3] Achilleine, one of the alkaloids found in yarrow, promotes blood coagulation.[10] There has been a dearth of studies, however, to substantiate the use of any of these components or their effects in the clinical setting.

Animal Studies

Taran et al evaluated yarrow essential oil vs. a standard concentration of chamazulenes in control oil vs. a neutral control oil in the healing of napalm burns in rabbits. Burns treated with the essential yarrow oil and the standardized chamazulene oil had a significantly faster time to eschar slough compared to control (seven days vs. 24 days, $P < 0.001$). Subsequent histological studies done on the burn tissue after complete healing revealed that the skin treated with the yarrow essential oil and the standardized chamazulene oil did not differ in appearance from normal skin, whereas the skin of healed control burns had significant distortion of the subdermis and dermis with cytoplasmic and nucleolar vacuolization.[11] The authors did not specify, however, the species of yarrow utilized for the study nor was a voucher specimen submitted.

Goldberg et al isolated and studied six constituents of the aqueous extract of yarrow flower heads. The anti-inflammatory activity of each fraction was assessed utilizing the mouse paw edema test.[12] Results were compared to known anti-inflammatory agents: corticotrophin, acetylsalicylic acid, dexamethasone, hydrocortisone, and indomethacin. Four of the six fractions produced reductions in inflammation greater than those induced by acetylsalicylic acid.

Clinical Studies

One randomized, placebo-controlled trial from The Netherlands using an herbal mixture of juniper, nettle, and yarrow in a 1:1:1 formulation showed no difference in indices of plaque formation or gingival health in 45 blinded volunteers with moderate gingival inflammation.[13] The study did include an in vitro portion in which the antibacterial activity of the pure herbal extract mixture of juniper, nettle, and yarrow against oral bacteria was assessed by the agar dilution method. Despite the fact that some antimicrobial activity was observed, the clinical portion of the study did not show any significant changes from the control rinse in the measured analyses of plaque formation, gum bleeding, or modified gingival index.

Adverse Effects and Contraindications

Yarrow is known to cause allergic contact dermatitis in sensitive individuals. Alpha-peroxyachifolid, the compound isolated from *Achillea millefolium* blossoms, is responsible for this effect.[14,15] The volatile oil of some species contains trace amounts of the chemical thujone, which is an abortifacient, and therefore should not be used by pregnant or lactating women.[16] Animal studies have shown achilleine, one of the alkaloids isolated from yarrow, to have in vivo procoagulant activity.[10] It should not be used in patients taking anticoagulants.

Conclusion

Yarrow research has a long way to go before the plant can be used with any assurance as a phytomedicine. There is a great deal of variability in constituent content based on ploidy level and environmental conditions. Commercial sources in this country are not well-defined enough to be certain of the genetic identity of the source plant. Even imported yarrow could be any one of a number of species. Therefore, reliable standardized products cannot be manufactured based upon the current level of expertise. At this time, yarrow remains a folk medicine and cannot be recommended for clinical use.

Recommendation

Because of the dearth of any randomized, blinded, controlled clinical studies regarding the use of yarrow and taxonomic classification problems within the species, yarrow cannot be recommended for use, either alone or in combination with other herbs. ❖

Dr. Marcolina is a board-certified internist and geriatrician in Issaquah, WA.

References

1. Castleman M. *The Healing Herbs: The Ultimate Guide to the Curative Powers of Nature's Medicines.* Emmaeus, PA: Rodale Press; 1991.
2. Leyel CF. *Culpepper's English Physician and Complete Herbal.* North Hollywood, CA: Wilshire Book; 1972.
3. Chandler RF, et al. Ethnobotany and phytochemistry of yarrow, *Achillea millefolium*, Compositae. *Econ Botany* 1982;36:203-223.
4. Zeylstra H. Why yarrow? *Br J Phytother* 1997;4: 184-189.
5. Figueiredo AC, et al. Composition of the essential oils from two populations of *Achillea millefolium* L ssp millefolium. *J Chromatogra Sci* 1992;30:392-395.
6. Afsharypour S, et al. Volatile constituents of *Achillea*

millefolium L. ssp. Millefolium from Iran. *Flavour Fragrance J* 1996;11:265-267.

