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Bitter Orange Safety Review • Ancient Cancer-Fighting Herbal Beverages • Ginseng for Memory • Ginkgo and Blood Pressure

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Number 89 | February – April 2011

Sage
Salvia officinalis

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Sage

Salvia officinalis

Family: Lamiaceae

Introduction

Sage, also known as common sage or garden sage, is a perennial that grows to a height of 3 feet with blue-violet blooms in summer.[1,2] *Salvia officinalis* originated in Southeastern Europe in the area that is now known as Albania and Bosnia.[3] Today, although cultivated in some European countries (e.g., Albania, Bulgaria, Croatia, Germany, Poland, Romania, Serbia and Montenegro, and Spain) and the United States, more than half of the world's supply is still wild-collected (mainly in Albania, Bosnia and Herzegovina, Croatia, Serbia and Montenegro), with increasing amounts being wild-collected under organic certification.[4-10]

Sage leaves are chewed whole; dried and ground into a powder; prepared as a fluid extract, tincture, or essential oil; or pressed fresh for the juice.[3] The genus *Salvia* is fairly large, containing hundreds of species not addressed in this profile, which are employed for a wide variety of applications in traditional medicine in the regions to which they are native.[11] Aside from *S. officinalis*, the most notable of these are Chinese sage root (*dan shen*; *S. miltiorrhiza*) and *S. divinorum* leaves, the reputed hallucinogen from Mexico.[11]

Sage *Salvia officinalis*. Photo ©2011 Steven Foster

History and Cultural Significance

The genus name *Salvia* derives from the Latin *salvere*, meaning "to save," perhaps referring the healing properties of plants in this genus.[3,12] *Salvia officinalis* was used medicinally by ancient societies in Greece, Egypt, and Rome.[3] Traditionally, it was employed to increase fertility, stop bleeding, heal minor skin wounds, treat hoarseness or cough, and improve memory function.[3] The English herbalist John Gerard (1545-1607) claimed that sage (usually a tea made from the leaves) was good for the head, brain, and memory,[13] and the physician/herbalist Nicholas Culpeper (1616-1654) also thought that it improved memory.[14]

In India, sage leaves were also used to treat intestinal gas, upset stomach, and infections of the mouth, nose, and throat.[3] Historically, sage has been used to promote regularity in a woman's menstrual cycle and to decrease breast milk production to facilitate weaning.[1,2] Since ancient times in most Mediterranean countries, sage has been popular as a culinary herb for its powerful and intense flavor, especially in meat and poultry dishes.[12]

Current uses of sage include the following: indigestion, treatment of inflammation of the mouth and throat, and excessive sweating, including that associated with peri-menopause; relief of pressure spots that result from the use of a prosthesis; and as a flavoring for food.[1-3,11-12,15] Sage oil has also been employed as a fragrance in soaps and perfumes.[1,3]

In 1985, the German Commission E approved the use of sage internally for dyspepsia (upset stomach or indigestion) and excessive perspiration, and externally for inflammation of the nose and throat.[3] One of the constituents of sage, salvin (a phenolic acid), has antimicrobial effects against *Staphylococcus aureus*,[1] a common bacteria responsible for skin and upper-respiratory tract infections. Sage has also shown strong antioxidant properties.[1,2] The German Standard License for sage leaf infusion indicates its use for inflammation of the gums and the mucous membranes of the mouth and throat, for pressure spots caused by prostheses, and in supportive treatment of gastrointestinal catarrh (inflammation of the mucous membranes).[2]

In 2009, the European Medicines Agency (EMA) published a final monograph which supersedes monographs of EU national authorities (including the German monographs) for the registration of traditional herbal medicinal products in the European Community that contain sage as an active ingredient.[16] Traditional uses approved for sage leaf (dry extract, herbal tea, liquid extract and tincture) are (a) for symptomatic treatment of mild dyspeptic complaints such as heartburn and bloating; (b) for relief of excessive sweating; (c) for the symptomatic treatment of inflammations in the mouth and throat; and (d) for relief of minor skin inflammations.[10] A prerequisite of registration is that the quality complies with the corresponding quality standards monographs of the *European Pharmacopoeia* (e.g., Sage Leaf PhEur or Sage Tincture PhEur). Concerning sage essential oil, the EMA has concluded that the risks do not outweigh

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the benefits; thus, a European Community herbal monograph will not be developed until new evidence of clinical safety and efficacy become available.[17]

In the United States, sage leaf is regulated as a food ingredient and as a dietary supplement component. Sage leaf is listed as GRAS (Generally Recognized as Safe) for use as a spice, seasoning, or natural flavor,[18] while sage essential oil is a GRAS flavoring agent.[19] For use of the essential oil as a flavoring, a quality standards monograph for "Dalmatian Type Sage Oil" is published by the United States Pharmacopeia Convention in the *Food Chemicals Codex*.[20] For therapeutic use, as part of the US Food and Drug Administration's (FDA) ongoing review of over-the-counter (OTC) drug products, the Dental Plaque Subcommittee of the Nonprescription Drugs Advisory Committee recently evaluated the safety and efficacy of sage oil combined with peppermint oil (*Mentha* x *piperita*, Lamiaceae). While the Subcommittee concluded that sage oil is safe for the intended use, they also concluded that there are insufficient data from controlled studies to permit final classification of the effectiveness of combined peppermint and sage oils as OTC active ingredients for the reduction of plaque and gingivitis.**[21]**

Modern Research

Note: Some of the studies mentioned below address *S. lavandulifolia* (*lavandulaefolia*), which is now recognized as a subspecies of *S. officinalis*, e.g., *Salvia officinalis* subsp. *lavandulifolia* (Vahl) Gams.[22] (Unless specified otherwise, the species studied was *S. officinalis*.)

Based on sage's traditional use as an aid to memory, preliminary pharmacological investigations were conducted into its bioactivity (*S. officinalis* and *S. lavandulifolia*) that led to more detailed *in vitro* studies which investigated the chemical constituents that might be responsible for aiding failing memory.[11] Results suggested that cyclic monoterpenes 1,8-cineole and alpha-pinene, as well as camphor, were responsible for the cholinesterase inhibition witnessed. Additionally, 1,8-cineole, alpha- and beta-pinene appeared partially responsible for the antioxidant effect of sage. Because Alzheimer's Disease (AD) is thought to be due, in part, to inflammation and damage caused by pro-oxidant compounds that act on the brain cells, and since cholinesterase inhibitors are a standard treatment for AD patients, clinical studies on sage were needed to determine if it might be an appropriate treatment for AD patients.

A 2010 clinical study investigated the effect of the essential oils of *S. officinalis* and other species on cognition and mood in 135 healthy adults (45 in each group of *S. officinalis*, *S. lavandulifolia*, [5 drops of each essential oil in 5 ml water, NHR Organic Essential Oils, Brighton, UK] and no aroma). [23] The *S. officinalis* group performed significantly better than the *S. lavandulifolia* and control groups on the quality of memory, specifically long-term or secondary memory with no impact on working memory performance. The authors state that they would not have predicted the non-significant difference between the *S. lavandulifolia* and no aroma based on previous research, but that one possible explanation could be the lack of standardization of the sage preparations. The *S. officinalis* findings compared favorably with those reported earlier following oral administration of sage in healthy young participants.

