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Turmeric in the Treatment of Dyspepsia

By Philippe O. Szapary, MD, and Michael D. Cirigliano, MD, FACP

THE MEDICAL LITERATURE SUGGESTS THAT TURMERIC (*CURCUMA longa*) extracts possess antioxidant, hypolipidemic, choleretic (stimulation of bile flow), cholekinetic (stimulation of gallbladder contraction), anti-inflammatory, anticarcinogenic, and antimicrobial activities.[1] Of all these purported benefits, perhaps the best-studied in humans are turmeric's choleretic and cholekinetic properties, making this ancient herb potentially useful in the treatment of dyspepsia.

Dyspepsia is a common condition seen in general practice, accounting for 2-4% of all primary care office visits.[2] The term nonulcer dyspepsia (NUD) refers to epigastric discomfort not associated with ulcer disease. In modern clinical practice in this country, the mainstay of treatment for NUD includes antacids, H_2-blockers, proton pump inhibitors, and antibiotics aimed at *Helicobacter pylori*, all of which may work in the short term, or may not work at all. In these patients, turmeric when used in doses of 1-3 g/d may improve dyspeptic symptoms.

History

Turmeric and its powdered rhizome were highly valued by early Asian civilizations because of its golden yellow color, reminiscent of sunlight. In Sanskrit, turmeric can be identified by 46 synonyms, including *pita* (fire/yellow) or *gauri* (brilliant).[3] Turmeric's distinctive color was thus exploited and used in commercial textile dyes. It was also noted that turmeric powder, because of its antimicrobial and antioxidant properties, preserved foods and prevented spoiling.[3] This is one of the reasons turmeric powder is used as a preservative and flavor enhancer in many Indian curry powders. In Western cuisine, turmeric is still used as a preservative in the pickling process, and as a dye and preservative in condiments like yellow mustard.

Extracts from *Curcuma longa*, also known as turmeric, have been used in Ayurvedic medicine for more than 2,000 years for a wide

Volume 3 • Number 5 • May 2000 • Pages 49-60

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variety of unrelated medical conditions from parasitic intestinal infections and skin cancer to liver disease. In traditional Chinese medicine, turmeric, also known as Jianghuang, has been used for dyspepsia, liver disease, and hyperlipidemia for more than two millennia and is listed in the Chinese Materia Medica.[4]

Source and Identification

Curcuma is a perennial herb indigenous to Southeast Asia and like ginger, belongs to the Zingiberaceae family. Of the genus *Curcuma*, two plants, *C. longa* and *C. xanthorrhiza* (Javanese turmeric) have medicinal properties.[3] *Curcuma longa*, also known as *C. domestica*, is by far the most commonly used and will be the focus of this review. The underground rhizome of *C. longa* (1/2 inch in diameter) is cultivated, boiled in water, air dried and cured into fingers, and then ground into powder. The major constituents of the powder include curcuminoids (2-5% by weight) and volatile oils (2-6%).[5] The majority of the biologic activity is believed to come from the curcuminoids, and to a lesser extent, the volatile oils that give turmeric its characteristic smell and taste.

Pharmacology

The major curcuminoids are curcumin, demethoxycurcumin (DMC), bisdemethoxycurcumin (BDMC), and cyclocurcumin.[5] The primary volatile oils, of which much less are known, are composed of sesquiterpenoids such as curcumone, turmerone, and zingiberene.[5] Of interest, a number of bioactive polypeptides have been identified, including turmerin.

Metabolism

Studies in rats and humans confirm that the majority of orally ingested curcuminoids are excreted in feces and that only very small amounts can be detected in serum and urine.[5] In vivo experimentation in rats using a very large oral dose of curcumin have found that 60% of curcumin is absorbed.[1]

In humans, curcumin is barely detectable in serum after a single 2 g oral dose of curcumin.[6] It is possible that curcumin undergoes transformation to unmeasured compounds in intestinal cell walls, and may be effective at very low concentrations. Interestingly, coadministering a small dose of piperine, an extract of black and long pepper used in Ayurveda, increased bioavailability of curcumin by 2,000% in one study.[6] The small amounts of curcumin that are absorbed in the serum are quickly metabolized by the liver to glucuronides of tetrahydrocurcumin and actively excreted into bile.[5]

Mechanism of Action

Curcuminoids' mechanisms of action have been extensively studied and are multifaceted. Curcuminoids have been shown to antagonize the effect of several spasmogens in isolated guinea pig ileum.[5] Curcumin may also stimulate the release of GI paracrine hormones from intestinal luminal cells. Curcumin has also been shown to increase hepatic cholesterol-7a-hydroxylase activity in rats, which stimulates bile acid synthesis.[7]

Turmeric extracts inhibit cyclooxygenase enzymes, like NSAIDs[8] and thus may be ulcerogenic, especially at higher doses.