7. Dastner G, et al. Volatile constituents of *Achillea millefolium*. *Planta Med* 1990;56:531.
8. Preitschopf A, et al. *Achillea millefolium*: Occurrence, ploidal level and preazulene variation. *Planta Med* 1989;55:596.
9. Haggag MY, et al. Thin layer and gas chromatographic studies on the essential oil from *Achillea millefolium*. *Planta Med* 1975;27:361-366.
10. Miller FM, Chow LM. Alkaloids of *Achillea millefolium*: Isolation and characterization of Achilleine. *J Am Chem Soc* 1954;76:1353-1354.
11. Taran DD, et al. The wound healing properties of the essential oils of yarrow and Yakut wormwood and khamazulen in napalm burns [in Russian]. *Voen Med Zh* 1989;8:50-52.
12. Goldberg AS, et al. Isolation of the anti-inflammatory principles from *Achillea millefolium* (Compositae). *J Pharm Sci* 1969;58:939-941.
13. Van der Weijden GA, et al. The effect of herbal extracts in an experimental mouthrinse on established plaque and gingivitis. *J Clin Periodontol* 1998;25: 399-403.
14. Hausen BM, et al. Alpha-peroxyachifolid and other new sensitizing sesquiterpene lactones from yarrow (*Achillea millefolium* L., Compositae). *Contact Dermatitis* 1991;24:274-280.
15. Davies MG, Kersey PJ. Contact allergy to yarrow and dandelion. *Contact Dermatitis* 1986;14:256-257.
16. Farnsworth NR. Potential value of plants as sources of new antifertility agents I. *J Pharm Sci* 1975;64: 535-598.

CME Questions

6. Coadministration of *Ginkgo biloba* should be avoided in patients using:
a. aspirin.
b. warfarin.
c. vitamin E.
d. All of the above

7. Which of the following has *not* been a reported side effect of *Ginkgo biloba* use?
a. Gastrointestinal distress
b. Depression
c. Rash
d. Bleeding

8. The mechanism of acupuncture analgesia may involve all of the following *except*:
a. stimulation of pain receptors.
b. gate-control.
c. participation of diffuse noxious inhibitory controls.
d. placebo effect.
e. nerve palsy.

9. The only type of dental pain for which acupuncture has been studied is postoperative dental pain.
a. True
b. False

10. Patients with a history of which of the following conditions should never use yarrow?
a. Atopy
b. Pregnancy or lactation
c. Deep venous thrombosis
d. All of the above
e. None of the above

11. Yarrow has the potential to interfere with anticoagulant medications.
a. True
b. False

Clinical Briefs

With Comments from John La Puma, MD, FACP

Curanderismo Use by Hispanic Patients

Source: Padilla R, et al. Use of curanderismo in a public health care system. *Arch Intern Med* 2001;161:1336-1340.

"CURANDERISMO ('THE HEALING') IS a centuries-old synthesis of Mexican Indian culture and beliefs. To evaluate the rate of use of curanderismo among Hispanic subjects seeking medical care at the Denver Health Medical Center, Denver, CO, we conducted a survey of 405 Hispanic subjects attending outpatient primary and urgent care clinics at Denver Health Medical Center, the public hospital system for Denver. The main outcome measure was independent predictors of use of curanderos. Of the 405 subjects, 118 (29.1%) (95% confidence interval [CI] 20.9-37.3) had been to a curandero at some time in their lives. Of all the subjects, 91.3% knew what a curandero was. Univariate analyses demonstrated an association between those who had been to a curandero and level of income, level of education, and whether the subject was bilingual. The results of fitting a stepwise logistic regression model revealed an independent

association with subjects who had been to a curandero and level of household income (> $20,000 vs. < $10,000), with an odds ratio (OR) of 2.19 (95% CI 1.20-4.01) (P = 0.01), and level of education (post-high school vs. elementary school), with an OR of 3.16 (95% CI 1.45-6.86) (P = 0.004). Many Hispanic patients who receive their health care at a public hospital system use the services of curanderos. This potentially has important implications for their health care."

