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Astragalus for Allergies • Herbs and Swine Flu • Harvesting Blood of the Dragon • Ginger and Menstrual Pain

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Turmeric

Curcuma longa

Family: Zingiberaceae

Introduction

The traditional spice and medicine turmeric (*Curcuma longa*, formerly *C. domestica*) is a low-growing perennial with lanceolate (sword-shaped) leaves and yellow flowers.[1,2] Native to Southeastern Asia, turmeric is currently cultivated in India, China, Japan, Indonesia, Taiwan, Africa,[3] Bangladesh, Sri Lanka, Burma (Myanmar), Thailand, Cambodia, Malaysia, and the Phillipines.[2] India is by far the largest consumer, producer, and exporter of turmeric rhizome (lateral fleshy roots), and the country also exports turmeric essential oil, turmeric oleoresin, and turmeric preparations.[4] The rhizomes are dried and ground into a golden yellow powder used in cooking and medicine.[1,2,3] They have a distinctive earthy fragrance.[5]

Turmeric *Curcuma longa* ©2009 Stevenfoster.com

History and Cultural Significance

The genus name *Curcuma* is the Latinized form of the Arabic *al-kurkum*, which originally meant *saffron* but now refers exclusively to turmeric.[6] The common name, turmeric, comes from the French *terra-mérite* (Latin *terra merita*), meaning meritorious earth—probably because ground turmeric resembles the earth pigment ochre, and perhaps because of the regard in which turmeric was held by ancient peoples. In many languages, the name for turmeric means yellow root, and it is known as Indian saffron in many European languages, although it is a cheap and unacceptable substitute for true saffron (*Crocus sativus*, Iridaceae).[6,7] Known as the "golden spice" or the "spice of life," turmeric has been held sacred and used medicinally in India for 4000 – 6000 years.[2,6] During India's Vedic period (ca. 1500 – 600 BCE), the orange-yellow rhizome of turmeric was called the "herb of the sun" and was regarded as the most outstanding healing herb.[2]

Turmeric is widely used in the Indian systems of medicine (Ayurveda, Siddha, and Unani) as well as in Eastern Asian systems (Traditional Chinese Medicine [TCM], Japanese Kampo, Korean, and Malay). In the Ayurvedic system, depending on what it is combined with, turmeric's main therapeutic uses are for treating disorders due to poison, ulcers, skin diseases and urticaria, urinary disorders, anemia, and chronic rhinitis/sinusitis.[8] It is also used in Ayurveda for anorexia, cough, diabetic wounds, biliary and liver disorders, and rheumatism.[2] Many Ayurvedic healers integrate the powder into a paste or lotion for the treatment of dry and flaking skin, skin sores and wounds, external inflammations, and painful arthritis.[1,2,9] In the Unani system, turmeric is used therapeutically to treat ulcers, rheumatoid arthritis, conjunctivitis, eye strain, hiccough, asthma, catarrh, and itching.[10]

Traditional medicinal practices in India and China tout the benefits of this bitter-tasting and slightly fragrant root as a digestive aid.[11] In TCM, turmeric is specifically indicated for treatment of amenorrhea (absence of menstrual periods), mass formation in the abdomen, rheumatic pain of the shoulders and arms, traumatic swelling and pain, and pricking pain in the chest and abdominal regions.[12]

Turmeric is incorporated into teas and is a base component in many culinary spice blends, specifically curry.[1,3,6] It is a component in *kedgeree* and *piccalilli* (England), *sofrito* (Africa), and *la-kama* (Morocco).[13] The fresh rhizome is preferred in Thailand, where it is grated and added to curry dishes and yellow curry paste.[6] Yellow rice, made by the addition of fresh or dried turmeric, is a dietary staple on the Eastern islands of Indonesia; in Bali, yellow rice is used as an offering to the Hindu deities. Turmeric has also become a staple

Continued on page 2

in Ethiopian cuisine.[5,13] Turmeric essential oil is used to improve the taste of stomach bitters, and the oleoresin is used in the food industry in sauces, soups, and instant meals.[13] Because of its brilliant color, turmeric has also been traditionally employed as a dye to color not only foods but cosmetics, paper, wood, and fabrics, specifically the golden robes worn by Thai Buddhist monks.[9]

Storing turmeric in its whole rhizome state is preferable as flavor and aroma dissipate quickly once the rhizome is powdered.[13] However, powdered turmeric has an almost unlimited life as a dye.

In 1985, the German Commission E approved turmeric for the internal treatment of indigestion.[1] The European Scientific Cooperative on Phytotherapy (ESCOP) recommends turmeric for mild digestive disturbances and minor biliary dysfunction.[14] In 2008, the European Medicines Agency (EMEA) published a draft monograph, which once final, will be relevant for traditional herbal medicinal product (THMP) registrations in all EU Member States, including Germany. It proposes therapeutic indications for "preparations" of turmeric (e.g., powdered rhizome, herbal tea, and 1:10 tincture with 70% ethanol) for the symptomatic relief of dyspepsia.[15] Also in 2008, Health Canada published its final monograph for turmeric for the purpose of natural health product (NHP) compendial product license applications. Health Canada approved uses of the dried rhizome or preparations of the rhizome (e.g., herbal tea infusion, 1:1 fluidextract and/or 1:5 tincture) as a carminative to help relieve flatulent dyspepsia and as a digestive aid.[16] Official quality standards are available in the currently valid editions of the *United States Pharmacopeia*, *British Pharmacopoeia*, *European Pharmacopoeia*, *Mexican Herbal Pharmacopoeia*, *Japanese Pharmacopoeia*, *Korean Herbal Pharmacopoeia, Pharmacopoeia of the People's Republic of China*, *Ayurvedic Pharmacopoeia of India*, *Unani Pharmacopoeia of India*, and others. Based on centuries of use as a common spice and modern toxicological research, turmeric and curcumin are generally recognized as safe (GRAS) for use in foods and dietary supplements.

Turmeric has been suggested as a safe, natural, and effective alternative to now-recalled cyclooxygenase inhibitors like celecoxib (Celebrex®) and rofecoxib (Vioxx®), as well as aspirin and ibuprofen.[1,17]

Modern Research

Curcumin, a collective noun for a group of phenolic compounds called curcuminoids, is the most active chemical component in turmeric; it accounts for 2-5% of the spice and is responsible for its characteristic yellow color.[2] Extensive *in vitro* and *in vivo* research over the past 50 years has indicated that curcumin may be helpful in a wide variety of conditions and diseases. It has demonstrated antioxidant, anti-inflammatory, hepatoprotective, antimutagenic, anticarcinogenic, antitumor, antibacterial, fungistatic, and wound-healing properties, among others.[2,13]

Clinical studies show that curcuminoids may be beneficial in the prevention and treatment of a number of types of cancer, including breast, colorectal, gastrointestinal, genitourinary, lung, leukemia, lymphoma, melanoma, ovarian, pancreatic, prostate, and sarcoma.[18-30] Treatment with encapsulated turmeric in one clinical study resulted in the alleviation of peptic ulcers.[31] A pilot study of 207 volunteers suffering from irritable bowel syndrome (IBS) suggested that a standardized turmeric extract (Cynara™ Turmeric, Lichtwer Pharma (UK) Ltd., Marlow, UK) might help reduce IBS symptoms, although placebo-controlled trials were needed.[32] A short-term study investigating the anti-rheumatic activity of curcumin found that its effects were comparable with those of phenylbutazone, an analgesic and anti-inflammatory drug.[33] Curcuminoids were also shown to produce a better anti-inflammatory response than placebo in postoperative inflammation in a small group of males who had hernia operations.[34] A pilot study suggested that turmeric paste applied externally is an effective and inexpensive treatment for scabies, a condition caused by skin mites.[35] Curcmin also shows beneficial effects on insulin resistance, a precursor of type 2 diabetes.[36] Turmeric extract has shown some potential in prevention and treatment of neurodegenerative conditions, including Alzheimer's disease.[37] Other clinical trials suggest that curcumin might be helpful in treating familial adenomatous polyposis, ulcerative colitis, hypercholesteremia, atherosclerosis, pancreatitis, psoriasis, chronic anterior uveitis, and arthritis.[28]

Turmeric has also shown promise in combination with other herbs. In one study, a combination of turmeric and Indian tinospora or *guduchi* (*Tinospora cordifolia*, Menispermaceae) was given to tubercular patients who were also receiving a treatment known to cause liver toxicity. That study found that the incidence and severity of hepatotoxicity was significantly lower.[38] Turmeric showed clinically significant results when studied in combination with Indian frankincense (*Boswellia serrata*, Burseraceae) for osteoarthritis of the knee.[39] Another clinical trial tested an eye drop preparation made from extracts of turmeric and 7 other herbs from the Ayurvedic tradition on patients with a number of ophthalmic disorders.[40] The herbal eye drop was successful in a variety of the conditions and no adverse effects were observed. Research demonstrates that the oral bioavailability of curcumin is limited and is enhanced by combining it with piperine, a compound found in black pepper (*Piper nigrum*, Piperaceae) and long pepper (*P. longum*).[41]

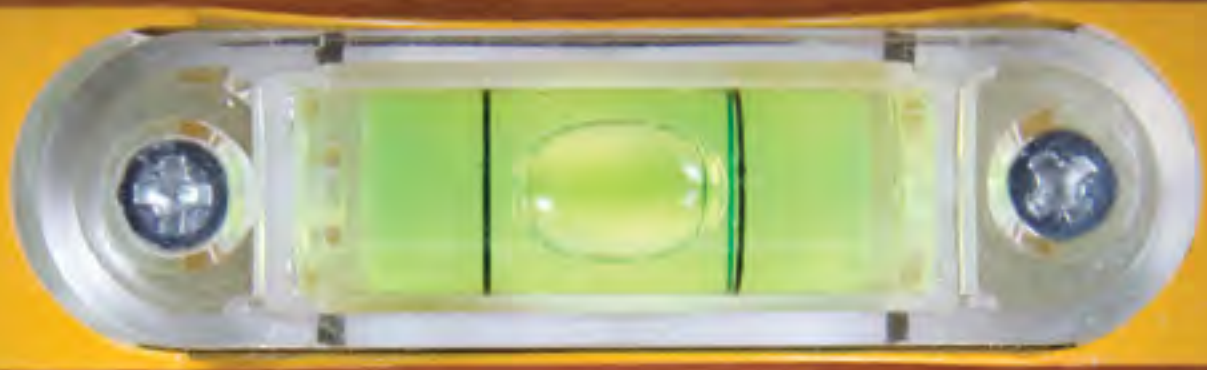
Future Outlook

In 2007, India accounted for over 71% of turmeric exports worldwide, followed by Vietnam (4.6%), China (2.7%), and Bangladesh (2.0%).[42] India exported no more than 10% of its annual production of 527,980 tons in 2002-2003. As of 2007, India had 162,950 hectares (402,658 acres) committed to turmeric cultivation with a production of 552,300 tons. In the most recently reported 12-month export trade data (April 2007 through March 2008), India exported 11,611.44 metric tons of fresh turmeric rhizome valued at USD $8.23 million and 42,380.57 metric tons of dried and/or powdered rhizome, valued at USD $33.95 million.[43] During the same period, India also exported 355,930 kg of turmeric oleoresin, 54,660 kg turmeric preparations, and 1,360 kg of turmeric essential oil.

Turmeric is susceptible to disease that can lead to a reduction in yield by as much as 80%.[2] It is also susceptible to abruptly fluctuating prices due to changing trade relations and competing turmeric production in a number of countries. Since a sustainable turmeric economy is only possible when these risks are minimized, a number of policy measures are being considered in turmeric-producing countries, including healthy seed production, quarantine regulations to restrict transporting seed from one state to another when disease is a problem, and education of farmers regarding post-harvest technology and the importance of keeping varieties separate since Alleppey and Madras turmeric are considered to be of higher quality than some others.[2,13] HG

—Gayle Engels

Continued on page 7



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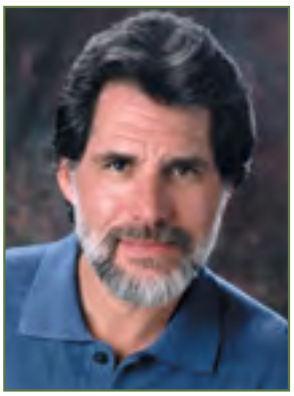
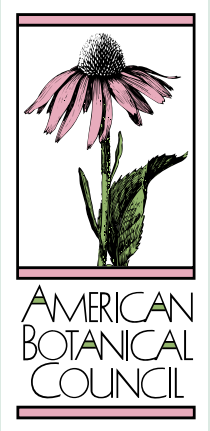


Although it was not our initial intention, our 3 feature articles in this issue all pertain in one way or another to medicinal plants of the tropics. Our cover story on *Ramuan*, the traditional medicinal plant culture of Malaysia, is a subject I've wanted to cover in *HerbalGram* for nearly 3 years. I had the opportunity to visit Kuala Lumpur, the vibrant and modern megapolis in Malaysia, in 2006 when I presented at a conference on Women's Health and Asian Traditional Medicine, and I was impressed by how the government of this rapidly economically-developing nation has committed to fostering research and product development based on Malaysia's rich array of medicinal plants. Our old friend, associate editor, and ABC Board of Trustee Chairman Steven Foster has written an article on the history and culture of Malaysia and how some of the more well-researched traditional herbal medicines are being developed for local and international markets—a salient example of modern efforts to commercialize a rich ethnobotanical tradition that is little-known in the West.

One of the major public health challenges of many tropical areas is combating malaria, particularly due to problems associated with the parasite's ability to develop resistance to conventional pharmaceutical drugs (the original drug having been the alkaloid quinine, derived from the bark of the South American *Cinchona officinalis* tree). In this issue, Kevin Spelman, PhD, a molecular biologist and herbalist, developing a theme from one of his primary herb teachers, Dr. Jim Duke, provides an essay on the benefits of multi-component plant-derived medicines and the pharmacological superiority of such (particularly in the fight against malaria) versus the single chemical entity drugs that have characterized the history of the development of the modern pharmaceutical industry. This has been a constant theme—one might call it a crusade—by Duke, who has written and spoken extensively on his preference for the putative benefits of chemically complex "herbal shotgun" remedies compared to pharmaceutical "silver bullet" drugs. This article was originally intended to serve as a lengthy sidebar to Spelman's cover story in *HerbalGram* #74, in which he discussed the nearly-forgotten Cinchona Gardens in Jamaica. On further reflection, however, it was decided that the topic warranted more in-depth coverage.

Continuing the tropical theme, our staff writer and assistant editor Kelly Saxton Lindner has written an account of how one small pharmaceutical company has developed a successful medicine from the red "dragon's blood" latex of the famed *sangre de drago* (*Croton lechleri*) tree of the Amazon's basin and montane areas. Widely used by indigenous healers of the area for a variety of applications, the latex contains proanthocyanidin oligomers, which Napo Pharmaceuticals has isolated into a drug for use in the life-threatening chronic diarrhea associated with HIV/AIDS, severe cholera-induced fluid loss, traveler's diarrhea, and irritable bowel syndrome, in which diarrhea is predominant. Napo has developed a program for sustainable harvesting of the trees' latex, with numerous economic and social benefits for the indigenous communities involved with the trees' re-planting and latex collection. As I write this, ABC is starting its annual "Pharmacy from the Rainforest" ethnobotany ecotours in the Peruvian Amazon and Andean highlands. One of my most salient memories of my dozen or so trips to the Amazon is taking the healing red sap of this tree and rubbing it in my hands, only to watch the red viscous liquid magically transform into a dry white powder! HG



Mission: Provide education using science-based and traditional information to promote responsible use of herbal medicine—serving the public, researchers, educators, healthcare professionals, industry, and media.

References

1. Blumenthal M, Goldberg A, Brinckmann J, eds. *Herbal Medicine: Expanded Commission E Monographs.* Austin, TX: American Botanical Council; Newton, MA: Integrative Medicine Communications; 2000.
2. Ravindran PN, Babu KN, Sivaraman K. *Turmeric: the Genus Curcuma*. Boca Raton, FL: CRC Press; 2007.
3. DerMarderosian A, Beutler JA, eds. *The Review of Natural Products: The Most Complete Source of Natural Product Information*. 3rd ed. St. Louis, MO: Facts and Comparisons, 2002.
4. Government of India Department of Commerce Export Import Data Bank. Accessed September 22, 2009.
5. Hemphill I. *The Spice and Herb Bible: A Cook's Guide.* Toronto: Robert Rose Inc.; 2002.
6. Turmeric (*Curcuma longa* L.). Gernot Katzer's Spice Pages. Available at: http://www.uni-graz.at/~katzer/engl/Curc_lon.html. Accessed August 31, 2009.
7. Poth S, Sauer G. *The Spice Lilies: Eastern Secrets to Healing with Ginger, Turmeric, Cardamom, and Galangal.* Rochester, VT: Healing Arts Press; 2000.
8. Ayurvedic Pharmacopoeia Committee. *Haridra*. In: *The Ayurvedic Pharmacopoeia of India*, Part I, Volume I, 1st Edition. New Delhi, India: Government of India, Ministry of Health and Family Welfare, Department of Ayurveda, Yoga & Naturopathy, Unani, Siddha and Homoeopathy (AYUSH). 1989;45-46.
9. McCaleb RS, Leigh E, Morien K, eds. *The Encyclopedia of Popular Herbs*. Roseville, CA: Prima Publishing; 2000.
10. Unani Pharmacopoeia Committee. *Zard Chob*. In: *The Unani Pharmacopoeia of India*, Part I, Volume I. New Delhi, India: Government of India, Ministry of Health and Family Welfare, Department of Ayurveda, Yoga & Naturopathy, Unani, Siddha and Homoeopathy (AYUSH). 2007;90-91.
11. Wichtl M, Brinckmann J. *Herbal Drugs and Phytopharmaceuticals*. 3rd ed. Stuttgart: Medpharm GmbH Scientific Publishers; 2004.
12. Chinese Pharmacopoeia Commission. Rhizoma Curcumae Longae. In: *Pharmacopoeia of the People's Republic of China*, Volume 1. Beijing, China: People's Medical Publishing House. 2005;260-261.
13. Teuscher E (ed), Brinckmann J, Lindenmaier M (trans). *Medicinal Spices: A Handbook of culinary Herbs, Spices, Spice Mixtures and Their Essential Oils.* Boca Raton, FL: CRC Press; 2006.
14. European Scientific Cooperative on Phytotherapy. *ESCOP Monographs*. 2nd ed. New York: Thieme New York; 2003.
15. European Medicines Agency (EMEA) Committee on Herbal Medicinal Products (HMPC). Draft Community Herbal Monograph on *Curcuma longa* L., Rhizoma. London, UK: EMEA. November 6, 2008. Available at: http://www.emea.europa.eu/pdfs/human/hmpc/curcuma_longa/45684508en.pdf.
16. Health Canada Natural Health Products Directorate (NHPD). Turmeric. In: *NHPD Compendium of Monographs*. Ottawa, ON: Natural Health Products Directorate. March 3, 2008. Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/prodnatur/mono_turmeric-curcuma-eng.pdf.
17. Duke JA, ed. *Handbook of Medicinal Herbs*. 2nd ed. Boca Raton, FL: CRC Press; 2002.
18. Cheng AL, Hsu CH, Lin JK, et al. Phase I clinical trials of curcumin, a chemopreventive agent in patients with high-risk or pre-malignant lesions. *Anticancer Res*. 2001;21:2895-2900.
19. Lal B, Kapoor AK, Agrawal PK, Asthana OP, Srimal RC. Role of curcumin in idiopathic inflammatory orbital pseudotumours. *Phytother Res*. 2000;14:443-447.
20. Aggarwal BB, Kumar A, Bharti AC. Anticancer potential of curcumin: preclinical and clinical studies. *Anticancer Res.* 2003;23:363-398.
21. Plummer SM, Hill KA, Festing MF, Steward WP, Gescher AJ, Sharma RA. Clinical development of leukocyte cyclooxygenase 2 activity as a systemic biomarker for cancer chemopreventive agents. *Cancer Epidemiol Biomarkers Prev*. December 2001;10(12):1295-1299.
22. Sharma RA, McLelland HE, Hill KA, et al. Pharmacodynamic and pharmacokinetic study of oral *Curcuma* extract in patients with colorectal cancer. *Clin Cancer Res.* 2001;7(7):1894-1900.
23. Sharma RA, Euden SA, Platton SL, et al. Phase I clinical trial of oral curcumin: biomarkers of systemic activity and compliance. *Clin Cancer Res.* 2004;10(20):6847-6854.
24. Garcea G, Jones DJ, Singh R, et al. Detection of curcumin and its metabolites in hepatic tissue and portal blood of patients following oral administration. *Br J Cancer.* 2004;90(5):1011-1015.
25. Garcea G, Berry DP, Jones DJ, et al. Consumption of the putative chemopreventive agent curcumin by cancer patients: assessment of curcumin levels in the colorectum and their pharmacodynamic consequences. *Cancer Epidemiol Biomarkers Prev.* 2005;14(1):120-125.
26. Anand P, Sundaram C, Jhurani S, Kunnumakkara AB, Aggarwal BB. Curcumin and cancer: an "old-age" disease with an "age-old" solution. *Cancer Letters.* In press.
27. Shishodia S, Chaturvedi MM, Aggarwal BB. Role of curcumin in cancer therapy. *Curr Probl Cancer.* 2007;31(4):243-305.
28. Goel A, Kunnumakkara A, Aggarwal BB. Curcumin as "Curecumin": from kitchen to clinic. *Biochemical Pharmacology.* 2008;75:787-809.
29. Dhillon N, Aggarwal BB, Newman RA, et al. Phase II trial of curcumin in patients with advanced pancreatic cancer. *Clin Cancer Res.* 2008;14(14):4491-4499.
30. Capodice JL, Gorroochurn P, Cammack AS, et al. Zyflamend in men with high-grade prostatic intraepithelial neoplasia: results of a phase I clinical trial. *J Soc Integr Oncol.* 2009;7(2):43-51.
31. Prucksunand C, Indrasukhsri B, Leethochawalit M, Hungspreugs K. Phase II clinical trial on effect of the long turmeric (*Curcuma longa* Linn) on healing of peptic ulcer. *Southeast Asian J Trop Med Public Health.* 2001;32(1):208-215.
32. Bundy R, Walker AF, Middleton RW, Booth J. Turmeric extract may improve irritable bowel syndrome symptomology in otherwise healthy adults: a pilot study. *J Altern Complement Med.* 2004;10(6):1015-1018.
33. Deodhar SD, Sethi R, Srimal RC. Preliminary study on antirheumatic activity of curcumin (diferuloyl methane). *Indian J Med Res.* 1980;71:632-634. Cited by: Ravindran PN, Babu KN, Sivaraman K. *Turmeric: the Genus* Curcuma. Boca Raton, FL: CRC Press; 2007.
34. Satoskar RR, Shah SJ, Shenoy SGT. Evaluation of anti-inflammatory property of curcumin (diferuloyl methane) in patients with postoperative inflammation. *Int J Clin Pharmacol Ther Toxicol.* 1986;24(12):651-654. Cited by: Ravindran PN, Babu KN, Sivaraman K. *Turmeric: the Genus* Curcuma. Boca Raton, FL: CRC Press; 2007.
35. Charles V, Charles SX. The use and efficacy of *Azadirachta indica* ADR ('Neem') and *Curcuma longa* ('Turmeric') in scabies. A pilot study. *Trop Geogr Med*. 1992;44(1–2):178–181.
36. Moon DO, Jin CY, Lee JD, et al. Curcumin decreases binding of Shiga-like toxin-1B on human intestinal epithelial cell line HT29 stimulated with TNF-alpha and IL-1beta: suppression of p38, JNK and NF-kappaB p65 as potential targets. *Biol Pharm Bull.* 2006;29(7):1470-1475.
37. Zhang L, Fiala M, Sayre J, et al. Curcuminoids enhance amyloid-B uptake by macrophages of Alzheimer's disease patients. *Journal of Alzheimer's Disease.* 2006;10:1-7.
38. Adhvaryu MR, Reddy NM, Vakharia BC. Prevention of hepatotoxicity due to anti tuberculosis treatment: a novel integrative approach. *World J Gastroenterol.* 2008;14(30):4753-4762.
39. Badria F, El-Farahaty T, Shabana A, Hawas S, El-Batoty M. Boswellia-curcumin preparation for treating knee osteoarthritis. *Alternative & Complementary Therapies.* 2002;341-348.
40. Biswas NR, Gupta SK, Das GK, et al. Evaluation of Ophthacare eye drops – a herbal formulation in the management of various ophthalmic disorders. *Phytother Res.* 2001:15(7);618-620.
41. Shoba G, Joy D, Joseph T, Majeed M, Rajendran R, Srinivas PS. Influence of piperine on the pharmacokinetics of curcumin in animals and human volunteers. *Planta Med.* 1998;64(4):353-6.
42. United Nations Commodity Trade Statistics Database (COMTRADE). Accessed September 22, 2009.
43. Government of India Department of Commerce Export Import Data Bank. Accessed September 22, 2009.

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features

Plumeria *Plumeria rubra* f. *acutifolia*

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The Difference between HerbMed® and HerbMedPro™

By Jacqueline C. Wootton, MEd

The American Botanical Council and the Alternative Medicine Foundation frequently receive inquiries on the difference between HerbMed and HerbMedPro. The answer to this question is partly historical. In 1998, there were many misconceptions about herbs; one particular double-think was to see them as both clinically ineffectual and yet dangerously unsafe—an apparent contradiction. However, the main misperception that the development of the HerbMed database set out to address was the claim that there was very limited clinical or scientific evidence to support their use. On the contrary, a search on a primarily conventional biomedical database, such as MEDLINE, returned an astonishingly large amount of high quality, published, peer-reviewed, scientific data on various aspects of herbs used for health.

Around the same time, medical informatics was expanding its reach to provide public access to the scientific and clinical data on which medical decisions are based so that not just medical practitioners, but patients too, could make informed decisions. PubMed, the publicly available interface for MEDLINE, was first released as an experimental database in 1996; in January 1998, it was redesigned and updated, then re-released.

PubMed was a powerful model and inspiration for the HerbMed database and name. In the same spirit of providing open information, our intention at the Alternative Medicine Foundation, Inc. was to make all of the HerbMed data freely available for the use of professionals and the public. Furthermore, in 1998, no other herbal information resource, either publicly or commercially available, provided evidence-based, categorized, structured and neutral information and research resources with direct links to research abstracts.

From 1998 to 2000, Soaring Bear, PhD, a research pharmacologist with a background in herbal medicine, helped design and build the prototype HerbMed database with an emphasis on speed and useful content, using minimal graphics. HerbMed has since been completely modified, re-categorized, the software rewritten, and the content hugely expanded by a succession of research pharmacologists and pharmacognosists.

In 1999, the HerbMed name was trademarked and both the underlying database and the public website that provided access to the herb records were known as HerbMed®. In 2001, the database was re-engineered to make it more robust and to enable multiple researcher-compilers to access and build the data through a secure administration site on the server. The newly engineered database made it

HERBMEDPRO ADDITIONS AND UPDATES (July 2009-August 2009)

New Herb Records

Common Name	Latin Binomial
Red clover	*Trifolium pratense*

Updated Herb Records

Common Name	Latin Binomial
Arnica	*Arnica montana*
Chocolate	*Theobroma cacao*
Evening primrose	*Oenothera biennis*
Tea, green/black	*Camellia sinensis*

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possible to create a professional interface for the database that was named HerbMedPro™.

The ambiguity of name remains; both the underlying database and the public website are still called HerbMed, but essentially, the public website (www.herbmed.org) provides pre-computed web pages of the herb records derived from the database that have to be republished periodically as new data is entered into each record. HerbMedPro, by contrast, provides immediate access to the data generated directly from the database, ensuring continuous updating to the records as new research data is entered and published.

So both HerbMed and HerbMedPro draw from the same underlying database, but HerbMed provides access to only a subset of the herb records and is not continuously updated. The initial objective of making all the data freely available had to be abandoned after the dot-com bubble collapse. One spin-off from the dot-com era was the trickle-down funding for open-access information. The realities of funding a sustainable operation provided the impetus for developing HerbMedPro, the subscription-based, professional version. Nonetheless, the public HerbMed website still provides full access to the 20 most popular herbs, with an additional new Herb of the Month available each calendar month.

HerbMedPro has other advanced features not found in HerbMed. While HerbMed provides a simple search function, HerbMedPro has an advanced search engine. You can search on individual entries or summaries, using author name, journal references, or specific keywords. For example, instead of searching through all the entries in the turmeric (*Curcuma longa*) record for articles on its effect on the prostate, the user can enter prostate as the search term and choose *C. longa* from the herb list to find just those articles.

Additionally, the user can search for herb actions and health indications, drawn from the underlying extra information fields in the database. For example, the user can search for articles that address any herbs that have anti-inflammatory actions that might be helpful in arthritis. The Dynamic Updates feature is available on both HerbMed and HerbMedPro, whereby search terms are provided for each herb, to automatically pull up all the most recent publications, from MEDLINE via PubMed, for any specific category of research.

HerbMedPro provides paid access to the entire database, either through direct individual membership (in HerbMedPro alone or via membership in ABC at the Academic level and higher) or by licensing. The membership option works best for individuals, academic and commercial research groups, and libraries providing the resource for their staffs and students. Licensing is ideal for governmental or private groups that wish to stream the database across to their own server to combine with other data resources, or to add functionality, extra data, and features.

HerbMedPro provides a powerful tool for those who regularly research the scientific literature on herbs, be they writers, educators, or product developers. Individuals can join via ABC's secure online ordering system. To determine if a higher level of membership or licensing is the better option for your organization, contact ABC at 512-926-4900. HG

Jacqueline C. Wootton, MEd, is founder and president of the Alternative Medicine Foundation, Inc, in Potomoc, Maryland and director of HerbMed and HerbMedPro.

Employee Profile: **Lindsay Stafford**

Stafford

Lindsay Stafford is an integral part of the ABC editorial department. She is responsible for a range of activities, including writing articles for *HerbalGram* and HerbalEGram, tracking and editing contributed articles, and creating and distributing each issue of HerbalEGram.

Lindsay is bright and highly motivated. After earning her bachelor's degree in journalism from the University of Texas, she worked as the resource center assistant for the National Center for Farmworker Health, a nonprofit that aims to improve the health of farmworker families. There she performed a host of editorial and administrative responsibilities but was not able to devote a sufficient amount of her work hours to writing. When we hired her at ABC, we promised her that she would have more writing assignments and less administrative tasks, and her exemplary and reliable work as a writer has not disappointed us.

Lindsay has already produced numerous articles for ABC, and she has proven to be extremely thorough in her work. She frequently puts extra effort into her articles, conducting a significant amount of background research and interviewing numerous potential sources. She also stays abreast of herb-related topics in the news and often proposes ideas for new *HerbalGram* or HerbalEGram stories.

In addition to her writing and editing responsibilities, Lindsay contributes to the tasks of coordinating peer review and fact-checking articles for publication in *HerbalGram* and HerbalEGram. She is in charge of compiling the Calendar and Access sections of each *HerbalGram* issue. She has helped to streamline the process of creating and distributing HerbalEGram issues each month using the Convio Internet platform software, and she has been instrumental in promoting and instituting improvements to that publication. Lindsay is also responsible for HerbalEGram's MediaWatch section, which requires that she review dozens of articles each month in the mainstream media and summarize the most compelling stories. She further proofreads ABC press releases and member advisories.

Lindsay studied Spanish in Spain and has done nonprofit work in Mexico several times, including a trip during which she worked on a small village farm. Recently she has been writing articles for *HerbalGram* that discuss herb-related issues in Latin American countries, and she has had to employ some of her rusty Spanish language skills—which she hopes to improve. At ABC, Lindsay most enjoys writing about the traditional and cultural uses of herbs. She strongly identifies as being a writer and is especially interested in narrative nonfiction and personal essay. HG

—Mark Blumenthal

Meet ABC Board Member Neil Blomquist: Respected Consultant and Businessman

Neil Blomquist's varied career experiences and enthusiasm for life, in addition to his company know-how and leadership abilities, make him a particularly valuable and interesting member of the American Botanical Council's (ABC) Board of Trustees.

Blomquist is most recognized for his time as chief executive officer (CEO) of Spectrum Organic Products Inc. (Petaluma, CA), one of the leading producers of organic culinary and nutraceutical oils and essential fatty acid supplement oils in North America.[1] Blomquist worked for Spectrum for 16 years in various positions. He was hired in 1989 as the director of sales and marketing, and in 1994 he became the president and chief operating officer (COO). In 2002, he became president and CEO.

Blomquist compares his time as COO and CEO of Spectrum to conducting an orchestra (oral communication, April 16, 2009). "Like a conductor, you have to make sure that each employee is playing their instrument to the best of their ability, and it also has to be in harmony to make beautiful music," said Blomquist. "Employees achieving the most they can in their position is the key to having a successful organization."

"He has the ability to conceptualize solutions to complex problems and develop a systematic blueprint to implement necessary changes," said fellow Board of Trustees member Morris Shriftman, CEO of Mozart Inc. in Petaluma, California (oral communication, May 8, 2009). "Neil is an astute businessman in all the traditional ways. Beyond those, he has the gentle touch of a compassionate human being, and he brings those qualities to his leadership in ways that get the job done while empowering, supporting, and nurturing talent in others."

Blomquist

At Blomquist's current consulting company, Sustainable Solutions LLC, he mentors the leaders of young companies, helping them create their own harmonious, well-structured organizations. He assists companies with their business plans, finances, marketing, management, and often, after his consulting-role is finished, serves on their board and continues his support. In fact, he's so popular as a consultant that he doesn't even have a website for his business. He finds he gets plenty of business from word of mouth.

Jeff Nibler, COO of the sustainable seafood company CleanFish™, met Blomquist 3 years ago when he began consulting with Sustainable Solutions (oral communication, April 20, 2009). Blomquist still advises him today and also serves on his Board of Directors. The areas Blomquist has helped him most, said Nibler, involve increasing employee efficiency as well as setting and obtaining goals.

"Neil is very low-key, non-imposing, easy to work with, and confident," said Nibler. "He's also very experienced in this market and has a personal passion for health and wellness that drives an individual to be just as passionate."

ABC has benefited from Blomquist's advisory role for the past 3 years. Many often ask him why he's on the board of a nonprofit focused on medicinal herbs when he's not necessarily a plant expert and has no formal training in any medicinal plant-related disciplines (he earned a BA in business administration and economics from the University of South Dakota in 1973). Though he is a long-time herb user and has a large amount of self-taught knowledge, his answer is that nonprofits, in particular, have to operate with higher-than-average business sense.

Blomquist said he hopes to see herbal medicine become more mainstream and more widely accepted amongst consumers. Blomquist himself has been committed to the movement for a long time and reflected fondly on the early 70s, when he and Mark Blumenthal, founder and executive director of ABC, preached the benefits of herbs to those who weren't quite as receptive as today's consumers. Blomquist said, "Though there has certainly been a transformation, this movement is still in its infant stage compared to where it could be."

"I had gotten to know Neil during a retreat of some friends in the Idaho mountains, and I was impressed by his clarity, sense of organization, and his basic gentleness," said Blumenthal. "Soon after I had learned that Spectrum had been sold to the Hain-Celestial group, I invited him to serve on the ABC Board of Trustees."

Blumenthal noted that, as a precondition to his acceptance, Blomquist visited the ABC headquarters, met ABC's employees, and learned more about the organization's people and programs. "He did his due diligence on us, and then, after consulting with his wife Monica, he accepted our offer," said Blumenthal. "He had offers from other organizations, and I feel deeply fortunate and grateful that he made a commitment to help expand and promote ABC's nonprofit educational mission and projects. Neil

knew that ABC's mission is an important component of the natural living lifestyle, and that herbal medicine is an inexorable trend that will continue to grow and help shape American culture in a positive and sustainable way."

"Mark's ever-expansive vision for ABC is well complemented by Neil's grounded and decisive leadership," said Drake Sadler, co-founder and chairman of the board for Traditional Medicinals®, an herbal tea manufacturer (e-mail, August 16, 2009). "Neil's values, integrity, and work ethic are very much aligned with the tremendous good work accomplished at ABC, and his presence adds a most valuable asset to the organization. Cultivating the right directors and advisors is critical for any business, and ABC has proven again that it can attract the professional talent needed for good governance and guidance."