A randomized, placebo-controlled, double-blind, balanced, 5-period crossover study in 2008 investigated the acute effects on cognitive performance of a standardized extract of sage (either 167 or 333 mg of a 70% dried ethanolic extract, Essential Nutrition, Brough, East Yorkshire, UK) in healthy adults (n=20) between 65-90 years of age.[24] The study found that administration of a standardized sage extract can improve cognitive function in healthy older people. Specifically, the authors saw dose-specific improvement in secondary memory performance for the 333 mg dose. Results corresponded to those found in earlier studies on younger populations and suggested that further investigations were warranted in larger numbers, other populations, and with different dosing regimens.

In a 2006, a double-blind, placebo-controlled, crossover study, 30 healthy participants received—on 3 separate days, 7 days apart—either 600 mg or 300 mg dried sage leaf or placebo.[25] Mood was assessed predose and at 1 and 4 hours post-dose, with each mood assessment being done before and after 20 minute performance of the Defined Intensity Stress Simulator (DISS) computerized multitasking battery. Improved ratings of mood in the absence of the stressor (pre-DISS) occurred with both doses, with the 300 mg dose reducing anxiety and the 600 mg dose leading to alertness, calmness, and contentedness. Reduced anxiety disappeared upon performance of the DISS. Results corresponded to those in other dose-dependent studies, and the authors suggested that further research was warranted into the potential use of sage in treating AD and natural aging, and the mechanisms responsible for the beneficial effects.

A 2005 placebo-controlled, double-blind, balanced, crossover study investigated the effect of *S. lavandulifolia* on mood and cognition in healthy young volunteers (n=24, 16 female, 8 male, 18-37 years old).[26] Single doses of placebo, 25 ml, and 50 ml of a standardized essential oil (Baldwins, London, UK) were given 4 times, 7 days apart. Participants were tested pre-dose and at 1, 2.5, 4, and 6 hours after dosing. Results showed consistent improvement for both doses on speed of memory, alertness, calmness, and contentedness.

In a 4-month, parallel group, placebo-controlled clinical trial in 2003 where 42 patients with mild to moderate AD were randomized to placebo or fixed dose of *S. officinalis* extract (1:1 in 45% alcohol, Institute of Medicinal Plants, Halejerd, Iran), the patients taking the sage extract showed a significantly better outcome on cognitive functions than placebo.[27] Additionally, agitation appeared to remain more frequent in the placebo group.

Human clinical studies on other aspects of sage have also been conducted. In 2009, a trial assessed the relative efficacy of a sage/echinacea (SE) spray and a chlorhexidine/lidocaine (CL) spray in the treatment of acute sore throat.[28] The SE treatment was a little better at reducing sore throat symptoms than the CL treatment during the first 3 days (63.8% vs. 57.8% at 3 days). No differences were noticed in secondary parameters and both were well-tolerated.

A 2007 prospective, randomized, double-blind, placebo-controlled study investigated the anti-inflammatory effects of a sage extract using the ultraviolet erythema test.[29] Test areas on the backs of 40 healthy volunteers were irradiated with the minimal erythema dose, then treated with 2% w/w of a commercially available sage extract (Flavex GmbH; Rehlingen, Germany), a 1% hydrocortisone control, 0.1% betamethasone control, placebo ointment, or no treatment. The sage extract significantly reduced the UV-induced erythema compared to placebo, and to a similar extent as the hydrocortisone.

A clinical study from 2001 has documented the benefits of a sage-rhubarb cream to decrease the duration of external lip eruptions caused by *Herpes simplex* (*H. labialis*).[30] The same study showed that the sage-rhubarb cream was also effective at relieving the pain and swelling that patients experience with herpetic flares.

Future Outlook

There is little specific information concerning the current market statistics for sustainable harvesting of sage. There are certified operators marketing organic wild-collected sage from European countries

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which requires implementation and inspection of sustainable wild-resource management plans. The European Herb Growers Association (EUROPAM) 2010 update on production of medicinal and aromatic plants (MAPs) in Europe, although not specific, indicates that commercial cultivation increased in Bulgaria while wild collection decreased; that sage remains one of the main medicinal herbs produced in Germany; and that it is still cultivated in Romania and in Greece in cooperatives.[31]

According to one source, Albania has traditionally been one of the world's leading sage producers.[32] It is one of Albania's most important MAPS exports and, in 2001, 1500 tons were exported with a market value of about $2.5 million (USD).

The US imports sage leaf tracked under the 10-digit Harmonized System Tariff Code (HS Code: 1211.9091.50). In 2009, the US imported 2,294.5 metric tons (MT), down 21% from 2008 imports of 2,909.1 MT, over 55% of which is exported by Albania.[33] After Albania, the second-largest supplier of sage leaf to the US is Germany. Although Germany is a producer of sage leaf, much of the German exports are likely re-exports of sage leaf originally from southeastern European countries (J. Brinckmann, e-mail, January 17, 2011).

Previous records indicate that worldwide production equaled 35 tons of sage essential oil in 1993, which was valued at $1,800,000.00.[34] Morocco produced 124.5 tons of dried leaves for export in 1993, but only 81.4 tons in 1996.[35]

Turkey is one of the most important sage-producing countries of the world. Due to overcollection of the herb in the wild that was posing a risk to native populations, a 2-year field study was undertaken to determine which of a number of methods would produce the best seedling quality for commercial cultivation of the plant.[36] The greenhouse seedbed method proved best because it resulted in the most vigorous seedling development and highest total fresh- and dry-weight herb production. A modified float system produced superior root development and less lateral root damage during transplantation. The authors stated that this was only preliminary data and that further studies were required to elucidate cultural requirements of *S. officinalis*.

—Gayle Engels

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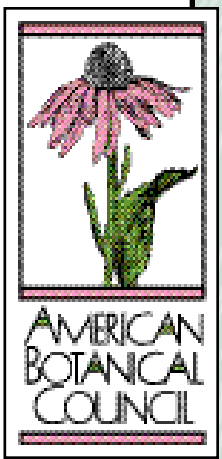


dear *reader*

There has been considerable confusion in the media, and even among health professionals, about the safety of the peel of bitter orange, or Seville orange (*Citrus aurantium*, Rutaceae). In September of last year, *Consumer Reports* again claimed—as it did in 2004—that bitter orange preparations can cause potentially serious adverse effects in humans. The article warned that this peel, which is the common ingredient in orange marmalade, and its extract are dietary supplement ingredients "to avoid." *Consumer Reports* relied on the monograph from the Natural Medicines Comprehensive Database for the information on which it based its conclusion.

In this issue, we present an extensively peer-reviewed safety review of bitter orange, in which the authors analyze the relevant chemical, pharmacological, toxicological, and clinical trial data on the herb. These experts conclude that much of the safety information reported in the popular media and in medical journals about the potential risks of bitter orange—and one of its principle active alkaloids *p*-synephrine—is erroneous and not supported by scientific or clinical data. We hope this review will help to clarify the confusion about the controversial herb's general safety as a dietary ingredient.