COMMENT

The authors review the ancient but still current "folk healing" tradition, which began in South America among native American tribes and is centered upon their beliefs of harmony with nature, spirit, and self. Curanderos and curanderas are spiritually chosen designates who "were given the power to heal the wounded spirit and cure the supernatural illness." Curanderos have inherited the role of the native American shamans who came before them, and much before the invading Spaniards. Most curanderos and curanderas are elders in the community, are not full-time practitioners, and are not expected to treat major medical illness. The authors cite a study of 16 curanderos which showed that "the setting for their practice is often their home. They generally use prayer, massage, herbs, and reassurance to treat their patients. In addition, curanderos frequently share their patients' social class, background, language, and religion."

Headache, empacho (pseudointestinal obstruction), nervios, and susto (fright) each were the cause of the visit to the curandero for more than 20% of subjects (who could name more than one reason for a visit); back pain, kidney problems, and diabetes registered less than 5% each. Because most subjects did not tell their physicians of these visits, it's also possible that they didn't tell their physicians of these symptoms—some of which could indicate serious pathology.

This study is useful, not because it indicates that curanderos can be curative or even therapeutic (it doesn't), but simply because many Hispanics remain medically indigent. As health care coverage becomes tighter, this population will continue to rely upon traditional methods of care. Most of their methods are benign, and some are likely to be highly beneficial—indeed, some already have been shown to be.

Recommendation

Ask your Hispanic patients who are indigent whether they see a curandero or use any treatments prescribed by anyone else. More often than you think, the answer will be yes. ❖

Fish Consumption and Depression

Source: Tanskanen A, et al. Fish consumption, depression, and suicidality in a general population. *Arch Gen Psychiatry* 2001;58: 512-513.

"A RECENT DOUBLE-BLIND, PLACEBO-controlled trial of 30 patients with bipolar affective disorder demonstrated a significant benefit of omega-3 fatty acid supplements on reducing episodes of severe mania and depression. Omega-3 polyunsaturated fatty acids (PUFAs) are now regarded as a promising but untested treatment as mood stabilizers. Consistent with these observations, several studies of patients with depression have reported depletions of omega-3 PUFAs in plasma or cell membranes. Previously, a cross-national comparison revealed a 50-fold lower annual prevalence of major depression, which was strongly predicted by higher fish consumption. Since fish is the major source of omega-3 fatty acids in the human diet, the frequent consumption of fish could lead to a high intake of omega-3 PUFAs, thus decreasing the risk of depression.

"Data were gathered on fish consumption, depression, and suicidality among a general population in Kuopio, Finland. A random sample of subjects (n = 3,004) aged 25 to 64 years was drawn from the National Population Register. The study questionnaires were mailed in spring 1999, and 1,767 subjects responded (59%). An ethical review board of the Kuopio University approved the study.

"Depression was estimated with the 21-item Beck Depression Inventory (BDI). A person was considered depressed if the BDI score was greater than or equal to 10. One of the BDI items screens the severity of suicidal tendencies. Suicidality was considered to be present if there were any thoughts of harming oneself. Fish consumption was estimated with a food-frequency questionnaire, which has been reported to be comparable with a seven-day food record. A subject was regarded as a frequent fish consumer if fish were consumed twice a week or more often.

"Both the risk of being depressed (odds ratio [OR] 0.63; 95% confidence interval [CI] 0.43-0.94; P = 0.02) and the risk of having suicidal ideation (OR 0.57; 95% CI 0.35-0.95; P = 0.03) were significantly lower among frequent lake-fish consumers compared with more infrequent consumers in a multiple logistic model even after adjustment for sex, age, marital status, education, employment status, work ability, area of living, financial status, general health, smoking, alcohol intake, coffee drinking, and physical activity. These results are also consistent with a study of 265,000 Japanese subjects followed for 17 years, which found a decreased risk of suicide among subjects with daily fish consumption compared with nondaily consumption.