Animal Studies

In a study done in rats fed a flatulent diet, curcumin feeding decreased gas production.[5] Curcumin administered at an IV dose of 25 mg/kg increased bile secretion in anesthetized dogs by 100%.[5] Other studies have confirmed these findings and also found a cholekinetic effect. Some investigators have found that curcumin prevented the formation of cholesterol gallstones in mice.[9]

Curcumin has been shown to increase mucin content in gastric juice of rabbits, thus possibly imparting a protective effect on the gastric mucosa.[5] This protective gastric effect is controversial, however, as one study has shown that curcumin when administered at high doses

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

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

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

Subscriber Information

Customer Service: 1-800-688-2421.
Customer Service E-Mail Address: customerservice@ahcpub.com
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Subscription Prices

United States
$219 per year (Student/Resident rate: $119).
Outside the United States
$249 per year plus GST (Student/Resident rate: $130 plus GST).
Back Issues
$37 per issue. Missing issues will be fulfilled by Customer Service free of charge when contacted within one month of the missing issue's date.

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Table 1

Comparison of commercially available turmeric products with other products used for dyspepsia

Product/ Manufacturer	Active Ingredient	Manufacturer's Suggested Use	Dyspepsia Dosing (Based on RCT)	Retail Price/Month (Based on NUD Dosing)
Zantac®	Ranitidine 150 mg	1 tablet PO bid	same	$41.15/month
Artichoke Leaf Extract (Enzymatic Therapy)	13-18% caffeylquinic acid	1 capsule PO tid	same	$20.50/month
Chamomile (Nature's Herb)	German chamomile flowers 354 mg/capsule	2 capsules PO tid	same	$11.07/month
Turmeric-Power (Nature's Herb)	Curcumin 300 mg Standardized to contain 95% curcuminoids	2-3 capsules qd	1 capsule qd	$6/month
Turmeric Extract (Source Natural)	Curcumin 350 mg/ bromelain 50 mg	1-3 capsules qd	1 capsule qd	$6/month

Source: Hospital of University of Pennsylvania outpatient pharmacy, online mail order companies

(100 mg/kg) PO to albino rats was actually ulcerogenic.[10] It appears that the ulcerative index of curcumin is dose dependent and approximately one-third that of the NSAID phenylbutazone.[11]

Clinical Trials

Searching MEDLINE, PubMed, NCCAM CAM Citation Index, IBIDS database, and the HerbMed™ database, we identified 12 clinical trials using turmeric or curcuminoids alone or with other herbs in humans. Of these 12 trials, only five of these trials specifically investigated the GI effects of turmeric derivatives and all of these trials were randomized, placebo-controlled trials (RCT).

One multicenter RCT done in Thailand reported the effect of turmeric powder compared with a combination antiflatulence product containing ginger, capsaicin, and cascara with placebo.[12] One hundred sixteen patients with clinically diagnosed non-specific dyspepsia were randomized to take 500 mg turmeric powder PO qid in capsule form for seven days.

Fifty-three percent of placebo patients were "improved or cured" compared to 83% of those assigned to the antiflatulence product and 87% of those in the turmeric group ($P < 0.008$ for either drug vs. placebo). At the end of the study, approximately 50% of subjects across all groups were satisfied with their treatment assignment. Problems with this study include the use of a nebulous, non-endoscopic definition of dyspepsia and the very short treatment period.

When treating a subset of NUD patients with functional biliary tract pain (i.e., no evidence of gallstones), a recent German group found that a proprietary combination product (Cholagogum F Nattermann®) containing 45 mg of curcumin and 4 mg of celandine given orally tid significantly reduced complaints of colicky right upper quadrant (RUQ) abdominal pain when compared to placebo over three weeks ($P < 0.01$).[13] No significant differences were noted in the incidence of early satiety, nausea, or vomiting.

This study implies that increasing bile flow may improve symptoms in these patients. This effect attributable to curcuminoids was recently demonstrated in another RCT in which 12 healthy volunteers received a 20 mg dose of oral curcumin or placebo, and had four serial RUQ ultrasounds over two hours.[14] Investigators found a 30% reduction in gallbladder volume two hours after receiving curcumin ($P < 0.001$).

Another RCT looking specifically at the healing rate of duodenal ulcers found that 6 g of turmeric powder given orally each day was no better than placebo at eight weeks.[15] Healing was actually worse in the turmeric group (2% healed) compared to the placebo group (15% healed) at four weeks. By the study's end, both groups demonstrated a 30% healing rate.

Another RCT compared turmeric powder 250 mg PO qid with a liquid antacid qid in healing endoscopically proven gastric ulcers in 60 patients.[16] After six weeks, 33% of gastric ulcers in the turmeric group had completely healed compared with 65% in the antacid group. Fifteen percent of the turmeric group was unchanged or

worse compared to 0% in the antacid group. These findings imply that large doses of turmeric may actually be ulcerogenic and retard healing rate in peptic ulcer disease (PUD).