When I lived in the mountains of northern New Mexico in the early 1970s, I learned about an interesting, locally used medicinal plant called osha (*Ligusticum porteri*, Apiaceae), the root of which has found a niche in the North American herbal market among herbalists, naturopathic physicians, et al. for its reputed respiratory benefits, among others. Almost all osha is wild-harvested, and attempts to grow small or large plots for commercial markets have not been successful. We present a graphically compelling 12-page review of osha by Christina Turi and Susan Murch of the University of British Columbia Okanagan, Kelowna, British Columbia.

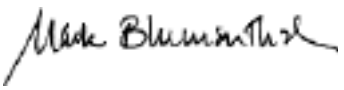
Except for occasional mention in *HerbalGram* reports on sustainability issues, and in 1 article on the ethnobotany of the American Southwest, we have not previously devoted much space in these pages to osha, for 2 basic reasons: First, there's been no published human clinical research on osha, and second, we did not want to run the potential risk of calling undue commercial attention to this plant due to our concerns about its sustainability. However, now we believe it is time to give this respected traditional medicine its due, despite the lack of data from human clinical trials.

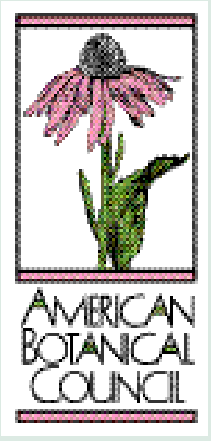
In the regulatory arena, one of the most important aspects of the FDA's final rule on cGMPs (current Good Manufacturing Practices) for dietary supplement manufacturers is that since June, *all* manufacturers of supplements, regardless of the company's size, must comply with the cGMP rule. One of the most important areas in this quality control pertains to the fact that all manufacturers must qualify their suppliers and their ingredients, as the suppliers themselves are not required to meet the cGMP rules for the ingredients they sell. Some industry trade organizations have proposed a mechanism to standardize information shared among suppliers and manufacturers regarding ingredient specifications, in order to make the communication of such information more streamlined. Presumably, this mechanism will eventually lower the cost of such communication (i.e., the Standardized Information on Dietary Ingredients initiative, or SIDI). Andrew Shao of the Council for Responsible Nutrition provides insights into this process.

Another of this issue's articles concerning herb quality comes from long-time ABC Advisory Board member Dennis Awang, a respected natural product chemist and author, and a former regulator for 20 years in Canada. In his guest editorial, based on a recent speech, he calls for more focus on the identity and quality of botanical ingredients in Canada, and, by extension, also in the United States.

The issue of botanical quality of herbal dietary supplements (in the United States) and natural health products (in Canada) is of great concern. While many ethical and responsible companies take great pains to ensure the proper identity and quality of the botanical raw materials and extracts they use in their finished products, unfortunately there are still those who do not exercise adequate measures to properly qualify their raw-material suppliers, who, as noted above, are exempted from the FDA's final rule on cGMPs. Thus, the ultimate onus of confirming proper identity and quality lies with the herbal supplement manufacturer.

In the coming year, within these pages and elsewhere, ABC will be publishing additional papers addressing herb quality as part of our contribution to community-wide efforts to ensure that consumers are able to obtain herbal products which are of acceptable and reliable quality.





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features

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departments

On the Cover
Sage *Salvia officinalis*.
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ABC by the Numbers in 2010

Despite a challenging economy, in 2010, the American Botanical Council successfully continued its mission to spread science-based information regarding herbal medicine and the uses of beneficial botanicals. Presented here is a quick review of some of the tactics, accomplishments, and milestones resulting from these efforts.

New Audiences

19,600,000 people! The power of television—and more specifically, PBS—is the catalyst for this amazing number of individuals who have been or soon will be exposed to ABC's unique nonprofit educational mission. ABC has video-recorded 14 "Herbal Insight" segments for the PBS series *Healing Quest*, co-hosted by singer-actor Olivia Newton-John and broadcast on 145 PBS channels across the United States. Each Herbal Insight segment, featuring ABC's executive director, Mark Blumenthal, focuses on the history, uses, and benefits of a single herb, making the science behind that herb easily accessible and interesting to the viewer. To view these segments, readers can check their local PBS listing or look on ABC's website (www.herbalgram.org) under "News."

Increased Media Education

As a reliable third-party educational resource, ABC is regularly contacted by the media for interviews regarding recent studies, reports, or articles on herbs and herbal products. In 2009, ABC participated in 64 interviews. In 2010, ABC gave 91 interviews to the media including: *The Wall Street Journal*, WebMD, *Martha Stewart Living*, *USA Today*, *Natural Foods Merchandiser*, and AARP. In addition, Mark Blumenthal coauthored an article for the Dr. Oz website. These media education efforts are essential to redirect the often misinformed articles on botanicals appearing in magazines, newspapers, and online publications throughout the United States and the rest of the world.

Increased Global Education

In 2009, ABC—primarily Mark Blumenthal—gave 34 lectures, speeches, and/or talks. In 2010, Blumenthal traveled 118,288 miles to 24 cities, 12 states, 7 countries, and gave 57 presentations that directly educated thousands of individuals. This amounts to his having traveled 4.75 times around the world.

Increased Internships for Pharmacy and Dietetic Students

Each year ABC offers internships for pharmacy doctoral students and students earning dietetic bachelor or master's degrees in their final year of study, helping them understand the vital role that herbs and medicinal plants play in self-care and healthcare. The interns' experiences at ABC are also designed

Employee Profile: **Ashley Lindstrom**

The responsibility of producing a magazine like *HerbalGram* requires a myriad of tasks. At the center of the activity is the managing editor.

This profile introduces our new managing editor, Ashley Lindstrom. She was hired last year as an assistant editor, but with the departure of our former managing editor—and despite applications from a number of qualified applicants—she was promoted to the position after working at ABC for only one month!

Ashley hails from San Antonio, Texas, and holds a master's degree in journalism from the University of Southern California in Los Angeles. She is cheerful and friendly, has a unique sense of personal style, and is fully committed to her new position at ABC. A former mezzo-soprano who sang opera and musical theatre in high school, Ashley made her stage debut in college as the titular character in a theatrical adaptation of *Mariette in Ecstasy*, which she followed up with a role as a homeless junkie in a lab production of *Bad Penny*. Thanks to a graduate-level elective class, Ashley is ABC's resident David Lynch expert, and her film column "Critical Darling" appears fortnightly in a San Antonio alternative weekly newspaper. When Ashley isn't writing, editing, or digging for treasures in a thrift store or vintage clothing shop, she volunteers for the local children's museum and an avant-garde theatre company.

In her role as managing editor, she respon-

to teach them how to find reliable information on the potentially beneficial role that herbs and other plant-based dietary supplements can play, and how to incorporate them responsibly into their future professional practice. In 2009, ABC provided 15 internships. However, last year the number of internships awarded was boosted to 21.