"Consequently, fish oils may alleviate depression and suicidal tendencies. However, large-scale intervention trials are needed before dietary recommendations to increase fish consumption or omega-3 PUFA intake could be applied to depressed patients or people in the general population."

COMMENT

We know that 13 oz of fish weekly can prevent sudden cardiovascular death. We think it may be the omega-3 fatty acids in cold-water marine fish that convey this benefit. Is it possible that these polyunsaturated fatty acids also have a psychoactive therapeutic effect?

These data for omega-3 fatty acid use are, of course, epidemiological—based on self-administered surveys and validated food-frequency questionnaires completed by 1,767 Finlanders. The data can only be associative, but there are other supportive data in this same population. An editorialist, who reported two years ago a preliminary, double-blind, placebo-controlled trial on the effect of omega-3 fatty acids in bipolar disorder, cites a study of Icelanders in which lack of seasonal mood change was correlated with omega-3 fatty acid intake. Iceland and Finland are on a similar latitude and share a similar diet. Taken together, these data are more than circumstantial, and seem to be pointing in an evidence-based direction.

Recommendation

Though it may be too early to prescribe fish oils for depression and mood disorders, it is not too early to ask your patients to eat more fish and less red meat for reducing the risk of sudden cardiac death and arterial aging. Patients who want to take fish oils for mood disorder ought not to combine them with anticoagulants. ❖

Acupuncture and Massage Therapies for Low Back Pain

Source: Cherkin DC, et al. Randomized trial comparing traditional Chinese medical acupuncture, therapeutic massage, and self-care education for chronic low back pain. *Arch Intern Med* 2001;161:1081-1088.

"BECAUSE THE VALUE OF POPULAR forms of alternative care for chronic back pain remains uncertain, we compared the effectiveness of acupuncture, therapeutic massage, and self-care education for persistent back pain.

"We randomized 262 patients aged 20 to 70 years who had persistent back pain to receive traditional Chinese medical acupuncture (n = 94), therapeutic massage (n = 78), or self-care educational materials (n = 90). Up to 10 massage or acupuncture visits were permitted over 10 weeks. Symptoms (0-10 scale) and dysfunction (0-23 scale) were assessed by telephone interviewers masked to treatment group. Follow-up was available for 95% of patients after four, 10, and 52 weeks, and none withdrew for adverse effects.

"Treatment groups were compared after adjustment for prerandomization covariates using an intent-to-treat analysis. At 10 weeks, massage was superior to self-care on the symptom scale (3.41 vs. 4.71, respectively; $P = 0.01$) and the disability scale (5.88 vs. 8.92, respectively; $P < 0.001$). Massage was also superior to acupuncture on the disability scale (5.89 vs. 8.25, respectively; $P = 0.01$). After one year, massage was not better than self-care but was better than acupuncture (symptom scale: 3.08 vs. 4.74, respectively; $P = 0.002$; dysfunction scale: 6.29 vs. 8.21, respectively; $P = 0.05$). The massage group used the least medications ($P < 0.05$) and had the lowest costs of subsequent care.

"Therapeutic massage was effective for persistent low back pain, apparently providing long-lasting benefits. Traditional Chinese medical acupuncture was relatively ineffective. Massage might be an effective alternative to conventional medical care for persistent back pain."

COMMENT

The senior investigator in this trial, Dr. Rick Deyo, has contributed greatly to the back pain literature for nearly two decades, and his other colleagues in Seattle—Drs. Cherkin and Barlow, and Ms. Street—all have contributed significantly as well. They teamed up with Eisenberg and Kaptchuk at Harvard to answer questions that are common in clinical practice about treatment of chronic low back pain.