Adverse Effects and Drug Interactions

Most animal studies have found turmeric and curcumin to be safe, even at high doses. For example, one study done in monkeys found no adverse effects at an oral curcumin dose of 800 mg/kg/d for three months.[17] There is one report of curcumin causing gastric ulcerations in mice at 50 mg/kg/d for six days[10] and another report of hepatotoxicity with exaggerated oral feedings with turmeric over just 14 days.[18]

In humans, turmeric is a Generally Recognized as Safe (GRAS) spice with typical consumption in Indian culture ranging from 0.1-3.8 g/d.[19] Published clinical trials do not report significant adverse events. Specifically, a clinical trial done in rheumatoid arthritis found curcumin to be well tolerated at doses up to 1,200 mg/d for two weeks (approximately 24 g/d turmeric powder).[20] Also, a published abstract from a Phase I trial of curcumin in patients with HIV found curcumin safe at doses of up to 2,000 mg PO qd for 18 weeks.[21]

There are no published reports of curcumin-drug interactions. One review raised the possibility of an interaction with antiplatelet agents as curcumin inhibits platelet aggregation in vitro. Animal studies have found that turmeric is safe in pregnancy but no human studies address this population. It is clear, however, that medicinal use of turmeric should be avoided in pregnancy as it may increase uterine contraction.[19]

There are several published case reports of contact dermatitis associated with turmeric powder when used topically. A search of the FDA adverse drug reaction (ADR) database identified 12 reports associated with turmeric or curcumin.[22] A review of these ADRs found that every case report was associated with multiherbal preparations, which included small amounts of turmeric and often included ma huang.

Formulations and Dosage

Turmeric is widely available commercially as a spice used in Indian cuisine but the doses required for a therapeutic effect in dyspepsia (1-3 g/d) precludes the practical use of this formulation in most Western diets. Turmeric is also available as a concentrated extract in capsule form standardized to curcumin content, as an alcohol extracted tincture, and as a tea. (*See Table 1.*) Since the curcuminoids and volatile oils are poorly water soluble, teas are not recommended.

In this country, turmeric and curcumin are found primarily in combination products marketed as antioxidants or for the treatment of arthritis. It is important to note that the anti-inflammatory doses of curcumin used in RCTs for arthritis treatment are at least four times higher than the doses found to be effective in dyspepsia.

International Practice

In Europe, carminative herbs like chamomile, artichoke leaf, and turmeric are frequently used in clinical practice for the treatment of dyspepsia. The German Commission E has approved the use of turmeric alone, and in combination with the herb celandine, for the treatment of dyspepsia.[23]

Conclusion

For simple NUD, it appears that curcumin or turmeric powder may decrease symptoms over the short run. No data exist to support its long-term use for this chronic condition. Turmeric should not be used in patients with active PUD as it may be ulcerogenic even at doses of 1 g/d. Turmeric should also not be used in patients with known cholelithiasis or chronic cholecystitis as this herb causes biliary contraction and could precipitate an attack. In the subset of patients with biliary dyskinesia, turmeric and curcumin seem to improve pain symptoms. To date, there are no studies directly comparing turmeric to artichoke leaf extract, the most popular herbal cholagogue used in Europe.

Recommendation

We caution against the indiscriminant use of medicinal turmeric for undiagnosed epigastric pain. This is based on data from RCT that suggest turmeric may impede healing of ulcers in PUD. Turmeric should also not be used in patients with known or suspected cholelithiasis. However, in patients whom you believe truly have NUD, turmeric powder 1-3 g/d or curcuminoids 50-150 mg/d is an inexpensive and likely effective remedy. ❖

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Vagus Nerve Stimulation for Epilepsy

By V. Jane Kattapong, MD, MPH

Illness is not something a person has. It's another way of being.

Jonathan Miller
The Body in Question

EPILEPSY WREAKS HAVOC IN PEOPLE'S LIVES; PATIENTS with epilepsy have to get used to another way of life. They give up much of their independence. They often have to give up driving. They cannot swim alone. They frequently miss school and work. They must always remember to bring their medications with them when they are away from home, and to take their medications regularly. Children may have difficulty in school. Severely affected individuals may be completely disabled and unable to work at all because of the seizures themselves, post-ictal symptoms of lethargy or confusion, or the sedation from multiple seizure medications. Thus, living with epilepsy may amount to another way of being.

A decrease in seizure frequency or severity may enable people with refractory epilepsy to achieve some semblance of normality in their lives.[1] Effective treatment of epilepsy may lessen the disability that patients experience. Vagus nerve stimulation (VNS) is one treatment modality that may decrease frequency and severity of seizures, as well as decrease the amount of sedating medications that patients must take.

Background

Epilepsy is generally defined as recurrent, unprovoked seizures.[2] Epilepsy occurs commonly; the risk of

developing epilepsy by age 80 has been reported to be 4%,[3] and it affects 0.5-1.0% of the population.[4] Epilepsy causes significant disability: Up to 50% of epilepsy patients experience either inadequate seizure control or disabling side effects of medication such as drowsiness, poor coordination, or poor concentration. Thus, disability from epilepsy occurs commonly.

Seizures are broadly classified as either generalized or partial in onset. Generalized seizures begin bilaterally in both hemispheres of the brain. Partial seizures have a localized onset and may evolve into generalized seizures.