Blomquist is more than just a plant-savvy businessman; he's also a man of many hobbies—past and present. In 1974, he rode a motorcycle from Oregon to Montana to visit his future wife Monica—and ended up staying for 11 years and having 2 children.[2] Though now he says he's more of a golfer than a biker, he's enjoyed an array of activities including skiing, hiking, fly-fishing, white-water rafting, and carpentry. He even built the first house that he shared with his wife, a 1,200 square-foot and 6-room building. A little-known talent of Blomquist, according to Shriftman, is his cooking expertise, especially his use of herbs: "Neil understands the origins of food, its growing and cultivation, and has a reverence for the land," said Shriftman, alluding to Blomquist's childhood farming experiences.

Blomquist's other career experiences include 6 months spent as a professional fisherman, a year as a journalist for the Beaverton paper in Oregon, and years as a natural food store owner. In 1976, a year or so after his unplanned relocation to Montana, he and his wife, along with another Montana couple, opened Cup of Sun, a natural and specialty food retailer in Kalispell, Montana, which they operated for 10 years.

"He is a trusted friend and great consigliore on many different levels—because of our many shared intellectual, cultural, and industry interests," said Shriftman. "The longer I know him the more I appreciate the depth of his character and integrity." HG

—Kelly Saxton Lindner

References

1. Neil Blomquist joins ABC Board of Trustees. *HerbalGram*. 2006;71:10.
2. Siguel E. Interview: Neil Blomquist, president of Spectrum Naturals (SN), Inc. Essential Fats Web site. Available at: http://www.essentialfats.com/blomquis.pdf. Accessed April 15, 2009.

International Report on Herbs and Swine Flu

More than 340,000 people around the world have contracted the Influenza A(H1N1) virus, and at least 4,100 people have died from it, according to data from World Health Organization (WHO) released in October 2009.[1] While hundreds of thousands die each year from seasonal flu, WHO warns that swine flu could cause more infections, as people have no immunity to it. The organization is therefore stressing the importance of an effective vaccine.[2] Many developing and heavily-populated countries, which will likely not be able to vaccinate the majority of their citizens, are turning to medicinal herbs with immune-boosting properties in attempts to help protect against the virus commonly known as swine flu.

Across China, the most populated country in the world, several plant-based initiatives are taking place to address H1N1; China's health ministry expects to vaccinate only 5% of its total population of 1.34 billion. As preventative measures, the education ministry is planning to give students free Traditional Chinese Medicine (TCM), and the State Administration of TCM is recommending people take the Chinese herbal mixture Lian Hua Qing Wen, versions of which contain forsythia (*Forsythia suspensa*, Oleaceae) fruit and honeysuckle (*Lonicera* spp., Caprifoliaceae) flower.[3]

Forsythia *Forsythia suspensa*. Photo ©2009 Jasmine Oberste www.chineseherbgarden.com

Honeysuckle *Lonicera japonica*. Photo ©2009 Jasmine Oberste www.chineseherbgarden.com

In Beijing, the Ditan Hospital reported that it used herbs to treat 117 H1N1 patients and experienced a 75% success rate.[4] Patients were given a tea and mouthwash containing 3 grams each of Japanese honeysuckle flower, isatis (*Isatis indigotica*, Brassicaceae),* mint (*Mentha* spp., Lamiaceae) leaves, and licorice (*Glycyrrhiza uralensis*, Fabaceae) root.

Capital Medicinal University in Beijing is conducting a clinical trial to assess if the roots, stems, and flowers of more than 10 Chinese medicinal herbs are effective and safe for treating H1N1 infections.[5]

"Such herbs has been used for thousands of years in China to treat flu and pandemic flu," said Cao Bin, MD, the principal investigator of the study (e-mail, September, 25, 2009). "But it is the first time we try to prove the safety and efficacy of Chinese herbs in the treatment of pandemic (H1N1)2009, following the principles of evidence-based medicine."

Researchers in neighboring Taiwan, meanwhile, have found that compounds from the roots of the Asian plant asafetida (*Ferula assa-foetida*, *F. foetida*, Apiaceae) are more effective at killing the H1N1 virus than prescription antiviral drugs.[6] Also commonly known as devil's dung or giant fennel, asafetida roots were used against the Spanish influenza in 1918, and researchers are now saying that these compounds "may serve as promising lead components for new drug development against this type of flu."

India, the second most populous country in the world, isn't expecting a vaccine to be available until April of 2010.[7] The government has decided to allow the local production of shikimic acid, a compound of non-nitrogenous acid found in various plants and used to make the antiviral drug oseltamivir (Tamiflu®). While the health ministry is recommending people with serious flu symptoms go to the hospital for treatment, it is suggesting that others with no-to-mild H1N1 symptoms can use traditional medicine to increase the strength of their immune systems.[8]

In Bangalore, known as the Garden City of India, an increasing number of people are purchasing Indian tinospora (*Tinospora cordifolia*, Menispermaceae), a deciduous climbing shrub with anti-inflammatory and anti-allergic effects and immune-boosting properties.[9,10] In the Indian tribal district of Dangs, where medicinal plants grow throughout the forests, the health department is giving tourists an herbal drink that also contains Indian tinos-

* Both leaf and root of isatis are used in TCM; the plant part for this formula was not specified.

pora,[11] as well as holy basil (*Ocimum tenuiflorum*, Lamiaceae), which exhibits adaptogenic, anti-inflammatory, and antioxidant activities,[12] and ginger (*Zingiber officinale*, Zingiberaceae) root, which has anti-nausea and anti-inflammatory effects.[13]

Though people around the world are seeking to prevent cases of H1N1 through the use of herbs, WHO has advised the public to not purchase any medicines to fight or prevent the virus unless prescribed by a healthcare practitioner.[14] Likewise, a US dietary supplements industry coalition advised consumers that "therapies for the treatment of swine flu should only be recommended by qualified healthcare professionals or public health authorities."[15] The coalition recognized that some dietary supplements "have much to offer in terms of enhancing general immune function" but said self-care for swine flu should be actively discouraged.

The US Food and Drug Administration (FDA) and the Federal Trade Commission (FTC) issued a warning that they will aggressively identify, investigate, and take regulatory or criminal action against individuals or businesses that wrongfully promote products as treatments for H1N1.[16] FDA has since sent more than 136 warning letters to offending websites that have promoted products using unapproved swine flu-related claims (such marketing was not necessarily promoted by the manufacturers of the products). FDA's "fraudulent product" list includes 4 herbal extracts, 2 teas, and at least 64 supplement products. The majority of the offending websites have since changed or removed the swine-flu related health claims from these products' marketing.

While most Americans will likely choose to get the H1N1 vaccine, the national media continues to document individuals and healthcare practitioners who focus on natural alternatives to vaccination for seasonal flu and/or swine flu.

The *San Francisco Chronicle*, for example, featured an article discussing a naturopathic doctor's flu prevention strategies of eating garlic (*Allium sativum*, Alliaceae) and maitake (*Grifola frondosa*, Polyporaceae), shiitake (*Lentinula edodes*, Tricholomataceae) and reishi (*Ganoderma* spp., Ganodermataceae) mushrooms, and taking additional herbs to support health.[17] Andrew Weil, MD, a national best-selling integrative medical author, explained on "Larry King Live" how astragalus (*Astragalus* spp., Fabaceae) and Chinese mushrooms can help increase immunity and resistance to colds and flu.[18]

Additionally, *The Denver Post* has featured several medical doctors' prevention advice, which also included taking astragalus, as well as vitamin D and probiotic supplements, turmeric (*Curcuma longa*, Zingiberaceae) root, and ginger. If flu infection does occur, a doctor in the article recommends taking a proprietary herbal extract made from the roots of *Pelargonium sidoides* (Geraniaceae) used traditionally in South Africa to treat various symptoms of upper respiratory tract infections.[19,20] HG

—Lindsay Stafford

References

1. Pandemic (H1N1) 2009—update 68. World Health Organization website. Available at: http://www.who.int/csr/don/2009_10_02/en/index.html. Accessed October 6, 2009.
2. What is the new influenza A(H1N1)? World Health Organization website. Available at: http://www.who.int/csr/disease/swineflu/frequently_asked_questions/about_disease/en/index.html. Accessed September 30, 2009.
3. Juan S. H1N1 could hit tens of millions. *China Daily*. September 12, 2009. Available at: http://www.chinadaily.com.cn/china/2009-09/12/content_8684701.htm. Accessed September 21, 2009.
4. Margolin C. Swine flu cured using Chinese herbs. *Alternative Health Journal*: July 25, 2009. Available at: http://www.alternativehealthjournal.com/article/swine_flu_cured_using_chinese_herbs/3705. Accessed September 18, 2009.
5. Capital Medical University. Chinese medicinal herbs treatment on novel influenza A (H1N1): multi-centre, prospective, randomized controlled study. NLM Identifier: NCT00935194. ClinicalTrials.gov. Available at: http://clinicaltrials.gov/ct2/show/NCT00935194: Accessed September 23, 2009.
6. Dawson J. Ancient Chinese remedy may work for flu. Inside Science News Service. September 10, 2009. Available at: http://www.livescience.com/health/090910-flu-remedy.html. Accessed September 18, 2009.
7. India to produce raw material for swine flu drug, toll touches 220. Indo-Asian News Service. September 17, 2009. Available at: http://www.hindustantimes.com/India-to-produce-raw-material-for-swine-flu-drug-toll-touches-220/H1-Article3-455026.aspx. Accessed September 18, 2009.
8. Chatterjee S, Chopra A. Cow urine, herbal remedies gain as India swine flu deaths climb. Bloomberg News. September 4, 2009. Available at: http://www.bloomberg.com/apps/news?pid=20601091&sid=arn2dLln.SPU. Accessed September 18, 2009.
9. Venugopal J. Amrutha Balli demand creeps up in flu time. Diligent Media Corporation. September 2, 2009. Available at: http://www.dnaindia.com/bangalore/report_amrutha-balli-demand-creeps-up-in-flu-time_1287147. Accessed September 18, 2009.
10. Oliff H. Indian tinospora shows positive results in treating allergic rhinitis. *HerbalGram.* 2006; 69:27.
11. In Dangs, herbal drink to ward off H1N1. *The Times of India*. August 31, 2009. Available at: http://timesofindia.indiatimes.com/NEWS/City/Surat/In-Dangs-herbal-drink-to-ward-off-H1N1/articleshow/4956006.cms. Accessed September 18, 2009.
12. Henson S. Health benefits of holy basil. *HerbClip*. August 31, 2008 (No. 030383-359). Austin, TX: American Botanical Council. Review of Basil as the holy Hindu highness by Duke JA. *Altern Complement Ther*. 2008;5-8.
13. Monograph on Ginger. *HerbClip*. December 29, 1995 (No. 122652-075). Austin, TX: American Botanical Council. Review of Zingiber officinale by Reading G. *ATOMS*. 1995;1(1).
14. World Health Organization. Warning on purchase of antivirals without a prescription, including via the Internet. Information Exchange System Alert No. 122. May 14, 2009. Available at: http://www.who.int/medicines/publications/drugalerts/Alert_122_Antivirals.pdf. Accessed September 21, 2009.
15. Industry coalition advises against use of dietary supplements as swine flu remedy, cure [press release]. Washington, DC: American Herbal Products Association; May 1, 2009.
16. FDA warns web sites against marketing fraudulent H1N1 flu virus claims [press release]. Silver Spring, MD: Food and Drug Administration; June 15, 2009.
17. Robbins N. Naturopath bridges gap in treatment, prevention. *San Francisco Chronicle*. September 21, 2009;C1.
18. Relative S. Astragalus vs. H1N1 (swine) flu virus suggests Dr. Andrew Weil. Associated Content. September 11, 2009. Available at: http://www.associatedcontent.com/article/2163091/astragalus_vs_h1n1_swine_flu_virus.html?cat=5. Accessed September 21, 2009.
19. Lofholm N. Natural remedies are all the rage as flu fears increase. *The Denver Post*. September 7, 2009;A-01.
20. Neustadt J. Special extract of traditional African herb Pelargonium treats bronchitis in clinical trial. *HerbalGram.* 2006; 71:32-33.

Tea: An Artist's Medium

Millions of people around the world drink tea (*Camellia sinensis,* Theaceae). The beverage is sipped for a variety of reasons, including its many tastes, medicinal properties, and ability to produce a soothing calm or gentle energy. Interestingly, many of the pleasures tea brings to its drinkers can also be brought to art.

Artist Jeffrey Axelrod stands in the kitchen of his San Francisco home with dozens of clear jars of brewed teas lining the table. Each jar contains 4–5 tea bags or heaps of loose leaf tea and less than one inch of water to make the teas as concentrated as possible. If the tea is watered down, every color looks the same once absorbed by the canvas, and Axelrod, who uses these teas to make art, needs vibrant variations of color.

"The thing I like most about the tea is that it has this warm organic feeling to it," said Axelrod (oral communication, July 9, 2009). "It doesn't matter if I put loose leaf in a jar or a tea bag—the end result is color."

The type of art Axelrod creates is called assemblage, which consists of a painted background covered by painted words and glued-on objects. The end result of many of his pieces is a whimsical, imaginative, and sometimes edgy collage of images, ideas, and emotions. Axelrod uses tea to paint many backgrounds and also uses tea to color the majority of some pieces.

Above: "Sonoma Before the Harvest," assorted teas and tea combinations, watercolor, and assembled objects. Painting ©2009 Jeffrey Axelrod

"Everything I do always has tea in it," he said. "Tea is my love."

Axelrod begins by dipping a one-inch paintbrush into the jars to paint a soft and glowing background on a canvas. Sometimes he'll use 5 to 7 teas for the background, and he has used up to 20 different teas in one piece.

Much of Axelrod's process of painting with tea is about experimentation, a likely reason he deems his kitchen a "laboratory." He mixes different teas to produce brighter colors and sometimes mixes teas with watercolors or has objects soak in tea overnight before assembling them onto the background. Often, Axelrod doesn't know the exact color that will be produced—an aspect of painting with tea that he enjoys. He does know that most teas produce warm and neutral colors, and that some kinds are better than others.

"Russian chocolate tea is my best brown; hibiscus is my best purple," said Axelrod.

Many different kinds of tea from numerous locations around the world make up Axelrod's palette, which currently consists of about 80 teas. While he's not too particular about these, there are a few brands he avoids, and he prefers to buy organic teas.

"Hot Air Balloons," tea and black Sharpie. ©2009 Austin Kleon

Axelrod has shown his artwork in several California-based art festivals, including the popular Sausalito Art Festival. When observers learn that he uses tea in such a great deal of his work, many are surprised, he said.

In May 2009, while exhibiting at the World Tea Expo in Las Vegas, Nevada, Axelrod met many tea manufacturers and tea enthusiasts who became interested in his work. Since then, he has started creating some marketing art, such as labels and posters, for several tea companies, including Rishi Tea, ITO EN®, and Florapharm®.

"Tea people are so passionate about the industry and are such nice people," Axelrod said of the experience. "I really enjoy working within the industry. It's like finding a new home."

Soon Axelrod might be using herbs in his artwork. He plans to make teas from some herbs that he purchased from an herb garden north of San Francisco.

"I'm going to play around with them. They're just so beautiful."

Though art made with tea is not common, others join Axelrod in their use of the herbal beverage for creative expression.

Austin Kleon, a writer/artist based in Austin, Texas, uses tea to create sketches that jump-start his creative juices.

"Tea is for when I want to smoothly sail through the day," he said (e-mail, July 14, 2009). "Coffee is for when I want to hack through the jungle."

On the mornings that Kleon opts for tea, he waits until his cup of tea has brewed and then drops the tea bag on an index card, which produces an unexpected variety of blobs, blurs, and smears.[1] He then hunts for images in the tea stains and creates sketches using a black Sharpie® felt pen. He got the idea from a fellow writer/artist, who got the idea from Dave Gray, the founder of the consulting and design firm XPLANE.

"I really love the color, honestly," said

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Kleon. "And it lends a kind of earthy, organic feel to line drawings."

Many of Kleon's tea sketches end up depicting lighthearted scenes, such as a "fat kid dancing," or another with people floating away in hot air balloons. Sometimes he will incorporate a process he learned from another artist's blog, which involves dividing the piece of paper or note card into a grid of panels, which he then uses to create cartoon narratives.[2]

"Not knowing what image will show up is part of the game," said Kleon. "You get to let your subconscious take over. It's like a Rorschach inkblot test. You could show the tea stain to 100 different people, and they'd see 100 different images."

Installation tea artwork by Michele Brody; dried paper tea bags featuring tea stains and transcribed conversations. ©2009 Michele Brody. Photo by Matthew Mancini

Similar to Axelrod and Kleon, Michele Brody uses tea to produce visual imagery. While doing this, she also actively explores, and engages others to explore, the emotions, experiences, and memories associated with drinking tea.

For the 2007 D.U.M.B.O. Art Under the Bridge Festival in Brooklyn, New York, Brody created a 3-day public installation in which she served passers-by cups of tea from a food cart.[3] While sharing this tea with strangers, Brody recorded their conversations and then transcribed their words onto the dried paper tea bags stained with vibrant purples, browns, and yellows. Later, the tea bags were mounted side-by-side to make a quilt of sorts, and similar installations were later featured at the Brenda Taylor Gallery and Lower East Side Tenement Museum, both in New York.

"It's really about creating this private space within the public realm where people come in, who are strangers, and share a cup of tea with me," said Brody (oral communication, July 16, 2009).

Like many of Brody's other creations, most of which also use organic materials like handmade paper or wheat grass seeds, the idea behind her tea projects is to sensitize people to time and how memories are stored, forgotten, and modified as time passes. She also intends for the installation to capture how a process that occurs over time can affect materials, as well as the process of oral histories and storytelling. In this case, the tea stains that are left behind on the bag serve as tangible images of the memories and experiences associated with drinking and sharing tea.

While aiming to look at how tea intertwines with all of these aspects, Brody doesn't ignore the visual art that the beverage creates on its own.

"In and of themselves, the tea stains on the bags are just beautiful," she said. "It's imagery that I could never create in and of my own as a painter. I wanted to incorporate these beautiful objects with the memory of sharing."

While a few people who stopped by her cart did not want to engage in conversation (this is New York, Brody reminds), many were quite open. Some spoke about the memory of drinking tea as a child when sick or drinking tea while traveling. Others shared their personal opinions toward tea, discussed technical definitions of tea, or explored why the United States does not have a deep tradition of drinking tea common in many other countries.

"We are a country that many people bring many, many practices to," she said of immigrants who have brought tea customs to the United States, adding that she thinks the country is experiencing a revitalization of tea drinking.

Another inspiration for Brody's tea projects has come from books that portray the common custom of offering tea to people as a welcoming gesture. Recently Brody read Rory Stewart's *The Places in Between*, a memoir about the author, who is Scottish, traveling on foot across Afghanistan in 2002.[4] Stewart was often made to feel welcome by strangers who offered him tea, Brody said.

"It intrigued me how tea is such a binder," she said of its ability to cross borders, histories, and religions. "Tea is so much more than just a beverage."

Additional examples of contemporary tea art, produced by a variety of artists, is available by visiting the tea sketches group on the interactive photo-sharing website Flickr at: http://www.flickr.com/groups/teasketches/pool/. HG

—Lindsay Stafford

References

1. Teabaggin': a cubicle pastime. Austin Kleon Web site. Available at: http://www.austinkleon.com/2009/05/26/teabaggin-a-cubicle-past-time/. Accessed July 14, 2009.
2. Teabaggin', Part Two. Austin Kleon Web site. Available at: http://www.austinkleon.com/2009/06/28/teabaggin-part-two/. Accessed July 14, 2009.
3. Tea house productions. Michelle Brody Web site. Available at: http://www.michelebrody.com/. Accessed July 8, 2009.
4. Bissell T. 'The Places in Between,' by Rory Stewart: a walk across Afghanistan. *New York Times*. June 11, 2006: Sunday Book Review. Available at: http://travel2.nytimes.com/2006/06/11/books/review/11cover_bissel.html. Accessed July 17, 2009.

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Efforts to Reduce Afghanistan's Illegal Opium Trade

As the producer of 93% of the world's opium, Afghanistan presents significant challenges to the international community.[1] US and UK forces have tried various methods to reduce poppy cultivation and disrupt heroin trade in Afghanistan. Another method for alleviating Afghanistan's opium problem has been proposed, which includes allowing Afghans to legally cultivate poppies for medicinal use.

Poppies (*Papaver somniferum*, Papaveraceae) have been used throughout the ages for medicinal and recreational purposes. The plant was mentioned in some of the earliest records of human civilization, including the Ebers Papyrus, an ancient Egyptian medical text written in about 1550 BCE.[2] Opium has been used for such purposes as pain-relief, to induce sleep, and to generate feelings of euphoria. Several of the known alkaloids of opium have been isolated for medical use, including the widely-used pain-reliever morphine and cough-suppressant codeine. The dangerous and highly addictive drug heroin is a derivative of the opium alkaloid morphine.

Opium farming and trade has been a major element of the culture and economy of some areas of Afghanistan.[1] Because this opium is typically trafficked as heroin and its trade has been a main source of funding for the Taliban, efforts have been made in recent years to stop Afghanistan's poppy cultivation.

The US government initially supported a policy of poppy eradication, but this typically harmed small farmers rather than powerful land owners, drug dealers, and the Taliban.[3,4] In mid-2009, the US government announced that it would shift away from eradication and instead focus on disrupting opium dealers, processors, and refineries. Increased counter-narcotics efforts by military operations in the summer of 2009 led to the destruction of hundreds of tons of poppy seeds, opium, and heroin in southern Afghanistan.[4] Government corruption in Afghanistan, however, may ultimately pose some challenges to this new US-led policy against Afghan drug trafficking.[3]

Some farmers have been forced or encouraged to replace their poppy fields with alternative crops.[1] In some cases, this practice has led to poverty for Afghan farmers and communities, as the replacement crops are often more difficult to grow and do not sell for nearly as much money as poppies.

One replacement crop that has been successful for some Afghan farmers, however, is saffron (*Crocus sativus*, Iridaceae)—the world's most expensive spice.[5,6] Farmers in some provinces of Afghanistan—particularly in Herat—have reportedly received support from the Afghan government, the US Agency for International Development, and the Italian-led Provincial Reconstruction Team to begin cultivating saffron in place of poppies. According to recent news articles, cultivation of this plant has proven extremely profitable, and both production of and demand for Afghan saffron has been rising in recent years. An article published in the *San Francisco Chronicle* in March of 2009 noted that the price of Afghan saffron has risen to an average of $1,360 per pound, and that this is roughly 38 times what poppy farmers in southern Afghanistan earn.[6] Saffron is an ingredient in fabric dyes and perfumes, and it has also been used medicinally. Researchers in Iran have demonstrated promising applications for saffron in treatment of mild-to-moderate depression and premenstrual problems in women.[7,8]

A potential plan for reducing opium trafficking in Afghanistan has also been proposed by the International Council on Security and Development (ICOS). Since 2005, ICOS has researched and promoted the idea of a "Poppy for Medicine" project in Afghanistan. Under this project model, Afghan farmers would legally cultivate poppies for local transformation into pharmaceutical-grade morphine, which could be sold to foreign governments at a relatively low cost. Such a project would serve as a counter-narcotics initiative while also contributing to Afghanistan's economic diversification and the global need for pain medicines.

Similar projects have previously been introduced in Turkey and India. According to Jorrit Kamminga, senior policy analyst for ICOS, the experiences of

those 2 countries were different but could be adapted to the unique situation of Afghanistan (oral communication, August 17, 2009).

Kamminga stated that the Poppy for Medicine project has already garnered support within Afghanistan and in countries interested in purchasing low-cost morphine, but ICOS has not yet been able to convince the US and UK governments to initiate the project. Because Afghanistan's government runs entirely on foreign assistance, and the country's counter-narcotics policies are directed by the United States and United Kingdom, the project would require US and UK approval. However, Kamminga stated that he hopes that US and UK government leaders will be more amenable to the idea of backing the Poppy for Medicine project in the near future.

"We've wasted 6 years and millions of dollars on a counter-narcotics policy that doesn't work," said Kamminga, referring to the practice of eradication. "We should at least try this and, if it doesn't work, move on and find other suitable alternatives for the short to medium term."

Kamminga stated that many countries are likely to be interested in importing morphine from Afghanistan, simply because they currently do not have enough. "There are vast amounts of unmet needs around the world. The World Health Organization has confirmed that 80% of the world's population does not have access to painkilling medicines like morphine."

He added that Afghanistan itself does not even have a sufficient supply of morphine. "It's ironic, since they produce 93% of the world's opium but are not able to produce enough painkilling medication for themselves."

In September 2009, The United Nations Office on Drugs and Crime released a report claiming that opium poppy cultivation in Afghanistan has gone down by 22%, that the number of poppy-free provinces has increased from 18 to 20, and that the price of opium has reached a 10-year low.[9] However, according to an article from the BBC, analysts have suggested that the fall in opium production may simply be a temporary tactic by suppliers to drive prices back up.[10] The UN report urged the international community to maintain progress in Afghanistan. It further noted that even though controlling drugs in Afghanistan will not solve all of the country's problems, the country's problems cannot be solved without controlling drugs.[9] HG

—Courtney Cavaliere

References

1. Callimachi R. No more opium, no more money for Afghan villagers. Associated Press; August 3, 2009.
2. Lee P. *Opium Culture: The Art and Ritual of the Chinese Tradition.* Rochester, VT: Park Street Press; 2006.
3. Bowman T. US drug agents target Afghan poppy pushers. National Public Radio. July 29, 2009. Available at: http://www.npr.org/templates/story/story.php?storyId=111174481. Accessed September 4, 2009.
4. 50 drug barons on US target list in Afghanistan. Associated Press; August 10, 2009.
5. Faizi F. Afghan farmers ditch opium for saffron. *Asia Times*; June 25, 2009. Available at: http://www.atimes.com/atimes/South_Asia/KF25Df01.html. Accessed August 4, 2009.
6. Palmer J. Saffron uproots poppies on farms in Afghanistan. *San Francisco Chronicle*; March 1, 2009;A8.
7. Moshiri E, Basti A, Noorbala A, Jamshidi A, Hesameddin Abassi S, Akhondzadeh S. Crocus sativus L. (petal) in the treatment of mild-to-moderate depression: a double-blind, randomized and placebo-controlled trial. *Phytomedicine.* 2006;13(9-10):607-611.
8. Minigh J. Saffron in the treatment of premenstrual syndrome. *HerbalGram.* 2008;78:33.
9. Afghanistan Opium Survey 2009 Summary Findings. United Nations Office on Drugs and Crime. September 2009. Available at: http://www.unodc.org/documents/crop-monitoring/Afghanistan/Afghanistan_opium_survey_2009_summary.pdf. Accessed September 10, 2009.
10. 'Sharp drop' in Afghan opium crop. BBC News; September 2, 2009. Available at: http://news.bbc.co.uk/2/hi/south_asia/8233010.stm. Accessed September 2, 2009.

Study Finds Astragalus and Mineral Formula Beneficial in Treating Seasonal Allergic Rhinitis

Reviewed: Matkovic Z, Zivkovic V, Korica M, et al. Efficacy and safety of *Astragalus membranaceus* in the treatment of patients with seasonal allergic rhinitis. *Phytother Res*. June 5, 2009: [Epub ahead of print].

The symptoms of seasonal allergic rhinitis (SAR)* include sneezing, runny nose, nasal passage obstruction, watery eyes, and itchy nose, throat, and eyes. The purpose of this randomized, double-blind, placebo-controlled clinical trial was to assess the efficacy of an "herbal-mineral complex" containing an extract of astragalus (*Astragalus membranaceus*, Fabaceae) root in the treatment of SAR. Astragalus is used in Traditional Chinese Medicine (TCM), and research has indicated that it stimulates the immune system.[1,2]

The trial was conducted from May to October 2007 at the University Hospital Dubrava in Zagreb, Croatia. Patients with histories of moderate to severe SAR and positive skin prick tests to grass or weed pollen were eligible. Patients with positive skin prick tests for tree pollen were excluded. (The reason for this exclusion was not explained but may have been due to possible overlap and confounding with the pollen seasons for grasses and weeds.) The patients provided blood samples and completed the self-administered mini Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ). The mini RQLQ includes 14 questions covering 5 domains: activity limitations, practical problems, nasal symptoms, eye symptoms, and other symptoms. Each item was rated on a 7-point scale from 0 (no impairment) to 6 (severely impaired). The total reflective symptom score (TSS) was also assessed. The TSS includes ratings of the severity of symptoms over the previous 24 hours on a scale of 0 (none) to 3 (severe). Individual symptoms included rhinorrhea (runny nose), nasal congestion, sneezing, and itching or burning eyes.

Forty-eight patients were randomized to take 2 capsules twice daily of either the astragalus complex (n=32) or an identical-appearing placebo containing lactose powder (n=16) for 6 weeks. Astragalus was harvested in the Hunan Province of China and extracted with water and ethanol (final drug-extract ratio: 18:1). The astragalus capsules contained 80 mg of astragalus extract standardized to contain 40% polysaccharides, plus calcium-aluminum-silicate.

The patients were evaluated at baseline and after 3 and 6 weeks of treatment. The patients and physicians separately rated the overall severity of signs or symptoms and the response to treatment on a 5-point scale from 1 (worsening) to 5 (significant improvement). A blinded cytologist performed nasal smears in order to assess the eosinophils on a 4-point scale from 0 (none) to 3 (almost all cells on smear eosinophils).

Out of 48 patients who began the study, 7 withdrew early (5 in the astragalus group and 2 in the placebo group). There was no statistically significant difference in the number of drop-outs between the groups. Reasons for withdrawal included severe SAR symptoms (n=3), lost to follow-up (n=2), and poor compliance (n=2). There were no statistically significant demographic or disease differences between the 2 groups at baseline. The patients were studied during their respective allergy seasons: grass pollen (May-June, n=26) and weed pollen (August-October, n=22).

After 3 weeks of the treatment, there was a statistically significant difference in the rhinorrhea score between the 2 groups (P=0.048). Other primary efficacy variables—TSS, mini-RQLQ score, and changes for immunoglobulin (Ig) E and IgG—did not show significant intergroup differences in individual symptom scores.

In contrast, at the end of the study the investigators and patients gave astragalus significantly higher efficacy ratings compared to placebo for the secondary variables (P=0.003 and P=0.025, respec-

* The acronym SAR used here should not be confused with SARS, the acronym for severe acute respiratory syndrome.

tively). In the astragalus group, significant improvements from baseline were observed for the symptoms of rhinorrhea, sneezing, and itching after 3 weeks (P=0.02, P=0.06, and P=0.04, respectively). The changes from baseline in the astragalus group were still significant after 6 weeks of treatment (rhinorrhea: P=0.01, sneezing: P=0.03, itching: P=0.03). There were no significant changes from baseline for individual symptom scores in the placebo group.

(After 6 weeks, the TSS in the astragalus combination and placebo groups significantly improved to baseline levels [p=0.001 and p=0.04, respectively]. An expert peer reviewer for *HerbalGram* suggests that this may indicate that the duration of the treatment period was too long; the symptoms may have disappeared because of less pollen exposure.)

The researchers also performed a post hoc analysis of the 22 patients with weed pollen allergies. There were significant differences between the placebo and astragalus groups after 3 and 6 weeks of treatment in TSS scores (3 weeks: P=0.037, 6 weeks: P=0.022) and mini RQLQ scores (3 weeks: P=0.017, 6 weeks: P=0.001). The patients and investigators gave significantly higher efficacy ratings to astragalus compared to the placebo (P=0.001 for both). During the study, 10 patients reported a total of 15 mild-to-moderate adverse events, including rhinosinusitis (the main outcome being studied), pharyngitis, enterocolitis (inflammation of the small intestine and colon), and nausea. According to the authors, none were considered to be connected to the study material (astragalus-mineral combination).

The authors conclude that this study provides "a significant number of positive signals" indicating that the herbal-mineral formulation of astragalus used in this study can be therapeutically effective against SAR. Multicenter clinical trials with larger samples of patients are needed to confirm the trends observed in this study.

An expert peer reviewer commented that the fact that astragalus demonstrated immune-stimulating effects should have been discussed in detail in the original study, noting that a 3 to 6 week duration of treatment should have been enough time to show measurable changes in the immune response of subjects, i.e., changes in indicators of immune system activity, such as ECP (Eosinophil Cationic Protein), tryptase (a serine proteinase found in mast cells associated with the immune response), IL (interleukin)-4, IL-5, and IL-13—none of which were measured in this trial—although, as noted, changes in nasal eosinophils were measured.

—Marissa Oppel, MS

References

1. Milot B. Astragalus review—immunostimulant and cardioprotective. *HerbClip*. October 31, 2003 (No. 060133-243). Austin, TX: American Botanical Council. Review of Anon. *Astragalus membranaceus* [monograph]. *Alternative Medicine Review*. 2003;8(1):72-77.
2. Upton R, ed. Astragalus—*Astragalus membranaceus. American Herbal Pharmacopoeia and Therapeutic Compendium: Astragalus Root.* Scotts Valley, CA: American Herbal Pharmacopoeia; 1999.

Astragalus *Astragalus membranaceus*. Photo ©2009 Steven Foster

Pilot Study Finds American Ginseng Helps with Cancer-related Fatigue

Reviewed: Barton DL, Soori GS, Bauer BA, et al. Pilot study of *Panax quinquefolius* (American ginseng) to improve cancer-related fatigue: a randomized, double-blind, dose-finding evaluation: NCCTG trial N03CA. *Support Care Cancer*. 2009. [e-pub ahead of print] DOI: 1007/s00520-009-0642-2.

American Ginseng *Panax quinquefolius*. Photo ©2009 Steven Foster

Cancer-related fatigue is the most common unmanaged symptom in patients who are undergoing chemotherapy, radiation therapy, biologic therapy, or have completed cancer therapy. The patients describe cancer-related fatigue as a feeling of being overwhelmingly tired and fatigued, which cannot be relieved by sleep. The purpose of this study was to investigate the potential of 3 doses of American ginseng root for alleviating cancer-related fatigue and to examine the potential toxicity of American ginseng. The only adverse side effect traditionally attributed to American ginseng (*Panax quinquefolius*, Araliaceae) is insomnia.

Patients (n = 290) with cancer-related fatigue, determined by a score of 4 or more on a screening questionnaire (with 10 being "as bad as you can imagine"), were included in this randomized, double-blind, placebo-controlled multicenter study (medical centers throughout the United States participated). Patients had to have cancer-related fatigue for at least 1 month and a life expectancy of at least 6 months. For 8 weeks, patients (n = 39 to 48 per group) received placebo or 750, 1000, or 2000 mg/day of American ginseng (4-year-old powdered root of Wisconsin-grown ginseng, encapsulated by Beehive Botanicals, Hayward, WI, and total ginsenoside content measured by Covance Labs, Madison, WI, at the start of the study to ensure at least 5% total ginsenosides).

Randomization was computer generated, but participants were stratified according to stage of disease, gender, baseline fatigue score (4–7 vs 8–10), and current treatment. The primary outcome measure was the Brief Fatigue Inventory. Secondary outcome measures included other validated questionnaires: the vitality subscale of the Medical Outcome Scale Short Form-36, the Pittsburgh Sleep Quality Index, the Global Impression of Change, and the Linear Analogue Self Assessment Scale. Patients reported toxicities (adverse effects) in a diary, and researchers also graded toxicities using the National Cancer Institute Common Toxicity Criteria. Baseline characteristics were similar among groups. Dropout rates were also similar.

There were no statistical differences between the placebo and ginseng groups on the primary or secondary endpoints. However, for the primary efficacy endpoint, there was a trend for greater positive effects with the highest dose of ginseng compared with placebo (P = 0.08). Also, the highest dose (2000 mg/day) was more effective than the other doses and more effective than placebo at improving vitality and quality of life.

Compared with the placebo group, more than twice as many patients in the 1000 and 2000 mg/day ginseng groups perceived a "moderate" to "very much better" improvement in fatigue at study end (placebo: 17% vs ginseng: 40%). In addition, more patients treated with 1000 and 2000 mg/day of American ginseng were satisfied with their treatment for fatigue than those treated with placebo. These data were obtained while patients were still blinded to their treatment group.

There were no significant differences among groups in the quantity, severity, or types of adverse effects, including sleep-related side effects. Patients in all groups reported various adverse effects: nausea, dizziness, nervousness, headache, trouble falling asleep, and trouble staying asleep.

The authors conclude that 1000 and 2000 mg/day of Wisconsin ginseng decreased fatigue more than placebo. They state that the most compelling evidence is the patient-reported improvement. Further, it is also compelling that there were no significant toxicities in the ginseng groups compared with the placebo group, despite the fact that the patients were undergoing cancer treatment and many had advanced disease. Based on *in vivo* studies referenced by this trial's authors, American ginseng may be producing its effect by modulating the neurotransmitters dopamine, norepinephrine, serotonin, and GABA.