Honored with the Varro E. Tyler Prize

In 2010, Mark Blumenthal was the recipient of the prestigious Varro E. Tyler Prize bestowed by the American Society of Pharmacognosy. Dr. Tyler was an early member of the ABC Board of Trustees and a mentor to Blumenthal. According to ASP, Blumenthal was given the award because of his enduring and dedicated service to the botanical supplement and phytomedicine communities, as well as his commitment to the development and dissemination of accurate information about the safety and benefits of botanicals.

Launched Educational Herbal E-Cards

Last year, ABC began offering registered users of its website and ABC members the opportunity to send beautiful herbal education electronic cards free of cost. Each E-card, designed by ABC, focuses on a specific herb, features stunning photography by Steven Foster, and provides science-based herbal education on the uses and benefits of the featured herb. There are currently 29 ABC E-cards covering health-related topics such as heart health, vision, and colds; botanicals for each birth month; holidays such as Mother's Day, Father's Day, and Valentine's Day; and a few all-occasion cards. Not only are these cards a pleasure to look at, they advocate spreading herbal medicine messages to new audiences and increase knowledge about the science behind correct herb uses. To date, E-cards have been sent to more than 4,895 people, presumably some of whom were previously unacquainted with ABC's nonprofit educational mission.

Hosted Visitors at the ABC Homestead

In 2010, more than 300 people visited ABC's office/homestead, located in Austin, Texas. Some were local Texans popping in to ABC to help celebrate HerbDay; others were visiting for the Council for Responsible Nutrition or the American Herbalists Guild conferences, both of which were held in Austin in October of last year. Other visitors included US Military/Baylor University Graduate Program in Nutrition students. The majority of visitors were treated to herb walks through ABC's 30+ medicinal demonstration gardens, including the newest Ayurvedic garden, dedicated in 2010.

Continued on pg. 14

sible for writing and editing articles for both *HerbalGram* and HerbalEGram (ABC's monthly e-newsletter), plus other non-serial publications (e.g., news releases, ABC member advisories, etc.). She is also responsible for communicating with authors and potential contributors to *HerbalGram* and HerbalEGram, as well as coordinating ABC's extensive peer-review process. (Unlike most peer-reviewed publications which normally rely on 2 expert reviewers, many *HerbalGram* articles—particularly the features—employ 3-5 or more reviewers. This requires significantly more time from ABC staff to compile reviewers' comments, communicate with the author(s), and complete the article for layout.)

Ashley also manages the *HerbalGram* proofreading process, and ensures (with Art Director Matt Magruder) that *HerbalGram* issues are completed on time with (hopefully) no errors. Ashley is also responsible for maintaining the inventory of all articles and their status in the editorial process, as well as the magazine's style sheet, which provides instruction and suggestions to *HerbalGram* contributors.

In addition to the above tasks, and others not listed, Ashley writes her own bylined articles for publication in *HerbalGram* and/or HerbalEGram, which entails researching subject matter, interviewing sources, writing and editing drafts, soliciting peer review, and occasionally securing photos/visuals to accompany articles. Her favorite topics include ancient plant-based medicine and herbal art.

Having such a full plate is common for employees of a nonprofit organization, where there are always more things to do than there are people to handle them. But Ashley takes the workload in stride, almost relishing it. As she told me one day in my office, "I'm never fully alive unless I'm in over my head."

–Mark Blumenthal

Continued from pg. 13

Published by ABC in 2010

4 issues of *HerbalGram* covering topics including: Replacing Animal-Based Remedies with Plants; Fair Trade Botanicals; Essential Oils & Drug Resistant Bacteria; Bacopa and Memory; Costa Rican Plants; The Rising of Herb Sales During the Recession; and Saffron and Alzheimer's.

12 issues of HerbalEGram, ABC's monthly e-newsletter featuring community and industry news, media watch links, PDFs of recently published books, a calendar of upcoming events, and new articles pertaining to the herbal community.

360 HerbClips, summaries and/or critical reviews (15 produced twice monthly) of clinical trials, articles, or other publications related to medicinal plants.

These publications are a benefit of ABC membership. More information about how to become an ABC member and thus support ABC's educational efforts is available by contacting ABC at 512-926-4900 or development@herbalgram.org.

In 2010, 14 ABC employees provided services to over 3,000 members in approximately 80 countries. The accomplishments outlined in this article are made possible mainly by the dedication of the many volunteers who offer their time and talents to keep ABC the premier herbal education organization, as well as to the members who provide the necessary resources to meet ABC's unique and essential nonprofit education mission. The ABC staff dedicates all of ABC's successes of 2010 to this wide and varied group of people who are interested in the beneficial roles that herbs and medicinal plants can and will play in self-care and healthcare.

—Denise Meikel

Join ABC in the Amazon!
See ad on pg. 25

Archaeological Oncology Project Uncovers Cancer-Fighting Compounds in Ancient Herbal Beverages

New research has revealed that some ancient cultures' botanical cancer treatments may in fact be viable. This news comes from from "Archaeological Oncology: Digging for Drug Discovery," a collaborative effort between the University of Pennsylvania Museum's (UPM) Biomolecular Archaeology Laboratory and Penn Medicine's Abramson Cancer Center in Philadelphia.

Archaeological Oncology researchers tested remnants of alcoholic herbal beverages from ancient Egypt and China, and found that several plant-derived compounds present in the samples showed lung- and colon-cancer-fighting activity.[1]

According to archaeochemist Patrick McGovern, PhD—the scientific director of the UPM Biomolecular Archaeology Laboratory for Cuisine, Fermented Beverages, and Health—the Egyptian and Chinese samples were selected for the Archaeological Oncology project in part because the lab had already been performing tests on them (oral communication, October 28, 2010). "[T]hey are very important samples, some of the earliest … and we went back and we reanalyzed them," said Dr. McGovern. "We just used a whole series of these more precise methods to start getting the compounds that would give us clues as to what the additives were."

Residue from an ancient Egyptian wine was procured from a jar dating back to ca. 3150 BCE; it had been buried with pharaoh Scorpion I of Dynasty 0.[1] (The potential general medicinal use of this wine sample was discussed in *HerbalGram* 2009; 83:22-23.) The substance was identified as a grape (*Vitus* spp., Vitaceae) wine through Liquid Chromatography Tandem Mass Spectrometry and Headspace Solid Phase Microextraction and Thermal Desorption Gas Chromatography-Mass Spectrometry (TD GC-MS). Researchers also determined that the wine contained "pine and/or terebinth tree resin" (*Pinus* spp., Pinaceae/*Pistacia* spp., Anacardiaceae). Based on the presence of 8 terpenoid compounds—including camphor, borneol, carvone, linalool, L-menthol, thymol, α-terpineol, and geranyl acetone—it is believed the wine contained Levantine herbs, likely savory (*Satureja* spp., Lamiaceae), wormwood (*Artemisia annua*, Asteraceae) and/or mugwort (*A. argyi*), tansy (*Tanacetum* spp., Asteraceae), balm (*Melissa* spp., Lamiaceae), senna (*Senna* spp., Fabaceae), coriander (*Coriandrum* spp., Apiaceae), germander (*Teucrium* spp., Lamiaceae), mint (*Mentha* spp., Lamiaceae), sage (*Salvia* spp., Lamiaceae), and thyme (*Thymus* spp., Lamiaceae).[1]