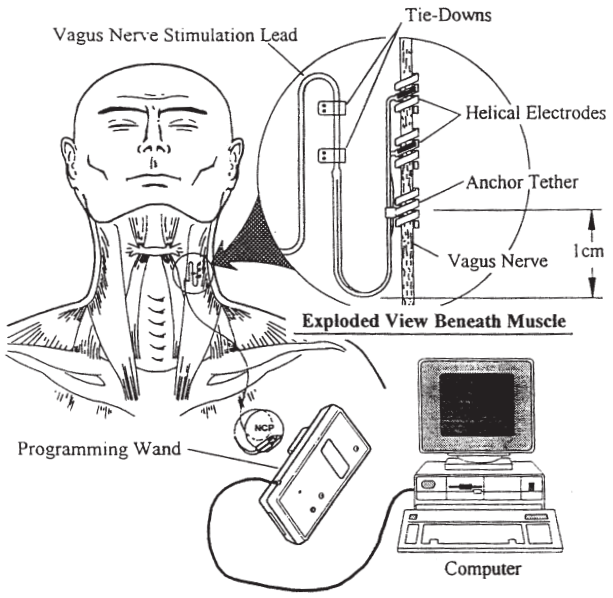
Procedure

In VNS, intermittent stimulation is administered to the left vagus nerve in the neck. The VNS is delivered via the NeuroCybernetic Prosthesis (NCP®), a vagal nerve stimulation device developed by Cyberonics, Inc. (Houston, Texas) for the treatment of epilepsy.[5] (*See Figure 1.*)

The device is a programmable signal generator which is implanted as an outpatient, or during an overnight admission, in the upper left chest. The generator is connected to a stimulating coil placed in close proximity to the left vagus nerve. Patients typically receive vagal nerve stimulation for 30 seconds every five minutes.[6] Since the device is programmable, signal duration and frequency can be modified as needed. In 1997, FDA approved the device for use as adjunctive treatment for partial-onset seizures for people over 12 years of age.

Figure 1

Implant detail of the vagus nerve stimulation pulse generator, the NeuroCybernetic Prosthesis (NCP®)



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Mechanism of Action

The mechanism of action of VNS for seizure control is not well understood. The vagus nerve normally supplies parasympathetic innervation to the pharynx, esophagus, trachea, bronchi, lungs, heart, stomach, small intestine, ascending and transverse colon, liver, and pancreas,[7] and has an integral role in regulation of respiratory, digestive, and cardiac function.[8]

In addition, the vagus nerve provides the brain with visceral sensory information from the head, neck, thorax, and abdomen.[2,9] The cell bodies of the vagus nerve sensory axons are contained in the nodoose ganglion. These cell bodies relay information to the nucleus of the solitary tract (NTS).[2] One pathway of the NTS provides an ascending projection conveying visceral sensory information to the forebrain.[10] This communication with the thalamocortical system may be the mechanism whereby VNS modulates seizure activity.

Vagus Nerve Stimulation in Adults

Long-term safety, tolerability, and efficacy of VNS were assessed in an open-label study of 454 patients with refractory epilepsy.[3] All patients had had continued seizures despite medical therapy. All patients had an NCP implanted in the anterior chest.

During the study, patients continued using antiepileptic drugs (AEDs) as needed. About half of the study participants were male and half were female. The average age of participants was 31 years, and the average duration of epilepsy was 21 years. The average number of seizures per day at baseline was about two, and the average number of AEDs used was two. Significant ($P < 0.0001$) seizure reductions were seen at predetermined time intervals, including three months, one year, two years, and three years.

To minimize the potential bias resulting in patient attrition, a "last-visit-carried-forward" analysis was performed, considering the status at the last visit to be the current condition. At three years, 43% of patients remaining in the study had experienced a > 50% decrease in seizure frequency. At three years, the most common side effects reported were hoarseness (19.3%) and cough (5.9%). Serious adverse events were limited to severe hoarseness in three individuals and shortness of breath in three individuals. There were no deaths of

study participants believed to be related to the VNS.

The total cost of VNS, including surgery and follow-up visits, is about $20,000 (personal communication, Cyberonics). This compares favorably with traditional epilepsy surgeries, such as temporal lobectomy, which can range from $20,000 to $100,000. Contraindications include the presence of a bilateral vagotomy or left cervical vagotomy.

Vagus Nerve Stimulation in Children

Evidence is starting to accumulate suggesting that VNS may be efficacious in children. The Pediatric VNS Study Group evaluated the use of intermittent left vagal nerve stimulation in children with medication-resistant epilepsy.[11]

In this study, essentially a meta-analysis of two double-blind, controlled trials of VNS efficacy, 60 children between 3½ and 18 with uncontrolled epilepsy were followed for up to 18 months. At 12 months, seizure reduction of 35% was found in 51 patients; and at 18 months, seizure reduction of 42% was found in 46 patients. Twenty-seven percent of patients had generalized tonic-clonic seizures, and 73% had partial-onset seizures. Differences in numbers between study enrollees and patients still enrolled at 18 months occurred because of patient dropout. However, an intent-to-treat analysis revealed little difference between analyses involving the entire group vs. the patients enrolled at the end of 18 months.