The authors have started recruiting patients in the North Central Cancer Treatment Group to enable them to conduct a larger, more definitive trial. The trial will be funded by the National Cancer Institute and supported by the Mayo Clinic, Rochester, MN. One thing that would be important to include in the next study/analysis is whether ginseng might have any adverse effects on cancer treatment outcome. None is expected, but this is an important variable that should not be overlooked. HG

—Heather S. Oliff, PhD

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Studies Assess Ginger for Treatment of Nausea During Pregnancy and Menstrual Pain

Reviewed: Ozgoli G, Goli M, Moattar F. Comparison of effects of ginger, mefenamic acid, and ibuprofen on pain in women with primary dysmenorrhea. *J Altern Complement Med.* 2009;15(2):129-132.

Reviewed: Ozgoli G, Goli M, Simbar M. Effects of ginger capsules on pregnancy, nausea, and vomiting. *J Altern Complement Med*. 2009:15(3):243-246.

Researchers from Iran recently conducted 2 trials to evaluate the safety and effectiveness of ginger (*Zingiber officinale*, Zingiberaceae) for treating female reproductive complaints. The first study compared ginger preparations to non-steroidal anti-inflammatory drugs (NSAIDs) for relieving dysmenorrhea (painful or difficult menstruation). The second study evaluated ginger as a treatment for nausea and vomiting during pregnancy.

Ginger *Zingiber officinale.*
Photo ©2009 Steven Foster

Dysmenorrhea is experienced by more than half of menstruating women. NSAIDs can be effective in relieving dysmenorrhea, but NSAIDs and other pain relievers commonly cause adverse side effects and are contraindicated in some people. Ancient medical texts refer to the use of ginger for relief of dysmenorrhea, but there are no published clinical trials to support its effectiveness. The researchers therefore conducted a study to compare the effects of ginger, mefenamic acid (a mild analgesic and fever-reducing NSAID used in some types of arthritis and for the relief of moderate short-term menstrual pain), and the NSAID ibuprofen on dysmenorrhea.

For the non-randomized, double-blind trial, the researchers recruited 150 female college students who were 18 years or older and had primary dysmenorrhea. The women completed a questionnaire that assessed menstrual characteristics and severity of pain. Those with moderate to severe dysmenorrhea were enrolled in the study and alternately allocated to 1 of 3 groups: the ginger group, the mefenamic acid group, or the ibuprofen group. Depending on their assigned group, the women were instructed to take either four 250-mg capsules of ginger rhizome powder (Zintoma; Goldaroo Company; Tehran, Iran), four 250-mg capsules of mefenamic acid (Ponstan; Razak Co.; Iran), or four 400-mg capsules of ibuprofen (Brufen; Roozdaru Co.; Iran) each day, beginning on the first day of their menstrual period and continuing for 3 days. After the 3 days, the women rated the severity of their dysmenorrhea, the degree of pain relief, and their satisfaction with the treatment. Only one menstrual cycle was studied.

All 150 women completed the study. There were no significant differences in baseline characteristics among the 3 groups. Dysmenorrhea severity decreased in all 3 groups (P values not reported) after 3 days. Severity of symptoms, improvement in pain relief, satisfaction with the treatment, and compliance with the capsules were not significantly different among the groups. None of the women reported any serious adverse side effects during the study.

The authors conclude that ginger is as effective as mefenamic acid and ibuprofen in decreasing menstrual pain. They also point out certain limitations of this study. The study subjects were alternately assigned to an experimental group rather than randomly assigned; however, baseline characteristics were similar among subjects in all 3 groups, and there is no indication of bias in group assignments. The study did not compare the effect of ginger on other menstrual symptoms, such as nausea, headaches, and fatigue. The scale used to rate dysmenorrhea severity was a verbal, 4-point scale, and the authors suggest that use of a 10-point visual analog scale or other standardized scale may detect more subtle differences in response among the experimental groups.

One issue the authors do not address is the dosage of comparator drugs used in this study. It is not clear if the doses selected for this study (1,600 mg ibuprofen and 1,000 mg mefenamic acid) are typical doses used for treatment of primary dysmenorrhea in the local population. In the United States, daily doses of 2,400-3,200 mg ibuprofen are commonly recommended for treatment of moderate or severe dysmenorrhea and may be more effective than the 1,600 mg dose of ibuprofen used in this study. The recommended dose for mefenamic acid is 1,500 mg per day. It is therefore unclear as to how much of a placebo-effect occurred in this study. It would have been better if a placebo group had been included for comparison. Another limitation is that the study was very brief; typically, dysmenorrhea studies are conducted over a 3 month period. In addition to correcting the limitations discussed by the authors, future trials should assess the safety and efficacy of ginger during several menstrual cycles, investigate a range of ginger doses, and include populations of women other than young college students.

The second study assessed the effects of 1,000 mg of ginger administered in capsule form on the severity of nausea and vomiting in pregnant women. Up to 90% of women experience nausea and vomiting during pregnancy. Little is known about the safety of anti-nausea drugs during pregnancy, so some pregnant women turn to herbs or other complementary therapies for relief. Ginger has long been used to relieve stomach upset in the traditional medicines of many cultures.

This single-blind, randomized, placebo-controlled trial was conducted at prenatal clinics and Isfahan Shahid Beheshti Hospital in Isfahan, Iran. Seventy healthy, pregnant women who were less than 20 weeks gestational age and who reported mild to moderate nausea with or without vomiting were enrolled in the trial. The women were randomly allocated to an experimental group or a matched control group. Women in the experimental group took four 250-mg capsules containing ginger root powder (Zintoma; Goldaroo Company; Tehran, Iran) daily for 4 days. Women in the control group took 4 placebo capsules containing lactose daily for 4 days. The women were instructed to take a capsule in the morning, at noon, in the afternoon, and at night.

Before starting the study, women rated the severity of their nausea and vomiting using a 10-point visual analog scale (VAS). The women were instructed to avoid fatty foods and to eat smaller, more frequent meals during the study. The women completed a questionnaire each day and recorded the severity of their nausea on the VAS twice a day (at noon and at bedtime). On the fifth day, the women were interviewed by a researcher to assess compliance with the dietary instructions and capsule use.

Of the 70 women who started the study, 67 completed the study (32 in the ginger group and 35 in the placebo group). There were no significant differences in nausea intensity between the 2 groups at baseline. Women in the ginger group reported significantly greater improvement in nausea than women in the placebo group ($P < 0.05$) during the 4-day trial. Nausea intensity declined in 84% of women in the ginger group and 56% of women in the placebo group ($P < 0.05$). The incidence of vomiting did not decrease significantly in the placebo group but decreased a significant 50% in the ginger group after 4 days ($P < 0.05$). None of the women reported any adverse side effects from the capsules. While compliance with the capsules was excellent in both groups, only about half of the women in each group reported complying with the dietary advice.

The authors conclude that daily treatment with 1,000 mg of ginger is a safe and effective way to decrease the intensity of nausea as well as the incidence of vomiting during pregnancy. However, the authors' conclusions that 1,000 mg is the appropriate dose cannot be asserted given that this study was not a dose-ranging study. Also, the authors' conclusion that this dose is safe cannot be asserted since there has been no long-term, follow-up studies of the infants, and, given the small sample size, only very large changes in pregnancy outcomes would have been seen.

The results of this study are consistent with 9 published randomized controlled trials, which have also evaluated the effectiveness of ginger for nausea and vomiting during pregnancy. In these trials, daily doses ranged from 1,000 mg to 1,500 mg and the ginger products included capsules containing ginger powder or ginger syrup, which is mixed with a beverage.

The authors point out that the short duration of this trial is a limitation. Another limitation that the authors did not discuss is whether the study was adequately blinded. Ginger capsules have a distinctive odor and flavor and it is possible that the people taking the placebo were aware that they had the placebo treatment. This could have contributed to the study outcome. Future trials should assess the safety and effectiveness of ginger over a longer period of time, should improve study blinding, and enroll pregnant women with severe nausea and vomiting to expand the understanding of this herb's effectiveness during pregnancy. HG

—Heather S. Oliff, PhD

Balancing Nature & Wellness

Malaysian Traditions of "Ramuan"

The History, Culture, Biodiversity and Scientific Assimilation of Medicinal Plants in *Malaysia*

By Steven Foster

Above photo: *Ramuan*, comprising a diverse mixture of ingredients, is a force for healing and beauty. Photo ©2009 Biotropics Malaysia Berhad. Photographed by S.C. Shekar

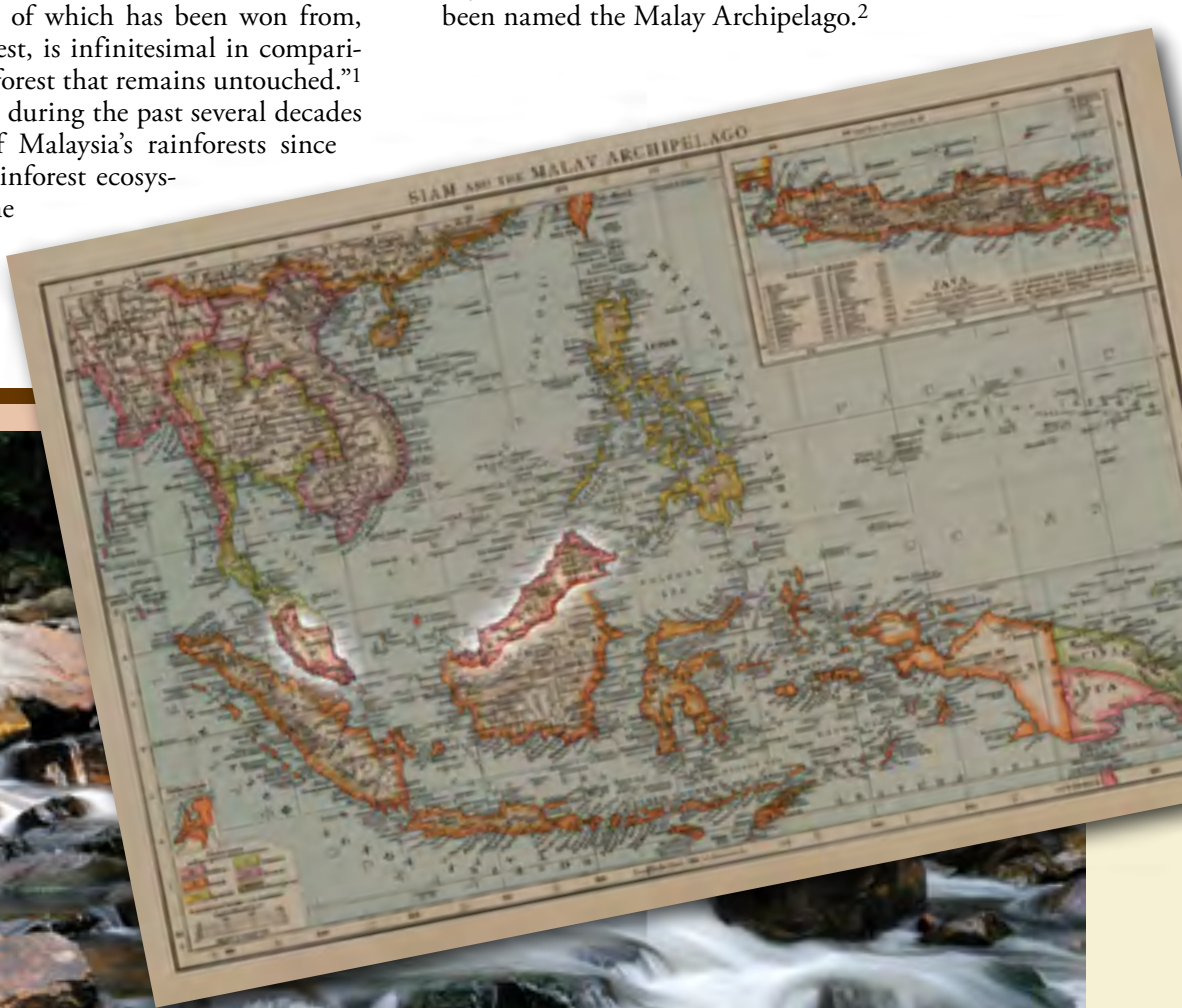
Right photo: **Hibiscus**, *Hibiscus rosa sinensis* Photo ©2009 Steven Foster

When many non-Malaysians think of Malaysia, they may likely envision a peninsula that juts out of Southeast Asia below Thailand, with the South China Sea to the east and the Indian Ocean to the west. However, Peninsula Malaysia represents only about 40% of the country's land area. Sixty percent of Malaysia's landmass, including the states of Sarawak and Sabah, is on the northern reaches of the island of Borneo, bordering adjacent Indonesian territory, and the Kingdom of Brunei. This hot, humid equatorial paradise is home to one of the oldest rainforests on Earth, along with swamp and mangrove forests. Over 58% of Peninsula Malaysia is covered in tropical rainforest.

Observing the vast expanse of vegetation in 1907, Sir William George Maxwell wrote that the entire peninsula appeared to be covered with forest. He added that "the inhabited area, every yard of which has been won from, and hacked out of the forest, is infinitesimal in comparison with the extent of the forest that remains untouched."[1] Although human activities during the past several decades have reduced the scale of Malaysia's rainforests since Maxwell's observations, rainforest ecosystems continue to define the country's geography.

In 1869, in the first edition of *The Malay Archipelago: The Land of the Orang-utan and the Bird of Paradise*, Alfred Russell Wallace, naturalist and contemporary of Darwin, provides a broad brushstroke view of the historical Malay Archipelago:

> Situated upon the Equator, and bathed by the tepid water of the great tropical oceans, this region enjoys a climate more uniformly hot and moist than almost any other part of the globe, and teems with natural productions which are elsewhere unknown. The richest of fruits and the most precious of spices are here indigenous . . . . It is inhabited by a peculiar and interesting race of mankind—the Malay, found nowhere beyond the limits of this insular tract, which has hence been named the Malay Archipelago.[2]



Historic map of Siam and the Malay Archipelago, *The Times London*, 1895. Courtesy of David Ramsey Collection.

Waterfall in the Taman Negara Rainforest National Park. Photo ©2009 Biotropics Malaysia Berhad. Photographed by Moriazi Mohamad

Global Trade—A Malaysian Tradition

The constant tropical climate, abundant rainfall, and its position along the Strait of Malacca, connecting ancient trading routes in the Andaman Sea in the Indian Ocean with the South China Sea, has made Peninsula Malaysia and the island city-state of Singapore, just to its south, a stopping point and trading center for many centuries. The strategic position also invited successive phases of outside influence over nearly two millennia.

It is hardly possible to enter a discussion about the medicinal and aromatic plants of Malaysia without considering the peninsula's location and the influence of the many civilizations and cultures that have visited, occupied, controlled, conquered, settled, and interacted with the Malay people for at least 3,000 years. Early outside influence came from India to the west. Chinese traders came to the area at least 1,000 years ago, as did Arab traders from the west. The Siamese, in what is now modern Thailand, and other Southeast Asians have left their mark as well. Through these many interactions, Hinduism, Buddhism, and Islam have layered their belief systems over millennia-old indigenous traditions. Europeans have influenced the region for nearly 500 years, including the establishment of large-scale cultivation of oil palm (from *Elaeis guineensis*, Arecaceae), rubber (from *Hevea* spp., Euphorbiaceae), and tea (*Camellia sinensis*, Theaceae).

Malaysia's rainforests provide precious medicinal plants and natural resources. Photo ©2009 Biotropics Malaysia Berhad. Photographed by S.C. Shekar

Geography

Malaysia is part of the geographic region of Malesia in Southeast Asia that includes the modern political entities of Malaysia, Indonesia, Papua New Guinea, and the Philippines. It is an area with a relatively uniform climate of high temperatures and predictable rainfall, intersected by the equator. Here, over 30,000 plant species are known to occur—perhaps 10% of the world's total number of plant species—with as many as half of these being endemic to the region. This ancient tropical flora, millions of years old, has evolved largely undisturbed by climatic and geological events, producing rainforests of remarkable age and diversity. Sea levels and climate variations have come and gone. Major, but often isolated, volcanic activity has contributed to the landscape. Notable geographically is the fact that in all of Malesia, only Peninsula Malaysia is connected to the adjacent continental landmass. As such, it serves as a bridge between Malesian floristic elements and those of the tropical Asian continent; the Peninsula itself has a flora of flowering plants, ferns, and gymnosperms numbering upwards of 10,000 species.[3]

Malaysia's tropical climate enjoys abundant rainfall from alternating northeast and southeast monsoons. The northeast monsoon occurs from mid-November until March, and the southwest monsoon occurs from May through September. Heavy rainfall, high temperatures, and consistently high humidity (about 80%) provide perfect conditions for tropical rainforests that cover about 80% of Malaysia. An immense and varied range of habitats and vegetation comprise Malaysia's rainforest formations. Low-lying coastal regions contain large-scale plantations, mostly on the west coast of the Peninsula. The flat coastal plains have extensive wetlands with mangrove and brackish-water swamp forest, creating a complex flora and fauna. Peat swamp forests fed by rainwater are found inland, and freshwater swamps fed by lakes and streams develop in river valleys.[3]

Biodiversity

Malaysia's rainforests are among the oldest in the world, estimated at 150 million years of age. They have produced astounding genetic evolution over the ages. One hundred years ago, rainforests covered nearly 100% of modern Malaysia. Human activity over the past 50 years has reduced the size of rainforest ecosystems, as the country set on a path of rapid economic development. Rubber and oil palm plantations, along with other crops, were established in former lowland forests suitable for agriculture. Environmental degradation was recognized and addressed at the national level as early as 1974, with the establishment at the National level of the Environmental Quality Act. A new federal Ministry of Natural Resources and environment was formed in 2004. Malaysia is a party to the Convention on Biological Diversity (CBD), the Convention on International Trade in Endangered Species of Wild Fauna and Flora (CITES), and the World Heritage Conventions, among other environmental and natural resource conventions and multilateral agreements.[4]

In 2001, the Global Diversity Outlook recognized Malaysia as one of the 12 mega-diversity centers of the

Bungan Kantan

Torch Lily

***Etlingera elatior* (Zingiberaceae)**

One of the largest flowers in the ginger family, *bungan kantan* is native to Indonesia, with leafy branches growing to over 20 ft in height. It is commonly grown as an ornamental in tropical regions due to the brilliant, red showy flowers' heads. In Malaysia, the flowerheads are harvested just as the flowers begin to open and are used to flavor Kedah rice noodles, a famous Malaysian dish. The interior of the flowerheads is also served raw as a healthful herb to eat with rice. Malays consider the raw flowerheads as a preventative for high blood pressure and treatment for diabetes. [Ref: Hassan WEW, Mahmood MP. *Healing Herbs of Malaysia*. Kuala Lumpur: Federal Land Development Authority; 2008.]

Photo ©2009 Steven Foster

Bunga Kenanga

Ylang Ylang

***Cananga odorata* (Annonaceae)**

The genus name *Cananga* is a phonetic derivation of the common Malay name kenanga. This large evergreen tree, native to Malaysia and Indonesia, is widely grown in tropical regions, where the flowers may bloom year round but are most abundant during the dry season. The greenish-yellow flowers display their greatest beauty in the fragrance of their essential oil—ylang ylang oil. In Malaysia, kenanga oil is believed to have aphrodisiac and antidepressant qualities, among others. It is used in aromatherapy to slow down rapid breathing, relieve anxiety, and to treat insomnia. In the absence of the oil, a handful of crushed fresh blossoms is smelled for its aromatherapy qualities. [Ref: Hassan WEW, Mahmood MP. *Healing Herbs of Malaysia*. Kuala Lumpur: Federal Land Development Authority; 2008.]

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world. The first edition of I. H. Burkill's 1935 tome *Dictionary of the Economic Products of the Malay Peninsula* noted 1,200-1,300 medicinal plants of Malaysia, an estimate still often quoted in the literature.[5] Out of more than 20,000 species of vascular plants, about 10%, or approximately 2,000 species, have documented medicinal qualities.[6] Given modern ethnobotanical, chemical, and pharmacological literature, the number of Malaysian medicinal plants is likely greater.

Foundations of Malaysian Medicinal Plant Knowledge

The 3 major races of Malaysia—Malays, Chinese, and Indians—use medicinal plants for their daily healthcare needs. In addition, the *Orang Asli*, the indigenous peoples of Malaysia, use medicinal plants as the basis for healthcare.[7]

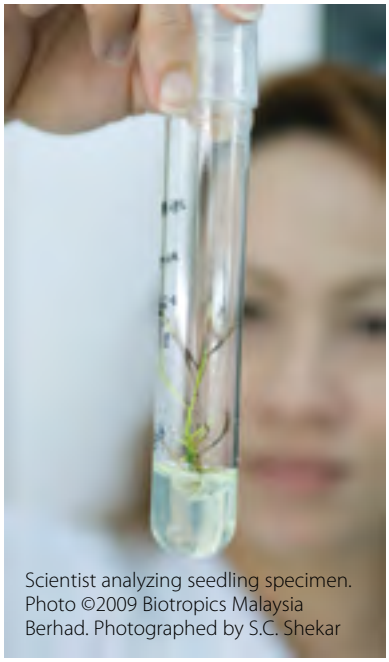
Europeans came to the region 500 years ago in search of valuable plant products, particularly the fabled and elusive spices of the East. Beyond such spices as nutmeg (*Myristica fragrans*, Myristicaceae) and clove (*Syzygium aromaticum,* Myrtaceae) were hints of the possibility of more botanical contributions for human benefit. Peter James Begbie, on observing indigenous medicine, wrote in 1834 of "the probability of this race yet revealing to us many medicinal shrubs which will prove highly valuable in compounds."[8]

Humans have occupied Malaysia for at least 40,000 years.[9] Most literature on medicinal plant use in Malaysia has emerged only in the last century. Books on Malay medicine featuring herbal ingredients were written in the 1880s in traditional Jawi script, thus were available only to educated Malays of the time. John Dermont Gimlette, an English physician, and I.H. Burkill, then director of the Singapore Botanic Gardens, translated an 1886 script by Munshi Ismail as *The Medical Book of Malayan Medicine.*[10] Burkill later wrote *A Dictionary of Economic Products of the Malay Peninsula* (2 vols. 1935, reprinted with additions, 1966),[5] a 2,444-page reference that still serves as the most comprehensive work on the Malay medicinal, herbal, and economic plants.

Expanding Knowledge Through Research

Until the 1980s, little further research or documentation of Malaysian medicinal plants occurred. In the 1980s, numerous ethnobotanical studies were carried out among indigenous groups and ethnic populations in Malaysia, including the Jah Het, Semai, Semaq Beri, Senoi, Hulu, and Temuan groups, as well as studies addressing traditional medicine practices among the Malay, Malaysian Indian, and Malaysian Chinese populations. However, less than a third of these studies were published in journals; the vast majority was technical reports, theses, dissertations and proceeding papers. Most are not readily available outside the originating institution.[11]

Most universities in Malaysia now have active research programs on medicinal plants, including ethnobotany, chemistry, pharmacology, pharmacognosy, and indigenous traditional systems of healthcare.[11] In the 1960s, phytochemical screening on Malaysian medicinal plants was a focus of Malaysian medicinal plant research, followed by isolation and structural elucidation of pure compounds. Since 1985, substantial support has been provided for research by the Malaysian government through its Intensified Research in Priority Areas (IRPA) program. Current research focuses on ailment-based medicinal plant assessment using bioassay-guided fractionation; research on biological, pharmacological, and toxicological activities; clinical trials; and herbal product development for both domestic and export markets. Malaysian institutions have also developed key strategic international alliances with major medicinal plant research groups in other countries.[12]



Scientist analyzing seedling specimen. Photo ©2009 Biotropics Malaysia Berhad. Photographed by S.C. Shekar

Malaysia has developed a national policy that embraces biodiversity and conservation while maintaining economic development.[4] During the Rio Earth Summit in 1992, Malaysian representatives strongly advocated an economic return for genetic or biological resources, as well as traditional knowledge. The potential for development of new genetic resources from its flora and traditional medical systems has sparked the development of a growing, government-supported biotechnology research and commercial development industry in the country.[4]

Scientist dispensing plant specimen. Photo©2009 Biotropics Malaysia Berhad. Photographed by S.C. Shekar

Towards A Regulatory Framework

Since 1992, all herbal products sold for human consumption, domestic and imported, must be registered with the Malaysian Ministry of Health to ensure their quality, safety, and efficacy. The Drug Control Authority of the Malaysian Ministry of Health must also license manufacturers, importers, wholesalers, and other suppliers. World Health Organization (WHO) guidelines are the basis for Malaysia's Code of Good Manufacturing Practices. Other regulatory controls to which herbal medicines are subject include the Medicines Act (covering advertising and sales, 1956; revised 1983), the Poisons Act 1952 (revised 1989), the Drug Sales Act 1952 (revised 1989), and the 1972 Wild Species Act.[12] The Drug Control Act prohibits traditional medicine products from

Bunga Kemboja

Plumeria, Frangipani, Lei Flower, Pagoda Tree

Plumeria rubra f. *acutifolia* (syn. *P. acuminata*; Apocynaceae)

To many travelers, plumeria is associated with Hawaii, as the flowers make beautiful leis. However, it is native to Mexico, South America, and the Caribbean. It came to Asia with Spaniards in the 17th century, where it was quickly adopted as a sacred tree whose flowers are used as an offering in Buddhist temples, and in Malaysia and Indonesia it is widely planted in Muslim cemeteries. It is Indonesia's national flower. In ancient Mexico, Aztec nobles always carried the flower while on public streets. Like many members of the dogbane family, the genus *Plumeria* produces a milky white, irritating sap; hence it was used to treat boils or warts. Root preparations were a traditional tonic for gonorrhea. The bark is used to treat scabies and skin diseases. The flowers are the source of the delicately intoxicating fragrance frangipani oil. [Refs: Hassan WEW, Mahmood MP. *Healing Herbs of Malaysia*. Kuala Lumpur: Federal Land Development Authority; 2008, and Mabberley DJ. *Mabberly's Plant-Book*. 3rd ed. Cambridge, UK: Cambridge University Press; 2008.]

Photo ©2009 Steven Foster

Limau Nipis

Lime

Citrus aurantifolia (Rutaceae)

The common English name of this familiar fruit, lime, is very similar to the Malay name limau nipis. Limau is a Malay word for citrus. This fast-growing, small evergreen *Citrus* species arrived in the Mediterranean region around the 9th or 10th centuries. Limes are known throughout the world and valued as a garnish for fish dishes and beverages. The tree is native to the Indo-Malay region. In Malaysia, the fruits are associated with spiritual ritual baths. Lime juice is used in ceremonial bathing of the bridegroom and in healing ceremonies before invoking spirits. As a love charm, a girl's name may be carved on the fruit skin. Female elephants are rubbed with lime juice to prevent a solitary male from leaving. Lime juice is used in Malaysian traditional medicine to treat premature graying, balding, and skin care. A leaf poultice is used to heal stretch marks after childbirth. A decoction of the leaves is used as a gargle for sore throat and to bathe feverish patients. [Refs: Hassan WEW, Mahmood MP. *Healing Herbs of Malaysia*. Kuala Lumpur: Federal Land Development Authority; 2008, and Burkill IH. *A Dictionary of the Economic Products of the Malay Peninsula*. 2nd ed. Kuala Lumpur: The Ministry of Agriculture and Cooperatives; 1966.]

Photo ©2009 Steven Foster

making therapeutic claims relative to the treatment and prevention of certain diseases. However, traditional claims relative to function, such as increase in strength and vitality, are permitted. Therapeutic claims can be made for herbal products with proven safety and efficacy, supported by clinical studies.[12]

The Scientific Committee of Malaysian Herbal Monographs is developing a standard protocol for quality control and identity standards. The first set of 20 monographs was published in 1999.[12] In 2001, the Institute for Medical Research, National Institutes of Health, Ministry of Health Malaysia, also established the Herbal Medicine Research Centre (HMRC). HMRC is charged with scientifically proving the safety and efficacy of herbal medicines, standardizing herbal products, coordinating research on herbal medicines in Malaysia and the activity of researchers in the field, and producing a Malaysian herbal pharmacopeia. HMRC includes an Information Unit, Bioassay Unit, Toxicology and Pharmacology Unit, and Phytochemistry Unit.[13]

Expanding Markets

As in much of the rest of the world, the market for medicinal plants among Malaysians is increasing. In 2000, it was estimated that the market for herbal medicine in Malaysia was about US $527 million. The figure is expected to increase to more than US $1.37 billion by 2010. Raw materials for herbal medicine are often imported from China, India, Indonesia, Hong Kong, Taiwan, and the United States. Even with market increases, Malaysia is thought to produce between only 5-10% of herbal medicines used by Malaysians, with the rest imported from the previously mentioned countries.[7,14]

According to a market assessment by Josef Brinckmann, vice-president of research and development at Traditional Medicinals, an herb tea manufacturer in Sebastopol, California, and editor of the *Medicinal Plants and Extracts* newsletter for the International Trade Centre's Market News Service, Malaysia is a net importer of 80% of the 38 natural product categories represented in international trade by the Harmonized System Code, in dollar value. Despite this figure, Malaysia is a leading exporter of a handful of natural ingredients, offsetting the overall categories of imports. The country is a leading exporter of cocoa butter, coconut oil, black pepper (*Piper nigrum,* Piperaceae), capsicum fruits (*Capsicum* spp., Solanaceae), essential oils, tea extracts, cinchona alkaloids (from *Cinchona* spp., Rubiaceae), and other plant and plant-derived ingredients. Following historical patterns, most of Malaysia's natural product exports are to Asian countries, particularly Thailand, Indonesia, Singapore, China, India, Japan, and South Korea. Malaysia is believed to be in a strong position to further develop export markets with the potential strong confidence in the Malaysian "brand," with its proven ability for scientific rigor and quality products.[15]

Unique medicinal plant products, especially for North American and European markets, provide excellent opportunities for Malaysia. Biotropics Malaysia, a government-linked company, was set up in 2007 to bring well-researched Malaysian natural products to the American, European and other international markets.

> If globalization is a historical phenomenon, then the Malay Peninsula is an early point of origin.

Malaysia's Unique Tradition—*Ramuan*

If globalization is a historical phenomenon, then the Malay Peninsula is an early point of origin. The intermingling of foreign cultures, civilizations, and religions, along with the ancient Malay social structures, evolved to create a traditional wellness system that is uniquely Malaysian, known today as *ramuan*, in which food, medicine, and beauty—inner health and outer beauty—blend in a multicultural approach to wellness that reflects the many cultures that are the people of Malaysia.[16]

Malay traditional medicine has an underlying theoretical framework akin to other Asian health systems. It is also heavily influenced by Arabic Unani medicine and its Galenic (Greco-Arabic) philosophy, but also incorporates adopted practices of the *orang asli* (indigenous peoples) and approaches of Indonesian, Chinese, and Indian traditional medicine systems. Similar to both Asian and Galenic philosophy, physical characteristics are believed to be constituted of the 4 elements—fire (*suprawi*), earth (*suddawi*), wind (*dammawi*), and water (*balpawi*). The nature of disease and medicines, meanwhile, is characterized as damp, cold, dry or hot, also drawing on the Indian-influenced concept of Pancha Indra—5 elements or senses. Influences from *orang asli* traditions include diagnoses based not only on physical characteristics but underlying spiritual or "spirit" influences, incorporating chants (*jampi*), prayers (*doa*), massage, abstinence[12] or strict prohibition (*pantang*), as well as color. The primary male healer is known as a *bomoh.* Single remedies or polyherbal prescriptions are dispensed in powders, capsules, pills, medicated oils, decoctions, infusions, simple distillates, pastes, and poultices.[10]

Traditional Malay practices were widely observed and recorded by European authors, but mostly in the context of folklore, superstition, or pagan rites. In 1900, Walter William Skeat detailed many folk traditions. The rites of the *bomoh,* he observed, were divided into 2 well-defined parts: (1) Diagnosis techniques including messages taken from the smoke of burning incense, reading coins thrown into water-jars, and reading parched rice floating on the surface of water; (2) Therapeutic rituals roughly classified into 4 types: (a) propitiatory ceremonies; (b) neutralization, or ceremonies seeking to destroy an evil principle; (c) expulsory for removing evil influence; and (d) revivification-restoring to health. The *bomoh*'s overriding fundamental principle was to preserve or restore the balance of the 4 elements, chiefly achieved by constant attention to and moderation in diet.[17]

The other primary practitioner in a Malay village is the *bidan* or *mak bidan*, often the most revered woman in a village. She performs vital tasks such as child delivery, advising mothers before and after birth, and advising young women on healthcare and health problems. The *mak bidan* is trained in the art of massage, which incorporates the use of aromatic and fixed oils, use of compresses and poultices, and hot stone massage to help rejuvenate a woman after childbirth, hasten blood flow to muscles, and help to regain youthfulness. This is not a single appointment with a massage therapist, but rather an elaborate healing and beauty-reviving ritual that lasts for 42 days and involves a wide range of herbal preparations and aromatic flowers, used internally and externally.[18]

Bunga Raya

Hibiscus, Rose-of-Sharon

***Hibiscus rosa-sinensis* (Malvaceae)**

Native to tropical Asia and Pacific Islands, Rose-of-Sharon arrived in Malaysia by the 11th century. It is referred to as "The Queen of the Tropic" and is the national flower of Malaysia. It is grown as an ornamental throughout the tropics and, in Malaysia, all parts of the plant are widely used in traditional medicine. The flowers are used for various menstrual irregularities and to treat fevers, coughs, and promote hair growth. The leaves and flowers are used for treating skin diseases, mumps, and fever. The leaves and roots are combined to treat skin eruptions. The mucilaginous root is used for coughs and fever. In China, juice from the petals has been used as a mascara to darken eyelashes. The flowers, fresh or cooked, are used as a purple food coloring for cooked vegetables and fruit preserves. [Ref: Hassan WEW, Mahmood MP. *Healing Herbs of Malaysia*. Kuala Lumpur: Federal Land Development Authority; 2008.]

Malaysian Herbs: Case Studies of Success

Tongkat Ali — Eurycoma longifolia

Tongkat Ali (*Eurycoma longifolia*, Simaroubaceae), has emerged as one of the most intriguing medicinal plants of Malaysia and adjacent countries. The name *tongkat ali* means "Ali's staff," a name which Burkill notes is common of plants in the genus *Smilax* and other tonics.[5] Other Malay names for *tongkat ali* translate into "bitter antidote," "bitter gall," "bitter jujube," "red jujube," "white jujube," "fold of the earth," and "vomit of the earth" (referring to use in cleansing rituals). It is also sometimes referred to by the common English name Long Jack. This small tree has attracted the attention of Chinese, Europeans, Indians, Indonesians, and others throughout the world.