They surveyed nearly 4,000 HMO enrollees six weeks after a primary care visit for back pain, not knowing how many still had pain, and enrolled the first 262 to respond, with 95% follow-up after one year. Typically, their patients were white, well-educated, and employed; 58% were women. Sixteen percent had massage previously for low back pain, but only 3% had acupuncture.

These data are the first that I know of to suggest strongly that massage is an effective short-term treatment for chronic low back pain. To find a licensed massage therapist, contact the American Massage Therapy Association, phone: (847) 864-0123, or web site: http://www.amtamassage.org.

In addition, Cherkin and colleagues present data to suggest cost-effectiveness as well, noting the use of massage therapists, treatment protocols, and long-term follow-up. The reason for the superior outcomes was not ascertained, but possibilities range from spending an hour in a relaxed environment to increased body awareness.

Recommendation

Massage therapy should be strongly considered, together with mobilization, exercise, and short-term analgesics, in the treatment of chronic low back pain, at least in an educated, employed population. Patients prefer it, these excellent data support it, and it appears to be cost-effective as well. ❖

In Future Issues:

Vitamin E for Diabetic Retinopathy

Deer Antler Velvet for Impotence

Gymnema sylvestre for Diabetes

Androstenedione as an Ergogenic Aid

Supplement to *Alternative Medicine Alert*
August 2001

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

Zinc

IN THE UNITED STATES, IT IS ESTIMATED THAT ADULTS AND CHILDREN GET TWO TO SIX COLDS each year, at a cost of more than $3.5 billion. A number of studies have evaluated the use of zinc lozenges to reduce the duration of symptoms associated with the common cold; results have been conflicting.

In one representative, positive study, time to complete resolution of symptoms was significantly shorter in the zinc group compared to the placebo group (median, 4.4 days compared to 7.6 days, respectively).[1] Patients taking one zinc lozenge (13.3 mg zinc from zinc gluconate) every two hours while awake experienced fewer days with coughing, headache, hoarseness, nasal congestion, nasal drainage, and sore throat. However, there was no difference in time to resolution of fever, muscle ache, scratchy throat, or sneezing, and the zinc group had significantly more side effects (nausea and bad aftertaste).

In recent studies, researchers have pointed to differences in product formulation to explain the variations in zinc studies.[2,3] Citric acid, tartaric acid, sorbitol, and mannitol may reduce efficacy by binding the free zinc ion in the mouth. Patients opting to try zinc lozenges, should select a zinc gluconate product that does not contain these additives.

Recommended Dietary Allowances (RDA)

5 mg/d for children 0-1 y	15 mg/d for males 11 y and older
10 mg/d for children 1-10 y	12 mg/d for females 11 y and older

Food Sources

Dietary sources of zinc include oysters, meat, dairy products, nuts, raisins, legumes, and whole grains.

Formulation

The amount of elemental zinc differs depending upon the zinc formulation: Zinc sulfate contains 23% elemental zinc (220 mg zinc sulfate contains 50 mg zinc). Zinc gluconate contains 14.3% elemental zinc (10 mg zinc gluconate contains 1.43 mg zinc).

Mechanism of Action

- Zinc is an essential trace element and a cofactor in many biological processes, including DNA, RNA, and protein synthesis.
- Zinc plays a role in the body's immune function, wound healing, reproduction, growth and development, behavior and learning, taste and smell, blood clotting, thyroid hormone function, and insulin action.

Clinical Uses

- To treat zinc deficiency associated with zinc-deficient diets, alcoholism, digestive diseases that result in chronic diarrhea, and restricticted diets, including anorexia nervosa.
- To treat the common cold and improve immune function.
- To treat blunted sense of taste (hypogeusia) and recurrent apthous ulcers.
- To treat Wilson's disease.
- To ensure normal development and growth in children.