Of the group of patients who did not complete the study, three left because of lack of efficacy, one left because the device eroded through the skin, and one died of aspiration pneumonia (unrelated to the device). The study authors concluded that VNS is a safe, effective adjunctive therapy for children with intractable epilepsy.

Side Effects

Relatively few side effects have been reported in association with vagus nerve stimulation. Side effects that have been reported include hoarseness, cough, paresthesias, headache, and shortness of breath.[3] In a blinded study of 254 epilepsy patients, no serious adverse events were found to be related to VNS.[12] One post-marketing case report described a 56-year-old man with mild mental retardation, right hemiparesis, and refractory partial seizures who developed bradycardia and transient asystole during lead diagnostic testing. The patient recovered completely with brief cardiopulmonary resuscitation. The manufacturer has stated that the occurrence of similar arrhythmias is expected to occur in about 0.1% of patients.[13]

The American Academy of Neurology's Assessment of Vagus Nerve Stimulation

The American Academy of Neurology's Subcommittee on Therapeutics and Technology Assessment reviewed the existing evidence in 1999[14] and found that the degree of improved seizure control attributed to VNS was comparable to that of the new AEDs. The subcommittee found that VNS for epilepsy was both effective and safe. Nevertheless, neurologists may be reluctant to offer VNS because it utilizes neither traditional pharmaceutical nor traditional surgical means of treatment.

Conclusion

VNS appears to be a safe, effective alternative to multi-pharmacy for patients with refractory epilepsy. Although current FDA approval covers usage for people over 12 years of age, it appears to be of benefit for younger children as well.

Recommendation

VNS may be beneficial as an adjunctive therapy in refractory epilepsy. This device is a nonpharmacologic treatment option that should be considered for epilepsy patients. ❖

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Goldenseal for Upper Respiratory Infections

By Dónal P. O'Mathúna, PhD

GOLDENSEAL REMAINS ONE OF THE MOST POPULAR herbs sold in the United States. In the first eight months of 1999, sales of echinacea and goldenseal, often formulated together, ranked fifth among herbal remedies sold through mainstream markets.[1] If your patients use herbal remedies, there's a good chance they take goldenseal as a "natural antibiotic" to treat and prevent colds and flu.

History and Harvesting

Goldenseal (*Hydrastis canadensis*) is a member of the buttercup family. It is a low-growing herbaceous perennial, characterized by a bright yellow rhizome (or underground thickened stem), from which it gets its name. Other common names include golden root, eye root, and ground raspberry, because of its small red fruit. It grows naturally in the woodland areas across much of the Eastern and Midwestern United States. Overharvesting of goldenseal in the 1980s and early 1990s led to concerns that it was becoming an endangered species, especially as it was difficult to cultivate. Much progress has since been made in this area, leading to significantly expanded agricultural acreage.[2]

Folklore

Native American tribes (including the Cherokee, Iroquois, Crow, Seminole, and Blackfoot) commonly used this herb as a diuretic and stimulant, as a treatment for stomach ulcers, and as a wash for irritated eyes and mouth sores. It was also an important source of yellow dye. European settlers first mentioned it in 1804 as a powerful "bitter" to increase appetite and facilitate digestion, and as a mouth and eye wash.[3] Goldenseal was enthusiastically promoted by the Eclectic medical doctors, who focused on herbal remedies and gave many American herbs their first scientific evaluations by carefully observing and recording their effects.[3] Many Eclectics were critical of overblown claims about goldenseal, such as its alleged ability to cure cancer.

With the decline of the Eclectics in the 1930s, goldenseal's use dropped off in the United States. Recent interest in goldenseal began when it was reported during the 1970s that oral ingestion would mask morphine in drug urinalysis. These claims have been shown to be without scientific merit, but they persist, and have broadened to include masking of marijuana and cocaine.[4]

Official Recommendation and Current Use

Goldenseal was officially approved as a medicinal herb in the United States Pharmacopoeia (1830-1840 and 1860-1926), and in the National Formulary (1888 and 1936-1955).[3]

Many pharmaceutical companies sold the root and preparations of it until the early 20th century. Goldenseal is now sold as a cure-all type of herb to prevent and treat colds and flu, strengthen the immune system, potentiate insulin, cleanse vital organs, and promote the functioning capacity of the heart, lungs, liver, spleen, pancreas, and colon.

Pharmacology

The active ingredients in goldenseal are a group of benzylisoquinoline alkaloids, the most abundant of which are berberine and hydrastine. Alkaloids are a diverse group of alkaline nitrogen-containing compounds made by many plants from a small group of amino acids. Many have pharmacological activity. The chloride salt of berberine is responsible for goldenseal's yellow color. Most of goldenseal's alleged medicinal effects have been linked to berberine, with recent studies confirming the lack of antibacterial activity of other constituents.[5]

Mechanism of Action

The mode of action of goldenseal and berberine in

humans is not understood well. Berberine (also isolated from barberry, Oregon grape root, golden thread, and several Chinese herbs) has antimicrobial effects, inhibiting the adherence of microorganisms to host cells.[5] Berberine has in vitro antimicrobial activity against a wide variety of microbes, including *Bacillus*, *Streptococcus*, and *Candida* organisms.[6] Antiviral activity has not been reported for berberine.