Burkill records "*Bedara laut,*" another name for *tongkat ali*, as being used in an infusion as a gargle for bleeding gums and a draught for dropsy (broadly, fluid retention) and ascites (excess fluid in the peritoneal cavity, a complication of liver cirrhosis, or possible spontaneous life-threatening bacterial infection). *The Medical Book of Malayan Medicine* suggests a deep respect for the herb as an ingredient in polyherbal prescriptions as a "neutralizer of poison" and "bitter antidote." The infusion is used for coughs, fever, and as an application for "caterpillar itch"—wounds caused by the bristles of the poisonous sea creature known as hairy sea-caterpillar or fireworm (*Chloeia flava*, Amphinomidae).[5]

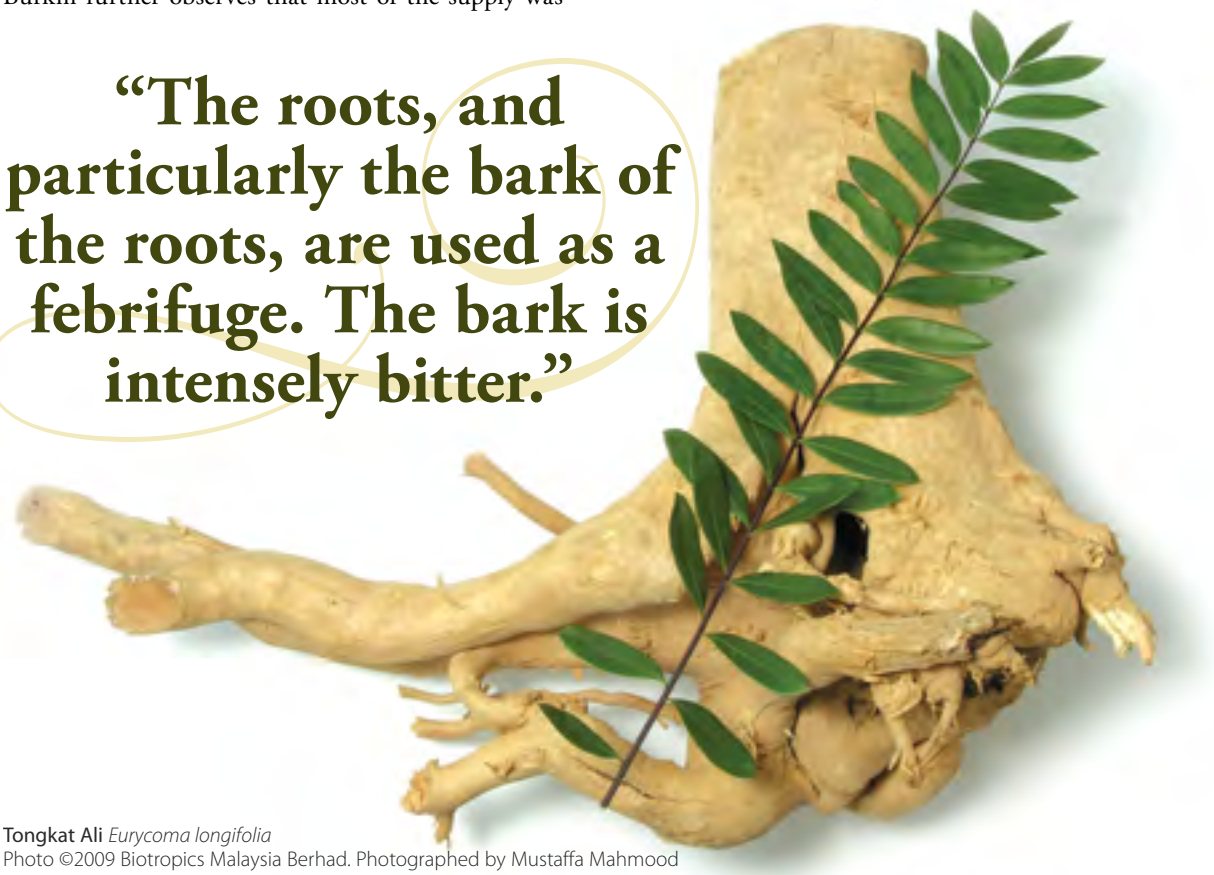
Burkill writes, "The roots, and particularly the bark of the roots, are used as a febrifuge. The bark is intensely bitter." Though plentiful on the Peninsula, Burkill further observes that most of the supply was imported via Singapore from Borneo (island home of 2 modern Malaysian states). In decoction, it is often mentioned in the literature for "intermittent fever" (malaria). Malays have been noted to drink the decoction in instances calling for a tonic, such as after childbirth. The pounded root bark was poulticed for headache, wounds, ulcers, and other sores.[5]

The source plant, *E. longifolia*, common in Indonesia and Malaysia, was named by William Jack (1795-1872), surgeon with the East India Company. Jack was one of the first to attempt a catalog of Peninsular Malayan plants.[19] A medium-sized tree to about 18 ft in height, it usually bears a single stem with pinnately compound leaves approximately 39 in. long and 30-40 leaflets in opposite pairs. Relatively inconspicuous flowers are borne in branched panicles, producing ovoid fruits, which are generally the size and shape of those of jujube (*Ziziphus jujube*, Rhamnaceae) and turn dark red when ripe. It is found as an understory tree in the lowland forests of Peninsula Malaysia, Indonesia, and other parts of Southeast Asia.[20]

The primary modern use for *tongkat ali* in the treatment of erectile dysfunction (ED) stems from its traditional reputation as an aphrodisiac. A recent study looking at Malaysian cultural differences in knowledge, attitudes, and practices related to ED used focus groups to evaluate data in 66 men of varying ethnic background. The researchers found that use of traditional remedies for preventing or treating ED were commonly recognized among all groups, particularly the use of preparations of *tongkat ali* root. It was also reported as a means to increase sex drive and desire.[21]

As the flagship of Malaysian traditional medicines, it has been the subject of relatively extensive

"The roots, and particularly the bark of the roots, are used as a febrifuge. The bark is intensely bitter."



Tongkat Ali *Eurycoma longifolia*
Photo ©2009 Biotropics Malaysia Berhad. Photographed by Mustaffa Mahmood

scientific research. One important research track has focused on claims of traditional use as an antimalarial. *In vitro* studies published in 1986 and 1991 showed a potential antimalarial effect of specific chemical fractions from the root.[22,23] In a 1995 study, a quassinoid mix in a semi-purified extract of the root showed that a dose-dependent complete inhibition of 6 Malaysian chloroquine-resistant *Plasmodium falciparum* cultures was achieved with 1.25-5.0 micrograms ml-l extract, 3 days post treatment.[24] The same researchers found that 3 of 9 isolated quassinoids showed antimalarial activity.[25] In a 2002 study, 2 compounds, 11-dehydroklaineanone and 15beta-O-acetyl-14-hydroxyklaineanone, showed potent plasmodicidal activity.[26] The quassinoids eurycomanone and 13,21-dihydroeurycomanone showed higher selective cytotoxicity to strains of *P. falciparum* in systematic bioassay-guided fractionation than 4 other quassinoids.[14] A recent *in vivo* study looked at the activity of whole standardized root extracts, alone and in combination with artemisinin, to assess antimalarial potential. Both oral and subcutaneous doses were given, and the combination of the 2 drugs, especially by the subcutaneous route, showed excellent results.[27] A 2008 study looking at *P. falciparum* growth stages found a methanol soluble isolate of the root had the greatest inhibitory effect at trophozoites stages of *P. falciparum*.[28] These and other studies relative to antimicrobial and cytotoxic activity have catapulted *tongkat ali* as a leading candidate for further antimalarial research.

Of equal interest to potential international markets are studies related to traditional use as an aphrodisiac. A 1997 study evaluated the effect of *tongkat ali* on the libido of sexually vigorous male rats and found a dose dependant stimulation of sexual arousal absent of genital stimulation, as measured by increased mounting frequencies.[29] Given a *tongkat ali* root extract for 10 days before a study, sexually experienced male rats exhibited greater orientation toward receptive females (as measured by sexual interest behaviors, environment response, self interest, and mobility) compared with controls.[30] In other studies, the same battery of tests proved to increase sexual interest in middle-aged rats that were retired breeders[31] and decrease mounting hesitation response compared to controls.[32] Yet another study, this one with sexually sluggish old male rats treated with *tongkat ali* extract, increased yawning and stretching, both regarded as ancestral vestiges of evolution associated with promoting sexual arousal.[33] The same research group studied the aphrodisiac effects in sexually inexperienced male rats, and in a series of tests over a 9 to 12 week observation period, the inexperienced male rats treated with *tongkat ali* root extract gained significantly more experience than the controls.[34] A pro-androgenic effect on the laevator ani muscle was shown in another study.[35] Clearly these small studies don't provide adequate scientific evidence to suggest throwing away Viagra®, but they do point to a scientific basis for the traditional use of *tongkat ali* as an aphrodisiac.

A joint study carried out by Massachusetts Institute of Technology and Malaysian research institutes indicated that the aphrodisiac activity of plants can be determined by the presence of 4.3 kDa peptide. This peptide, found in *tongkat ali* root, may be responsible for its aphrodisiac attributes, as it is a potent phytoandrogen shown to increase testosterone levels in rat leydig cells.[36,37] Patents have been granted on the identity of the peptide, its extraction, and its use in increasing testosterone synthesis, and an extract based on an exclusive license of this patent is produced in Malaysia and marketed as LJ100 in the United States.[38] At the cellular level, *tongkat ali* has been found to increase the level of cGMP (cyclic guanosine monophosphate), which produces smooth muscle relaxation in the corpus cavernosum, allowing blood flow that leads to an erection. It also increased levels of cAMP (cyclic adenosine monophosphate), enhancing metabolism of sugar utilization, which helps to explain its energy-boosting effects.[39] Antianxyolytic activity has also been experimentally confirmed.[40] Ergogenic effects were demonstrated in a study on men, including modulation of testosterone level, reduction of body fats, and increased muscle strength and size.[41] It is also purportedly used as a natural energizer and sexual stimulant and potential health supplement in the maintenance and regulation of healthy ageing in men.[42]

Tongkat Ali *Eurycoma longifolia* trees. Photo ©2009 Biotropics Malaysia Berhad. Photographed by Mustaffa Mahmood

Kacip Fatimah — Labisia pumila

Labisia pumila (syn *L. pothoina*, *Ardisia pumila*; Myrsinaceae, also placed in the Primulaceae family) is known in Malaysia as *kacip fatimah*. *Labisia* is a small genus of about 7 species of subherbaceous perennials found in Southeast Asia.[43] *Labisia* means "a spoon," as the small depression of the corolla resembles the bowl of a spoon. Many Malay names for the plant are dedicated to the prophet Mohammed's only daughter, Fatimah. *Kacip fatimah* is sometimes called *kunci fatimah*, which roughly translates into "Fatimah's key;" *selosoh fatimah* means "Fatimah's childbirth medicine;" and *rumput siti fatimah* is "grass of our lady Fatimah." Other common names include *tadah mata hari* (intercepting the sun) and *bunga belangkas hutan* (woodland king-crab's flower), among others. King-crab's flower honors the Malay's fondness for imagery as king crabs are commonly seen in pairs, which is regarded as a happy matrimonial pair.[5]

As a protective medicine, a decoction of the whole plant is administered after childbirth, but also before birth to expedite delivery. The decoction is also used for the treatment of dysentery, intestinal gas, and dysmenorrhea, as well as for a condition described as "sickness in the bones."[5]

In Malaysia, *kacip fatimah* has not only been used for centuries, but it is taken on a regular basis by Malay women today. The fresh or dried plant is boiled in an earthen cooking pot, either alone or in decoction with other herbs. The herb, or formulations with other herbs, is readily available in powders or extracts in pills, capsules, mixtures with tea or coffee, and as a canned beverage. The decoction is given 1-2 months before childbirth. Modern perceptions of its health benefits include being a useful herb to contract the uterus after childbirth; firm and tone abdominal muscles; tighten the vaginal wall and tissue; allay painful or difficult menstruation, cramping, and irregular periods; and to generally alleviate fatigue and promote emotional well-being. Used regularly it is believed to increase vitality, libido, and energy.[16] The decoction of the leaves and roots is valued to help delay conception and regain strength after childbirth.[20]

Three varieties are found in Malaysia: the 2 major varieties used in commercial products, *L. pumila* var. *alata* and *L. pumila* var. *pumila*, as well as *L. pumila* var. *lanceolata*. Quality control studies have identified morphological, microscopic, and chromatographic methods to differentiate between the 3 Malaysian varieties of *L. pumila*.[12] An herb or subshrub, with creeping rhizomes, growing from 12-18 in. in height, *kacip fatimah* is found on the floor of damp forests at elevations from about 200 to 2,300 ft. The distinctive elliptical-lanceolate, glabrous leaves are dark green above, usually with lighter-green margins, and tinged reddish-purple beneath. The leaves may be over a foot long and up to 5 in. wide. The small white-pink flowers occur in spike-like panicles in the leaf axils. They produce a small round, red berry when ripe.[20] The plant contains benzoquinoid derivatives, alkenyl resorcinols, and triperpenoid compounds.

Kacip Fatimah *Labisia pumila*
Photo ©2009 Biotropics Malaysia Berhad. Photographed by Mustaffa Mahmood

Kacip fatimah has been one of the most widely used herbs by women in Malaysia for hundreds of years.

In an investigation of 6 commercial herb products available in Malaysia, 5 products intended for use before childbirth were found to contain *L. pumila* var. *alata* root, and one product intended for use after childbirth contained *L. pumila* var. *pumila* leaf. Since *Labisia pumila* is often associated with habitats where tin mining occurs, with soils rich in tin, the authors of the study also investigated the tin, aluminum and iron content of *Labisia* plant samples. A relatively high iron content in *L. pumila* var. *alata* root (107.3-111.6 ppm) suggests the plant may help prevent anemia in pregnant women. Possible estrogenic activity had been proposed as an explanation for traditional use by pregnant women, and two small studies have shown a tendency toward possible estrogenic activity.[44]

Kacip fatimah is generally considered safe for human consumption when used in the form of a traditional decoction. A pilot study on post-menopausal women indicated dosages of up to 560 mg/day as safe for consumption.[45]

Given its wide use by Malay women during pregnancy, Zaizuhana et al. investigated the effect of *kacip fatimah* aqueous extracts at different dosage levels and time intervals on mammalian bone marrow cells using micronuclei formation to assess the potential genotoxicity and mutagenic effect of the herb. Using what was admittedly a limited experimental design, they did not observe any mutagenic potency or genotoxic effects, but urge further research.[46]

A study by Effendy et al. looked at the possible liver and kidney toxicity of a petroleum ether extract of the roots of *L. pumila* var. *alata* administered subcutaneously for 7 days in laboratory animals at 3 different concentrations. The treatment groups showed mild-to-moderate hemorrhage lesions in the kidneys and liver degeneration, with the greatest abnormalities occurring in the group that received the highest dose of the extract. The authors concluded

that a toxin might be present in the plant and that further studies should be carried out to determine safety. This study, however, used high doses over a short period of time in a petroleum ether extraction system as a subcutaneous injection, which is a very different preparation and will yield a complete set of different compounds than those found in traditional and conventional products using water as the extraction solvent. These purely experimental results therefore have no relevance to real-world usage by humans, where solely water decoctions are used.[47]

An evaluation of the potential teratogenicity of an aqueous extract of *L. pumila* var. *alata* root at up to 1000 g/kg/day in an animal model did not show any teratogenic effect, though what was deemed as a statistically insignificant increase in body weight of pregnant animals was observed. This study furthers scientific data on the relative safety confirmed in toxicological studies conducted to date.[48]

Another study looked at female reproductive toxicity and potential effects of a *L. pumila* var. *alata* aqueous extract on pregnancy and labor in rats. The authors observed no signs of reproductive toxicity or complications in pregnancy, delivery, and early pup growth in rats. There was no observable adverse effect at levels equivalent to 800 mg/kg/day.[49]

Researchers from Oman and Malaysia recently looked at the effects of an aqueous extract of *kacip fatimah* on maintaining integrity of the aortic wall in laboratory animals. Aortic stiffness is a potentially useful measure of cardiovascular health and predictive sign of cardiovascular disease. A patent-pending water extract of *kacip fatimah* was given at a dose of 17.5 mg/kg/day orally in drinking water. After 3 months of treatment, with another group receiving estrogen therapy, the authors concluded that the *L. pumila* var. *alata* water extract helped to maintain the integrity and morphology of the aortic wall in a manner similar to that of estrogen. They note, too, that the results were consistent with previous studies with *kacip fatimah* that showed an estrogenic effect. It was theorized that the herb may have possible cardio-protective effects and may be suitable for treating menopause-induced aortic stiffness.[50]

Kacip fatimah has been one of the most widely used herbs by women in Malaysia for hundreds of years. Based on the growing number of products in the Malaysian market, with claims of enhanced vitality and libido over the last 10 years, the Government of Malaysia has been providing support to universities, research institutes, and government agencies to evaluate the identity, safety, pharmacology, and human experience with *L. pumila*. Government interest in the herb provides funding for establishing a basic scientific understanding of the traditional use, pharmacognosy, chemistry, pharmacology, and toxicology of *kacip fatimah*. A patent has been filed for an aqueous extract and on-going clinical trials, if positive, will not only confirm the traditional knowledge of many generations of Malaysians but also increase international interest in the herb.

Kacip Fatimah *Labisia pumila*
Photo ©2009 Biotropics Malaysia Berhad. Photographed by Mustaffa Mahmood

Conclusion

While many developing countries have hoped and waited for a drug or chemical company to discover a blockbuster compound that might bring revenue to the country from native flora, Malaysia has explored the potential of its own biodiversity that includes upwards of 20,000 species of vascular plants. In the past decade, there has been government support for scientific investigation of the traditional remedies used by its diverse populations, establishment of educational and research programs at nearly every university, and engagement in public policy debates about the potential and future of its biodiversity. Inventories of medicinal plant resources are ongoing. The historic literature produced by European and Asian immigrant populations of recent centuries has been thoroughly explored for what it might reveal of use for today, both in terms of public healthcare and commercial development. *Ex situ* and *in situ* conservation efforts have also been established. Collaborative efforts between Malaysian scientists and institutions in the developed world have yielded chemical compounds of potential interest, like calanolide A, a coumarin of the *bintangor* trees of Sarawak *Calophyllum lanigerum* and *C. teysmanii* (Clusiaceae) that has shown activity against the HIV virus.

Strategies and a framework for managing biodiversity and strategic planning for the future are under development in accordance with the Convention on Biodiversity (CBD), of which Malaysia is a member. Given its great diversity, Malaysia has been the focus of international attention in biodiversity issues, both in terms of conservation and in view of habitat destruction in the cause of economic development. Malaysian biologists have stressed the importance of protecting habitats and valuing biodiversity for the intrinsic and future economic value of genetic resources.[51,52] This echoes the conservation concern from many tropical countries—that potentially useful genetic materials can be brought to market in a sustainable manner that also promotes economic development. HG

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References

1. Maxwell WG. *In Malay Forests*. Edinburgh and London: William Blackwood and Sons; 1907.
2. Wallace AR. *The Malay Archipelago: The Land of the Orang-Utan and the Bird of Paradise*. New Edition ed. London: MacMillan and Co., Limited; 1906.
3. Jones DT. *Flora of Malaysia - Illustrated*. Kuala Lumpur, Malaysia: Oxford University Press; 1993.
4. Division CaEM. *Biodiveristy in Malaysia.* Kuala Lumpur: Ministry of Natural Resources and Environment;2006.
5. Burkill IH. *A Dictionary of the Economic Products of the Malay Peninsula*. 2nd ed. Kuala Lumpur: The Ministry of Agriculture and Cooperatives; 1966.
6. Herbal Medicine Research Center IfMR. *Compendium of Medicinal Plants Used in Malaysia.* Kuala Lumpur: Aktif Bestari Sdn. Bhd.; 2000.
7. Batugal P, Kanniah J, Lee S, Oliver J, eds. *Medicinal Plants Research in Asia: Volume: 1: The Framework and Project Work Plants*. Serdang, Selango, DE, Malaysia: International Plant Genetice Resources Institute - Regional Office for Asia, the Pacific and Oceanate (IPGRI-APO); 2004.
8. Begbie PJ. *The Malayan Peninsula: Embracing its History, Manners and Customs of the Inhabitants, Politics, Natural History, etc., from it's Earliest Records*. Madras, India: Printed for the Author at the Vepery Mission Press; 1834.
9. Kemp BM. Mitochondrial DNA and the African exodus. *Anthropological Currents.* 2006;47(2):213.
10. Gimlette JD, Burkill IH. The Medical Book of Malayan Medicine. *Garden's Bulletin Staright's Settlements.* 1930;6(1):323-421.
11. Mat-Salleh K, Latiff A, Nazre A. What do we know about our medicinal and cultural important plants: Current status of Malyasian ethnobotany. *International Conference on in-situ Biodiversity Conservation in the New MIllenium.* Kots Kinabalu, Sabah, Malaysia2000.
12. Jamal AA. Malay traditional medicine: an overview of scientific and technological progress. *Tech Monitor.* 2006;Nov-Dec:37-49.
13. Centre HMR. http://www.imr.gov.my/org/hmrc.htm#2. Accessed August 23, 2009
14. Chang S, Ali RM. Inventory, documentation and status of medicinal plants research in Malaysia. *Medicinal Plants Research in Asia.* 2004;Vol. 1:120-127.
15. Brinckmann JA. Market Survey 2007: Market for Malaysian Natural Ingredients Used in Cosmetic, Dietary Supplements and Pharmaceutical Products. *3rd International Congress on Traditional Medicine and Materia Medica (ICTMMM)*. Putra World Trade Centre, Kuala Lumpur, Malaysia: Power Point Presentation; 2007.
16. Bodeker G. *Health and Beauty from the Rainforest: Malaysian Traditions of Ramuan*. Kuala Lumpur: Editions Didier Millet; 2009.
17. Skeat Ww. *Malay Magic Being an Introdution to the Folklore and Popular Religion of the Malay Peninsula*. London: Macmillan and Co., Ltd.; 1900.
18. Zakaria M, Mohd MA. *Traditional Malay Medicinal Plants*. Kuahal Lumpur: Penerbit Fajar Baki, Sdn. Bhd.; 1994.
19. Ridley HN. *The Flora of the Malay Peninsula*. London: L. Reeve & Co., Ltd.; 1922.
20. Hassan WEW, Mahmood MP. *Healing Herbs of Malaysia*. Kuala Lumpur: Federal Land Development Authority; 2008.
21. Low WY, Wong YL, Zulkifli SN, Tan HM. Malaysian cultural differences in knowledge, attitudes and practices related to erectile dysfunction: focus group discussions. *International Journal of Impotence Research.* 2002;14:440-445.
22. Chan KL, O'Neill MJ, Phillipson JD, Warhurst DC. Plants as sources of antimalarial drugs. Part 31 *Eurycoma longifolia*. *Planta Med.* 1986;52(2):105-107.
23. Kardono LB, Angerhofer CK, Tsauri S, Padmawinata K, Pezzuto JM, Kinghorn AD. Cytotoxic and antimalarial constituents of the roots of Eurycoma longifolia. *J Nat Prod.* Sep-Oct 1991;54(5):1360-1367.
24. Ang HH, Chan KL, Mak JW. Effect of 7-day daily replacement of culture medium containing *Eurycoma longifolia* Jack constituents on the Malaysian Plasmodium falciparum isolates. *J Ethnopharmacol.* 1995;49(3):171-175.
25. Ang HH, Chan KL, Mak JW. In vitro antimalarial activity of quassinoids from *Eurycoma longifolia* against Malaysian chloroquine-resistant Plasmodium falciparum isolates. *Planta Med.* 1995;61(2):177-178.
26. Jiwajinda S, Santisopasri V, Murakami A, et al. In vitro anti-tumor promoting and anti-parasitic activities of the quassinoids from *Eurycoma longifolia*, a medicinal plant in Southeast Asia. *J Ethnopharmacol.* 2002;82(1):55-58.
27. Mohd Ridzuan MA, Sow A, Noor Rain A, Mohd Ilham A, Zakiah I. *Eurycoma longifolia* extract-artemisinin combination: parasitemia suppression of Plasmodium yoelii-infected mice. *Trop Biomed.* 2007;24(1):111-118.
28. Sholikhah EN, Wijayanti MA, Nurani LH, Mustofa. Stage specificity of pasak bumi root (*Eurycoma longifolia* Jack) isolate on Plasmodium falciparum cycles. *Med J Malaysia.* 2008;63 Suppl A:98-99.
29. Ang HH, Sim MK. *Eurycoma longifolia* Jack enhances libido in sexually experienced male rats. *Exp Anim.* 1997;46(4):287-290.
30. Ang HH, Sim MK. *Eurycoma longifolia* Jack and orientation activities

in sexually experienced male rats. *Biol Pharm Bull.* 1998;21(2):153-155.
31. Ang HH, Lee KL. Effect of *Eurycoma longifolia* Jack on orientation activities in middle-aged male rats. *Fundam Clin Pharmacol.* 2002;16(6):479-483.
32. Ang HH, Ngai TH, Tan TH. Effects of *Eurycoma longifolia* Jack on sexual qualities in middle aged male rats. *Phytomedicine.* 2003;10(6-7):590-593.
33. Ang HH, Lee KL, Kiyoshi M. Sexual arousal in sexually sluggish old male rats after oral administration of *Eurycoma longifolia* Jack. *J Basic Clin Physiol Pharmacol.* 2004;15(3-4):303-309.
34. Ang HH, Sim MK. *Eurycoma longifolia* increases sexual motivation in sexually naive male rats. *Arch Pharm Res.* 1998;21(6):779-781.
35. Ang HH, Cheang HS. Effects of *Eurycoma longifolia* jack on laevator ani muscle in both uncastrated and testosterone-stimulated castrated intact male rats. *Arch Pharm Res.* 2001;24(5):437-440.
36. Asiah O, Jordan B, Lessard PA, et al. Genetic diversity of *Eurycoma longifolia* inferred from single nucleotide polymorphisms. *Plant Physiol.* 2003;131(3):1294-1301.
37. Asiah O, Nurhanan MY, Mohd Illam A. Determination of bioactive peptide (4.3 KDA) as an aphrodisiac marker in six Malaysian plants. *Journal of Tropical Forest Science.* 2007;19(1):61-63.
38. Sambandan TG, Rha C, Kadir AA, Aminudium N, Saad JM, inventors; Government of Malaysia, Massachusetts Institute of Technology, assignee. Bioactive fraction of *Eurycoma longifolia.* US patent 7,132,117. February 14, 2001.
39. Pihi AHL. Current status of the effect of *Eurycoma longifolia* (tonkat ali) extacts as a sexual stimulant agent. Paper presented at: Seminar on Medicinal Plants Programme & Abstracts. 2002; Kuala Lumpur.
40. Ang HH, Cheang HS. Studies on the anxiolytic activity of *Eurycoma longifolia* Jack roots in mice. *Jpn J Pharmacol.* 1999;79(4):497-500.
41. Hamazah S, Yosuf S. The ergogenic effects of *Eurycoma longifolia* Jack: a pilot study. *Br. J. Sports Med.* 2003;37:465.
42. Tambi MI. Standardized watersoluble extract of *Eurycoma longifolia* (LJ100) on men's health. *IJA.* 2005;28((Suppl. 1)):27.
43. Mabberley DJ. *Mabberly's Plant-Book*. Third Edition. Cambridge, UK: Cambridge University Press; 2008.
44. Houghton PJ, Jamal JA, Milligan S. Studies on *Labisis pumila* herb and its commercial products. *J. Pharm. Pharmacol.* 1999;51((Supplement)):236.
45. Hazlina NH, Bekabar WN, Mohamad WB, et al. Pilot study on the safety and cardiovascular effects of BioLabisia(TM) on post-menopausal women. *International Medical Journal.* 2009;16(2):137-148.
46. Zaizuhana S, Puteri JNMB, Noral'ashikin Y, Muhammad H, Rohana AB, Zakiah I. The in vivo rodent micronucleus assay of Kacip Fatimah (*Labisia pumila*) extract. *Trop Biomed.* 2006;23(2):214-219.
47. Effendy AWM, Siti-Nurtahirah J, Hussin ZM. The side effects of Kacip Fatimah extract on liver and kidney of white rats. *Journal of Sustain. Sci & Mngt.* 2006;1(1):40-46.
48. Faud WEM, Sulaiman SA, Islam MZ, Wahab MSA, Jamalullail SMS. Evaluation of the teratogenicity of aqueous extract of *Labisia pumila* var. *alata* in rats. *Malaysian Journal of Medical Sciences.* 2005;12(2):13-21.
49. Ezumi MFW, Amrah SS, Suhaimi AWM, Mohsin SSJ. Evaluation of the female reproductive toxicity of the aqueous extracts of *Labisiai pumila* var. *alata* in rats. *Indian J Pharmacol.* 2006;38(5):355-356.
50. Al-Wahibi A, Nazaimoon WM, Norsyam WN, Farihah HS, Azian AL. Effect of water extracts of *Labisia pumila* var. *alata* on aorta of overiectomized sprague dawley rats. *Pakistan Journal of Nutrition.* 2008;7(2):208-213.
51. Latiff A, Zakri AH. *Protection of Traditional Knowledge, Innovations and Practices: The Malayan Experience.* Geneva: Universiti Kebangsaan Malaysia; 30 October - 1 November 2000.
52. Latiff A. Valuing the Bioviersity of Medicinal Plant Species in Malaysia. Paper presented at: Sustainable Management and Utilization of Medicinal Plant Resources, Proceedings of the International Conference on Medicinal Plants; 5-7 December, 2005.

Sweet Annie *Artemisia annua*. Photo ©2009 Martin Wall

"Silver Bullet" Drugs vs. Traditional Herbal Remedies: Perspectives on Malaria

By Kevin Spelman, PhD

The hunt for active constituents in that characterize modern, single chemical entity drugs—is just over 2 centuries old. This method of drug development, which emphasizes chemical simplicity, has resulted in important—but sometimes temporary—treatment options. Multi-component remedies have often been neglected by researchers in favor of silver bullet drugs, due to difficulties in understanding their activity, biases within the medical establishment, and other factors. Some research indicates, however, that chemically-complex mixtures can be safer and more effective than single isolates, and they may also be less likely to result in drug resistance. With multidrug resistance becoming a leading obstacle to curing malaria and protecting against infection,[1] it is critical both to understand the history of analytical chemistry as it has impacted the modern view on antimalarial drugs and to reevaluate the potential of using multi-compound treatments such as herbal remedies.

The Rise of Silver Bullet Screening within Pharmacology

As chemistry was maturing in the 19th century, the developing field of analytical chemistry, with its ability to isolate and purify the active ingredients of plants, was foundational in early drug research and development.[2] Alkaloids, a widely diverse group of constituents, were some of the first principals isolated from plants. The historical record suggests that Charles Derosne was the first to extract plant alkaloids; he extracted a mixture of 2 alkaloids from opium (from *Papaver somniferum,* Papaveraceae) in 1803.[3] During the same time period, Friedrich Wilhelm Adam Sertürner was purifying constituents from opium and in 1817 succeeded in isolating morphine.[3,4] Over the next 5 years, Pierre Joseph Pelletier and Joseph Bienaimé Caventou, 2 French pharmacist-chemists at the Ecole de Pharmacie of Paris, isolated a number of noticeably active compounds from plants.[3] One of the alkaloids, quinine, from the South American cinchona tree (*Cinchona* spp., Rubiaceae), would later become an antimalarial drug that would change the political and economic landscape of Africa and other tropical areas.[3,5,6]

Also during the 1800s, François Magendie, known as the father of experimental pharmacology and a teacher of the renowned French physiologist Claude Bernard, began experimenting with Javanese arrow-poisons and eventually found that the active constituent was strychinine. He and Pelletier later demonstrated that emetine was the primary active substance of ipecac, although they were unable to isolate a pure substance. (It was later shown that their emetine was a mixture of at least 3 alkaloids.[7]) Magendie took pharmacology further into a reductionist direction by promoting the use of isolated principles from plants. In 1821 he published a pocket formulary for practicing physicians entitled (translated from French) "Formulary for the preparation and use of several new drugs, such as nux vomica, morphine, prussic acid, strychinine, veratrine, the cinchona alkaloids, emetine, iodine."[7] This work was essentially a guide to using isolated alkaloids in clinical medicine. The silver bullets of modern pharmacology had arrived.

Half a century later, the physician Thomas MacLagan successfully used salicylic acid, a metabolite of salicin (from the bark of willow [*Salix* spp., Salicaceae]) in a clinical trial on patients with rheumatism.[8] By the late 19th century, clinical trials such as MacLagan's and the groundbreaking physiology experiments of Claude Bernard and Magendie had fertilized the medical sciences to the point that pharmacology, which had formerly been seen as having limited relevance to the medical sciences, was elevated to a respectable ranking among the medical disciplines. Further, Oswald Schmiedeberg and his students at the University of Strasbourg laid many of the intellectual and experimental foundations of pharmacology,[2,9] while Friedrich Bayer[8] and Charles Frederic Gerhardt,[10] through the production of acetylsalicylic acid, laid the foundation for the synthetic processing practices of what would become the pharmaceutical industry.

One of the foundations of pharmacology thus came to be the isolation and purification of constituents from plant medicines, which were already being used in various non-purified forms.[2,9] In fact, about half of the *United States Pharmacopoeia* (USP) at the beginning of the 20th century were still "impure" multi-constituent plant medicines.[11] Many of the 19th century and early 20th century medical journals documented case studies substantiating the effectiveness of plant medicines in their crude form.

Early efforts in the development of pharmacological agents were based on observations of outcomes within living systems exposed to substances. This strategy provided such drugs as aspirin in the West, as well as both the Ayurvedic and Chinese pharmacopeias in Asia. As the understanding of pathogenesis advanced, research strategies moved to *in vivo* animal models, followed by *in vitro* cellular models, which produced such drugs as the antibiotic penicillin from fungi and the anticancer drug cisplatin from an inorganic potassium salt.[12] However, with increasing technology came sharper focus on single etiological agents; currently most drug discovery is confined to single protein targets. Medicinal chemists insist on single target-based screens because the alternative—studying multiple interactions—until recently, was not technologically possible and was considered too complex.[13]

Safety and Effectiveness of Medicinal Plants vs Drugs

The medical sciences have drastically changed their focus over the last 200 years. Not only have they moved from complex molecular mixtures to single molecules, but they have also shifted their focus to disease models of decreasing complexity, from the living to the inanimate.[12] Williamson points out that when complex extracts were simplified to one molecule, scientists did not realize until much later that the specific mode of activity and the adverse side effects were altered, sometimes producing more serious adverse effects. And Vickers comments that an unspoken oversight of the medical sciences is that the rationale for the approach of isolation and purification of active constituents from "crude drugs" has never been made explicit.[11]

Although it has been suggested that the isolation and purification of active constituents from plants can provide the advantage of precise dosing and decreases the possible adverse events induced by other plant constituents, statistics suggest that pure compounds have their own risks. Analysis of data suggests single chemical drugs produce in the realm of 1000-10,000 times higher toxicity than medicinal plant preparations (although such data are

not always directly comparable). A 2006 report by the Institute of Medicine put the number of medication errors causing injury to Americans at 1.5 million per year.[14] Considering that the reports of adverse events are estimated to be underreported by a factor of 10, this is a remarkable figure.[15] Detailed analysis of data from 55 countries published in the *British Medical Journal* noted that adverse events from herbal remedies are "a tiny fraction of adverse events associated with conventional drugs," and the risk of using herbal remedies is "fewer than synthetic drugs."[16]

Moreover, the belief that "therapeutic reproducibility" is superior because of the precise dosing of an isolated chemical strongly ignores the large variation in drug metabolism. For example, caffeine and other drug metabolism varies at least 60-fold in healthy subjects.[17] Thus, if an individual is exposed to a concentrated chemical and has a slow metabolism, severe toxicity may occur. The likelihood of this happening with a medicinal plant, which is inherently a dilute mixture of chemicals, is, relatively speaking, significantly less likely.[16]

Critics of medicinal plants argue that the low concentration of any one phytochemical in a plant creates a mixture of compounds too dilute to have an effect. However, Rajapakse et al. have demonstrated that very low concentrations of any one chemical will contribute to a chemical mixture's activity, even if that chemical does not show activity when isolated.[18] This notion particularly challenges the research on herbal medicine that has suggested that some are void of activity because of failure to find a single active constituent. This also challenges research that equates activity of a plant with a single isolated chemical contained within a plant or plant part.

Further, attempts as early as 1928 demonstrated that the pharmacological activity of combinations of constituents often had different activity that could not be predicted by the activity of the isolated constituents.[1] In other words, the efficacy of medicinal plants often cannot be reduced to a single constituent. Thus much of the research on medicinal plants that seeks a pharmaceutical gem from a jungle of phytochemistry is incomplete as it neglects the possibility of synergic, additive or antagonist activity of multi-constituent remedies.[19]

Neema Daudi of Karagwe, Tanzania drinking **Sweet Annie** (*Artemisia annua)* tea. Photo ©2009 Keith Lindsey

The chemical complexity inherent to multi-constituents, however, is not without disadvantages. Medicinal plants/multi-component remedies represent a particular challenge in understanding molecular modes of activity. That this is a particularly complex issue is demonstrated by the attempts to use information theory to cope with the complexity of the multi-component nature of herbal remedies.[20,21] This issue still remains to be solved and will continue to delay significant pharmacological research on medicinal plants. But until modes of activity are clearly elucidated, outcome studies provide meaningful data.

Pharmacological research in itself will also need to break out of its current research methodologies to fully understand medicinal plant activity. The inability of contemporary science to describe systems composed of diverse elements that engage in nonlocal interactions has limited pharmacology, as well as many other areas of science.[22] Constructs such as complexity theory and information theory offer model systems that provide a more complete approximation of natural processes. In addition, systems biology and network pharmacology offer approximations of physiology one step closer to real time cellular interactions and as a result, may substantially increase the understanding of multi-component remedies interfacing with cellular networks.