According to a review published in the *International Journal of Oncology*, these herbal ingredients suggested to the researchers that the wine was likely intended to dispense a drug, as there are numerous records of ancient Egyptian prescriptions for herbal wines and beers.[1]

The ancient Chinese beverage tested by the Archaeological Oncology project had been preserved as a liquid inside a bronze jar from ca. 1050 BCE, found in the Changzikou Tomb in the Henan Province.[1] Analysis by TD GC-MS exposed camphor and α-cedrene in the liquid, as well as "benzaldehyde, acetic acid, and short-chain alcohols characteristic of rice [*Oryza sativa*, Poaceae] and grape wines."[1] Through further testing, the researchers were able to determine that the beverage was rice-based, and that the

Patrick McGovern and Melpo Christofidou-Solomidou examine an ancient shard. Photo ©2010 Abramson Cancer Center Laboratory, University of Pennsylvania Health System.

aromatic compounds, camphor and α-cedrene, may have come from China fir (*Cunninghamia lanceolata*, Cupressaceae), a type of chrysanthemum (*Dendranthema* spp., Asteraceae), or perhaps 1 or 2 species of the genus *Artemisia* (such as wormwood or mugwort).[1]

"If an *Artemisia* species explains the presence of camphor and α-cedrene, then the plant's leaves had probably been steeped in rice wine, as is still done in TCM [Traditional Chinese Medicine]," wrote the researchers in their review.[1]

In vitro testing, an additional activity of the Archaeological Oncology Project, found artemisinin, a compound originating in wormwood, to be active against both lung and colon cancers. Artesunate—a less toxic "semi-synthetic analogue" of artemisinin—proved even more effective than artemisinin against colon cancer and several other cancers. Additionally, compounds derived from the ancient beverages, including borneol, isoscopoletin, and ursolic acid, also inhibited tumor growth in laboratory tests.[1]

According to John Riddle, PhD, distinguished professor emeritus of history at North Carolina State University, modern civilization has "absolutely" lost many effective, ancient, botanical treatments for cancer (e-mail, October 28, 2010). In an article titled "Ancient and Medieval Chemotherapy for Cancer," published 25 years ago, Dr. Riddle asserted that "The modern scientist might employ the history of a drug, especially in the works of the leading medical authorities, as a starting point for conducting animal and clinical tests. Important clues exist in the historical records about which drugs might be worth testing… For too long we have believed that the past was filled with more superstition and stupidities than with experienced judgment about medicine."[2]

Dr. McGovern plans to persist in testing ancient beverages to find clues for contemporary medical treatment. "We're hoping to get an NIH [National Institutes of Health] grant," said Dr. McGovern, "to continue this research, looking at other parts of the world where humans were also exploring their environment and trying to discover perhaps medicinal compounds that could be dissolved into alcoholic beverages."

Beverages from Peru, southern France, and Scandinavia have been targeted for future testing, and Dr. McGovern would also like to analyze samples from the Near East.

The researchers would have moved forward with clinical testing of artesunate's anti-cancer effects; however, according to Dr. McGovern, a team of Germans independently discovered those effects around the same time, and has already commenced clinical trials. "The way that medical people look at it," said Dr. McGovern, "if someone's already beat you to that, there's no reason to do more on that particular compound. We just have to find other compounds that are effective, too."

— Ashley Lindstrom

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The Plant List: The First Comprehensive Inventory of Most Known Plant Species

"If the names are unknown, knowledge of the things also perishes."[1] **–Carl Linnaeus**

A single plant can be given multiple scientific names over time.[2] More than 3,000 scientific names exist for only 19 species of *Mentha* (Lamiaceae), for example, and thousands of additional plants have multiple names (A. Tucker, e-mail, September 25, 2010). This is the result of plant systematists disagreeing with the original author's naming, an unawareness that particular plants have already been named, or the changing of plant names to reflect evolving knowledge of relationships among plant species. Based on the widely used "principle of priority," the "correct" name of a species should be the first name published according to guidelines set out in the International Code of Botanical Nomenclature.[3] Often, the oldest plant names are found in the 1753 book *Species Plantarum*, written by Carl Linnaeus, a Swedish botanist who is referred to as the father of taxonomy.

Still, these numerous names continue to cause confusion and problems, especially in the case of geographically widespread plants and commercially used plants like medicinal herbs. "We need clear, definitive names to facilitate communication among plant scientists and those in the commercial world, to be sure that we are all using the same name in the same way," said John Wiersema, PhD, a botanist at the US National Germplasm Resources Laboratory and director of the GRIN (Germplasm Resources Information Network) database (e-mail, October 28, 1010). "Any piece of information on a particular taxon is largely meaningless if the name to which it is associated cannot be accurately represented."

"We need clear, definitive names to facilitate communication among plant scientists and those in the commercial world, to be sure that we are all using the same name in the same way."

Seeking to solve this problem, the Royal Botanic Gardens, Kew, and the Missouri Botanical Garden (MOBOT) are currently creating a more definitive and comprehensive list of plant names that indicates which names are accepted as correct and which are synonyms.[4] "The Plant List," as the project is called, was started by Kew and MOBOT in 2008 as an initiative addressing the Global Strategy for Plant Conservation's (GSPC) first target goal, which calls for "a working list of all known plant species" by 2010. According to GSPC's website, such a list "is considered to be a fundamental requirement for plant conservation."[5] The GSPC was enacted in 2002 by the Convention on Biological Diversity, an international treaty that aims to stop the "continuing loss" of the earth's plant diversity, as well as to encourage sustainable use and benefit-sharing of plants.[6]

Botanists and other scientists, as well as information technology specialists at Kew and MOBOT have been developing and testing a new process to generate the list, which consists of merging existing resources through an automated, rules-based approach.[4] The heuristic informatics method captures taxonomic knowledge into a rulebase, and computers are then used to aid in sorting out the millions of plant name records from Tropicos, Kew's World Checklist of Selected Plant Families, The International Compositae [Asteraceae; daisy family] Alliance, International Legume [Fabaceae] Database and Information Service (ILDIS), and plant name information from the International Plant Name Index (IPNI).

Several media sources have reported that the project will eventually cut the global list of plant names by 600,000, making the number of plant species names about 400,000.[7] The project is not exactly cutting plant names from existence, however. "The significance of The Plant List," said a Kew spokesperson, "is not to provide a few names and delete the non-current ones, but rather to identify the names which are used and have been used in the past, and as far as possible link the names which refer to the same species to facilitate information retrieval and study" (B. Friedlander, e-mail, October 29, 2010).

"There are around 1,000,000 Latin names for plant species," said the spokesperson. "The estimates for the number of [actual] plant species vary from around 250,000 to 440,000. Our work on The Plant List to date suggests that the number of species is likely to be nearer the high end of that range. Thus plants have on average between 2 and 3 names; plants which are widespread and used tend to have several synonyms. This obviously is a problem. Some work we have done at Kew suggests that if you search online resources for a medicinal or nutritional plant using just one of the alternative names of a species, you might only find 20% of the information about the species. The point of The Plant List is to alert people that more than one name for a species might exist and if they are interested in finding out about that species, they need to search using the alternative names (synonyms)."