Goldenseal is believed to relieve colds and flu by increasing the flow of mucous and causing the release of more antibodies.[7] Goldenseal allegedly acts in humans as an "alterative," an herbalist's term for substances that gradually produce beneficial changes in the body by stimulating natural healing processes. In this case, goldenseal's GI effects are said to result from "increasing deficient flow but decreasing excessive flow" of various mucous secretions.[7]

Animal Studies

One animal study examined goldenseal's effect on the rat immune system.[8] Animals given goldenseal in their drinking water showed significantly elevated IgM antibody levels compared to control rats during the first two weeks, but not in the four subsequent weeks. Levels of IgA antibodies did not differ between the two groups.

Another animal study provides some support for goldenseal's relief of cold symptoms.[9] Mice with drug-induced diabetes were fed a diet containing 6.25% by weight of goldenseal to investigate its reputation as a natural diabetes treatment. No significant changes in plasma glucose and insulin concentrations were detected, but hyperphagia and polydipsia were significantly reduced.

Clinical Studies

A search of MEDLINE, TOXLINE, and International Pharmaceutical Abstracts (using the terms goldenseal, golden seal, hydrastis, and berberine) found no clinical studies using goldenseal. Several goldenseal monographs also were consulted, and none reported clinical studies. A clinical study of giardiasis and berberine found it active against *Vibrio cholerae*, protozoa, and fungi.[10]

Goldenseal contains 2-4% of berberine, so one would have to take 26 commercial 500 mg goldenseal capsules daily to obtain the berberine dose typically given in the referenced clinical studies. Twenty-six capsules (or 13 g) daily far exceeds the usual recommended dose.[7]

Formulation

Goldenseal reportedly enhances the effects of echinacea and is frequently added to other herbal preparations. It is available as dried root and rhizome in capsules, tinctures, extracts, tablets, salves, and ointments. For colds and flu, one or two 500 mg capsules are recommended 2-3 times daily. Alternatively, one teaspoonful of herb (the contents of 2 or 3 capsules) or tincture can be added to a cup of boiling water to make a tea taken three times daily. Stronger mixtures are recommended for external use only.

Adverse Effects

Large doses or prolonged use of goldenseal can cause nausea, vomiting, paresthesia, hypertension, and respiratory failure. Fatalities have been reported.[11] Goldenseal (10 capsules; strength not reported) is one of several berberine-containing herbs used as abortifacients.[7] Berberine displaces serum-bound bilirubin, raising blood levels and increasing the risk of brain damage in infants with previously raised bilirubin levels.[12]

Adulteration

Widespread use of goldenseal has led to over-collection and deforestation of the plant, leading to high prices and adulteration with less expensive berberine-producing herbs.[13] These include Chinese goldthread (*Coptis chinensis*), yellow root (*Xanthorhiza simplicissima*), and Oregon grape (*Mahonia aquifolium* or *Berberis vulgaris*), which have different overall effects. Oregon grape in particular has been associated with adverse effects, especially diarrhea, nephritis, confusion, and stupor.[14] The European Union's drug regulating agency in 1996 listed Oregon grape as an Herbal Drug with Serious Risks because of its berberine content.[7]

Conclusion

The likely active ingredient in goldenseal has in vitro antibacterial, antifungal, and antiparasitic activity. However, its systemic efficacy, especially against viral infections, remains unproven. One animal study showed it may induce short-lasting immune system stimulation.

Recommendation

Given goldenseal's serious adverse effects, its popular use for colds and flu appears unwarranted. Goldenseal certainly should not be used during pregnancy or lactation. Traditional usage has primarily been as a topical antimicrobial, and berberine does have broad antimicrobial activity. Ironically, goldenseal has fallen prey to the same tendency toward overuse as have prescription antibiotics, resulting in endangerment of the plant's wild variety. ❖

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CME Questions

28. Which of the following statements about curcumin is/are true?
a. It has been shown to increase bile acid flow.
b. It has been shown to heal peptic ulcers.
c. It has been shown to increase gallbladder contraction.
d. a and c.

29. The following statements about turmeric are correct *except*:
a. turmeric is a spice.
b. turmeric can be used as a food colorant.
c. turmeric possesses antioxidant properties in vitro.
d. turmerin is the most bioactive constituent of turmeric.

30. All of the following statements about turmeric are true *except*:
a. turmeric has documented anti-inflammatory activity in humans.
d. turmeric is most useful when used as a tea.
c. turmeric may retard healing of duodenal ulcers.
d. turmeric should not be used in patients with gallstone disease.