> Many of the 19th century and early 20th century medical journals documented case studies substantiating the

Multiple Constituents of Herbs and the Importance of Synergy

It is a rare medicinal plant that has only one bioactive constituent.[3,7] Rather, medicinal plants commonly contain numerous active constituents. Messina et al. point out that the allelochemicals of a single plant can have complementary and overlapping activities on human physiology, including alteration of biotransformation enzyme activities, anti-inflammatory effects, stimulation of the

immune system, hormone metabolism, and antimicrobial effects.[23]

The medicinal plant sweet wormwood, also known as Sweet Annie (*Artemisia annua,* Asteraceae), source of the antimalarial drug artemesinin, contains constituents that improve pharmacokinetic parameters, as well as at least 9 other compounds that contain antimalarial activity.[24] Some of the flavonoids of *A. annua* appear to potentiate the mode of activity of artemesinin.[25] Two polymethoxyflavones, casticin and artemitin, although inactive against the malaria-causing protozoa *Plasmodium* spp., have been found via *in vitro* models to selectively enhance the activity of artemisinin against *P. falciparum*.[26] Two additional flavones that show very little direct growth inhibitory activity, chrysosplenol and chrysoplenetin-D, appear to target the P-glycoprotein pumps known as multi-drug resistance (MDR) efflux inhibitors.[27] This provides further possible potentiation of artemisinin against malaria,[28] since resistance of *P. falciparum* to mefloquine and structurally related drugs has been found to be due to the P-glycoprotein pump.[29,30]

The same phenomenon is seen in plants from which alkaloidal drugs are extracted. Rarely do the alkaloidal plants limit their production to only one alkaloid; usually they yield a complex mixture, possibly dominated by one or 2 alkaloids, but often accompanied by literally dozens. For example, the Madagascar periwinkle (*Catharanthus roseus*, Apocynaceae), from which the cancer drugs vincristine and vinblastine are derived, contains close to 100 distinct alkaloids.[3] Yet resistance to vincristine and vinblastine is a well known occurrence.[31] It may be worth considering whether some of the co-occurring constituents of *C. roseus* could mitigate the development of resistance.

Above photo: Women harvest **Sweet Annie** (*Artemisia annua)* leaves at Tooro Botanical Gardens in Fort Portal, Uganda. Photo ©2009 Keith Lindsey

Below photo: Women sort **Sweet Annie** (*Artemisia annua)* leaves at Tooro Botanical Gardens in Fort Portal, Uganda. Photo ©2009 Keith Lindsey

In *Cinchona* spp. there are at least 7 alkaloids, as well as other groups of constituents, that contribute to the antimalarial activity.[32] During World War II, the US military experimented with a mixture of cinchona alkaloids named totaquine.[33] Totaquine was easy to produce, even with cinchona bark of low quinine content, and it could have been a relatively inexpensive drug. The military concluded that totaquine was as effective as quinine in terminating acute attacks of malaria but had a slightly higher rate of nausea and blurred vision. They also found that the 2 alkaloids cinchonine and cinchonidine were less toxic than quinine.

A more recent study done with a mixture of 3 cinchona alkaloids—quinine, quinidine, and cinchonine—demonstrated a synergic effect against a culture of *P. falciparum*.[34] Additionally, the *Plasmodium* strains that were resistant to quinine were up to 10 times more susceptible to the alkaloid mixture than any of the single alkaloids. It is possible that *Plasmodium* resistance could be at least delayed, if not avoided, with prudent use of such therapeutic mixtures.

As has been seen in multiple examples over the last 40 years, whether it be insect resistance to DDT, bacterial resistance to antibiotics, or *Plasmodium* spp. resistance to the antimalarial drugs chloroquine and mefloquine, resistance to a single agent is predictable.[35] Resistance to mefloquine was found within 6 years in areas where it had been widely used (Thailand, Cambodia, and Vietnam).[36] On the other hand, it has been shown in various research models that the development of resistance of microbes is greatly attenuated by multi-component remedies.[27,37-41] For example, *Heliobacter pylori* exposed to the antibiotic clarithromycin for 10 exposures, sequentially, develops resistance. But when exposed 10 sequential times to essential oil of lemongrass (*Cymbopogon citratus*, Poaceae), consisting of at least 23 different terpenoids—16 of which have known antimicrobial activity[24]—*H. pylori* was unable to develop resistance.[37]

Although often led by clinical trial and error, the strategy of using multiple compounds is already being used in clinical medicine. Drug cocktails have proven successful in the treatment of other complex diseases. Cancer, hypertension, and psychiatric treatment protocols have taken to achieving maximum efficacy by targeting several biochemical pathways simultaneously, exploiting synergy, and minimizing toxicity.[42] In addition, multicomponent remedies, or "multitargeting," is becoming a theme of infectious diseases. Physicians are now using drug cocktails to compensate for resistance in tuberculosis found in the inner cities. Cocktail therapies for AIDS and bacterial, fungal, and viral infections suggest that multitarget perturbations are useful therapeutic strategies.[43] Polypharmacy is increasingly being accepted as a reducer of microbial resistance.

Support for Multi-Compound Remedies from Evolution and Biological Networks

Natural products have been described as a population of privileged structures selected by evolutionary pressures to interact with a wide variety of proteins and biological targets.[44] From an evolutionary standpoint, many plant compounds are selected to enable plants to survive their biological environment. Depending on the mode of activity, allelochemicals (plant compounds generated for protection) must survive the metabolic processes of herbivores to be effective in their role against herbivory.[28,45-47] Thus, these molecules, once absorbed, commonly have functional activity on various biochemical pathways of the herbivores that consume them. Natural selection would eventually eliminate plants that generated costly allelochemicals but could not effectively protect themselves by delivering these compounds to the herbivore.[28] It follows that the phytochemical matrix surrounding these allelochemicals should, *by natural selection,* enhance absorption to allow the allelochemicals to reach their biochemical niche.[48]

Experimental models demonstrate that co-occurring compounds of medicinal plants play a role in enhancing the bioavailability and distribution of various phytochemicals. For example, the absorption of hypericin, the antiviral compound in St. John's wort (*Hypericum perforatum*, Clusiaceae), is significantly enhanced in the presence of its naturally occurring flavonoid components.[49] Similarly, artemisinin is absorbed faster in humans from a tea preparation of *Artemisia annua* than from tablets of pure artemisinin. This appears to be due to the co-occurring plant constituents, which seem to generate a high extraction efficiency of the lipophilic artemisinin in boiling water.[50]

Further, although one could argue that plant-human interactions were selected to repel and potentially harm humans, there are hypotheses suggesting the contrary. Plants may have

Illustrations of failed drugs that target a single protein, and ignore a sophisticated network system of disease

Fields of **Sweet Annie** (*Artemisia annua)* grow in front of African huts at Okoboi, North-East Uganda. Photo ©2009 Keith Lindsey

selected compounds to encourage humans to feed on them and in the process enhanced early human health as well as encouraged propagation of themselves.[51] Ehrlich and Raven suggested over 4 decades ago that the study of species interacting with one another have been narrow in scope and ignore the reciprocal aspects of these interactions.[52] While much understanding of the interactions among species has been gained since Ehrlich and Raven's work, their comment does seem pertinent to the idea of human and plant interactions as an evolutionary force influencing human physiology. An evolutionary perspective, when followed logically, would suggest that exclusively using isolated compounds to induce shifts in mammalian physiology is unsupported by the evolutionary process. On the contrary, exposure to one chemical at a time, from an evolutionary time scale, is completely novel to biology. For over 200 million years of evolving mammalian physiology, ingestion of foods and medicines, by way of plants, have always been multi-component mixtures of nutrients and secondary metabolites.

Systems biology, meanwhile, has shifted the investigational emphasis from the molecular level to the system level, recognizing that cellular physiology is organized as genes, proteins, and small molecules in *intermolecular networks*.[53] The interactions among these components generate potential multi-step pathways, signaling cascades and protein complexes composed of redundant, convergent, and divergent pathways.[1,54] In this paradigm, the core ecological milieu of cellular activity in health and disease, which were originally postulated as relatively disconnected linear pathways, are now recognized as a complex interdependent web of regulatory, structural, and metabolic signaling pathways among cells: Pharmacology is evolving from understanding the function of individual proteins to understanding how networks of proteins interact.[53]

In disease processes, there are numerous risk factors and defective proteins out of balance with each other that provide various pharmacological targets.[55,56] In addition, many of the physiological systems and their interactions dynamically shift as a disease improves or worsens.[57] There is often one major or easily definable defective target for a given disease, but collateral proteins that can act in a network are likely to be involved. With this in mind, the focus on a single protein to treat disease processes may not necessarily provide therapeutic efficacy.[58]

Illustrations of failed drugs that target a single protein, and ignore a sophisticated network system of disease processes, are numerous. For example, in the treatment of inflammatory bowel disease, many agents developed by targeting a specific molecule are proving to be either insufficiently effective or totally ineffective.[58] Another example is the drug Iressa (gefitinib), which targets the protein EGFR to treat lung cancer. While this drug, which has been designed to have high selectivity for EGFR, generates an extraordinary response in 10% of those taking it, 90% of lung cancer patients show little-to-no response.[59]

Conversely, many highly efficient drugs, such as the non-steroidal anti-inflammatory drugs (NSAIDs), saliclyate, metformin, and the blockbuster drug Gleevec (imatib mesylate), affect many targets simultaneously.[60] Ágoston et al, in a comparison of various pharmacological strategies, found that multiple but partial perturbations of selected targets in a network are almost always more efficient than the knockout of a single, carefully selected target.[43] This is likely due to the redundant pathways of cellular networks that are not inhibited by a single chemical.[60] (Case in point—Gleevec was originally formulated to target a single protein but has been found to hit multiple targets, which has been postulated to be the reason for its success.)

Thus, the hunt for high-affinity, high selectivity compounds, which has dominated pharmacological research, is not necessarily ideal for efficient perturbation of a cellular network.[60] Low-affinity multi-target drugs such as plant extracts, on the other hand, may achieve significant alteration of a cellular network.[43,60]

Recent technological developments (e.g., Matrix Assisted Laser Desorption Ionization—Time of Flight, gene microarrays) to facilitate probes of interconnected pathways should add to the understanding of how cell networks interact by providing previously unattainable information about physiological processes. Information about protein abundance, phosphorylation state, and metabolite concentration are leading to more complex pharmacological models. Of great significance, "omics" experiments capture a glimpse of the activity of cellular networks by genomic, proteomic, and metabolomic profiles.[54] Thus a snapshot of the cellular dynamics can be observed. Since natural products are often too complex to allow chemists to explore their structure-activity relationships,[45] "omics" methodology may offer important insights into the mode of activity of complex traditional remedies.[61,62]

A union between systems biology, network pharmacology, and medicinal phytochemistry might reveal that nature's strategy of activating multiple pathways simultaneously to elicit network regulation is likely safer and frequently more effective.

This strategy plays to the strength of plants, which have been selected, over millions of years, to modulate cellular networks and interconnected pathways. Medical sciences are increasingly able to appreciate, using network pharmacology models, the complex strategy of using multiple compounds. An evolutionary perspective, as well as a systems biology viewpoint, support the idea that chemical matrices are not only the evolutionarily established norm for shifting physiological processes, but may be superior for interfacing with the robust and complex cellular systems of life, including humans.[60]

The Treatment of Malaria with Medicinal Plants

Malaria, in addition to being the most pernicious parasitic disease of humans, is also the most prevalent. Current statistics suggest that malaria kills between 2.7 to 3 million people each year, with the majority being children under the age of 5 years.[63] *Plasmodium* spp. has generated resistance to all classes of antimalarial drugs, and as a result there has been a doubling of malaria-attributable child mortality in eastern and southern Africa.[64] Disturbingly, malaria is so common in certain tropical areas that "low transmission areas" are defined as a person acquiring *Plasmodium* spp. infection less than 3 times a year. Conversely, in some tropical areas new malaria infections are acquired more than once each day and can be asymptomatic.[65] Current estimates suggest that approximately 300 million people on the planet are infected with *Plasmodium* spp.

Of the 4 species of malaria parasites that infect humans—*P. falciparum, P. vivax, P. ovale, P. malariae*—the most deadly is *P. falciparum*. If falciparum malaria is treated appropriately, the mortality is a mere 0.1%.[65] However, *P. falciparum* parasites, especially from Southeast Asia, are particularly known for developing drug resistant strains and these strains can produce a mortality rate of 15-20%.[66]

Predictably, there are reports of *in vitro* resistance of *Plasmodium* spp. to artemisinin derivatives[67,68] as well as reports of recrudescence in patients treated with artemisinin derivatives.[69] This is of particular concern due to the increase in demand of artemisinin-derived drugs, from 22,000 treatment courses in 2001 to an estimated 200 million in 2008.

Treatment cost and income are important variables affecting the choice of malaria treatment and contributing to drug resistance. The majority of malaria-ridden countries spend less than US $10 per capita annually on health, creating a situation where even US 50 cents becomes a prohibitive cost of treatment.[65] Perhaps partially due to such economics, the recommended treatment in many high-transmission areas are antimalarial drugs (i.e., chloroquine or sulfadoxine-pyrimethamin) that are partially or completely ineffective.[70] As a result of cost and lack of access to healthcare facilities, medicinal plant preparations remain a popular choice for the rural poor.[71] Studies report up to 75% of African patients with malaria use medicinal plants, while in French Guiana 33% report regular use of herbal remedies to prevent febrile illnesses and malaria.[72] Mothers in rural Africa commonly start malaria treatment of their children with herbal therapies before they initiate pharmaceutical treatment.[73]

Treatment of malaria by the poor often involves buying whatever they can afford and not necessarily the correct dosage for effective treatment, which can contribute to drug resistance. Thus, it could be that new pricey pharmaceuticals (or even cheaper, older pharmaceutical antimalarials) *combined with* properly used medicinal plant preparations might stave off drug resistance. Considering that recent treatment strategies to reduce the emergence of de novo resistance relied on antimalarial drug combinations,[70] it follows that if a plant contains compounds that are antimalarial (and antimalarial plants commonly have multiple antimalarial compounds), a combination of properly-dosed medicinal plant extracts with an inexpensive pharmaceutical antimalarial may greatly facilitate elimination of the malarial parasite.

Willcox has pointed out that there are 1,277 plant species from 160 families listed that have been used to treat malaria.[74] (Of these, 5 were listed as "endangered," 13 were listed as "vulnerable," and 3 were listed as "near threatened.") In northeast India, 65 medicinal plants from 38 different families have been reported to treat malaria,[75] and in South Vietnam, 46 plants traditionally used for malaria have shown activity through *in vitro* testing.[76] Approximately 64% of the traditional malaria remedies in Kenya have been found in an *in vitro* model to exhibit anti-plasmodial activity.[77] Of the 1,277 plants Willcox listed,[74] 47 species are used on 2 continents and 11 species are used on all 3 tropical continents as antipyretics or antimalarials. The plants used on more than one continent for the treatment of malaria could provide an informed beginning for the search for effective antimalarials, whether they be low cost traditional remedies or high-tech combination cocktails made from isolates.

> Pharmacology is evolving from understanding the function of individual proteins to understanding how networks of proteins

Notable mentions of medicinal plants include *Terraplis interretis*, which showed high rates of adequate clinical response* in testing to the point of clinical cure.[74] Additionally, *Cryptolepis sanguinolenta* (Asclepiadaceae) has demonstrated activity roughly equal to that of chloroquine; *Cryptolepis* cleared fever 12 hours faster and cleared parasites within 24 hours.[74] *Bidens pilosa* (Asteraceae) has shown activity against drug resistant *P. falicparum* parasites *in vitro* and *in vivo* in rodents. *Strychnopsis thouarsii* (Menispermaceae) appears to be useful for prevention of malaria due to activity against the hepatic stage of *Plasmodium*.[78]

Studies with plants traditionally used for malaria treatment from various parts of the world have intriguingly shown inhibitory activities against both chloroquine-sensitive and resistant strains of *P. falciparum*.[79] Some of these medicinal plants, worthy of further research, include *Coscinium fenestra* (Menispermaceae), *Psidium guajava* (Mytraceae), *Vangueria infausta* (Rubiaceae), *Struchium spargano-phorum* (Asteraceae), *Cinchona succirubra*, *Tithonia diversifolia* (Asteraceae), *Cedrela odorata* (Meliaceae), and *Pycnanthus angolensis* (Myristicaceae).[80] Traditional remedies of Kenya, which include *Vernonia lasiopus* (Asteraceae), *Rhamnus prinoides* (Rhamnaceae), and *Ficus sur* (Moraceae), also show notable antiplasmodium activity. Some, such as *V. brachycalyx* and *V. lasiopus*, showed a stronger effect on resistant *Plasmodium* strains than on nonresistant strains.[77] *V. lasiopus,* which was found to potentiate chloroquine, also showed antiplasmodial activity comparable to *Cinchona*.[77]

Despite the prevalent use of traditional remedies for malaria, with or without pharmaceuticals, there seems to be few organizations dedicated to researching medicinal plant species as home remedies or sources of drugs to treat *Plasmodium* spp. infections. The Research Initiative on Traditional Antimalarial Methods (RITAM), Doctors for Life, Insect Centre of Insect Physiology and Ecology (ICIPE), Action for Natural Medicines (anamed), and the Plant Medicine Innovation Group, however, have dedicated their energies towards the political, economic, and research efforts of medicinal plants and other issues related to health and malaria.

*World Health Organization defines adequate clinical response as the absence of parasitaemia on day 14 or absence of fever (regardless of parasitaemia), without previously meeting the criteria for an early treatment failure.

Racks built for storing **Sweet Annie** (*Artemisia annua)* leaves at Tooro Botanical Gardens in Fort Portal, Uganda. Photo ©2009 Keith Lindsey

Sweet Annie *Artemisia annua.* Photo ©2009 Martin Wall

Below photo: Innocent Balagizi Karhagomba of Bukavu, D R Congo drinking **Sweet Annie** (*Artemisia annua)* tea. Photo ©2009 Keith Lindsey

Many of these researchers believe that medicinal plants have the potential of solving the medical and societal issue of multi-drug resistance.[41,81-86] Anamed's work of training local people to cultivate *A. annua* and then treat malaria with the tea is reported to be successful and has likely led to a significant reduction in deaths. (K. Lindsey, personal communication, April 30, 2009). While some physicians are suggesting combinations of antimalarial drugs to prevent *Plasmodium* spp. resistance,[38,87] the esteemed ethnobotanist James A. Duke—a veteran of malaria ridden areas—suggests that the use of teas or ethanolic extracts of *A. annua*, with its 9 different antimalarial compounds, might prove as efficacious as using multiple costly drugs.[6,28] Duke's suggestion, that extracts of *A. annua* are a natural "cocktail" therapy, could lead to self-reliance therapy that is readily available to impoverished areas where the death rates from malaria are high.

Although *Plasmoidal* recurrence was an issue in one study using a tea of *A. annua*,[88] as previously mentioned, the recrudescence issue could possibly be addressed by a different dosing strategy or extraction method. There are positive studies, at least in the short term, to support the use of an *A. annua* tea for the treatment of malaria.[88,89] In addition, Willcox reports on Chinese studies performed with ethanolic extracts,[90] which resulted in better outcomes than those studies using the teas. The recrudescence rate in the formal clinical trials using the tea of *A. annua* is likely due to the short half-life of artemisinin, which does not kill all stages of *Plasmodium*, and the short duration of treatment in these studies. This is of concern because recrudescence is a risk for resistance. On the other hand, de Ridder et al comment that *A. annua's* traditional use in China for 2000 years for fevers is apparently without the emergence of resistance.[91] Another option to avoid recrudescence might entail combining *A. annua* with *Cinchona,* or other medicinal plants, which have constituents with an extended half-life.

Considering the number of plant extracts that have shown activity against *Plasmodium* spp. and the research that has suggested promising results of some traditional remedies, it seems unlikely that there would not be more species that could be explored. Given that effective medicinal plant extracts could shift the benefit:cost ratio from dollars to pennies, and that many known antimalarial plants, including *A. annua,* grow prolifically in tropical equatorial climates, this could significantly change the societal and economic burden of disease in many parts of the world. In addition, properly planned cottage industries of producing plant-based remedies for the treatment of malaria and other disorders could generate income for rural communities. Nevertheless, until enough resources are marked for allowing research on the potential of medicinal plants as a low cost, easily accessible solution, this potential may never be known. It is this author's opinion that if political and economic issues are removed from the labyrinth of malaria treatment, then medicinal plants, often readily available and affordable as opposed to pharmaceuticals, may provide at least a partial solution to one of the planet's leading causes of mortality.

Opportunity for Pharmaceutical Companies

Unfortunately, most multinational pharmaceutical organizations have down-scaled, or terminated, their natural products operations. Basso points out that this is in spite of natural products having between a 25-50% share of the top-selling 35 ethical drugs from 2000-2003.[80] Newman reports that between 1981-2002, 74% of drugs approved for cancer therapy were either natural products or based on natural products.[92] Of 119 chemical compounds extracted and isolated from plants to make conventional drugs, an impressive 74% have the same or related use as the indigenous cultures that use them.[93] Thus, it is obvious that, besides providing important drug leads, natural products exploration and the respectful observation of people that still rely on plants as medicine have much to offer, including economic incentive for pharmaceutical companies.

But modern pharmaceutics effectively severed the connection between plants, foods, and medicines during the 20th century journey in search for disease-curing silver bullets. The abandonment of searching natural products for drug leads has been accompanied by an inexorable rise in the cost of generating new drugs. Such methods as high-throughput screening have been reported as having not had a significant impact on the derivation of new drugs.[94] Random searches through combinatorial libraries, which are typically not based on biologically relevant properties, according to one estimate, lead to hits at a rate of 1:10,000.[95,96] Conversely, combinatorial libraries based on natural products—compounds that, by default, have been *selected for biological activity* through the high-throughput screening of the evolutionary process—increase the likelihood of finding active compounds.[97] Similarly, ethnobotanical leads have yielded positive activity in the order of 2 to 5 times higher than random screening.[98] Such statistics indicate that an obvious source of new drug discovery lies in natural products.[99] It seems quite likely that the increasing cost of generating new-to-nature molecules will generate a gap in medical care that will reconnect plants and human health at a new level of technological sophistication.[100]

> There are 1,277 plant species from 160 families listed that have been used to treat malaria.

Current data leads away from the use of single compounds to treat infectious disease such as malaria and suggests that combinations of antimalarials that have different modes of activity will reduce the chance of plasmodial resistance.[38] In spite of this research, there still exists a strong bias for reductionistic pharmacological models—structure- and function-based studies based on isolated compounds perturbing single targets. However, recently a number of research groups are screening compounds that stick to several targets and some are attempting to engineer "promiscuous drugs."[101] But this is a high tech, expensive solution that ignores the currently existing options of specific medicinal plant extractions, which are often overlooked because they contain promiscuous compounds. If science in the 21st century is to truly advance beyond drugs that temporarily cure, yet later induce microbial resistance, the public, as well as the scientific establishment, must actively acknowledge and support research—both theoretical and applied—utilizing network pharmacology models and the multi-constituent properties of indigenous plants, rather than single-constituent pharmaceuticals.

Furthermore, large pharmaceutical companies have often focused research efforts exclusively on generating drugs that target conditions of wealthy, developed countries, while neglecting the needy in poverty-stricken countries, who are in need of life-saving drugs.[80] More effort should be made by the pharmaceutical industry to address the healthcare problems of poverty-stricken areas. Fortunately, recent efforts by non-governmental organizations (NGOs), nonprofits, and other non-commercial entities have

stepped into the area to fill the development gap. In addition, traditional healers and modern phytotherapists, who have provided a lifetime of work observing the effects of medicinal plant extracts on disease processes, perpetuate the knowledge of medicinal plant effects. These practitioners' noteworthy efforts are often in the face of considerable resistance from much of the medical establishment as well as the social fabric of industrialized nations.

A Call to Action

Comprehensive evaluations of medicinal plants are urgently needed before more plant species are lost and knowledge of specific traditional medicines becomes irretrievable. While the study of a medicinal plant and its many components—some of them unidentified or having unknown properties—is theoretically, economically, and technically challenging, it should not be abandoned for sake of investigative expediency. Research into the multi-component nature of medicinal plant remedies offers a segue way into more complex therapeutics.[34] Thus, the issue of using herbal remedies to alleviate human suffering is not one of merely assessing efficacy and safety,[1] but a matter of the medical community's struggle to understand a pharmacological paradigm that embraces the complexity of bio-molecular networks.

Sweet Annie *Artemisia annua*. Photo ©2009 Martin Wall

Changing research perspectives are leading to models that allow the observation of multiple perturbations of biological networks, in addition to multiple targets. This perceptual shift, coupled with the latest pharmacological models based on systems biology, build a paradigm in which multicomponent remedies, such as medicinal plants, are recognized as sophisticated pharmacological agents. Moreover, these multicomponent remedies may offer improved efficacy and safety over isolated silver bullets.[43,102]

Implementation of network pharmacological models, which would lead to more complex therapeutic agents, could result in delayed antimicrobial resistance, decreased infectious morbidity, and less healthcare expenditures. But certain challenges have held drug therapeutics in the simplistic model that encourages the search for silver bullets. One obstacle, a limited collection of analytic tools, has been solved with the newest generation of high-tech analytical tools. Microarrays and related technologies are now economically feasible to the point that running hundreds of arrays are possible. Such an approach will demand more statistical, mathematically, and computational prowess. But if successful, this could generate improved therapeutics based on patient specific treatments and dietary guidelines, resulting in less human suffering and decreased economic burden. A second obstacle, a clashing of philosophies, is in the process of resolving. Ohno and collegues suggest that further progress will be made when all parties involved give up their subjective certainty and allow unbiased and more methodologically relevant investigations of medicinal plant species.[37]

After a hundred years of technological innovation, plants are still the primary source of leads for pharmacologically active compounds. The United Nations Convention on Biological Diversity takes the noteworthy stance that evolution has been selecting and perfecting diverse bioactive molecules for millions of years.[103] The evolution of the science of pharmacology is likely to grow considerably beyond the current tenants of isolation, selectivity, and potency if it takes a cue from the 300 million years of plant evolution that have perfected a complex chemical means of defense against microbes and other predators. The study of phytochemical defense offers an opportunity to expand the foundational philosophy and techniques of the search for new drugs: They may best be utilized, not as expensively manufactured silver bullets hitting a single target, but as multi-component, broad-spectrum, pleiotropic molecular cocktails interfacing with cellular networks. This natural technology has been harnessed by traditional cultures for many centuries.

It is a scientific imperative for the progress of medicine that the time-tested methods of traditional medicine and the hi-tech modern pharmaceutical approaches coalesce. Both traditional and conventional healthcare systems seek to alleviate human suffering, both systems have merit, and both systems provide therapeutic options. All parties must learn to stretch pharmacological principles, beyond simplistic modeling and economic gain, to therapeutics based on improving the human condition. We must not let prejudice against therapeutics that are complex and not fully understood impede the use of life-saving remedies. Furthermore, where plant species intersect with medicine, we must keep an eye towards species preservation, sustainability, and the ethics of interfacing with traditional cultures. HG

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References

1. Borisy AA, Elliott PJ, Hurst NW, et al. Systematic discovery of multicomponent therapeutics. *Proc Natl Acad Sci U S A.* 2003;100(13):7977-7982.
2. Drews J. Drug discovery: a historical perspective. *Science.* 2000;287(5460):1960-1964.
3. Bruneton J. *Pharmacognosy Phytochemistry Medicinal Plants*. Paris: Lavoisier; 1995.
4. Huxtable RJ, Schwarz SKW. The isolation of morphine--first principles in science and ethics. *Mol. Interv.* 2001;1(4):189-191.

5. Jarcho S, Torti F. *Quinine's predecessor : Francesco Torti and the Early History of Cinchona*. Baltimore: Johns Hopkins University Press; 1993.
6. Yarnell E, Abascal K. Botanical treatment and prevention of malaria, part 2 selected botanicals. *Alternative and Complementary Therapies.* 2004:277-284.
7. Singer CJ, Underwood EA. *A Short History of Medicine*. 2d ed. Oxford: Clarendon Press; 1962.
8. Sneader W. The discovery of aspirin: a reappraisal. *BMJ.* 2000;321(7276):1591-1594.
9. Koch-Weser J, Schechter PJ. Schmiedeberg in Strassburg 1872-1918: the making of modern pharmacology. *Life Sci.*1978;22(13-15):1361-1371.
10. Lafont O. [Clarification on publications concerning the synthesis of acetylsalicylic acid]. *Rev Hist Pharm (Paris).* 1996;43(310):269-273.
11. Vickers A. Botanical medicines for the treatment of cancer: rationale, overview of current data, and methodological considerations for phase I and II trials. *Cancer Invest.* 2002;20(7-8):1069-1079.
12. Lansbury PT. Back to the future: the 'old-fashioned' way to new medications for neurodegeneration. *Nat Rev Neurosc.* 2004;5:S51-S57.
13. Nussbaum RL, Ellis CE. Alzheimer's disease and Parkinson's disease. *N Engl J Med.* 2003;348(14):1356-1364.
14. Institute of Medicine. *Preventing Medication Errors: Quality Chasm Series.* Washington, DC: Institute of Medicine of the National Academies; 2006.
15. Lasser KE, Allen PD, Woolhandler SJ, Himmelstein DU, Wolfe SM, Bor DH. Timing of new black box warnings and withdrawals for prescription medications. *JAMA* 2002;287(17):2215-2220.
16. Ernst E. Herbal medicines put into context. *BMJ.* 2003;327:881-882.
17. Kalow W, Tang BK. Caffeine as a metabolic probe: exploration of the enzyme-inducing effect of cigarette smoking. *Clin Pharmacol Ther.* 1991;49(1):44-48.
18. Rajapakse N, Silva E, Kortenkamp A. Combining xenoestrogens at levels below individual no-observed-effect concentrations dramatically enhances steroid hormone action. *Environ Health Perspect.* 2002;110(9):917-921.
19. Cech NB. Rigorous science for the study of holistic herbal medicine: Challenges, pitfalls, and the role of mass spectrometry. Paper presented at: 226th ACS National Meeting; September 7-11, 2003; New York, NY.
20. Gong F, Liang YZ, Xie PS, Chau FT. Information theory applied to chromatographic fingerprint of herbal medicine for quality control. *J Chromatogr A.* 2003;1002(1-2):25-40.
21. Liang YZ, Xie PS, Chan K. Quality control of herbal medicines. *J Chromatogr B Analyt Technol Biomed Life Sci.* 2004;812(1-2):53-70.
22. Gallagher R, Appenzeller T. Beyond Reductionism. *Science.* 1999;284(5411):79.
23. Messina M, Lampe JW, Birt DF, et al. Reductionism and the narrowing nutrition perspective: time for reevaluation and emphasis on food synergy. *J Am Diet Assoc.* 2001;101(12):1416-1419.
24. Duke J. Dr. Duke's Phytochemical and Ethnobotanical Databases. *Artemisia annua*. Accessed July 28, 2005.
25. Bilia AR, Lazari D, Messori L, Taglioli V, Temperini C, Vincieri FF. Simple and rapid physico-chemical methods to examine action of antimalarial drugs with hemin: its application to Artemisia annua constituents. *Life Sci.* 2002;70(7):769-778.
26. Elford BC, Roberts MF, Phillipson JD, Wilson RJ. Potentiation of the antimalarial activity of qinghaosu by methoxylated flavones. *Trans R Soc Trop Med Hyg.* 1987;81(3):434-436.
27. Stermitz FR, Scriven LN, Tegos G, Lewis K. Two flavonols from Artemisa annua which potentiate the activity of berberine and norfloxacin against a resistant strain of Staphylococcus aureus. *Planta Med.* 2002;68(12):1140-1141.
28. Spelman K, Duke JA, Bogenschutz-Godwin MJ. The Synergy Principle in Plants, Pathogens, Insects, Herbivores and Humans. In: Kaufman PB, ed. *Natural products from plants.* Vol 2e. Boca Raton, Fla.: CRC Press; 2006:475-501.
29. Uhlemann AC, McGready R, Ashley EA, et al. Intrahost selection of Plasmodium falciparum pfmdr1 alleles after antimalarial treatment on the northwestern border of Thailand. *J Infect Dis.* 2007;195(1):134-141.
30. Duraisingh MT, Cowman AF. Contribution of the pfmdr1 gene to antimalarial drug-resistance. *Acta Trop.* 2005;94(3):181-190.
31. Colombi M, Guffanti A, Alietti A, et al. OPP-EBV-CAD regimen as salvage treatment in advanced refractory or resistant multiple myeloma. *Leuk Lymphoma.* 2000;40(1-2):87-94.
32. Duke J. Dr. Duke's Phytochemical and Ethnobotanical Databases. *Cinchona* spp. Accessed January 21, 2006.
33. Most H. Clinical Trials of Antimalarial Drugs. In: United States. Army Medical Service., Coates JB, Anderson RS, Havens WP, eds. *Internal medicine in World War II.* Vol II. Washington: Office of the Surgeon General, Dept. of the Army; 1961:525-598.
34. Druilhe P, Brandicourt O, Chongsuphajaisiddhi T, Berthe J. Activity of a combination of three cinchona bark alkaloids against Plasmodium falciparum in vitro. *Antimicrob Agents Chemother.* 1988;32(2):250-254.
35. Levy SB. *The antibiotic paradox: how the misuse of antibiotics destroys their curative power*. 2nd ed. Cambridge, MA: Perseus Pub.; 2002.
36. Nosten F, van Vugt M, Price R, et al. Effects of artesunate-mefloquine combination on incidence of Plasmodium falciparum malaria and mefloquine resistance in western Thailand: a prospective study. *Lancet.* 2000;356(9226):297-302.
37. Ohno T, Kita M, Yamaoka Y, et al. Antimicrobial activity of essential oils against Helicobacter pylori. *Helicobacter.* 2003;8(3):207-215.
38. White N. Antimalarial drug resistance and combination chemotherapy. *Philos Trans R Soc Lond B.* 1999;354(1384):739-749.
39. Tegos G, Stermitz FR, Lomovskaya O, Lewis K. Multidrug pump inhibitors uncover remarkable activity of plant antimicrobials. *Antimicrob Agents Chemother.* 2002;46(10):3133-3141.
40. Stermitz FR, Cashman KK, Halligan KM, Morel C, Tegos GP, Lewis K. Polyacylated Neohesperidosides From Germanium caespitosum: Bacterial Multidrug Pump Inhibitors. *Bioorg Med Chem Lett.* 2003;13:1915-1918.
41. Poitrineau K, Brown SP, E HM. Defence against multiple enemies. *J Evol Biol.* 2003;16(6):1319-1327.
42. Cavalli A, Bolognesi ML, Minarini A, et al. Multi-target-directed ligands to combat neurodegenerative diseases. *J Med Chem.* 2008;51(3):347-372.
43. Ágoston V, Csermely P, Pongor S. Multiple, weak hits confuse complex systems: A transcriptional regulatory network as an example. *Phys Rev E.* 2005;71(5):1-8.
44. Koehn FE, Carter GT. The evolving role of natural products in drug discovery. *Nat Rev Drug Discov.* 2005;4(3):206-220.
45. Brewer S. The relationship between natural products and synthetic chemistry in the discovery process. In: Wrigley SK, ed. *Biodiversity: new leads for the pharmaceutical and agrochemical industries.* Vol 257. Cambridge: Royal Society of Chemistry; 2000:59-65.
46. Papadopoulou K, Melton RE, Leggett M, Daniels MJ, Osbourn AE. Compromised disease resistance in saponin-deficient plants. *Proc Natl Acad Sci U S A.* 1999;96(22):12923-12928.
47. Wu H, Haig T, Pratley J, Lemerle D, An M. Biochemical basis for wheat seedling allelopathy on the suppression of annual ryegrass (Lolium rigidum). *J Agric Food Chem.* 2002;50(16):4567-4571.
48. Spelman K. Ecological Pharmacology: Humans and plants coherently couple through phytochemistry. *UnifiedEnergetics.* 2006;2(5):40-45.
49. Butterweck V, Lieflander-Wulf U, Winterhoff H, Nahrstedt A. Plasma levels of hypericin in presence of procyanidin B2 and hyperoside: a pharmacokinetic study in rats. *Planta Med.* 2003;69(3):189-192.
50. Rath K, Taxis K, Walz G, Gleiter CH, Li S-M, Heide L. Parmacokinetics study of artemsinin after oral intake of a traditional preparation of Artemisia annua L. (annual wormwood). *Am J Trop Med Hyg.* 2004;70(2):128-132.
51. Wynne-Edwards KE. Evolutionary biology of plant defenses against herbivory and their predictive implications for endocrine disruptor susceptibility in vertebrates. *Environ Health Perspect.* 2001;109(5):443-448.
52. Ehrlich PR, Raven PH. Butterflies and plants: A study in coevolution. *Evolution.* 1964;18(4):586-608.
53. Ideker T, Lauffenburger D. Building with a scaffold: emerging strategies for high- to low-level cellular modeling. *Trends Biotechnol.* 2003;21(6):255.
54. Nikolsky Y, Nikolskaya T, Bugrim A. Biological networks and analysis of experimental data in drug discovery. *Drug Discov Today.* 2005;10(9):653.
55. Gerard C, Rollins BJ. Chemokines and disease. *Nat Immunol.* 2001;2(2):108-115.
56. Cooper RS. Gene-environment interactions and the etiology of common complex disease. *Ann Intern Med.* 2003;139(5 Pt 2):437-440.
57. Jia W, Gao WY, Yan YQ, et al. The rediscovery of ancient Chinese herbal formulas. *Phytother Res.* 2004;18(8):681-686.
58. Mencher S, Wang L. Promiscuous drugs compared to selective drugs (promiscuity can be a virtue). *BMC Clin Pharmacol.* 2005;5(1):3.