According to the Kew spokesperson, who noted that the project is a work in progress, the list currently contains 301,000 accepted species names, 480,000 synonym names, and 240,000 remain un-assessed as being either accepted or synonyms. Remaining work includes the adding of important data sets to the resource, such as key names resources on legumes, composites, and grasses (Poaceae), so that the working list is as comprehensive as possible.[4] Kew recognizes that the list has its limitations, including a lack of coverage of ferns and fern allies (pteridophytes, about 10,000 species) and algae (about 30,000 known species), variable completeness and accuracy in synonymy information for flowering plants other than monocots, and weak coverage of Southeast Asia and genera that start with letters in the latter half of the alphabet.

"It will not be perfect, but for the first time we will concentrate the available information in one place," said the spokesperson. "One of the reasons this has not been done before is that different sources of synonymy information sometimes conflict and these differences need to be resolved." The final list was published at the beginning of the New Year at www.theplantlist.org.

Though Kew and MOBOT did not work with the American Herbal Products Association (AHPA), which publishes the smaller subset of common and Latin names of most herbs used in commerce in the United States, *Herbs of Commerce*, 2nd edition, this will not affect the quality of the final product, said Michael McGuffin, AHPA's president (e-mail, October 25, 2010). "The institutions involved are highly authoritative," he said, "and there is every reason to believe that they will produce an excellent and comprehensive final product." Still, *Herbs of Commerce* will remain as is. "The Kew/MOBOT project appears to be of a very broad scope," he continued. "The purpose of *Herbs of Commerce* seeks to provide a unified nomenclature for just over 2,000 herbs used in dietary supplements. These decisions were made on a case-by-case basis, usually deciding in favor of names that reflected or facilitated common use."

Likewise, GRIN will continue to base its plant classifications on primary sources, such as taxonomic articles published in scientific literature, and will use secondary sources, such as The Plant List, "only when more primary sources of information are lacking, or perhaps to alert us to the need to further evaluate a particular taxon," said Wiersema. Though there has been no organized effort similar to The Plant List between GRIN and its partners, taxonomic experts from these organizations continuously try to indicate and employ the most "correct" and current taxonomic acceptance of any name, he continued. According to Wiersema, the resources being used for The Plant List, which have been critically reviewed by taxonomic specialists for certain groups, will be adequate for some plant families. "For many other families this remains to be seen," he added. A reviewer of this article noted that, while The Plant List will be imperfect, a list with errors and omissions is a better starting place than no list at all, and that the manpower and funding to create a totally complete list of all names do not exist.

Before Linnaeus published *Species Plantarum*, biologists used various naming practices, which often included long series of Latin names, such as one of the pre-Linnaean names for the common briar—*Rosa sylvestris alba cum rubore, folio glabro*.[8] Additionally, these names could be altered whenever a biologist wanted to do so. About this time, many new botanical and animal specimens were being brought back to Europe from the New World, further increasing the need for a more definitive and organized nomenclature system.

In *Species Plantarum*, Linnaeus introduced the binomial system of scientific naming by combining the genus name and the specific, descriptive epithet designating the species. For example, the scientific binomial of garlic is written as *Allium sativum*, *Allium* being the genus, *sativum* being the epithet, and *Allium sativum* being the species (in the family Alliaceae or Lilliaceae, depending on modern taxonomic preference). Thus his name for common briar became *Rosa canina* (Rosaceae). Though this system has been used throughout much of history, it was not until 1930 that international representatives officially agreed upon using it and *Species Plantarum* as the source for oldest botanical names.[9] Among additional requirements laid out in this agreement—the International Code of Botanical Nomenclature—is the rule that to be official, botanical names must be published in a normal botanical publication that is delivered to at least 2 botanical organizations.

The Plant List website is available at: www.theplantlist.org.

—Lindsay Stafford

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NCCAM Prioritizes Several Herbs for Mechanistic Research Grant

The National Center for Complementary and Alternative Medicine (NCCAM) of the US National Institutes of Health (NIH) has designated several herbs as funding priorities for a recent $8.1 million grant project.[1] "Mechanistic Research on CAM Natural Products" is sponsored by NCCAM, the National Cancer Institute (NCI), and the Office of Dietary Supplements (ODS).[2] It funds only research on the action mechanisms of natural products, so studies on products' clinical efficacy will not be funded by this particular project. Acceptance of applications began November 1, 2010.

While the investigation of herbs' and other CAM products' efficacy is essential and ongoing at NCCAM, understanding how the substances work in humans to produce specific outcomes is also important.[2] And, according to NIH's grant announcement, "Despite the widespread use of these products, insight into potential biological mechanisms of action frequently is lacking." Additionally, the composition of many natural products, botanicals especially, is complex and makes understanding their action mechanisms significantly more difficult.

NCCAM has listed the following herbs as areas of priority in regards to the mechanistic research grant project:[1]

- Ashwagandha (*Withania somnifera*, Solanaceae)
- Astragalus (*Astragalus membranaceus*, Fabaceae)
- Devil's claw (*Harpagophytum procumbens*, Pedaliaceae)
- Echinacea (*Echinacea purpurea*, Asteraceae)
- Ginseng, Asian (*Panax ginseng*, Araliaceae) & American (*P. quinquefolius*)
- Hops (*Humulus lupulus*, Cannabaceae)
- Milk thistle (*Silybum marianum*, Asteraceae)
- Thunder god vine (*Tripterygium wilfordii*, Celastraceae)
- Turmeric (*Curcuma longa*, Zingiberaceae)

Devil's Claw *Harpagophytum procumbens*. Photo ©2011 Steven Foster

More specifically, NCCAM will focus on funding ashwagandha research that investigates whether a more systemic type of activity is responsible for the herb's diverse effects on the body, which include anti-leishmanial activity, immune modulation, decreased anxiety, and possible prevention of neurodegenerative diseases and cancer. Accepted research might examine such physical responses to the herb as changes in gene, protein, or regulatory RNA expression or localization.

Echinacea *Echinacea purpurea*. Photo ©2011 Matthew Magruder

Though recent research has identified several active components of astragalus, NCCAM would like to fund research that aims to "fully characterize the bioactive compounds" of this herb and its activities and mechanisms of action, particularly looking at complex polysaccharides.

Research on devil's claw funded by this particular NCCAM grant would, in part, aim to identify a biomarker of anti-inflammatory activity (other than the harpagoside compound), as well as study the herb's documented analgesic properties, analgesic mechanisms of action, and the compounds responsible for these effects.

Because some *in vitro* activity of echinacea has depended on the plant part and extraction method used, funded studies would seek to identify both optimal species and extraction methods. Also, research would focus on identifying components responsible for immune activities and marker components for standardization and pharmacokinetics, and clarifying the biological signature.

As for ginseng research, NCCAM is encouraging investigations using systems biology approaches to study the potential

Milk Thistle *Silybum marianum*. Photo ©2011 Steven Foster

action mechanisms of specific components, such as individual ginsenosides and ginseng-derived glycans or terpenoids from different ginseng species or preparations.