31. What are the two broad classifications of seizure types?
a. Psychomotor and motor
b. Generalized and partial
c. Childhood and adult

32. Common side effects of vagus nerve stimulation for epilepsy include:
a. nausea.
b. jaw pain.
c. hoarseness.
d. vomiting.

33. The NeuroCybernetic Prosthesis (NCP®) delivers electrical stimulation to:
a. the right and left vagus nerves.
b. the right vagus nerve.
c. the left vagus nerve.
d. alternating right and left vagus nerves.

34. The active ingredients in goldenseal belong to the group of plant chemicals called:
a. flavonoids.
b. diterpenes.
c. alkaloids.
d. steroids.

35. Which group of patients should most certainly limit or avoid use of goldenseal?
a. Older men
b. Teenagers
c. Immunosuppressed adults
d. Pregnant women

36. The active ingredient in goldenseal has shown activity as an:
a. insulin-regulating compound.
b. antibacterial agent.
c. estrogen replacement agent.
d. antiviral agent.

Reader Question

Comment: Your journal in no way represents the facts about SAMe. [See *Alternative Medicine Alert*, December 1999, pp. 133-135.] SAMe has to be taken with B-vitamins (folic acid and B_6); none of the references cited required that SAMe be taken in that condition. Please respond to this, as you are misinforming the public. SAMe is, indeed, the most effective antidepressant ever made available to the public.

John A. Rush, PhD, ND
Orangevale, CA

Response: *You are correct that none of the trials of SAMe published to date discuss B-vitamins. If SAMe raises homocysteine levels, then taking folic acid along with SAMe might be helpful. There is still considerable controversy, however, whether patients who have elevated levels of homocysteine benefit from taking folic acid.*[1] *In addition, as I discuss in my article, there is also very little evidence that oral SAMe is an effective antidepressant.*

Barak Gaster, MD
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University of Washington, Seattle

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Editor's Note: Dr. Rush acknowledges no significant financial interest in SAMe, its manufacturers, or distributors.

Clinical Briefs

With Comments from John La Puma, MD, FACP

(-)-Hydroxycitric Acid and Weight Loss

Source: Kriketos AD, et al. (-)-Hydroxycitric acid does not affect energy expenditure and substrate oxidation in adult males in a post-absorptive state. *Int J Obes Relat Metab Disord* 1999;23:867-873.

AVAILABLE AS AN HERBAL SUPPLEMENT, (-)-Hydroxycitric acid [(-)-HCA] is promoted as a weight loss agent. It is hypothesized that (-)-HCA can increase fat oxidation by inhibiting citrate lyase, an enzyme that plays a crucial role in energy metabolism during de novo lipogenesis. The indirect inhibition of the cytosolic pool of citrate by (-)-HCA and the subsequent reduction in acetyl coenzyme A and oxaloacetate alter steps in the citric acid cycle that promote fat oxidation.

We hypothesized that supplementation with (-)-HCA would result in an increase in fat oxidation and metabolic rate, reflected by an increase in beta-hydroxybutyrate and energy expenditure (EE) and/or a decrease in respiratory quotient (RQ). Furthermore, during moderately intense exercise, we hypothesized that (-)-HCA supplementation would increase the rate of lactate conversion to glucose in the liver. No studies have investigated the effects of (-)-HCA supplementation in conjunction with a typical daily dietary composition (approximately 30-35% fat) on metabolic processes that could influence body weight regulation in humans.

Sedentary adult male subjects (n = 10, age 22-38 years, body mass index 22.4-37.6 kg/m^2) were enrolled in a randomized, double-blind, placebo-controlled, crossover study involving three days of (-)-HCA (3.0 g/d) or placebo supplementation. Four laboratory visits were conducted: Protocol A with and without (-)-HCA treatment with no exercise; and Protocol B with and without (-)-HCA treatment with moderately intense exercise (30 min at 40% maximal aerobic fitness [VO_{2max}] and 15 min at 60% VO_{2max}). EE (by indirect calorimetry) and RQ were measured for 150 min following an overnight fast. Blood samples were collected for the determination of glucose, insulin, glucagon, lactate, and beta-hydroxybutyrate concentrations.

In a fasted state and following three days of (-)-HCA treatment, RQ was not significantly lowered during rest (Protocol A) nor during exercise (Protocol B) compared with the placebo treatment. Treatment with (-)-HCA did not affect EE, either during rest or during moderately intense exercise. Furthermore, the blood substrates measured were not significantly different between treatment groups under the fasting conditions of this study. These results do not support the hypothesis that (-)-HCA alters the short-term rate of fat oxidation in the fasting state during rest or moderate exercise, with doses likely to be achieved in humans while subjects maintain a typical Western diet.

COMMENT

These University of Colorado investigators add to the clinical work done on the enzyme HCA, in the rind of the fruit *Garcinia cambogia*, which might reduce how much fat the body actually makes. But according to this and most human evidence I've seen, it doesn't work. The only human studies that support its use and show some weight loss combined 750 mg HCA with a low-calorie diet and exercise (a combination for the ages).