59. Cohen MH, Williams GA, Sridhara R, et al. United States Food and Drug Administration Drug Approval Summary: Gefitinib (ZD1839; Iressa) Tablets. *Clin Cancer Res.* 2004;10(4):1212-1218.
60. Csermely P, Agoston V, Pongor S. The efficiency of multi-target drugs: the network approach might help drug design. *Trends Pharmacol Sci.* 2005;26(4):178-182.
61. Hudson J, Altamirano M. The application of DNA micro-arrays (gene arrays) to the study of herbal medicines. *J Ethnopharmacol.* 2006;108(1):2-15.
62. Chavan P, Joshi K, Patwardhan B. DNA microarrays in herbal drug research. *Evid Based Complement Alternat Med.* 2006;3(4):447-457.
63. Grellier P, Depoix D, Schrevel J, Florent I. Discovery of new targets for antimalarial chemotherapy. *Parasite.* 2008;15(3):219-225.
64. Korenromp EL, Williams BG, Gouws E, Dye C, Snow RW. Measurement of trends in childhood malaria mortality in Africa: an assessment of progress toward targets based on verbal autopsy. *Lancet Infect Dis.* 2003;3(6):349-358.
65. White NJ. Antimalarial drug resistance. *J Clin Invest.* 2004;113(8):1084-1092.
66. Rathod PK, McErlean T, Lee PC. Variations in frequencies of drug resistance in Plasmodium falciparum. *Proc Natl Acad Sci U S A.* 1997;94(17):9389-9393.
67. Jambou R, Legrand E, Niang M, et al. Resistance of Plasmodium falciparum field isolates to in-vitro artemether and point mutations of the SERCA-type PfATPase6. *Lancet.* 2005;366(9501):1960-1963.
68. Krishna S, Woodrow CJ, Staines HM, Haynes RK, Mercereau-Puijalon O. Re-evaluation of how artemisinins work in light of emerging evidence of in vitro resistance. *Trends Mol Med.* 2006;12(5):200-205.
69. Menard D, Matsika-Claquin MD, Djalle D, et al. Association of failures of seven-day courses of artesunate in a non-immune population in Bangui, Central African Republic with decreased sensitivity of Plasmodium falciparum. *Am J Trop Med Hyg.* 2005;73(3):616-621.
70. WHO. *Antimalarial drug combination therapy. Report of a technical consultation.* Geneva, Switzerland: WHO; 2001.
71. Dzator J, Asafu-Adjaye J. A study of malaria care provider choice in Ghana. *Health Policy.* 2004;69(3):389.
72. Vigneron M, Deparis X, Deharo E, Bourdy G. Antimalarial remedies in French Guiana: A knowledge attitudes and practices study. *J Ethnopharmacol.* 2005;98(3):351.
73. Malik EM, Hanafi K, Ali SH, Ahmed ES, Mohamed KA. Treatment-seeking behaviour for malaria in children under five years of age: implication for home management in rural areas with high seasonal transmission in Sudan. *Malaria J.* 2006;5(60).
74. Willcox ML, Bodeker G. Traditional herbal medicines for malaria. *BMJ.* 2004;329(7475):1156-1159.
75. Bora U, Sahu A, Saikia AP, Ryakala VK, Goswami P. Medicinal plants used by the people of Northeast India for curing malaria. *Phytother Res.* 2007;21(8):800-804.
76. Nguyen-Pouplin J, Tran H, Tran H, et al. Antimalarial and cytotoxic activities of ethnopharmacologically selected medicinal plants from South Vietnam. *J Ethnopharmacol.* 2007;109(3):417-427.
77. Muregi FW, Chhabra SC, Njagi EN, et al. Anti-plasmodial activity of some Kenyan medicinal plant extracts singly and in combination with chloroquine. *Phytother Res.* 2004;18(5):379-384.
78. Carraz M, Jossang A, Franetich J-F, et al. A Plant-Derived Morphinan as a Novel Lead Compound Active against Malaria Liver Stages. *PLoS Med.* 2006;3(12):e513.
79. Tran QL, Tezuka Y, Ueda JY, et al. In vitro antiplasmodial activity of antimalarial medicinal plants used in Vietnamese traditional medicine. *J Ethnopharmacol.* 2003;86(2-3):249-252.
80. Basso LA, da Silva LHP, Fett-Neto AG, et al. The use of biodiversity as source of new chemical entities against defined molecular targets for treatment of malaria, tuberculosis, and T-cell mediated diseases - A Review. *Mem Inst Oswaldo Cruz.* 2005;100(6):575-606.
81. Duke JA, Bogenschutz-Godwin MJ. The Synergy Principle at Work in Plants, Pathogens, Insects, Herbivores, and Humans. In: Kaufman PB, ed. *Natural products from plants*. Boca Raton, Fla.: CRC Press; 1999:183-206.
82. Spelman K. Philosophy in phytopharmacology: Ockham's Razor vs. synergy. *J Herbal Pharmacotherapy.* 2005;5(2):31-47.
83. Gilbert B, Alves LF. Synergy in plant medicines. *Curr Med Chem.* 2003;10(1):13-20.
84. Williamson EM. Synergy and other interactions in phytomedicines. *Phytomedicine.* 2001;8(5):401-409.
85. Wagner H. Phytomedicine Research in Germany. *Environ Health Perspect.* 1999;107:779-781.
86. Bland J. Alternative therapies--a moving target. *Altern Ther Health Med.* 2005;11(2):20-22.
87. Chawira AN, Warhurst DC, Robinson BL, Peters W. The effect of combinations of qinghaosu (artemisinin) with standard antimalarial drugs in the suppressive treatment of malaria in mice. *Trans R Soc Trop Med Hyg.* 1987;81(4):554-558.
88. Mueller MS, Runyambo N, Wagner I, Borrmann S, Dietz K, Heide L. Randomized controlled trial of a traditional preparation of Artemisia annua L. (Annual Wormwood) in the treatment of malaria. *Trans R Soc Trop Med Hyg.* 2004;98(5):318-321.
89. Mueller MS, Karhagomba IB, Hirt HM, Wemakor E. The potential of Artemisia annua L. as a locally produced remedy for malaria in the tropics: agricultural, chemical and clinical aspects. *J Ethnopharmacol.* 2000;73(3):487-493.
90. Willcox M. Artemisia species: from traditional medicines to modern antimalarials—and back again. *J Altern Complement Med.* 2009;15(2):101-109.
91. de Ridder S, van der Kooy F, Verpoorte R. Artemisia annua as a self-reliant treatment for malaria in developing countries. *J Ethnopharmacol.* 2008;120(3):302-314.
92. Newman DJ, Cragg GM, Snader KM. Natural products as sources of new drugs over the period 1981-2002. *J Nat Prod.* 2003;66(7):1022-1037.
93. Gurib-Fakim A. Medicinal plants: traditions of yesterday and drugs of tomorrow. *Mol Aspects Med.* 2006;27(1):1-93.
94. Proudfoot JR. Drugs, leads, and drug-likeness: an analysis of some recently launched drugs. *Bioorg Med Chem Lett.* 2002;12(12):1647-1650.
95. Jansen RC. Studying complex biological systems using multifactorial perturbation *Nat Rev Genet.* 2003;4(2):145-152.
96. Martin EJ, Critchlow RE. Beyond mere diversity: tailoring combinatorial libraries for drug discovery. *J Comb Chem.* 1999;1(1):32-45.
97. Brohm D, Metzger S, Bhargava A, Müller O, Lieb F, Waldmann H. Natural products are biologically validated starting points in structural space for compound library development: solid-phase synthesis of dysidiolide-derived phosphatase inhibitors. *Angew Chem Int Ed Engl.* 2002;41(2):307-311.
98. Lewis WH, Elvin-Lewis MP. Basic, quantitative and experimental research phases of future ethnobotany with reference to the medicinal plants of South America. *Ciba Found Symp.* 1994;185:60-72; discussion 72-66.
99. Butler MS. The role of natural product chemistry in drug discovery. *J Nat Prod.* 2004;67(12):2141-2153.
100. Ray SD, Patel N, Shah N, Nagori A, Naqvi A, Stohs SJ. Pre-exposure to a novel nutritional mixture containing a series of phytochemicals prevents acetaminophen-induced programmed and unprogrammed cell deaths by enhancing BCL-XL expression and minimizing oxidative stress in the liver. *Mol Cell Biochem.* 2006; 293(1-2):119-136.
101. Frantz S. Drug discovery: Playing dirty. *Nature.* 2005;437(7061):942-943.
102. Wagner H, Ulrich-Merzenich G. Synergy research: Approaching a new generation of phytopharmaceuticals. *Phytomed.* 2009;doi:10.1016/j.phymed.2008.12.018.
103. Raskin I, Ribnicky DM, Komarnytsky S, et al. Plants and human health in the twenty-first century. *Trends Biotechnol.* 2002;20(12):522-531.

Sweet Annie *Artemisia annua*. Photo ©2009 Martin Wall

Blood of the DRAGON

The Sustainable Harvest and Replanting of the *Croton lechleri* Tree

By Kelly Saxton Lindner

Croton lechleri tree.
Photo ©2009 Ricarda Riina

Many people indigenous to the Peruvian Amazon lack options when it comes to employment. Some have to travel 6 hours by powerboat to sell fish to the nearest town, which can occasionally result in the fish spoiling before they arrive at their destination. Some Peruvians have few agricultural crops that they can farm to financially support their families other than coca (Erythroxylum coca, Erythroxylaceae)—the leaves of which are traditionally chewed in the highlands as a way to increase energy and prevent altitude sickness and sometimes used to produce cocaine. Because of such limited work opportunities, some Peruvians find it difficult to pay the registration fees required to enroll their children into school and purchase even the most minimal of school supplies, such as pencils and books. Some are also unable to build hospitals, high schools, soccer stadiums, and other things that could improve their communities.

However, several communities in Peru are now able to obtain necessities by working with Napo Pharmaceuticals Inc. of San Francisco, California.* These communities help to sustainably harvest the latex of a tree in the Peruvian rainforest, which Napo then turns into a drug that has been shown to be effective in treating various forms of diarrhea (including cholera- and HIV-related diarrhea). This drug may be able to successfully treat these diseases on a global level in the near future.

What is the Blood of the Dragon?

Sangre de drago or "dragon's blood"—also referred to as *sangre de grado*—is the red latex found in a number of tree species from the genus *Croton* (Euphorbiaceae), common in the lower montane and rainforest basin regions of several Andean countries (Colombia, Ecuador, Peru, and Bolivia), as well as northern Argentina and southeastern Brazil.[1] Although many species of trees from the family Euphorbiaceae produce a milky white sap, *Croton lechleri* and other species found in Mexico, Central America, and tropical and subtropical South America are all characterized by their viscous red latex.

The latex of *C. lechleri*—which is dark red when taken from mature trees but lighter in color, sometimes orange, within younger trees[2]—has been used by healers for centuries to treat diarrhea and various ailments, including gastrointestinal problems, respiratory infections, skin infections, mouth disturbances, wounds, and herpes simplex.[1,2,3,4] The traditional dose of latex is 5–10 drops applied topically over lesions or mixed in water, juice, milk, or alcohol and ingested 1 to 3 times a day for up to 3 weeks.[3] There are no known adverse events related to the internal use of the latex,

*Napo's name derives from a major tributary of the Amazon, which flows out of the province of Napo in Ecuador and joins the Amazon downstream from Iquitos, the former rubber-tapping center in Peru.

Left photo: A *Croton lechleri* tree used by Napo for reforestation in the buffer zone near Parque National Cordillera Azul in Northern Peru. Several thousand small seedlings cover the forest floor. The area is prepared to maximize production of seedlings as part of natural forest regeneration and reforestation process. Photo ©2009 Steven R. King

and because of the tree's wide distribution and the historically recognized effectiveness of its sap, it's one of the most common traditional medicines in Latin America.

Napo has been researching and working with *C. lechleri* for many years, and its intellectual property (obtained from the now-defunct Shaman Pharmaceuticals, which had employed an ethnobotanical approach to drug discovery) goes back over 20 years. Napo has endeavored to find the best growing conditions for *C. lechleri*, the most effective ways of sustainably harvesting and replanting the tree, the most productive methods for collecting the latex, and the best ways to efficiently employ local indigenous people, who are in need of adequate income. (Most earn a relatively minuscule amount of money compared to wages in developed countries). Over the last 2 decades, more than 30 studies on the biology, ecology, distribution, economics, and reforestation have been conducted by scientists in different Andean countries regarding *Croton* trees. Napo selected *C. lechleri* because of its biological activity and because it is a well known and widespread pioneer tree species.[3] Studies have found that in rainforest areas of the Andean Amazon region (at a general altitude of 300–700 meters), there's an average density of 3 to 10 of these trees per hectare. The general altitude range of the tree is 300–2,000 meters.

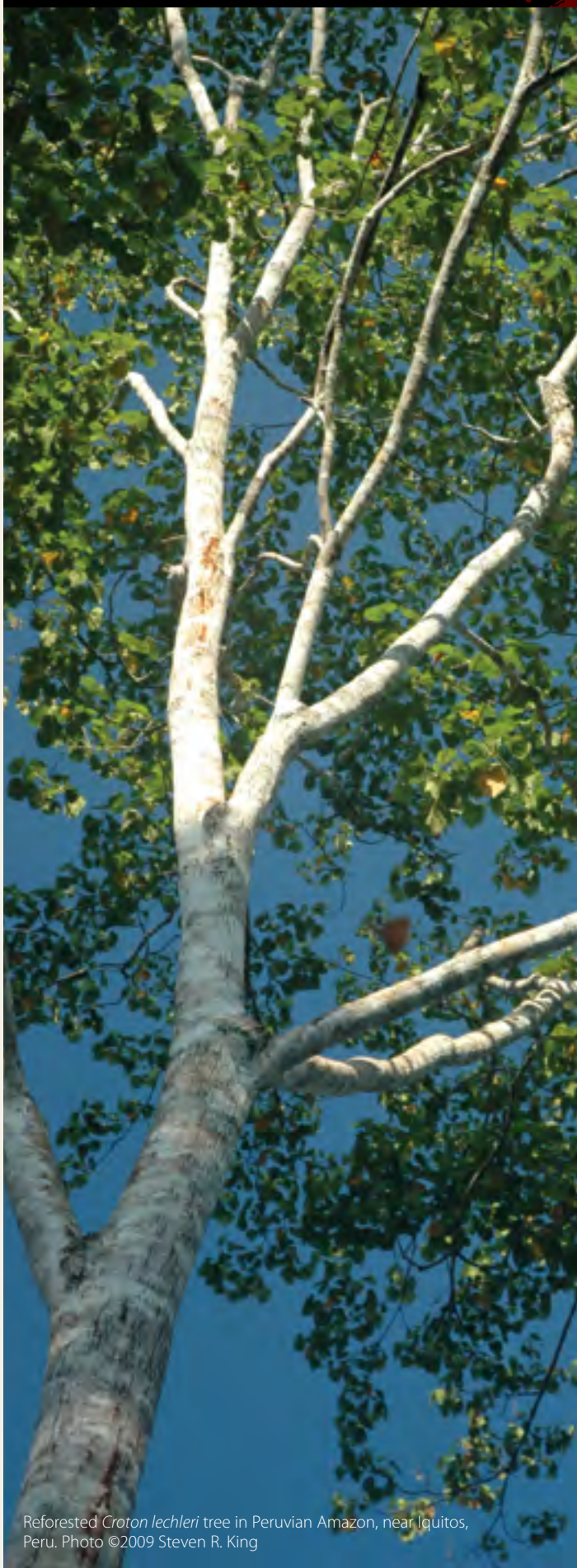
Napo has used the tree's latex to create a drug able to combat HIV/AIDS-related diarrhea, severe cholera-induced fluid loss, traveler's diarrhea, and diarrhea-predominant irritable bowel syndrome (IBS). This drug, made with a highly purified proanthocyanidin oligomer called crofelemer, which Napo has isolated from the *C. lechleri*'s latex, has shown overall effectiveness in approximately 1,700 randomized patients in double-blind, placebo-controlled, clinical trials, with no apparent adverse effects, even in patients as young as 3 months of age.[2,3] There have been many pre-clinical and clinical trials conducted on crofelemer, and Napo has received fast-track status from the US Food and Drug Administration (FDA) for its development of crofelemer for its IBS and HIV indications.[5,6,7,8,9]

Napo has entered into an agreement with Direct Relief International (DRI), a medical assistance and disaster relief agency based in Santa Barbara, California, to provide the drug at cost to children afflicted with cholera and diarrheal diseases of developing countries once its safety and efficacy has been fully established in children.[10] Napo also plans to collaborate with the International Centre for Diarrhoeal Disease Research (ICDDR) in Bangladesh for the same purpose; Napo has already collaborated with ICDDR on studies treating adult cholera patients with crofelemer.

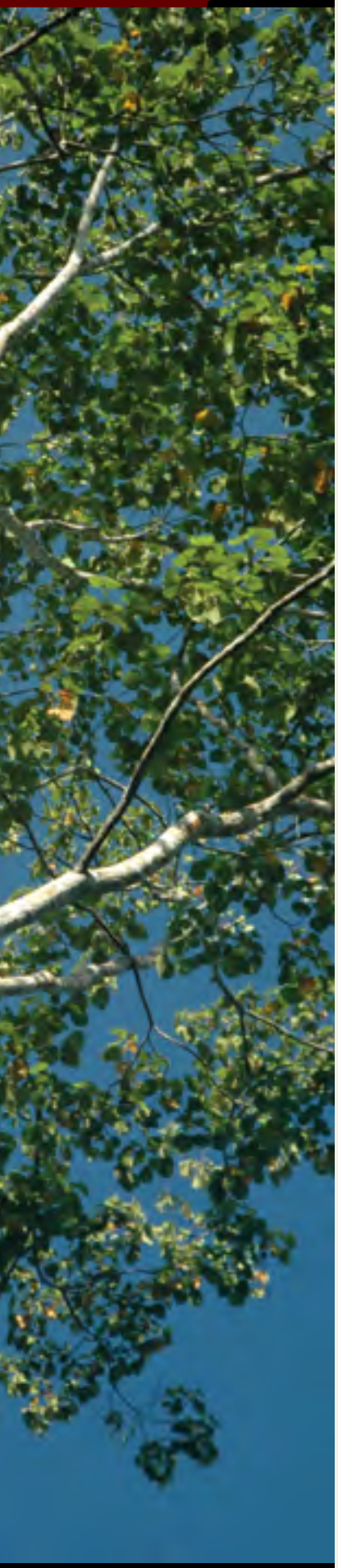
Cholera is an infection that causes severe diarrhea, which leads to dehydration and can cause death, sometimes within the first 6–18 hours of infection.[11] Every year approximately 2.5 million children under the age of 5 die due to dehydration caused by various forms of diarrhea, such as cholera. This occurs primarily in developing countries, and it stems from such causes as limited access to clean water. Since crofelemer has an anti-secretory mechanism of action that blocks chloride ions and subsequent water secretion, this keeps the gut from losing too much excess fluid and can prevent dehydration-related death caused by cholera or HIV-related diarrhea.[2,11,12] In fact, it improves bowel function in many conditions that involve prominent secretory diarrhea. Crofelemer's effectiveness on diarrhea-predominant IBS is still being evaluated, but it has been shown to reduce pain in this condition, which is one of the primary complaints of those who suffer from IBS.[13] Crofelemer also acts locally on the gastrointestinal tract, instead of being absorbed into the body, which gives it a higher level of efficacy than other treatments and limits the potential for adverse effects.[2,12] Most antidiarrheal agents paralyze or slow processes in the gut, causing constipation, and cannot be taken for more than 24 hours.

Tapping versus Felling

Researchers at Napo originally hoped that *C. lechleri* trees could be harvested much like the rubber tree (*Hevea brasilensis*, Euphorbiaceae), through the use of a machete or tapping tools to tap or cut the bark and drain



Reforested *Croton lechleri* tree in Peruvian Amazon, near Iquitos, Peru. Photo ©2009 Steven R. King



There are no known adverse events related to the internal use of the latex, and because of the tree's wide distribution and the historically recognized effectiveness of its sap, it's one of the most common traditional medicines in Latin America.

Reforestation of wild collected *Croton lechleri* sapling in secondary forest near Huallaga River in Peruvian Amazon.
Photo ©2009 Steven R. King

desired latex while leaving the tree standing and healthy.[3] The *Hevea* species can be tapped repeatedly for latex without damage to the tree. *Croton lechleri*, however, demonstrated a high mortality rate when this tapping method was implemented and did not yield much latex.[14]

To understand why their efforts toward tapping *C. lechleri* were not successful, employees of what is now Napo sent bark samples to the Royal Botanic Gardens in Kew, England, where Paula Rudall, PhD, head of the micromorphology section at Kew, examined the differences between *Croton* and *Hevea* bark. Dr. Rudall found that the laticifers, which produce the latex in the *Hevea* trees, are articulated and regenerate when cut. Species such as chicle (*Manikara zapota*, Sapotaceae), which is used to make chewing gum, and jelutong (*Dyera costulata*, Apocynaceae), which has a lightweight wood used in many things like pencils, are also articulated, meaning that they can be tapped repeatedly without destruction to the trees.[3] The laticifers in *Croton* species are non-articulated and do not regenerate when cut. Dr. Rudall concluded that this morphological difference is what causes the *Croton* trees to "go dry" faster when tapped and causes the high mortality rates in the trees.

Therefore, it was decided that it was actually more sustainable to cut down the whole tree and drain all available latex at once, which creates a much higher yield of latex than tapping, and then replant a new tree in its place. The fact that *C. lechleri* has been documented to be a fast growing pioneer tree species also greatly influenced this decision.

The Harvesting of *Sangre de drago*

Local people with experience harvesting *C. lechleri* latex taught the company that the best yield of latex is obtained early in the morning (although observations show that harvesting during the full moon actually tends to yield the most latex). Workers typically harvest during the hours of 4:30 am and 9:30 am, since too much heat from the sun can cause the tree to lose water and yield less latex. Rainwater can also dilute the latex, so dry weather conditions are recommended. Through years of research, collectors have determined that it is best to harvest trees that have reached their 6th or 7th year or older and are about 27 cm (10–11 inches) in diameter at a minimum, as this increases the yield of latex.[4] If harvested in this manner, these trees can consistently yield an average of 3 to 4 liters of latex per tree.

To perform the harvesting, first a slash is cut into the tree's bark to make sure that the tree has latex, as sometimes a tree is too young or damaged to produce. The tree is left standing if there is very little or no latex. If the tree has sufficient latex, it is then felled onto 2 precut perpendicularly laid logs and propped so that the base of the tree is higher than the top. Full shallow circles are cut into the bark 1 cm wide, every 15 cm, with a special knife called a *rasqueta*, which looks similar to a hooked or bent machete. Plastic containers are placed under each cut to catch the latex as it drains.

Napo continues to refine its knowledge of the best ways to harvest. In fact, Mario Pariona, a conservationist who works with one of Napo's 3 harvesting

Latex of *Sangre de drago*. Photo ©2009 Michael Powers

Young *Croton lechleri* trees growing as a result of natural germination in Chimbana, Peru. Photo ©2009 Steven R. King

"The *Croton* tree has managed to be a source not only of medicine but also a source of jobs for indigenous people and farmers in the rainforest of the Amazonia in Peru"

and replanting subsidiaries in Peru, says that each day he and others go into the Andean or Amazonian towns to find out more about the best harvesting conditions from locals. For instance, they attempt to discern "how to select the trees with the best contents of latex, how to define the suitable diameter of the trees for the harvest, the best seasons for the extractions, and moon phases and hours of the day for the best results," said Pariona (written communication, July 15, 2009).

Cesar Gregorio Lozano Diaz, who oversees 4 primary harvesting and reforestation sites for Napo, provides daily breakfast, lunch, and dinner to his employees, in addition to lodging when they are harvesting and replanting far from home, roofing for their homes when they need it, and registration fees for their children to attend school. Each site employs between 25 to 30 workers and can involve up to 69 families at times.

"It's a whole community endeavor, and I am pleased and proud that they have an appreciation for what they're doing and take great pride in it," said Lozano (oral communication translated by S. King, July 28, 2009). "They know what they're doing is helping the world." Lozano added, "The Peruvian Amazon jungle is beautiful, rich, and unique with some of the best biodiversity in the world. Like the lungs of the planet, the Peruvian Amazon absorbs carbon and protects the world." Besides its use in creating a useful drug, Napo hopes that *C. lechleri* may be planted and harvested in many tropical areas all over the world, which may aid in the removal of carbon dioxide (CO2) from the atmosphere.

Lozano's whole family is involved in this business. His daughter works out all the logistics of the paperwork, his brother helps translate paperwork, and his wife supports and helps with everything Lozano does, including cooking for the workers when they need a meal.

"The *Croton* tree has managed to be a source not only of medicine but also a source of jobs for indigenous people and farmers in the rainforest of the Amazonia in Peru," said Dina Límaco, who also oversees harvesting and replanting sites for Napo. The communities of the workers she oversees have been provided with assistance in building new schools, a football stadium, and a health center, where there is a permanent nurse and a doctor who visits weekly (oral communication, July 17, 2009). Límaco also helps with the little things: "Most of the time they ask for occidental medicine [conventional Western medicine], implements to play football, small motors for their boats, and books and

different things for their schools. But the most important thing we offer them is jobs. This provides a better way of living for them and their children."

Límaco also noted that the workers are paid according to the appropriate standard set by the Ministry of Work in Peru.

Reforestation and Agroforestry

Napo has assisted in the planting of 317,000 *C. lechleri* trees so far and has established a ratio of 3 to 5 trees planted for every tree harvested.[3]

Lozano trains and assists workers in building temporary greenhouses, where some *C. lechleri* saplings stay for a few months before being transplanted into an area cleared of weeds. The trees are planted 4 meters apart and checked every 3 months for the first 2 years to make sure no weeds or any plants are crowding them. Once the trees reach 10 meters in height, they are left as is and drained for latex at age 6 or 7 (written communication from C. Lozano, July 20, 2009). The trees grow at a rapid rate of 3 to 4 meters per year, especially during their first 2 years.[3,14,15]

Heart-shaped leaf of rapidly growing, reforested *Croton lechleri*.
Photo ©2009 Steven R. King

These trees grow naturally in a large variety of soils, altitudes, and climates, though they tend to occur most frequently near rivers and streams.[14,15] They also easily propagate through natural germination. After the tree's 5th year, it produces thousands of seeds, for the germination of new *C. lechleri* seedlings. Sometimes those who reforest need to space out these saplings after a certain age for the best results, but other than that, this type of reforestation requires little maintenance.

"Basically you've got a tree that is naturally extremely widespread, abundant, and that grows 1 foot a month in the first 2 years and can easily create other trees," said Steven R. King, PhD, vice-president of sustainable supply at Napo (oral communication, June 9, 2009), "I wish I could take credit for this, but it was nature that created *Croton lechleri*."

In 1998, some employees of Napo were involved in publishing an educational manual about sustainably harvesting and replanting *C. lechleri*, of which 5,000 free copies were distributed across Latin America. "El Manejo Sostenible de Sangre de Drago o Sangre de Grado Material Educativo" (The Sustainable Harvesting of the Blood of the Dragon for Commercialization) was reproduced by the Ministry of Agriculture in Peru, which also distributed thousands of copies throughout Peru.[14,15] The Agrarian Development Agency of Loreto, Peru, took this even further by creating its own manual, "Cultivo de Sangre de Grado, " which was very close to a reproduction itself.

"They pretty much took one entire section of our manual and reproduced it with very little difference," said Dr. King, with a laugh. "It was the best example of positive piracy I've ever seen."

In 1999, a book was published in Spanish explaining the harvesting as well as the value of the tree and its latex: *Dessarrollando Nuestra Diversidad Biocultural: Sangre de Grado y el Reto de su Produccsión sustentable en el Perú* (*Improve our Biocultural Diversity: Blood of Dragon and the Challenge of its Sustainable Production in Peru*).[16] This book was written and edited by Peruvian forester Elsa Meza, who has done extensive work with *C. lechleri* and indigenous communities in Peru over the past 15 years.

C. lechleri is considered a great candidate for agroforestry, since it grows well with bananas, oranges, coffee, etc., serves as a windbreaker, provides shade, increases the nutrients in the soil, and helps prevent erosion.[3] It can also coexist with livestock once it reaches 5 feet in height, which makes it viable for silvopastoral systems, which integrate trees with forage and livestock.

Napo has also replanted 170,000 trees in a buffer zone right outside of the *Parque Nacional Cordillera Azul* (National Park of the Blue Mountain Range) in Chimbana, Peru.[3] Buffer zones are areas that have income-generating activities, such as the harvesting or replanting of *C. lechleri* for Napo, which deter people from reducing the rich diversity of a national park by venturing inside to hunt, collect plants, or harvest primary trees to generate income.

Quality Control of *Sangre de Drago* and Distribution

After the harvesting, the latex is poured into 10-gallon containers and transported by boat or car to the quality control/trans-shipment site of the Napo subsidiary companies in Iquitos, Yurimaguas, Lima, and other Peruvian cities. There, it is inspected by a supervisor and, if acceptable, funneled into 55-gallon drums through a filter that will catch any extraneous plant material that might have been accidentally acquired during harvesting.

Collection by volunteers of *Croton lechleri* seedlings for transplant to a temporary nursery for reforestation work. Photo ©2009 Michael Powers

Croton lechleri trees planted in a secondary forest as reforestation work in Northern Peruvian Amazon. Photo ©2009 Michael Powers

"It's a whole community endeavor, and I am pleased and proud that they have an appreciation for what they're doing and take great pride in it."

Members of a local community that is collaborating in reforestation process near Chimbana, Peru. Photo ©2009 Steven R. King

The drums are then sealed, and the raw latex is shipped to Glenmark Pharmaceuticals Ltd., one of Napo's partners in Mumbai, India. Extraction and partial manufacturing in Peru is being planned once the crofelemer has achieved US FDA approval.

The latex of *C. lechleri* has a distinctive odor, color, and texture, so it is difficult for anything to masquerade as *sangre de drago*. The latex happens to smell a great deal like barbeque sauce and has a very distinctive taste: "Once you smell that smell and taste that taste, you know what it's supposed to smell and taste like," said Dr. King.

The latex has the look of blood, although perhaps a little browner. If placed on the skin, it tends to cling, although it feels watery at the same time. If a person dabbed *sangre de drago* onto his or her hands and rubbed them together, the latex would first turn to a creamy texture but eventually dry and turn into a fine white powder.

If a shipment passes the quality control tests, the proanthocyanidin compound is isolated, purified, and made into tablets. Currently Napo and its partners Salix Pharmaceuticals, Inc. in Raleigh, North Carolina, and Glenmark are working on the larger scale manufacture of crofelemer. In Peru, Napo is focusing only on replanting at present but will begin harvesting again soon to prepare for mass distribution. The drug is expected to be distributed in India as soon as 2010, and in the United States in 2010/2011, according to Dr. King, depending on how fast some of the regulatory work is accomplished.

Fair Trade

According to Dr. King, Napo is committed to fair trade, sustainable management, and conservation of both tropical forests and the cultural diversity that is a key part of the fabric of Amazonian rainforests. He explained that Napo is committed to ensuring the sustainability of *C. lechleri*.

"A tree called *Cinchona officinalis*, the source of quinine, was heavily harvested, and if seeds had not been smuggled out of the country to be cultivated in Asia and Africa, it would have likely been intensively overharvested," said Dr. King. "Even the famous national tree of Brazil, rosewood [*Caesalpinia echinata*], was nearly wiped out for its perfume, a form of medicine for some. If we overdo it now, this medicine won't exist later, so we thought it best to err on the side of caution." He added, "It's the right thing to do."

It is for these reasons that Napo (when it was previously Shaman Pharmaceuticals) founded the Healing Forest Conservancy (HFC) in 1990. HFC is a nonprofit organization whose mission is to return benefits and profit-sharing to the indigenous people who work with Napo in harvesting or replanting medicinal plants or who have traditional knowledge of the medicinal plants in question.[3] Napo also tries to accomplish fair trade through its B Corporation subsidiary Crofelemer Access Program (CAP) Global. CAP primarily works to provide economic alternatives to tropical deforestation in rainforest areas of different biodiversity-rich Andean nations.

"We and our collaborators have tried to always include specific acknowledgement to local and indigenous people and/or authors whenever possible," said Dr. King. "I have been told that they want the world, their children, and future generations to know what ethnomedicine and indigenous science they've provided to the world's medicine

Planted *Groton lechleri* in reforestation site of Cuyana, Peru.
Photo ©2009 Steven R. King

chest. It is an appropriate source of cultural pride and one that has not been properly accorded indigenous people except in general terms—rarely in the medical or scientific community." HG

References

1. Latex Source: Origins of Crofelemer [unpublished manuscript]. San Francisco, CA: Napo; June 30, 2009.
2. Lindner K. Trials show Crofelemer is effective for treating diarrhea associated with cholera and other infectious pathogens. HerbalEGram. February 2009;6(2).
3. Borgesi J, King S, Hughes K, Meza E, Nelson S, Romero C. Conservation of biocultural diversity and benefit sharing mechanism in the Amazon: *Croton lechleri*, a traditional indigenous resource [conference presentation]. Presented at the INPI/EC seminar "Role for Intellectual Property Protection in the Field of Biodiversity and Traditional Knowledge." September 9-11, 2001.
4. Jones K. Review of sangre de drago (*Croton lechleri*): a South American tree sap in the treatment of diarrhea, inflammation, insect bites, viral infections, and wounds: traditional uses to clinical research. *J Alt Compl Med*. 2003;9(6):877-896.
5. Bardhan P, Sharma A, Bolmall C, et al. Safety and efficacy of a novel anti-secretory anti-diarrheal agent Crofelemer (NP-303) in the treatment of adult acute infectious diarrhea and cholera, with or without the use of antibiotics. 13th International Conference on Emerging Infectious Diseases in the Pacific Rim—Focused on Enteric Diseases [abstract book]. Kolkata, India; April 6–9, 2009.
6. DiCesare D, DuPont HL, Mathewson JJ, et al. A double blind, randomized, placebo-controlled study of SP-303 (Porvir) in symptomatic treatment of acute diarrhea among travelers to Jamaica and Mexico. *Am J Gastroenterol*. 2002;97:2585–2588.
7. Gabriel SE, Davenport SE, Steagall RJ, Vimal V, Carlson T, Rozhon EJ. A novel plant derived inhibitor of cAMP-mediated fluid and chloride secretion. *Am J Physiol*.1999;276:G58–G63.
8. Holodniy M, Koch J, Mistal M, et al, A double blind, randomized, placebo-controlled phase II study to assess the safety and efficacy of orally administered SP-303 for the symptomatic treatment of diarrhea in patients with AIDS. *Am J Gastroenterol*.1999;94:3267–3273.
9. Ubillas R, Jolad SD, Bruening RC, et al. SP-303, an antiviral oligomeric proanthocyanidin from the latex of *Croton lechleri* (sangre de drago). *Phytomedicine*.1994.1:77–106.
10. Napo Pharmaceuticals completes dose selection phase of ADVENT trial [press release] San Francisco, CA: Napo; August 4, 2009.
11. Crofelemer Fact Sheet. Napo Pharmaceuticals, Inc. Website. Available at: http://www.napopharma.com/products/crofelemerFS2.pdf. Accessed May 21, 2009.
12. Saxton K. Company seeks patients for clinical trial on natural pharmaceutical for HIV-related diarrhea. HerbalEGram. July 2008;5(7).
13. Mangel A, Chaturvedi P. Evaluation of crofelemer in the treatment of diarrhea-predominant irritable bowel syndrome patients. *Digestion*. 2008;78:180–186.
14. King S, Meza E, Ayala F, et al. *Croton lechleri* and the sustainable harvest and management of plants in pharmaceuticals, phytomedicines, and cosmetics industries [conference presentation]. Presented at the International Symposium on Herbal Medicine. Honolulu, HA; April 30, 1997.
15. Baltazar E, Ayala F, Castañel M, et al. Sustainable harvesting of sangre de drago and sangre de grado for commercialization [manual]. San Francisco, CA: Shaman Pharmaceuticals and the Healing Forest Conservancy; 1998.
16. Rodriguez A, Mendoza C, Castro D, Ramos M, Fonceca M, Meza E. *Dessarrollando Nuestra Diversidad Biocultural: Sangre de Grado y el Reto de su Produccsión sustentable en el Perú*. Lima, Peru: Imprenta PROPACEB; 1999.