Prioritized hops research would seek to establish better understanding of its phytoestrogenic principles, including receptor or tissue specificity, and which components are responsible for any sedative activity and their action mechanisms.

Further, NCCAM will focus on funding milk thistle research that investigates the *in vitro* and *in vivo* activity of the plant's individual components and how the components work collectively, as well as studies into mechanisms associated with the hepatoprotective and chemopreventive activities and the herb/drug interactions of silymarin, an extract of milk thistle.

Thunder god vine research that receives NCCAM funding from this particular grant would focus on identifying compounds other than triptolide that might influence the plant's overall activity. Lastly, turmeric studies would investigate the metabolites responsible for activity and their tissue distribution, pharmacokinetics, and pharmacodynamics, as well as the bioavailability of individual curcuminoids compared with different formulations of mixtures and extracts.

Additional CAM areas of interest for the mechanistic action grant project include beta-glucans, coenzyme Q 10, polyphenols (e.g., flavonoids, catechins, anthocyanins), probiotics, polyunsaturated fatty acids (PUFAs), and vitamin D. According to NCCAM, this listing of research priority areas is not exhaustive and might change over time as new science emerges and brings with it new priorities. More detailed information on these research priorities, as well as examples of responsive projects funded by this grant is available at www.nccam.nih.gov/grants/CAMNP/priorities/?nav=upd.

—Lindsay Stafford

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Convention on Biological Diversity's 10th Conference of the Parties

International Body Sets New Voluntary Goals for Protection of Animals, Plants, Traditional Knowledge

In 2002, member parties of the Convention on Biological Diversity (CBD) laid out global conservation and sustainability targets to be met by the end of the decade, and labeled 2010 the "International Year of Biodiversity." But as 2011 quickly approached on the heel of reports that one-fifth of the world's plant and vertebrate species are threatened with extinction,[1] there was unequivocal agreement that the Convention and its members failed to achieve their goals.[2] Now, CBD member parties have returned from their most recent international meeting with new policies to guide their conservation efforts through 2020.

CBD is an international treaty that aims to conserve the world's biological diversity, encourage sustainable use of its components, and promote fair and equitable sharing of benefits that come from genetic resources. The European Union and 192 member countries make up its governing body, called the Conference of the Parties (COP), which meets every 2 years to review the Convention's progress, adopt new goals and programs, and provide policy guidance.[3] Though the United States helped write the first draft of the Convention more than 20 years ago, the US Congress has not yet ratified it, leaving the nation unable to vote as a Party. The United States is the only major country and one of only 3 countries total (alongside Andorra and the Holy See) that have not ratified the convention.[4]

Seven thousand delegates gathered for the 10th COP (COP 10) from October 18-29, 2010, in Nagoya, Japan, and adopted 47 decisions.[5] These included a 2011-2020 Strategic Plan, the Nagoya Protocol on Access to Genetic Resources and the Fair and Equitable Sharing of Benefits Arising from their Utilization, and an updated and revised Global Strategy for Plant Conservation (GSPC). Though several parties consider some of these decisions to be imperfect, many are calling the reaching of consensus—which came after days of long negotiations—a historical achievement.[6]

The Strategic Plan

The Strategic Plan is considered a useful, flexible framework that country parties should use to revise or develop national and regional targets while taking into account their own priorities and capacities. The targets, summarized below, are to be met by 2020.[5]

Target I: Address underlying causes of biodiversity loss by mainstreaming biodiversity action across government and society

(a) Ensure that people are aware of the values of biodiversity and what they can do to conserve and use it sustainably.

(b) Integrate biodiversity values into national and local development and poverty-reduction strategies and ensure that planning processes are being incorporated.

(c) Eliminate, phase out, or reform incentives (e.g., subsidies) that are harmful to biodiversity, and develop and apply positive incentives for the conservation and sustainable use of biodiversity.

(d) Ensure that governments, businesses, and stakeholders have implemented plans for sustainable production and consumption and have safely and ecologically used natural resources.

Target II: Reduce direct pressures on biodiversity and promote sustainable use

(a) Halve, or bring to zero, the rate of natural habitat loss and significantly reduce degradation and fragmentation.

(b) Sustainably manage and harvest all fish and invertebrate stocks and aquatic plants through legal approaches that ensure fisheries do not adversely impact

Standing ovation for the adoption of the Nagoya Access and Benefit Sharing Protocol at 1:28 a.m.
Photo ©2011 KK Davis

threatened species and ecosystems.

(c) Sustainably manage areas of agriculture, aquaculture, and forestry so that biodiversity is conserved.

(d) Reduce pollution levels so they are not detrimental to ecosystems and biodiversity.

(e) Identify and prioritize invasive alien species and pathways, control or eradicate priority species, and implement measures to prevent their introduction and establishment.

(f) Minimize the multiple anthropogenic pressures on coral reefs and other vulnerable ecosystems impacted by climate change or ocean acidification.

Target III: Improve the status of biodiversity by safeguarding ecosystems, species, and genetic diversity

(a) Conserve at least 17% of terrestrial and inland water areas, and 10% of coastal and marine areas, especially areas of particular importance for biodiversity.

(b) Prevent the extinction of known threatened species and improve and sustain their conservation status, particularly of those in most decline.

(c) Maintain genetic diversity of cultivated plants and farmed and domesticated animals and their wild relatives, including economically and culturally valuable species.

Target IV: Enhance the benefits to all from biodiversity and ecosystem services

(a) Restore and safeguard ecosystems that provide essential services, taking into account the needs of women, indigenous and local communities, and the poor and vulnerable.

(b) Enhance biodiversity's contributions to carbon stocks through conservation and restoration, including restoration of at least 15% of degraded ecosystems.

(c) Ensure that the Nagoya Protocol on Access to Genetic Resources and the Fair and Equitable Sharing of Benefits Arising from their Utilization is in force and operational, consistent with national legislation, by 2015.

Target V: Enhance implementation through participatory planning, knowledge management, and capacity building

(a) Ensure that each Party has started implementing an effective, participatory, and updated national biodiversity strategy and action plan by 2015.

(b) Respect and recognize indigenous and local communities' customary use of biological resources, traditional knowledge, innovations, and practices.

(c) Improve, widely share, and transfer biodiversity's science base, technologies, values, functioning, status and trends, and consequences of its loss.

(d) Mobilize and substantially increase financial resources for effectively implementing the Strategic Plan 2011-2020.

Controversy Over Benefit Sharing Decisions

Perhaps the most contentious element of CBD COP 10 was the Nagoya Protocol for Access and Benefit Sharing (ABS), mentioned in the Strategic Plan's Goal IV.[5] One of CBD's main objectives is to promote fair and equitable sharing of benefits that come from genetic resources, such as plants, fungi, and pathogens, and member parties have discussed a treaty on this subject for many years.

After many late-night sessions and last-minute negotiations, the ABS Protocol was passed and adopted at COP 10. It will go into effect in 2015. "The final hours at Nagoya were very tumultuous," said Katherine Davis, ABS advisor for Botanic Gardens Conservation International (e-mail, December 6, 2010). "The negotiating group worked at speed to try to finish, but still failed to reach agreement on the last key core points. So the Japanese presidency, with everything at stake, swooped in with some proposed compromises and managed to get agreement—this final maneuver added in some of the most ambiguous text."