This well-designed, high-tech (they measured body composition by DEXA using a bone densitometer!) study notes that obesity is a chronic disease requiring lifestyle modification for a long-term solution. The authors also point out that the daily cost of 3 g/d of HCA approaches $40, and it's not uncommon for people to waste their money in just this way.

Recommendation

Garcinia and HCA are not recommended for weight loss, short- or long-term. Refer patients to a medically sound weight management program for assistance with the skills needed to change their eating and fitness habits. ❖

Noni Juice and Renal Patients

Source: Mueller BA, et al. Noni juice (*Morinda citrifolia*): Hidden potential for hyperkalemia? *Am J Kidney Dis* 2000; 35:310-312.

"WE REPORT THE CASE OF A MAN with chronic renal insufficiency who self-medicated with an alternative medicine product known as noni juice (*Morinda citrifolia*). The patient presented to the clinic with hyperkalemia despite claiming adherence to a low-potassium diet. The potassium concentration in noni juice samples was determined and found to be 56.3 mEq/L, similar to that in orange juice and tomato juice. Herbal remedies and alternative medicine products may be surreptitious sources of potassium in patients with renal disease."

COMMENT

These Purdue and Indiana University authors report, and an editorial comments upon, a surreptitious source of hyperkalemia in a patient with chronic renal insufficiency. The editorial notes a Chinese herbal nephropathy, associated with carcinogenic phytotoxins.

Even without toxic herbs, juices, and medications, patients with kidney disease do not have it easy. Most of their nutritional prescriptions are hard to follow, perhaps especially so in these days of high-protein, fast-food craziness. Either these patients have to watch everything they eat, or they have to change their way of cooking, eating, and shopping so that they learn how to plan, and make eating in a low-protein, low-potassium, usually low-sodium, low-calorie, high-calcium way second nature. Many aren't able to do this. Their kidney function deteriorates; they develop complications; they require dialysis; they get a new kidney; or they don't; they die, or stay on dialysis.

Noni juice is available refrigerated or frozen in some health food and specialty markets. It is often, as it was in this case, sweetened with white grape juice. The noni tree grows in India, Samoa, Tahiti, Southeast Asia, and Australia, and the juice of its fruit is reported to be a cure all. Though 1 oz/d is recommended, containing only 1.66 mEq of potassium, popular daily usage is (and testimonials report) much greater quantities.

Recommendation

Who knows what's really in noni juice? But suspect supplementation of juices and other processed dietary supplements when a renal patient's numbers don't make sense. ❖

Iridology to Identify Toxins

Source: Ernst E. Iridology: Not useful and potentially harmful. *Arch Ophthalmol* 2000;118:120-121.

MORE THAN 1,000 LICENSED NATUROpathic physicians practice in the United States, and iridology is described as "the most valuable diagnostic tool of the naturopath." Some therapists are using iridology as a basis for recommending dietary supplements and/or herbs. Several iridology organizations exist: The National Iridology Research Association is an iridologists' service organization; the International Association of Iridologists is the leading organization for European-style iridology and runs training programs; and the Bastyr Naturopathic College in Seattle, Wash., has an elective course on iridology (J. Colton, e-mail communication, December 2, 1998). In the United States, insurance programs do not normally cover iridology, but in some European countries, they do. In Germany, for instance, 80% of the Heilpraktiker (nonmedically qualified health practitioners) practice iridology. Ophthalmologists may therefore ask what is iridology and how valuable is it?

COMMENT

Iridology is knowledge about the iris, especially about the connection between its pigmentation and organ dysfunction. Each iris is divided into three major and three minor zones; some iridologists divide the iris, like an hour, into 60 parts; others divide it into 100 parts. Each part relates to an organ or an internal function. Maps of the right iris correspond to the right side of the body; maps of the left iris correspond to the left. Careful photographs of both irides are often taken by iridologists, and examined. Neural connections are responsible for the correlation between the iris and organ function.

Iridology is practiced by some homeopaths and naturopaths. Iridologists do not claim to diagnose particular illnesses, but instead, to identify toxicities and dysfunction. Specific natural remedies can, at an iridologist's recommendation, prevent illness from developing. If it does, then the credit goes to the iridologist.

Ernst identifies four controlled, masked evaluations of the diagnostic validity of iridology: One study evaluated patients with renal disease, gallbladder disease, ulcerative colitis, coronary heart disease, asthma, pleurisy, gastroenteritis, and an upper respiratory infection. Sample size ranged from 1-146; all trials were small; all involved at least one and two involved several iridologists. All studies, according to Ernst, were adequately designed and masked, and consisted largely of evaluating color photographs of the iris. None found any diagnostic accuracy with iridology.

These data suggest that iridology is a waste of time and money. But how many patients have been reassured that their irideal maps were normal while their real pathophysiology continued to brew? How many patients receive diagnoses of "toxicity" they don't really have?

Recommendation

The practice of iridology should be thought of as crystal ball reading—what you see is, or is not, what you get. Tell your patients to save their money. ❖

In Future Issues:

Praying with Patients: How? When? Where?

Isoflavones for Menopause