Blood red latex exuding from laticifers of *Croton lechleri*.
Photo ©2009 Steven R. King

Impact of Current Good Manufacturing Practices for Dietary Supplements on Small Manufacturers

For the past 2 years, staff at the small herb company Herbs, Etc. has been preparing for an inspection of Good Manufacturing Practices (GMP) from the US Food and Drug Administration (FDA). In hopes of being GMP-compliant, many of the 27 employees have attended GMP seminars and webinars, thoroughly read and reread FDA's GMP rule, and discussed the rule section-by-section in weekly meetings. Additionally, they have upgraded certain aspects of the company's operations, including the hiring of a new full-time employee to review and approve manufacturing documentation for quality assurance purposes. Though it has been a tremendous amount of work, Daniel Gagnon, owner of the Santa Fe, New Mexico-based Herbs, Etc., said he is glad the GMP rule has been implemented.

"These regulations were really needed," said Gagnon (oral communication, August 31, 2009).

FDA issued the final rule on GMPs for dietary supplements on June 25, 2007.[1] According to the rule, compliance with GMPs (sometimes referred to as cGMPs) should help to ensure that manufacturers are producing unadulterated and properly-labeled dietary supplements and using a consistent and reliable process. The final rule applies to all domestic and foreign companies that manufacture, package, label, or hold dietary supplements distributed in the United States. The compliance requirements are being implemented in 3 phases: large companies (more than 500 employees) needed to be compliant by June 25, 2008; small companies (fewer than 500 but more than 20 employees) needed to be compliant by June 25, 2009; and very small companies (less than 20 employees) have until June 25, 2010, to be compliant.

The generalized activities necessary for GMP compliance include:

- Having qualified staff members employed
- Having physical plants designed or built to protect against adulteration
- The use of appropriate equipment and utensils
- The use of master manufacturing and batch production records
- Employing quality control procedures
- Holding and distributing dietary supplements and manufacturing materials in ways that ensure that quality is not negatively affected
- Recording each product's GMP-related complaints and retaining these records for 1 to 2 years

Industry reaction to the final rule has included criticism of FDA's lack of specific guidance for manufacturers and concerns regarding potential costs for small and very small businesses.[1,2] Feedback has especially focused on the wording, organization, and length of the rule, which many consider confusing. FDA is currently being sued by a group of plaintiffs who claim the agency is violating the Fifth Amendment requirement that laws not be vague, alleging that some supplement manufacturers are unable to understand the rule.[3] Though this lawsuit lacks probability of success, it voices concerns held by some in the industry.

The American Herbal Products Association (AHPA), the leading trade association focused exclusively on botanicals, petitioned FDA in July of 2007 to reconsider and amend 7 aspects of the final rule for being potentially confusing, destructive to dietary ingredient manufacturers, or contrary to the public interest.[4]

"They ignored us," said Michael McGuffin, president of AHPA (oral communication, August 26, 2009).

Other trade associations have voiced similar concerns. The Council for Responsible Nutrition (CRN), a trade group representing many large dietary ingredient and dietary supplement companies, commented in October of 2007 that it strongly opposes the rule's inclusion of the *Petition to Request an Exemption From 100 Percent Identity Testing of Dietary Ingredients*.[5] The Natural Products Association (NPA), the trade association for health food retailers and manufacturers, meanwhile, requested that FDA provide a definition or guidance on how to properly qualify suppliers of dietary ingredients.[6] FDA is working on releasing such guidance, but nothing has been published thus far.

FDA Inspection Activities

FDA says it is limiting "any disruption for dietary supplements produced by small businesses" by enforcing compliance requirements in phases based on business size, but it also recognizes that the rule will have a "significant economic effect on small businesses."[1] The agency estimated that the annual costs of GMP compliance would be $69,000 per year for large businesses and $46,000 for very small businesses, with small businesses bearing the largest costs at $184,000. Though many have commented that FDA's figures are largely underestimated, Brad Williams, a manager in FDA's Division of Dietary Supplements, said it is too soon to analyze the actual costs for companies (oral communication, August 27, 2009).

As of August 9, 2009, FDA had inspected 12 large manufacturers, said Williams. He added that the agency encountered difficulty in correctly identifying manufacturer size during the first phase of inspections. Initially relying upon company sales as an indicator of company size, it soon became apparent that many smaller companies have significant sales. If inspectors happened to show up to what they believed was a large manufacturer, and discovered it wasn't, the company was inspected according to food

GMPs, said Williams. (Prior to the implementation of the dietary supplement GMPs, all dietary supplement manufacturers had to comply with existing GMPs for food manufacturers, which are oriented towards ensuring proper sanitation measures.)

Of the 12 manufacturers inspected, FDA issued only one untitled letter, which is less severe than a warning letter, to a New Jersey firm, and the manufacturer is currently making corrections, said Williams. This doesn't mean all other companies were without errors, however.

"We have not found perfect compliance everywhere," he added.

FDA expects to begin inspecting small businesses very soon, and inspections of large firms will continue. After June 2010, all firms must comply, irrespective of their size. Although a 2008 FDA report estimated that more than 200 companies would be inspected during the 2009 fiscal year, it is now known that the number will be much less.

"Actually, we won't come close to that," said Williams.

When carrying out inspections and taking follow-up actions, FDA will treat all firms equally, no matter what size the business, said Williams. When a manufacturer is inspected, the business' management receives a list of observations from the FDA inspectors, who then submit the observations to their district office for a decision on what, if any, actions should be taken. Sometimes an inspector observes problems that can be corrected on the spot. Other times, problems are observed that will take longer to correct, and the inspector is given a verbal commitment that the firm will correct the errors. Depending on the type and seriousness of errors, FDA might do a follow-up inspection. Firms with more serious observations tend to be inspected more frequently, he added.

"Our inspectors do not go in with the intent of closing down a business," said Williams, adding that inspections are generally a learning opportunity for both the company and for FDA.

The University of Mississippi (UM) has been participating in the training of FDA inspectors on dietary supplement GMPs and will continue to do so through next year, said Ikhlas Khan, PhD, director of UM's FDA training program and a research professor at UM's National Center for Natural Products Research (e-mail, September 15, 2009). The training focuses on the straightforward aspects of the GMP rule, such as sanitation, batch records, personnel training, and record keeping, as well as the more difficult activity of identity testing, he added.

"[Inspector training is] important since [dietary supplement] GMPs are different than drugs and foods and requires different skill sets," said Dr. Khan.

Impact on Businesses

With GMP inspections now entering their second phase, the rule's impact can be better observed.

"I'm sure all of us are nervous, no matter how big or how small, because when FDA comes in, it's a big deal," said Gagnon of Herbs, Etc., who is also the chairperson of AHPA's small business committee.

Among small and very small businesses, Gagnon said he has noticed 2 main reactions to the GMP rule, with the most common response being thorough preparation. The remaining small and very small companies, which are usually not members of trade organizations, seem to be saying that if they get inspected, they will shut down their business, he continued.

Some of these companies might think that attempting GMP compliance will be too complicated, too expensive, too tedious, or

that the necessary business-oriented preparation goes against the "healing" philosophy that initially brought them into the small herbal industry, said Gagnon.

"I think we're going to see a lot of the smaller companies disappear at the end of the year," he said, adding that this will be a huge loss to the industry because these small businesses contribute a great deal to industry education and innovation.

He added that many of the smaller businesses that primarily manufacture vitamin and mineral supplements, which often contain numerous ingredients, might have a harder time in achieving compliance than other companies. Identifying and/or certifying the ingredients of such products is much more difficult and expensive than identifying whole materials and simpler formulas, and it often requires finding the right testing technology and completing more tests, he added.

AHPA's McGuffin echoed the significance of the complexity of a company's products when considering impact.

"If the operation is pretty simple, you have less work to do than if it is very complicated," he said. "There is much greater ease in identifying herbs in whole form than when you have powdered or extracted it."

For this reason, he said, it seems that larger companies are not necessarily having an easier time than the smaller ones.

GMP Standards and Experiences Elsewhere in the World

Other countries have implemented their own GMP standards and procedures for dietary supplement companies. In 2003, Health Canada approved the Natural Health Products Regulations (NHPR), Part 3 of which includes GMP regulations for natural health products, such as dietary supplements.[1] Under this rule, manufacturers, packagers, labelers, and importers must qualify for and obtain a site license by demonstrating that they meet GMP requirements.

NHPR resulted from extensive and ongoing consultation with the industry, which probably prevented potential confusion over the regulation, said Robin Marles, PhD, director of the Bureau of Clinical Trials and Health Sciences at the Natural Health Products Directorate at Health Canada (oral communication, August 27, 2009). Before implementing the rule, the government held meetings, discussions, and workshops with industry from 2000 until 2003. The rule was phased in over 2 years, about 900 site licenses were issued, and the inspection process is now getting under way, said Marles. He added that the government continues to consult with the industry, hold nation-wide workshops, and release and revise guidance regularly as issues are identified.

The herbal industry in Australia is also GMP-regulated. The Australian Code of GMP for Medicinal Products, which includes complementary medicines such as herbs,[2] is generally the same as GMP regulations for pharmaceutical manufacturers. Those regulations are therefore considered to be superior to GMP regulations in countries where herbal preparations are regulated as foods (e.g., dietary supplements), said Robert Forbes, founding director of Robert Forbes & Associates, a regulatory consultancy firm in Australia specializing in complementary medicines (dietary supplements), foods, and cosmetics.

References

1. Health Canada. Good manufacturing practices guidance document. August 2006: Version 2.0. Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/prodnatur/gmp-bpf-eng.pdf. Accessed September 3, 2009.
2. The regulation of complementary medicines in Australia-an overview. Therapeutic Goods Administration Website. Available at: http://www.tga.gov.au/cm/cmreg-aust.htm. Accessed September 4, 2009.

"It seems like it's a lot of work for everybody," said McGuffin.

According to McGuffin, companies that manufacture *and* sell original products are also likely to be more significantly impacted by GMP compliance. Because some of the manufacturing activities required for GMP compliance might appear to be expensive or confusing, some of these businesses will probably transition to using contract manufacturers, he said. Though he anticipates a move away from integrated companies to those focused either on marketing or on manufacturing, this will not be a universal shift, he added.

With most of the supplement industry hard at work to be GMP-compliant, it remains to be seen if the new regulations will have an impact on supplement quality and price.

"I think it's inevitable that [the rule] will achieve what it set out to do as long as it is enforced," said McGuffin.

The biggest impact on supplement quality will most likely be for manufacturers who thought they were producing quality products but were making unintentional errors, he said. As companies in the industry increase their manufacturing diligence, most of those mistakes will be prevented, or once realized, will be corrected.

"The quality of supplements from high quality companies are still [going to be] excellent, just as they were 5 years ago, 10 years ago," McGuffin added.

"I think [the rule] will be a tremendous help," said Gagnon. "I think it's making a lot of companies have to step up. The consumer basically wins in that process."

Because the processes needed to ensure the quality of products often impose higher costs on the manufacturers, they usually pass this on to consumers, he continued.

"I don't think its going to be a tremendous cost [on consumers]. It will be hardest for small to medium size supplement manufacturers who do vitamins and minerals. For them [affordability] is going to be a real challenge," said Gagnon. HG

—Lindsay Stafford

References

1. Food and Drug Administration. 21 CFR Part 111 Current good manufacturing practice in manufacturing, packaging, labeling, or holding operations for dietary supplements: final rule. *Federal Register*. June 25, 2007; 72(121):34751-34958.
2. Heller L. GMP inspections should focus on Utah, California. Nutraingredients-USA.com. January 20, 2009. Available at: http://www.nutraingredients-usa.com/Regulation/GMP-inspections-could-focus-on-Utah-California. Accessed September 3, 2009.
3. Starling S. FDA sued over 'unclear' GMP rules. Nutraingredients-usa.com. August 12, 2009. Available at: http://www.nutraingredients-usa.com/Regulation/FDA-sued-over-unclear-GMP-rules. Accessed September 3, 2009.
4. AHPA petitions FDA to reconsider some parts of cGMP [press release]. Silver Spring, MD: American Herbal Products Association; July 27, 2007.
5. Shao A. Re: Docket no. 2007N-0186, CFSAN 200736. Petition to request an exemption from 100 percent identity testing of dietary ingredients: current good manufacturing practice in manufacturing, packaging, labeling, or holding operations for dietary supplements. October 24, 2007. Available at: http://www.crnusa.org/pdfs/CRN_GMP_IFR_Comments102407.pdf. Accessed September 3, 2009.
6. Association requests clarification on the Interim Final Rule (IFR) Exemption Petitions for reduced identity testing under the dietary supplement cGMPs [press release]. Washington, DC: Natural Products Association; October 25, 2007.

AHPA and CRN Comment on FDA's Proposed Policy on Economically Motivated Adulteration

The US Food and Drug Administration (FDA) issued a *Federal Register* notice on April 6, 2009, requesting public comments regarding economically motivated adulteration (EMA).[1] Comments were requested on "ways in which the food (including dietary supplements and animal food), drug, medical device, and cosmetic industries, regulatory agencies, and other parties can better predict and prevent economically motivated adulteration with a focus on situations that pose the greatest public health risk."[1] The deadline to submit comments was early August 2009.

Some examples of EMA mentioned in the notice have involved serious health risks. Melamine added to some milk-based infant formulas (to increase nitrogen levels and give the impression of higher protein content) was responsible for the death of 6 infants in China.[1] There were also 150 deaths in the United States between 2007–2008 associated with the intravenous anticoagulant drug heparin, which was contaminated with oversulfated chondroitin sulfate that was not detected during the original quality tests (these tests have now been updated to recognize this contaminant). The illegal substitution of diethylene glycol for glycerine was responsible for the death of 70 children in 1996 in Haiti and 50 children in Nigeria between 2008 and 2009. An example of an EMA in a dietary supplement, not mentioned in the notice, was the FDA's discovery in 2009 of unapproved steroids added to body-building products of American Cellular Lab of Pacifica, California.[2] These products were being illegally marketed as dietary supplements.

The FDA notice called for suggestions on how to combat this mounting problem as well as ways to clarify the agency's working definition of EMA. The current working definition is as follows:

> EMA [is] the fraudulent, intentional substitution or addition of a substance in a product for the purpose of increasing the apparent value of the product or reducing the cost of its production, i.e., for economic gain.[1] EMA includes dilution of products with increased quantities of an already present substance (e.g., increasing inactive ingredients of a drug with a resulting reduction in strength of the finished product, or watering down of juice) to the extent that such dilution poses a known or possible health risk to consumers, as well as the addition or substitution of substances in order to mask dilution.

On August 3, 2009, the American Herbal Products Association (AHPA) submitted comments to the FDA, including a suggested revision of the above EMA definition. AHPA suggested the replacement of the word "product" with "ingredient, component, or product" to clarify that a product should be considered adulterated when it contains an adulterated ingredient or component.[3,4] AHPA also pointed out in its comments that a definition of adulteration should not be limited to a situation that poses a health risk: "Whether or not any specific instance of EMA presents a health risk should not be a factor in defining intentional adulteration for economic gain as economically motivated adulteration."[4]

AHPA also suggested the addition of the following sentence to the revised definition of EMA, to discourage the addition of substances that can cheat quality tests, as well as highlight the problem of products that achieve certain desired effects by substituting illegal undeclared drugs: "EMA also includes, but is not limited to, the addition or substitution of substances in order to allow an adulterated ingredient or product to conform to identity and other quality tests used for genuine articles, or in order to have a physiological effect that is dependant upon the added or substituted substance."

"I believe the definition we've provided will assist [the FDA] because it'll make it clearer what is meant by economically motivated adulteration," said AHPA President Michael McGuffin (oral communication, September 15, 2009).

"They're not doing this because of big problems with herbs. They've recognized that adulteration is rampant," said McGuffin, pointing out that adulterated herbs and supplements were not even mentioned among the FDA's examples of EMAs in the *Federal Register* notice. "Deliberate adulteration does no one any good except the cheater."

In comments submitted to the FDA by the Council for Responsible Nutrition (CRN), Andrew Shao, PhD, vice-president of scientific and regulatory affairs at CRN, referred to EMA as a "'two-way street.' If there are willing buyers of sub par raw materials, whose true actives are substituted with or 'cut' by less expensive (and at times dangerous) materials, there will always be willing sellers. Manufacturers that knowingly accept economically adulterated raw materials, whether through failure to qualify suppliers, failure to properly identify materials by using outdated, nonspecific assays, or by just turning a blind eye, should be reprimanded by FDA…FDA can only hold these companies accountable by increasing the frequency and intensity of inspections of manufacturers' facilities."[5] He further wrote that CRN encourages the FDA to work collaboratively with the dietary supplement industry to develop guidelines for ingredient supplier qualification, as this would likely reduce instances of EMA.

According to Shao, "EMA is a serious, and in some instances, dangerous issue. At a minimum, it undermines consumer confidence and, at the extreme, costs lives."

It is unclear at press time when the FDA plans to have a revised definition of EMA or what new policies may be implemented to combat this problem. HG

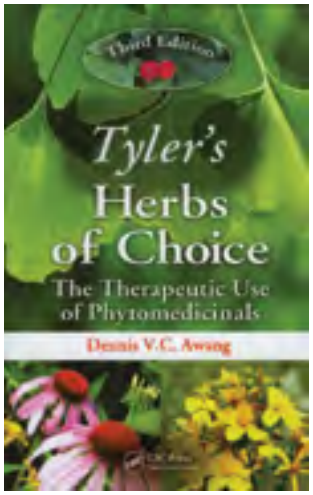
—Kelly Saxton Lindner

References

1. Food and Drug Administration. Economically motivated adulteration; public meeting request for comment. 74 *Federal Register* 64; April 6, 2009.
2. Lindner K. Drugs illegally marketed as supplements also mislabeled by media. HerbalEGram: September 2009; 6(9).
3. AHPA urges FDA to address 'spiking' in EMA definition [press release]. Silver Spring, MD: American Herbal Products Association. August 5, 2009.
4. McGuffin M, Young A. Comments of the American Herbal Products Associations on Economically Motivated Adulteration. Silver Spring, MD: American Herbal Products Association; August 3, 2009.
5. Shao A. Response to Docket No. FDA–2009–N–0166. Economically Motivated Adulteration. Washington, DC: Council for Responsible Nutrition; July 31, 2009.

Tyler's Herbs of Choice: The Therapeutic Use of Phytomedicinals, 3rd edition by Dennis V.C. Awang. Boca Raton, FL: CRC Press, Taylor & Francis Group; 2009. Hardcover; 269 pages. ISBN-13: 978-0-7890-2809-9. $89.95. Available in ABC's online store.

Those who had the pleasure of knowing the late Prof. Varro E. Tyler (1926–2001), affectionately known to friends and colleagues as "Tip," almost universally describe him in a single phrase, "a consummate gentleman." His tireless work as a pharmacognosist, pharmacy professor, dean and university vice-president, author, and mentor to at least 2 generations of scientists deserves accolades. Tyler, like many natural products scientists of his generation, was trained in classical pharmacognosy, imparting skills to identify and assess plant materials based on botanical, microscopic, and chemical characteristics, along with organoleptic assessment. Tyler, and colleagues of his era, saw their once-flourishing academic discipline decline to what nearly became a historical footnote, then rise from the ashes of obscurity to become a global phenomenon.



The academic discipline of pharmacognosy arose in the late 19th century to define a scientific basis for plant drugs that dominated the market and *materia medica* of the era. As pharmacy and pharmacy education shifted away from plant drugs, pharmacognosy nearly disappeared as an academic discipline. The conventional drug market and research shifted from crude drugs (herbs) to single isolated chemical entities, and pharmacognosy itself became an information foundation for new drug discovery from natural sources. The caveat, of course, was that any lead from nature or the pharmacognosist's laboratory would provide pharmaceutical companies with chemical building blocks for a new (it hoped) synthetic compound, readily defined, easily patented, and free from the confounding endless variation that nature served-up. Tyler's published research up until 1980 reflects the prevalent trend of that point in history.

In the 1970s, crude drugs in the form of herbs and herbal teas again appeared in the American market, masquerading as health foods and food additives, rather than as the "drugs" that those like Tyler had always known them to be. Tyler was annoyed by marketing hyperbole, unscientific extolment of the virtues of herbs in what he viewed as uncritical "advocacy" literature along with products of quality he might have thought were akin to floor sweepings. He became an outspoken and tireless critic of what he termed "paraherbalism" and an advocate of what he deemed "rationale herbalism."

His view earned him the ire of unabashed herbal advocates, who made a concerted effort to discredit his information; criticisms that in large part, if viewed critically rather than emotionally, only go to support Tyler's own assertions. The great irony on what often seemed to be fear-based personal attacks on Tyler, is the fact that he was at the very core of being one of the greatest proponents of the use of herbal medicine in modern society. However, he insisted that the use of herbs must have rational scientific context, including the regulation of herb products. Ultimately, Tyler and his critics sought the same outcome—the acceptance by modern society of the rightful place of herbs in healthcare.

He felt the Germans had taken a largely rational approach to their regulation of herbs as "drugs," and he became a tireless advocate for at least a conversation about adopting useful elements of the German regulatory system. His advocacy led to the eventual publication of an English translation of the German Commission E monographs by the American Botanical Council.

Tyler may have sometimes erred in his conclusions not to recommend a particular herb for a particular use because scientific evidence did not support traditional use. He might have expressed his conclusions less emphatically, and perhaps more appropriately worded his opinions to state that science doesn't support traditional claims—not because science refuted the claim, but because no scientific research had yet been published on the subject.

Therefore, the works of Tyler have to be understood in the context of Tyler's own worldview. Those who knew him may surmise that it was not useful or wise to engage him in a debate about the scientific validity of homeopathy or the value of organically produced crops versus conventionally grown crops. Yet, they could still sit on his back porch with him and enjoy a mutually favorite Czech beer or discuss mutual literary collecting interests.

It is predictable that a belief that the moon could influence plants would be met with disdain by Tyler. However, if research indicating such a phenomenon was conducted, published, *and* met with scientific consensus, Tyler would accept the new data or proof and revise his beliefs accordingly.

When one compares various editions of his books, his acceptance of new findings is clearly evident. Tyler's words, written with eloquence, dusted with subtle wry humor, and peppered with a skeptic's contempt, will make his titles among the 20th century herb books that are remembered in 2 centuries' time. Whether one agreed with him or not, he always produced a good read. Tyler's own words reflect a snapshot in time, yet contain wisdom of timeless value. The contemporary value of Tyler's work, therefore, requires revision.

Despite some of his critical writings on herbs, with his positive and negative assessments in several editions of *The Honest Herbal* (revised by this reviewer as *Tyler's Honest Herbal* in 1999), Tyler surprised many of his colleagues with the initial publication of *Herbs of Choice* in 1994. In this book, he made a rational case for notice and acceptance by conventionally-trained health professionals of numerous herbs that he deemed adequately supported by both empirical data and modern clinical trials.

Tyler would have been pleased to find that the third edition of his *Herbs of Choice* is revised and authored by his friend and colleague Dennis Awang, a natural products chemist and a former Canadian regulatory official. They share a love for accurate use of language, scientific thought, and appropriate regulation of herb products. In the new third edition of *Tyler's Herbs of Choice*, Dr. Awang has updated the book with new published studies on important herbs found in the modern market for which scientific evidence supports therapeutic use, whether in selfcare or healthcare.

Like Tyler, Awang does not accept science just because it is published in a scientific journal. He is critical of government-funded

research on herbs in the United States with findings primarily published in prestigious medical journals because "some [are] blatantly deficient in appreciation of herbal scientific parameters." Awang reviews various negative studies on St. John's wort (*Hypericum perforatum*, Hypericaceae) and echinacea (*Echinacea* spp., Asteraceae), among others, and explains the deficiency of the science. Tip Tyler would smile and nod his head in agreement.

In the new edition, herbs that have been the focus of significant research in the last decade such as andrographis (*Andrographis paniculata*, Asteraceae), butterbur (*Petasites hybridus*, Asteraceae), gotu kola (*Centella asiatica*, Apiaceae), bacopa (*Bacopa monnieri*, Plantaginaceae) and bitter orange (*Citrus aurantium*, Rutaceae) have been added. Awang, a leading expert on feverfew (*Tanacetum parthenium*, Asteraceae), has thoroughly revisited this subject. As in previous editions, the third edition of *Tyler's Herbs of Choice* is arranged by body systems, conditions, or biological effects, spanning 8 of the book's 10 chapters. Chapter 1, "Basic Principles," contains a good deal of practical information with guidelines for using herbal medicines, herbal dosage forms, definitions, and discussion on herb quality. It also retains Tyler's signature discussions on paraherbalism, rational herbalism, and homeopathy, among other herbal polemics. An Appendix, "The Herbal Regulatory System," has been updated and expanded by Paul N. Brown and Michael Chan, untangling this evolving milieu of new Good Manufacturing Practices (GMPs) and their effects on the confidence of herb quality. An excellent overview of the current Canadian regulations on herbal products is also included.

Mainstream medical healthcare providers know that a large percentage of patients use herbal dietary supplements as medicines and, in most cases, do not discuss that use with their healthcare provider. Perhaps the harried practitioner avoids broaching the subject with patients because of lack of knowledge of the subject matter. They were simply not schooled in clinical applications of herbs. *Tyler's Herbs of Choice*, 3rd edition gives those readers a valuable tool for sorting the wheat from the chaff. It is a practical handbook, written by authors with keen knowledge of the multidisciplinary herbal scientific literature, its strengths, and deficiencies. Tyler and Awang have nuanced expertise in the many facets of natural product science, which adds to the book's depth and accuracy.

The greatest value of *Tyler's Herbs of Choice*, 3rd edition is its ability to give medical practitioners the confidence to understand, recommend, and advise on herbs and phytomedicines of clinical value.

—Steven Foster
President, Steven Foster Group, Inc.
Eureka Springs, AR

Plant Spirit Healing: A Guide to Working with Plant Consciousness by Pam Montgomery. Rochester, VT: Bear & Company; 2008. Paperback; 222 pages. ISBN-13: 978-1-59143-077-3. $16.00.

With a title like the one Pam Montgomery has chosen, an open-minded reader is a prerequisite. Written in her straightforward, personal style, Montgomery lays out her truth in this guide to the "triple spiral path of healing," which engages the heart, soul, and spirit of not only humans, but of plants. The whole book, including the fascinating mirror-image color photographs by Linda Law, is a kaleidoscopic journey.

It is interesting to read why Montgomery opted to choose the word *spirit* over the word *energy* in the title of the book. Using the word *energy* could have lent credibility, since so-called "energy medicine" is now a category being researched by the National Center for Complementary and Alternative Medicine (NCCAM) at the National Institutes of Health. Montgomery says that, after much reflection, she chose the word *spiritual* because "energy in scientific terms refers to the ability of a physical system to do mechanical work…it has only been recently that energy as a force existing in a unified field has been discussed, and, even though the word *spirit* has not entered scientists' vocabulary, it is on the verge of recognition in connection to this life force."

Pioneering semantics is nothing new to Montgomery. Her first book, *Partner Earth: A Spiritual Ecology* (Destiny Books, 1997), was one of the first titles to use the term *spiritual ecology*. Now that term is more ubiquitous in this time of concern for the global climate, though it has been primarily employed by religious-affiliated organizations to cement the idea that sacred work includes taking good care of the planet. Montgomery clearly differentiates her brand of spirit from organized religion.

Montgomery liberally uses the works of others in short quotes and other references, drawing from a wide array of experts—some expected, such as well-known physicist James Lovelock, author of the groundshaking *Gaia: A New Look at Life on Earth,* and others less known or fading from memory. Montgomery's reminding readers of the late Swedish painter and activist Monica Sjoo and the late Romanian writer and historian Mircea Elaide, who wrote what is considered a foundational text on shamanism in 1951, adds admirable quality to the book. One of the newer scientific researchers noted in this book is Anthony Trewavas, a leader in plant neurobiology, a field that is dispelling the notion that plants are passive entities. This research is showing that plants are actually actively engaged in life comparative to animals. Montgomery also cites her herbal contemporaries, including Rosita Arvigo, Susun Weed, and Matthew Wood. The substantial and well-written foreword, titled "Reclaiming the Invisible," is by provocative herbal author Stephen Harrod Buhner.

Plant Spirit Healing is divided into 3 sections that take the reader through the theoretical framework, practical application, and finally, summaries of 10 specific plants. Chapters open with one of the author's journal entries dated over the past several years. Each passage refers to a time and a place on her land in the verdant hills of Danby, Vermont and frames the teaching offered in that chapter. The words she shares from her diary stem from her direct personal awareness of a place; perhaps along the stony creek that tumbles down Marble Mountain, following moose tracks or wild turkeys, or huffing up Eagle's Nest Trail. She writes simply, in conversation with the reader, about how these places, the plants, animals, rocks and water, time of day and celestial events, affect and move her. These entries introduce the ideas conveyed in the chapter and solidify the idea that direct interaction and relationship with nature is core to plant spirit healing.

Key to everything, Montgomery emphasizes direct experience as *the* teacher. She refers to personal experiences she has had with clients and students to help readers understand the tenet of each chapter. In Chapter Nine, titled "Healing Oneself, Others, and the Planet with Plant Spirits," she tells a story about a student ill with Lyme disease who responded to a year of plant spirit healing by saying, "It's not like Lyme disease is miraculously whisked away. It's that I take up more of the space and there's no room for Lyme disease."

Readers may experience a thread of mystery running throughout the text about how to best use the plants for healing. Montgomery encourages readers to experiment with techniques. The chapter on foundational healing modalities opens with a journal entry about the uniqueness of each falling snowflake. Likewise, "There are many ways to give the healing gifts of a plant spirit to another," Montgomery says. This chapter specifically discusses formalized modalities of healing that the author has employed, including 5-element Chinese medicine, the chakra system, and the medicine wheel. But Montgomery writes, "I urge you to explore deeply the ones that speak to you… the healing comes through your co-creative partnership with the plant spirits. The most important aspect of Plant Spirit Healing is your relationship to the plants…."

The last chapter is on the individual herbs, titled "Plant Allies." The introduction reminds readers that it is the mingling of energies from a relationship between plant and human on a heart, soul, and spirit level that allows true healing and that this relationship will be different for everyone. While products such as teas, tinctures, oils, incenses, and flower essences have their place, Montgomery says, "Remember, you are the author of your own experience, making you an authority." The 10 herbs listed as plant allies include mugwort (*Artemisia vulgaris*, Asteraceae), which, among other uses, is held to be the "all in one" for alignment of the spinal cord. Sacred basil (*Ocimum sanctum*, Lamiaceae) is the author's indispensable ally, and an infused body oil is made by soaking the leaves for 6 weeks. Other herbs include dandelion (*Taraxacum officinale*, Asteraceae), calendula (*Calendula officinalis*, Asteraceae), St. John's wort (*Hypericum perforatum*, Clusiaceae), hawthorn (*Crataegus* spp., Rosaceae), angelica (*Angelica archangelica*, Apiaceae), agrimony (*Agrimonia pilosa*, Rosaceae), rose (*Rosa* spp., Rosaceae), and surprisingly, birthroot (*Trillium erectum,* Melanthiaceae), which has been used for parturition. Contemporary herbalists are in general agreement that trilliums should not be harvested, nor sold on the marketplace. The United Plant Savers organization lists it as "At Risk," and the US Department of Agriculture lists it as threatened or endangered in some eastern states. Granted, there is no suggestion to harvest the plant, and all of the stories shared about it seem to indicate that it was only the energy that was being tapped. Nonetheless, it is cause for wonder why mention was not given of its threatened existence.

The book has an index and a bibliography, which are useful to readers interested in exploring more about some of the fascinating people and topics that are touched upon in the text.

Montgomery thoroughly acknowledges the wisdom inherent in indigenous cultures and how this is a natural progression of an intrinsic connection with nature. Indeed, her book seems to be designed as a guide to accessing the "indigenous soul," as she calls it. That *Plant Spirit Healing* is a top seller for its publishers signals that not only is it written in an accessible way, but that the modern audience resonates with the idea that people and plants share root and bough. While the perennial quest to maintain humans at the pinnacle of creation continues to dominate scientific and religious endeavors, further experimentation continues to mount evidence that life forms are more similar than different. Modern science and indigenous knowledge and

New Book Profiles

A Practical Guide to Licensing Herbal Medicinal Products. Thomas Brendler, L Denzil Phillips, and Stefan Spiess. London, UK: Pharmaceutical Press; 2009. Hardcover; 770 pages. ISBN–13: 978-0-85369-784-8. $395.00

This book, supported by the UK's Medicines and Healthcare products Regulatory Agency (MHRA), provides guidance on how to legally market herbal medicinal products in the United Kingdom. By 2011, every herbal product that is judged as medicinal by the MHRA will require a registration under the Traditional Herbal Medicinal Product Directive (THMPD). Containing all legal guidelines and forms—as well as instructions on how to fill out all relevant applications, where to send them, and the costs involved—this resource can help manufacturers obtain that registration and follow necessary quality standards and other requirements.

Stockley's Herbal Medicines Interactions: A Guide to the Interactions of Herbal Medicines, Dietary Supplements and Nutraceuticals with Conventional Medicines. Elizabeth Williamson, Samuel Driver, and Karen Baxter (eds). London, UK: Pharmaceutical Press; 2009. Hardcover; 423 pages. ISBN–13: 978-0-85369-760-2. $89.95. Available in ABC's online store.

This reference provides over 150 monographs with data on the most commonly used herbal medicines, dietary supplements, and nutraceuticals. Each monograph contains information on synonyms and related species, constituents, uses and indications, pharmacokinetics, and interaction overviews. Detailed information on kinds of interactions is also provided, such as interactions that could occur with antidiabetic medications, cardiovascular drugs, foods, herbal medicines, vitamins, and more.

Integrative Oncology. Donald Abrams and Andrew Weil. New York, NY: Oxford University Press; 2009. Hardcover; 601 pages. ISBN–13: 978-0-19-530944-7. $35.00. Available in ABC's online store.

Integrative Oncology is the first text in the Weil Integrative Medicine Library series, all of which will focus on various forms of integrative medicine. This emerging field treats the body, mind, and the spirit, making use of both conventional and alternative medicine. Andrew Weil, MD, series editor, is a well-known expert and leader in this overarching field. This book specifically provides information for both practitioners and consumers on integrative oncology—integrative medicine used in the treatment or prevention of cancer. Included are up-to-date and extensively referenced chapters on a wide spectrum of issues in a reader-friendly format featuring key points, sidebars, and tables.

belief grow closer, and the popularity of books like Montgomery's contribute to the open-mindedness of the general population. This attitude slowly but surely affects public policy that funds scientific research.

Like her previous book, this new one adds to a growing body of herbal literature that reaches beyond "this for that" or identification guidebooks. Herbalists and others who have a relationship with the doctrine of vitalism can be expected to find much appeal in Montgomery's book. Contrarily, those connecting more with the evidence-based doctrine that currently captivates healthcare regulatory bodies worldwide will surely find much to criticize. In this camp will be those concerned that books like this cast an illegitimate pale on the herbal field, taking it further from conventional acceptance. Even as these different orientations divide herbalists, one thing is certain: politics and science have trended back toward the acknowledgement that the relationship between the human species and nature is powerful. Now, emphasis on this relationship is a dominant political and market force as focus turns to planetary health. In addition, there is agreement that each individual's relationship to nature, reflected by lifestyle and specific decisions, have powerful effects on the planet and personal health.