- To treat and prevent peptic ulcers.
- To treat acrodermatitis enteropathica.
- As adjunctive treatment in many chronic diseases, including sickle cell disease, Hansen's disease, macular degeneration, and diabetes.
- To treat muscle cramps in zinc-deficient cirrhosis patients.
- Topically, to treat acne, herpes simplex infections, resistant trichomonas infections, and leg ulcers; to speed wound healing; to improve outcomes in burn patients; in toothpastes and mouthwashes to prevent dental plaque formation and gingivitis; and in ophthalmic products to soothe eye irritation.
- Intravenously, zinc is used as a component of total parenteral nutrition.
- When used parenterally, immediately post-head trauma, zinc improves the rate of neurological recovery.

Adverse Effects/Toxicity

- Zinc taken orally can cause nausea and vomiting, watery diarrhea, irritation and corrosion of the gastrointestinal tract, acute renal tubular necrosis, and interstitial nephritis.
- Toxicity presents with flu-like and central nervous systems symptoms including fever, coughing, nausea, vomiting, diarrhea, epigastric pain, lethargy, fatigue, neuropathy, and dehydration.
- Zinc gluconate lozenges can leave a bad aftertaste and may cause nausea.
- Zinc-induced copper deficiency has been associated with sideroblastic anemia, neutropenia, and impaired immune function at doses of 400 mg/d and greater.
- Zinc supplementation might reduce HDL levels and test results and increase the LDL to HDL ratio.
- Zinc supplementation can increase $HgbA_{1C}$ in type 1 diabetics.

Interactions/Nutrient Depletion

- Concomitant use with captopril, chlorthalidone, deferoxamine, and loop and thiazide diuretics can increase urinary zinc elimination.
- Concomitant use with amiloride and potassium-sparing diuretics can decrease urinary zinc elimination.
- Chlorthalidone can increase serum zinc levels.
- Concomitant use with interferon alfa-2b might be effective for treating necrolytic acral erythema associated with hepatitis C.
- With the exception of doxycycline, concomitant use with all tetracylines decreases zinc and tetracyline absorption.
- Concomitant use with cisplatin might increase the cytotoxicity of cisplatin when in the presence of chelate ethylenediaminetetraacetic acid, as compared to cisplatin treatment alone.
- Concomitant use with fluoroquinolones reduces zinc absorption and serum levels of fluoroquinolones.
- Penicillamine can reduce serum levels of zinc; concomitant use with penicillamine can reduce the effects of zinc from food or supplements.
- Concomitant administration with foods containing bran, protein, phytates, calcium, or phosphorus may decrease supplemental zinc absorption through a nonspecific binding function.
- Concomitant caffeine use can decrease zinc absorption.
- Concomitant zinc use can decrease copper absorption and increase zinc excretion.
- Iron taken in solution can inhibit the absorption of zinc, but foods fortified with iron do not.
- Use with caution in people who are homozygous for hemochromatosis.
- Avoid or use with caution with zinc ophthalmic solutions in glaucoma patients.
- Zinc absorption is reduced in people with rheumatoid arthritis.
- When testing blood for zinc and other trace elements, avoid powdered gloves to reduce the potential of sample contamination.

References

1. Mossad SB, et al. Zinc gluconate lozenges for treating the common cold. A randomized, double-blind, placebo-controlled study. *Ann Intern Med* 1996;125:81-88.
2. Garland ML, Hagmeyer KO. The role of zinc lozenges in treatment of the common cold. *Ann Pharmacother* 1998;32:63-69.
3. Marshall S. Zinc gluconate and the common cold. Review of randomized controlled trials. *Can Fam Physician* 1998;44:1037-1042.

Resources

Pelton R, et al. *Drug-Induced Nutrient Depletion Handbook*. Hudson, OH: Lexi-Comp; 1999.

Zinc. Facts about Dietary Supplements. Office of Dietary Supplements. National Institutes of Health. Available at: http://www.cc.nih.gov/ccc/supplements/zinc.pdf. Accessed: May 21, 2001.

Natural Medicines Comprehensive Database [database online]. Stockton, CA: Therapeutic Research Center, Inc., 2000.