Pam Montgomery has offered her view of how to live better on the planet. Her voice contributes to a long, contentious conversation mitigated too often by greedy, commercial interests. She cuts to the chase when she says, "We are committed to the earth, the green beings, and the water, treating them as if they are relatives…." Perhaps it is only by cultivating a relationship of deep knowing with the earth, as that of a close relative, that we can bring authenticity to the concepts of green and sustainable. After all, "He who knows nothing, loves nothing," the notorious 16th century physician known as Paracelsus supposedly said.

Montgomery takes her place among other out-spoken Vermonters, such as the highly influential godfather of environmentalism, George Perkins Marsh (1801–1882). In *Man and Nature*, written in 1864, he came to the same conclusion as Montgomery when he wrote, "All nature is linked together with invisible bonds and every organic creature, however low, however feeble, however dependent, is necessary to the well-being of some other."

—Cascade Anderson Geller
Herbalist
Portland, OR

The Meaning of Tea: A Tea Inspired Journey by Scott Chamberlin Hoyt and Phil Cousineau (ed). New York, NY: Talking Leaves Press; 2009. Paperback; 362 pages. ISBN-13: 978-0-615-20442-0. $24.95. Available in ABC's online store.

The New Tea Companion: A Guide to Teas Throughout the World by Jane Pettigrew and Bruce Richardson. London, UK: National Trust Books; 2008. Hardcover; 256 pages. ISBN-13: 978-0-9793431-7-9. $22.95.

More than coffee, more than Coca-Cola®, the most widely drunk prepared beverage in the world is tea. Steeped from the dried and otherwise variably-processed leaves of *Camellia sinensis* (Theaceae), tea has engendered a deep role and relationship with people in Asia throughout history and has become the dominant beverage in China, India, Southeast Asia, Russia, and England. It rivals coffee in the Middle East, Saharan and sub-Saharan Africa, Continental Europe, and (in the past 300 years or so) North America.

Author Scott Chamberlin Hoyt mentions in the introduction of *The Meaning of Tea* that his bookshelf groans under the weight of many books written on the subject of this mythic, popular, compelling beverage.

So why another book on tea? For Hoyt, it's part of his personal journey, the past 10 years of which have been an alluring relationship with tea and the plant from which it is brewed. The author has a longstanding

Native American Medicinal Plants. Daniel E. Moerman. Portland, OR: Timber Press; 2009. Paperback; 799 pages. ISBN–13: 978-0-88192-987-4. $39.95.

This abridged edition of the now-classic *Native American Ethnobotany* in a dictionary format, instead of an encyclopedic format, contains information on about 250,000 medicinal uses of 2,700 plant species commonly used in Native North American cultures. This book also features indexes organized by tribe, usage, and common name, which make the information easily accessible.

The Encyclopedia of Herbs: A Comprehensive Reference to Herbs of Flavor and Fragrance. Arthur O. Tucker and Thomas Debaggio. Portland, OR: Timber Press; 2009. Hardcover; 604 pages. ISBN–13: 978-0-88192-994-2. $39.95.

Written by 2 herb experts and including more than 500 species of herbs, this compendium contains detailed profiles that can be used to grow and use many medicinal plants. Each entry typically contains the plant's botanical name and family, growing information (height, hardiness, light requirements, water consumption, required soil type, and pH), its name in various languages, a history of the plant, its chemistry, and culinary and landscape uses.

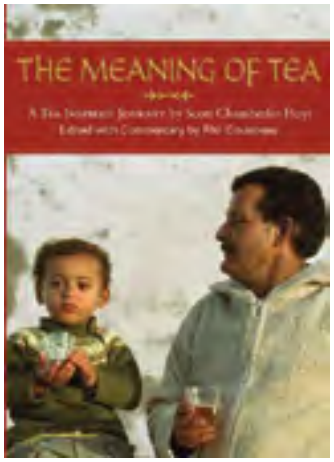
Botanical Medicine: From Bench to Bedside. Raymond Cooper and Fredi Kronenberg (eds). New Rochelle, NY: Mary Ann Liebert, Inc., 2009. Hardcover; 237 pages. ISBN–13: 978-1-934854-05-1. $99.00. Available in ABC's online store.

More than 20 scientific experts contributed to this book. It serves as a guide to anyone interested in botanical research, moving from the field to the phytochemistry laboratory to the development of a clinically useful product. Organized into 3 sections, it contains details on selection and quality of botanical products, preclinical and clinical approaches, and a practitioner's view of the challenges faced by those interested in exploring botanical products.

Clinical Botanical Medicine, 2nd ed. Eric Yarnell, Kathy Abascal, and Robert Rountree. New Rochelle, NY: Mary Ann Liebert, Inc., 2009. Hardcover; 438 pages. ISBN–13: 978-0-913113-46-2. $99.00.

This updated edition gives significantly expanded information on how herbs can be used effectively in common clinical conditions. It further focuses on "poorly explored aspects of botanical medicine," such as beneficial cooperation among compounds within a plant (or plants), and how the plant used as a whole can influence the potential toxicity of some of its parts. Organized into 2 parts, this book includes information on botanicals to treat or prevent specific diseases or conditions, as well as broader issues in botanical medicine.

interest in Eastern thought and is intrigued by all things Asian. So when he decided to study tea, he was easily predisposed to traveling to Asia—and elsewhere—to film dozens of tea growers and producers, tea sellers, and tea drinkers for his highly-praised 74-minute documentary, also called "The Meaning of Tea." That documentary was re-released this year in a multi-language version. This book contains the transcripts of his filmed interviews of over 50 people. In all, he and his film crew shot over 120 hours of footage that produced over 2000 pages of transcripts, which have been edited to create this book.



"There is no better time for the rest of us to adopt the practices of tea drinkers," says Phil Cousineau, the book's collaborator and editor. "Considering that the fallout of our weakened economy includes millions of stressed-out, overstretched people, this book offers a simple avenue to wellness, calm, and meaning through tea."

The book is divided into 7 sections, each based on a geographical area: India, Morocco, America, Japan, France, England and Ireland, and Taiwan. Each section also follows the order of the 7 cups of tea alluded to in "The Song of Tea" by the Tang Dynasty poet Lu Tong (790–835 CE):

The first drink sleekly moistened my lips and throat;
the second banished my loneliness;
the third expelled the dourness from my mind;
the fourth broke me out in a light perspiration;
the fifth bathed every atom of my being;
the sixth lifted me higher to kinship with the immortals;
the seventh is the utmost I can drink.[1]

But this gem contains much more than the interviews. Hoyt's book is about the philosophy of tea and tea drinking, as well as the intimate personal relationship people have with tea.

As director, writer, producer and food activist Deborah Koons Garcia writes in the foreword to the book, "Reading Hoyt's wonderful book and watching his beautiful film, I learn much that sets me pondering the amazing substance called tea." She continues, "Right now we can appreciate that tea is hand cultivated and hand picked, that it is enjoyed everywhere, a kind of global connective tissue."

"What does tea mean to you?" asks Cousineau, in one of his commentaries, referring to the primary question asked to each interviewee. "What does it mean to grow it, sell it, drink it, cut business deals, or arrange marriages and funerals over it? What is it that *moves* people to bare their souls over a cup of tea? By *meaning*, I mean its value, its virtue, its inner significance, its intent, and its purpose."

The book shows Hoyt's penchant for meaning and skill as a philosopher of tea, going beyond being a documentarian of people's relationship with the beverage. Sprinkled throughout the book are proverbs, aphorisms, and quotes (some about tea, some about life—of course, the point of this book is that, for millions, tea *is* life!) from Buddha, Confucius, Rabindranath Tagore, the Bible, Samuel Johnson, Carl G. Jung, Joseph Campbell, JRR Tolkien, Jack Kerouac, James Joyce, Alexander Pushkin, and Monty Python's Flying Circus, among others.

The book even includes an excellent summary in the final pages on the many documented health benefits of tea—an area of continual clinical and epidemiological research—by Pamela Yee, MD, an integrative physician in New York City.

As much as Hoyt's book is about the meaning and relationship people have with tea, and as much as it may be focused on the essence of drinking tea, his book is not about the history of tea, the details of the actual rituals surrounding the drinking of tea, the many types of tea, or how tea is grown and produced. This kind of detailed information, however, can be found in another recently published book on tea—Jane Pettigrew and Bruce Richardson's *The Tea Companion*. Both authors are tea experts: Pettigrew is the author of 13 books on tea and Richardson is a professional tea blender and writer.

Beautifully illustrated with color photos, old paintings and drawings, and black-and-white engravings, this book is a small, coffee-table-like book that is so compelling that it is hard to put down once opened. And, like many reference-like books, one can pick it up almost anywhere and read a few short pages and find interesting and compelling information about the history and lore of tea.

The *Companion* is divided into 3 main parts: (1) the history of tea; (2) tea production, including leaf grades, blends of teas, and brewing tea; and (3) the main part, with information on over 100 teas from around the world, including descriptions of their tastes, brewing tips (including specific water temperatures, important for proper brewing!), and photos of the dried and wet tea leaves and brewed teas.

The authors have included sections on the recent rise in popularity of high quality specialty teas in the United States, organic tea production, and explanation of the puerh tea phenomenon. This popular tea is made from a large-leaf variety of *Camellia sinensis* that traditionally grows in Yunnan, China.

Tea, in its many forms, is a healthful and helpful beverage. Its popularity has grown quickly in the past decade, in the United States and worldwide. For an insightful and inspiring look into the role that tea has enjoyed and will continue to play in various cultures, and the physical, psychological, and spiritual benefits that tea can contribute to everyone who takes the time to brew and enjoy it, both these books are highly recommended.

—Mark Blumenthal

Reference

1. Blofeld J (translator). *The Chinese Art of Tea*. Boston, MA: Shambhala Publications;1997.

Shari Lieberman
1958–2009

Shari Lieberman, PhD, a leader in the field of natural nutrition, died July 20, 2009, in Florida from complications related to metastatic breast cancer.[1] She was 51.

"Dr. Shari," as she was called, had many guest spots on television and radio shows and was generally regarded as a nutrition and mineral supplements expert.[2] She privately practiced as a clinical nutritionist in New York City for over 20 years, published scientific research, and presented at US and international conferences. Dr. Lieberman was a prolific writer and wrote in a way that appealed to the general public. She helped explain 28 basic vitamins and minerals to the layperson with her best-selling book, *The Real Vitamin & Mineral Book* (Avery/Penguin Putnam, 4th edition, 2007), co-authored with Nancy Bruning.

"Shari always encouraged me to study the conventional medical options in sufficient detail so I can explain to mainstream medical skeptics of natural medicine where natural products can be appropriately used in conventional therapies," said David Wales, president of American BioSciences Inc. (e-mail to M. Blumenthal, August 20, 2009).

Dr. Lieberman also co-authored *Mineral Miracle: Stopping Cartilage Loss & Inflammation Naturally* (Square One Publishers, 2006) with Alan Xenakis, and she co-authored the *User's Guide to Detoxification* (Basic Health Publications, 2005) and *User's Guide to Brain-Boosting Supplements* (Basic Health Publications, 2004) with James Gormley, in addition to writing many other books.

"Shari helped get the message out about the benefits of healthy eating, supplements, and herbal medicine," said Jack Challem, a health writer known as The Nutrition Reporter™ (e-mail, August 28, 2009). "And she walked the walk—taking very good care of herself."

Dr. Lieberman earned her PhD in clinical nutrition and exercise physiology from The Union Institute in Cincinnati, Ohio.[2] She was a certified nutrition specialist, a fellow of the American College of Nutrition, a faculty member of the University of Bridgeport's School of Human Nutrition graduate program, a board member of the Certification Board for Nutrition Specialists, a past president of the American Association for Health Freedom, and the recipient of the National Nutritional Foods Association's (now the Natural Products Association) 2003 Clinician of the Year Award.

According to co-author Gormley, vice president and senior policy advisor of Citizens for Health and past editor-in-chief of *Better Nutrition* magazine, Dr. Lieberman's "Nutrition Hotline" Q&A column was one of the longest-running and most popular departments in *Better Nutrition* (e-mail, August 18, 2009).

"I think she, more so than anyone else, popularized the concept of *optimal* nutrition," said Gormley. "I will miss Shari's brilliant mind, her easy and infectious laughter, and warmth as a caring, wonderful healer, author, educator, and amazing human being."

Alexander Schauss, PhD, CEO and senior director of natural and medicinal products research at AIBMR Life Sciences, Inc., met Dr. Lieberman in the 1980s. He described her as someone who was hard to forget because of her "vivacious personality, good looks, obviously fit body, and that unforgettable New York accent" (e-mail, August 26, 2009). He added, "It was obvious by looking at her that she practiced what she preached."

Dr. Schauss described one point in Dr. Lieberman's life that was very painful: "An attempt was made to strip her of her RD by a team of quackbusters [anti-health fraud activists] who saw her public visibility and advocacy of healthy foods and dietary supplements a threat to their agenda to suppress such information. The battle was in New York state, and although most people thought she was handling it well, it actually tore her up inside. She prevailed in her battle with the American Dietetic Association and quackbusters in the end, and kept her RD credentials, but it proved a painful experience."

Dr. Lieberman was described by several of her colleagues as being passionately committed to the health of American consumers. "Time and again she fought for what was right," said Challem. "She was gentle among friends, but could also be a tough fighter, defending the use of supplements."

But it was her infectious enthusiasm, her smile, and her passion for nutrition that her colleagues mentioned the most: "Her ability to always be motivated easily trickled off to those around her," said Douglas S. Kalman PhD, RD, director of business development at Miami Research Associates (e-mail, August 21, 2009). "Shari never stopped trying to grow and do so in various areas of the nutrition industry and academic sectors. Please continue to read Shari's writings, buy her books, and live life like she did, with authenticity, pride, a smile, and zest."

Dr. Lieberman is survived by her husband Agusto (Augusto) Benvenuto. The New York Chiropractic College is naming a scholarship after her for its graduate nutrition program. HG

—Kelly Saxton Lindner

References

1. Maharam L. RIP Shari Lieberman, PhD, CDN. July 23, 2009. Ask the Running Doc page. Runner's World Website. Available at: http://runningdoctor.runnersworld.com/2009/07/rip-shari-lieberman-phd-cdn.html. Accessed August 30, 2009.
2. About Dr. Sheri. Dr. Sheri Website. Available at: http://www.drshari.net/index.asp. Accessed September 9, 2009.

Craig Winters 1951–2009

Craig Alan Winters, a tireless activist for environmental and natural health causes, died July 3, 2009, from complications related to cancer.[1] He was 58 years old.

Among his many endeavors, Winters co-founded the influential grassroots organization Citizens For Health (CFH) in 1991. Interested in natural health for most of his life, Winters was concerned that Americans could potentially lose access to dietary supplements, herbs, and alternative health services, said Alexander Schauss, PhD, CEO and senior director of natural and medicinal products research at AIBMR Life Sciences, Inc (oral communication, August 13, 2009).

"There was a lot of really weird stuff going on at the time," said Dr. Schauss, referring to US Food and Drug Administration (FDA) raids on alternative healthcare clinics and health food stores, as well as proposed regulations to give FDA broad regulating authority over dietary supplements. Such authority would have restricted what information could be provided about the benefits of dietary supplements, even by physicians and medical associations.[2] It was feared that many supplements would have to be submitted to FDA for pre-market drug approval based on evidence of their therapeutic efficacy, he added. This would have effectively removed most supplements from consumer access until each was individually approved via a costly and time-consuming process similar to how new drugs are approved before being allowed onto the market.

Later in 1991, Winters was appointed CFH's chairman of the board. Though this was initially an unpaid volunteer position, he threw all of his energy into CFH and ended up leaving his full-time salaried job, added Dr. Schauss.

"He just had this tremendous spirit to do anything he could to educate people on matters of health, always cognizant that he was not a physician," said Dr. Schauss.

Soon CFH focused its work on the Health Freedom Act of 1992 and later on the passing of the Dietary Supplement Health and Education Act of 1994 (DSHEA). Winters vigorously researched the issues associated with DSHEA, as well as the members of Congress who were unsure of or against passing the legislation. He shared information and brainstormed strategies with Dr. Schauss, who would then travel to Washington, DC to speak with members of Congress and their staff, sometimes persuading them to become co-sponsors of DSHEA.

"Craig had tremendous organizational skills," Dr. Schauss said. "He literally wouldn't get off the phone for hours and hours. He was always behind the scenes, but in a very, very constructive and productive way."

Dr. Schauss recalled a time that Winters spent an hour-and-a-half explaining DSHEA to employees at a natural health store in Rhode Island after discovering that the wife of Sen. John H. Chafee (R-RI) often shopped there. The next time Sen. Chafee's wife visited the shop, the store's employees were well informed and could talk with her about DSHEA. She allegedly returned home to speak with her husband, who ended up not only voting for passage of the bill in a key Senate committee, but also signed on as a co-sponsor of DSHEA, said Dr. Schauss.

Winters also came up with the idea to create local CFH chapters and letter writing campaigns around the United States in order to educate citizens and increase the base of supporters who would communicate with members of Congress, Dr. Schauss continued.

"It was remarkable what transpired from that point on," he said.

DSHEA was eventually passed by Congress without one dissenting vote, and signed into law by President Bill Clinton on October 25, 1994.[3] Winters and the other CFH staff members cried when they heard the news. Soon after, Sen. Orrin Hatch (R-UT) formally recognized the role that CFH and its members played in lobbying for passage of the bill, and the House sponsor of DSHEA, Rep. Bill Richardson (D-NM), thanked CFH, said Dr. Schauss.

"Without Craig's ongoing support of this campaign, I'm really not sure if DSHEA would exist today or not," he added.

Once the battle for DSHEA was won, Winters' energy and passion for natural health and the environment did not stop. Concerned about the effect that genetically-modified (GM) food could have on people's health and the environment, Winters co-founded The Campaign to Label Genetically Engineered Foods (CLGEF) in the late 1990s.[1]

"He saw how big the problem was, and he saw a need to tackle the issues head on," said Cameron Woodworth of Green Designs Internet Solutions and former communications director for CLGEF (e-mail, August 18, 2009).

Winters worked with Rep. Dennis Kucinich (D-OH) on legislation to require labeling of GM foods, encouraged citizens to send letters to their Congress members, and communicated information with the public through speeches, debates, and CLGEF's website, he continued.

"In Europe, genetically engineered foods are labeled," said Woodworth. "Craig thought that Americans deserved this right as well."

Though Congressman Kucinich has introduced several labeling acts and bills to the House of Representatives from 2000 until 2006, none have been successful.

"Craig had hoped that things might change under the Obama administration," said Woodworth.

During his life, Winters spent time as a representative for a natural products company, taught a class on nutrition in the natural products industry at Bastyr University, and helped co-found EarthSave Seattle to promote the benefits of eating a plant-based diet.[1,4] He also helped transform CLGEF into The Campaign, which additionally focused on issues such as food irradiation, toxic fertilizers, global warming, and solar energy.

Winters is survived by his parents Robert and Lillian Winters and a brother. Before his death, Winters requested that all donations to The Campaign, which recently ceased operations, be sent to the Institute for Responsible Technology, which continues to work for the labeling of GM foods, said Dr. Schauss. (PO Box 469, Fairfield, IA 52556 or www.responsibletechnology.org.)

While working so tirelessly, Winters maintained his unique stamina and focus and always motivated others to stay positive, said Dr. Schauss, adding, "He did more in his years than most people do in two lifetimes."

"[Craig] saw a problem, a need, and he took action," said Woodworth. "Folks in the natural foods industry are deeply saddened that he is gone. He leaves a legacy of standing up for what is right, for being brave enough to step up and play a leadership role, for being able to stay positive and active even though the problems facing us are great." HG

—Lindsay Stafford

References
1. Woodworth C. In Memoriam – Craig Winters (1951-2009). Organic Consumers Association website. Available at: http://www.organicconsumers.org/articles/article_18453.cfm. Accessed August 18, 2009.
2. Williams L. FDA steps up effort to control vitamin claims. *New York Times*. August 9, 1992: Section 1 Page 1. Available at: http://www.nytimes.com/1992/08/09/us/fda-steps-up-effort-to-control-vitamin-claims.html?pagewanted=all. Accessed August 18, 2009.
3. Dietary Supplement Health and Education Act of 1994. Center for Food Safety and Applied Nutrition website. Available at: http://vm.cfsan.fda.gov/~dms/dietsupp.html. Accessed August 14, 2009.
4. Craig Winters 2004 Pioneer Award recipient [press release]. Port Townsend, WA: Natural Products Association Northwest; November 6, 2004.

Fernando Cabieses Molina
1920–2009

Fernando Cabieses, MD, a respected neurosurgeon, educator, artist, author, and friend of traditional herbal medicine, passed away in Lima, Peru on January 13, 2009. Dr. Cabieses was founder of Peru's National Institute of Traditional Medicine. He was also one of the world's foremost authorities on the effects of many of Peru's most popular traditional herbal medicines, including coca (*Erythroxylum coca*, Erythroxylaceae), maca (*Lepidium meyenii*, Brassicaceae), *ayahuasca* (*Banisteriopsis caapi*, Malpighiaceae), *sangre de drago* (*Croton lechleri*, Euphorbiaceae), and *uña de gato* (*Uncaria tomentosa*, Rubiaceae), among others. An advisor to the World Health Organization Committee for Traditional Medicine, Dr. Cabieses was a strong proponent of the rational integration of traditional medical practices into national healthcare systems.

Dr. Cabieses once said that "surgery is an admission of the impotence of modern medicine," and his vision of medical practice (and healing) embraced such unquantifiable concepts as love, soul, and spiritual awakening. He was a great teacher, both due to his skill at communicating and his ability to listen. In spite of being a figure of international prominence, he humbly treated all humanity as equal, sharing freely and learning deeply from shamans and Nobel laureates alike.

Born in Merida, Yucatan, Mexico in 1920, he moved to Peru at the age of 15 with his father, who was in consular service. He studied biology and medicine in Lima, at the Universidad Nacional Mayor San Marcos (UNMSM) from 1937 to 1945, then specialized in neurology and neurosurgery in the School of Medicine at the University of Pennsylvania, studying under Carl Schmidt, MD, early investigator of the pharmacological activities of ephedrine.

Upon his return to Peru in 1950, Dr. Cabieses introduced the surgical treatment of cerebral aneurisms and epilepsy. He became clinical professor of neurosurgery at the University of Miami, Florida, as well as professor emeritus of medicine at UNMSM. Dr. Cabieses was founder and rector of the Universidad Cientifica del Sur, where, conscious of the tendency toward excessive automation and dehumanization in medical education in Peru, he devised a novel program of intensive medical training in clinics and hospitals throughout Lima.

He was distinguished with honorary professorships at the Peruvian national universities of Trujillo (1962), Cajamarca (1963), Cuzco (1982), and Lambayeque (1985), and was awarded the degree of Doctor Honoris Causa at the Universidad Inca Garcilaso de la Vega (2006). Dr Cabieses was a member of the American Medical Association, the American College of Surgeons, and of numerous other academic and professional organizations. He was the founding director of the Peruvian Museum of Health Sciences, and he served as the first director of the Museum of the Nation.

Dr. Cabieses was intensely interested in the history of medicine in Peru, and he published numerous scientific articles and books illustrating that traditional medical practices remained vibrant in remote areas of the country. This awareness led eventually to his founding of the National Institute of Traditional Medicine, which aimed to improve healthcare in Peru and beyond through promoting the study and identification of Peruvian medicinal plants.

Recognizing the phenomenal biodiversity of Peru, its role in the evolution of numerous systems of traditional medicine, and its global contributions to agriculture, Dr. Cabieses was a tireless supporter of biodiversity conservation. He initiated the CAMBIE prize to honor individuals for their promotion of conservation in Peru, as well as to raise awareness of the benefits of maintaining these resources intact for future generations.

During the First Peruvian Congress of Medicinal Plants and Phytotherapy in Lima (2000), he was recognized for his contributions, both nationally and internationally, in the fields of research, education, and the diffusion of knowledge of the medicinal plants of Peru. Recognized for his contributions to cultural interchange and understanding, he was appointed president of the International Council of the Ibero-American-Israeli Cultural Institute. He was also honored by being named *Amauta*—a quechua language word meaning "person of great wisdom" and professor—by the University of Cuenca and the Pontificia Universidad Católica de Ecuador.

I had the honor and privilege to work with Dr. Cabieses since 1997, during which time our collaboration produced 15 scientific papers and contributed to the discovery of over a dozen new Peruvian plant species, including one new genus that a group of scientists hope to name in his honor soon. His gentle humor, inquisitive nature, and generosity will be missed by innumerable friends and colleagues.

Dr. Cabieses is survived by his wife and daughter. HG

—James Graham, PhD, adjunct associate professor, Department of Medicinal Chemistry and Pharmacognosy, University of Illinois at Chicago and research associate in botany, Field Museum

Sources
1. Unger T. Fernando Cabieses obituary. *El Comercio.* January, 15, 2009.
2. Cardenas M. Interview. *El Comercio.* April 7, 2007.

November 1–4: International Society for Nutraceuticals & Functional Foods 2009 Annual Conference. San Francisco, CA. This event presents dozens of distinguished speakers and presenters from around the world, who will discuss a variety of nutraceutical and functional food issues. Topics include: nutraceuticals for arthritis, brain health, type-2 diabetes, cancer, weight control, and other conditions; nutraceutical oils; marine nutraceuticals; nutraceutical and functional beverages; pre, pro, and synbiotics; traditional foods and health promotion; and nuts and dried fruits products, among many other topics. For more information, visit the website at: http://isnff.org/viewpage_plain/cms/id/42/2009_Annual_Conference.

November 5–6: American Institute for Cancer Research Annual Conference: Food, Nutrition, Physical Activity, and Cancer. Washington, DC. This conference opens with a plenary session discussing intervention trials to establish relationships between diet and cancer, and includes the participation of several experts in the field. Several split sessions will follow and address topics including: the role of phytochemicals in herbs, spices, and fruit in cancer prevention and treatment; evidence of nutrition, health behaviors, and cancer survivorship; regulatory sites and implications of bioenergetics; and cancer prevention policy. The conference closes with a plenary session on physical activity in cancer prevention and control. For more information, visit the website at: www.aicr.org/conference.

November 5–7: American Holistic Medical Association Conference: Holistic Health Now. Cleveland, OH. This conference serves to educate and entertain doctors, healthcare practitioners, and others who are interested in holistic health. Throughout the 3-day conference, attendees can learn from speakers such as Tieraona Low Dog and Ben Kliger, experience diverse educational exhibits, and enjoy healthy international cuisine and a live dance band at the Saturday night gala. The conference also provides concurrent sessions, CME's to help fulfill educational requirements, and networking opportunities. For more information, visit the website at: http://www.holisticmedicine.org/displayconvention.cfm?conventionnbr=6313.

November 6–8: Organic & Natural Products Fair, China. Shanghai, China. This event is organized by the Organic Food Development Center of the State Environmental Protection Administration and is the largest exhibition of organic and natural products in China. A group of international exhibitors will present their products amid a multifunctional trading and conference platform. For more information, visit the website at: http://www.onp-china.com/.

November 11–13: SupplySide West. Las Vegas, NV. As the world's largest event for healthy and innovative ingredients, attendees will have extensive networking opportunities, as well as experience hundreds of exhibitions featuring thousands of ingredients. Exhibitors include developers and marketers of foods, beverages, dietary supplements, and cosmeceuticals. The additional educational program features workshops on energy shots, beverages, FDA GMPs, stevia, the economy and consumers, and probiotics. The event will also feature distinguished speakers from within the industry. For more information, visit the website at: http://www.supplysideshow.com/west/.

November 12-13: International Conference of the Society for Integrative Oncology: Revitalizing Cancer Care. New York, NY. The New York Academy of Medicine's sixth annual conference will focus on comprehensive interdisciplinary programs and whole systems research. Information will be presented on clinical practice and research evidence for Ayurveda, homeopathy, naturopathy, and Traditional Chinese Medicine. The conference's goal is to fuse the evidence from a collection of healthcare practices in order to derive improved models of integrative systems that can benefit current oncology patient management. Several distinguished doctors and professors will also speak, including opening keynote speaker Dr. Dean Ornish. For more information, visit the website at: http://www.integrativeonc.org/.

November 17–19: Natural Ingredients Europe 2009. Frankfurt, Germany. At this global business platform, attendees from the natural ingredients industry can exhibit their products or services, learn about others' products, and hear from influential industry speakers. Products at the trade show include new, innovative, and organic products, as well as products of companies from specific geographic regions around the world. Attendees will have the opportunity to take part in discussions on the latest innovations in food manufacturing and processing, the industry's newest developments, and how to control costs, reformulate existing products, and develop ideas into products. For more information, visit the website at: http://ni.ingredientsnetwork.com.

November 18–20: BioFach India 2009. Mumbai, India. Taking place at the Bombay Exhibition Centre, this international organic trade fair brings together international experts from the organic market. The trade fair serves the purpose of presenting India's organic-product potential to many attendees and providing the Indian market with a strong international networking opportunity. The program includes top-ranking speakers and participants, and discussions on political guidelines, organic certification, current market trends, and export conditions for Indian products. For more information, visit the website at: http://www.biofach-india.com.

November 18: SteviaWorld Europe. Frankfurt, Germany. With the stevia market gaining ground in the United States, this event will discuss the key issues surrounding stevia within the European market. Topics to be addressed include: the status of regulatory approval, finding a supply of cultivated stevia, new flavor masking and sweetness enhancement solutions, incorporating stevia sweeteners into product portfolios, ensuring product quality and integrity, recent agronomy advances, and the future of stevia sweeteners. Leading industry players will lead these discussions, including the president of Morita Kagaku Kogyo Co., Ltd. the first company to commercialize the stevia sweetener. The event also presents a networking opportunity as attendees will include agronomists, growers and regulators, product developers, marketing managers, food science researchers and technologists, and many others. For more information, visit the website at: http://www.cmtevents.com/aboutevent.aspx?ev=091146&.

December 1–5: 4th Global Summit on Medicinal and Aromatic Plants. Sarawak, Malaysia. This event provides a forum to discuss and share ideas on information and experiences for the promotion and development of medicinal and aromatic plant industries. Attendees will include research scientists, traditional health practitioners, academicians, representatives from the medical and pharmaceutical industries, conservation biologists, biochemists, NGOs, government agencies, and more. An educational session will take place, along with an exhibit of herbal and related products. For more information, visit the website at: http://www.gosmap.in/.

December 4–5: 6th International Conference: Functional Foods for Chronic Diseases: Diabetes and Related Diseases. Denton, TX. This conference brings together experts in medicine, biology, and the food industry to discuss the relationship between functional foods and the prevention and treatment of chronic

diseases. Topics covered include the advances of phytotherapy and food therapy for diabetes and other related chronic diseases, such as cardiovascular diseases and obesity. A special focus will be given to the creation of functional and medicinal foods with new properties. For more information, visit the website at: http://www.functionalfoodscenter.net/Conference_2009.html.

January 21–24: 7th Annual Scripps Center for Integrative Medicine's Natural Supplements: An Evidence-Based Update. San Diego, CA. Informative and comprehensive, this conference features renowned faculty who will present an overview of natural supplements in evidence-based practice while emphasizing disease states. Conference attendees will learn how to address and manage dietary supplement use, as well as earn continuing education credits. Additional topics of focus include regulation, resources, research and efficacy in commonly utilized areas such as pain management, cardiovascular health and diabetes, women's health, and mental health and neurology. Attendees can also participate in botanical garden tours and the research competition, which awards top poster presentations with cash prizes and publication in the *Journal of Complementary and Alternative Medicine*. For more information, visit the website at: http://www.scripps.org/events/natural-supplements-an-evidence-based-update.

More calendar listings at
www.HerbalGram.org

In this department of *HerbalGram*, we list resources such as publications, organizations, seminars, and networking opportunities for our readers. A listing in this section does not constitute any endorsement or approval by *HerbalGram*, ABC, or its Advisory Board.

USP Dietary Supplements Compendium (USP-DSC) has recently been published in its Sixth Edition by the US Pharmacopeia (USP). Updated and published every 2 years, this reference guide combines the latest *USP–National Formulary* standards with information from the *Food Chemicals Codex*. It also features information from regulatory and industry documents, such as the Dietary Supplements Health and Education Act (DSHEA) of 1994. Developed for dietary supplement manufacturers, contract laboratories, and distributors, this reference can be used as a tool for companies striving to comply with the US Food and Drug Administration's (FDA) Good Manufacturing Practices (GMPs) for dietary supplements. The USP-DSC guides readers on how to qualify raw materials, prepare for internal quality control and GMP audits, set and validate SOPs, conduct in–process and batch–release tests, and accurately package, label, and store products. Available at: http://www.usp.org/products/dietary-SupplementsCompendium/.

The European Food Safety Authority (EFSA) has recently released guidance documents discussing how to assess the safety of botanical materials and preparations intended for use in food (dietary) supplements. Aimed at helping food manufacturers evaluate the safety of ingredients they might use in their products, the first of these documents offers a 2-tiered set of scientific criteria on how to prioritize and determine the safety assessment of botanical ingredients. The remaining documents, composed by an EFSA panel of experts, provide tested examples of the safety assessment approach, and an updated and merged compendium of botanicals reported to contain toxic, addictive, psychotropic, or other substances of concern that require specific attention while assessing safety. Available at: http://www.efsa.europa.eu/EFSA/efsa_locale-1178620753812_1211902880387.htm.

Ecosystem Services Experts Directory is a searchable online database of international experts on ecosystems and ecosystem functions, including affiliates of universities, nonprofits, and corporate, government, or international organizations. The directory is a joint project of several international non-governmental organizations (NGOs), e.g., the World Resources Institute, Earthwatch Institute, and the International Union for Conservation of Nature. Updated regularly, the directory aims to be a resource for those who need specific information or guidance on a particular ecosystem trend or environmental management practice. All experts in the directory have 5 years in a research or practitioner role related to ecological functions and/or services, as well as advanced degrees in ecosystem-related fields, e.g., water resources, wetlands, climate regulation, and agriculture. Available at: http://projects.wri.org/ecosystems/experts.

Nutrients, an international, peer-reviewed journal of issues related to food science and nutrition has recently been launched and is freely available online. *Nutrients* does not restrict the length of its articles and manuscripts in order to encourage scientists to publish their experimental and theoretical results in as much detail as possible so that results can be reproduced by others. Aside from providing reviews, research papers, and short communications, the journal also welcomes manuscripts on research proposals and research ideas, manuscripts concerning summaries and surveys on research cooperation and projects, and electronic files or software regarding the full details of the calculation and experimental procedure. Subject areas include: macro, micro, essential, and bioactive nutrients; nutrient requirements and sources; plant, animal, and marine products; sustainability; human nutrition; functional foods; nutraceuticals; dietary supplements, and more. Available at: http://www.mdpi.com/journal/nutrients/.

Office of Dietary Supplements (ODS) recently expanded its website's coverage of the ODS Analytical Methods/Reference Materials (AMRM) Dietary Supplements Program, intended to encourage the development of validated analytical methods and reference materials for dietary supplements to meet the needs of manufacturers, regulators, contract laboratories, academicians, and researchers. On the newly-added AMRM webpage, ODS provides more detailed information about activities and resources for researchers in this area. The webpage's main topics include: an AMRM program description; reference materials for dietary supplement analysis; dietary supplements laboratory quality assurance program; analytical methods for dietary supplements; training, education, and outreach; related resources; and a glossary. Available at: http://ods.od.nih.gov/AnalyticalMethods.

Publications

American Herb Association Quarterly Newsletter: $20/yr. AHA, P.O. Box 1673, Nevada City, CA 95959.

Australian Journal of Medical Herbalism: quarterly publication of the National Herbalists Association of Australia (founded in 1920). Deals with all aspects of Medical Herbalism, including latest medicinal plant research findings. Regular features include Australian medicinal plants, conferences, conference reports, book reviews, rare books, case studies, and medicinal plant reviews. AUD/$95 plus AUD/$15 if required by airmail. National Herbalists Association of Australia, 33 Reserve Street, Annandale, NSW 2038, Australia.

Medical Herbalism: Subtitled "A Clinical Newsletter for the Herbal Practitioner." Edited by Paul Bergner. $36/yr, $60/2 yrs. Canada $39/yr. Overseas $45/yr. Sample/$6. Medical Herbalism, P.O. Box 20512, Boulder, CO 81308.

Other

American College of Healthcare Sciences, ACHS.edu is the only accredited, fully online college offering degrees, diplomas, and career-training certificates in complementary alternative medicine. ACHS is committed to exceptional online education and is recognized as an industry leader in holistic health education worldwide. Visit www.achs.edu, call (800) 487-8839, or stop by the College campus located at 5940 SW Hood Ave., Portland OR 97239..

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