"The debate has always been in part about righting the wrongs of colonialism and neo-colonialism, and ensuring that the countries of origin will be involved in, and able to set the terms for, the development of profitable products from genetic resources—versus over-regulation that could make such development too complex and costly for profits ever to ensue," Davis continued. "There's a tension between sovereignty and cooperation—countries want to make their own rules, but they want other countries to be more responsive to their regulations."

As the medicinal plant trade often includes the exchanging of resources, knowledge, and benefits among developed and developing countries or indigenous groups, the Nagoya Protocol has the ability to affect industry practices. This, however, will ultimately depend on the extent of related actions taken by members. Selected elements, summarized below, instruct member parties to do the following:[5]

- Ensure that parties who supply genetic resources are given fair and equitable benefits (monetary and non-monetary) arising from the using of genetic resources, their subsequent applications, and commercialization. These benefits should be intended and used for conserving biodiversity and sustainability.
- Ensure that access to genetic resources is decided by the country of origin of the resources or a party that has acquired resources in line with the Convention, and shall be handled in a fair, transparent, and legal way.
- Ensure that traditional knowledge of genetic resources from indigenous and local communities is accessed with their involvement and previously informed consent, and that mutually agreed upon terms have been established.
- Promote and encourage non-commercial research, especially which contributes to conservation and sustainability and that would be used to address threats to human, animal, and plant health.
- Practice trans-boundary cooperation between local and indigenous groups, as well as between these groups and other parties, and respect their laws and community procedures.
- Ensure that genetic resources are utilized within the policies of the Protocol and take necessary measures to support compliance and transparency, such as permits and checkpoints.

"It's pretty amazing that the Protocol did get adopted, given the last-minute nature of the negotiations," said Davis. "It is not a very elegant document but it does pull the main issues together and tackle compliance." Though the passing of the Protocol is commendable, the document is not perfect in all parties' eyes. During COP 10's closing session, delegates from Venezuela expressed that it does not adequately stop biopiracy, and others from Africa and Asia said it is not the best document but that they would accept it as a starting point.[5] Representatives from Bolivia

voiced their disagreement with the Protocol, saying that many countries' viewpoints were left unaddressed, as was recognition of indigenous groups' contributions. Additionally, concerns about access to research material for conservation purposes remain, said Danna Leaman, chair of the Medicinal Plant Specialist Group of the International Union for the Conservation of Nature's (IUCN) Species Survival Commission (SSC). "How national legislation deals with this issue is still to be determined" (e-mail, December 2, 2010). Leaman noted that SSC will be publishing a policy document on this issue in the upcoming months.

Concern with Loss of Plant Diversity

An additional important decision made by COP 10 was the updating and revising of the GSPC, which aims to stop the "continuing loss of plant diversity," as well as focus on sustainable use and development and benefit-sharing that contributes to poverty alleviation.[7] The new targets are summarized below:

- Create an online flora of all known plants.
- Assess the conservation status of as many known plant species as possible.
- Secure at least 15% of each ecological region or vegetation type through using effective management and/or restoration techniques.
- Protect at least 75% of the most important areas for plant diversity of each ecological region.
- Sustainably manage at least 75% of production lands in each sector.
- Conserve at least 75% of known threatened plant species *in situ*.
- Make available at least 75% of threatened plant species in *ex-situ* collections, preferably in the country of origin, and at least 20% available for recovery and restoration programs.
- Conserve 70% of the genetic diversity of crops, including wild relatives and other economically valuable plant species, while respecting, preserving, and maintaining associated indigenous and local knowledge.
- Put effective management plans in place to prevent new biological invasions and to manage important areas for plant diversity.
- Ensure that international trade endangers no species of wild flora.
- Ensure that all wild-harvested plant-based products are sourced sustainably.
- Maintain or increase plant-related indigenous and local knowledge, innovations, and practices in order to support customary use, sustainable livelihoods, local food security, and healthcare.

"From our perspective, the most important decision regarding plants was the adoption of the revised and updated GSPC," said Suzanne Sharrock, director of global programs for BGCI (e-mail, November 11, 2010). "A significant number of countries voiced support for the GSPC, highlighting both the need to continue to have a specific strategy for plants, as well as the desire to ensure that GSPC targets are incorporated into national biodiversity strategies and action plans. BGCI is working on the development of a toolkit to assist national implementation of the GSPC. This will include identification of methodologies and case studies related to the conservation and sustainable use of medicinal plants."

Other groups have also been taking steps toward implementing GSPC-related initiatives. Royal Botanic Gardens, Kew, for example, has been working in partnership with Missouri Botanical Garden (MOBOT) for several years to create a list of most of the world's plant species and their accepted and synonym names.[8] Additionally, MOBOT joined CBD's international consortium of scientific partners at the beginning of COP 10,[9] and Kew's Millennium Seed Bank Partnership has thus far conserved 10% of the world's plant species *ex situ* and aims to have 25% by 2020.[10]

In addition, the MPSG continues to work on contributing to specific toolkits for local protected areas managers, as called for by the GSPC update, said Leaman. It is also working with the FairWild Foundation to create a means for business investment in sustainable and equitable use of medicinal plants, as well as with the CITES (Convention on International Trade of Endangered Species) secretariat and national CITES authorities to develop more effective means for monitoring trade in medicinal plant species and to improve methods for non-detriment findings. Finally, IUCN, the World Health Organization, World Wildlife Fund, and TRAFFIC are revising the 1993 Guidelines on the Conservation of Medicinal Plants to reflect the many advances in policy and practice (The original document can be found at http://cmsdata.iucn.org/downloads/medgd_en___complete.pdf.)

Future Outlook

COP 10 made additional decisions, such as the Strategy for Resource Mobilization, which lays out financing of the initiatives, a ban on geo-engineering, and an urging of world governments to be cautious in releasing synthetic life into the environment.[5] Additionally, many delegates urged the United States to quickly ratify the CBD.[4]

Considering the unmet 2010 biodiversity targets, the new goals' ability to produce significant progress remains to be seen. The targets are completely voluntary and are implemented in the form of member countries' national biodiversity plans, aspects which give no guarantee that actions will be completed or even initiated and how true to the Convention they will be.[6] "Now we need countries to spring into action and actually set up their national focal points and competent national authorities," said Davis.

"Of course the adequacy of these decisions depends entirely upon the commitment of the parties and more broadly on public and corporate willingness to meet the targets set by COP 10," said Leaman. "The principal players for medicinal plants include the pharmaceutical/herbal products [industries], resource management authorities, health authorities, and of course, consumers."

Another source of doubt over the potential success of the 2020 targets is inadequate funding, cited as one of the reasons for the unmet 2010 targets. While Japan, the host country of the meeting, pledged $2 billion toward the new policies, few other parties have shown the same dedication.

"For medicinal plants," Leaman continued, "the major challenge in understanding and reporting on status and trends will be funding and capacity for conservation status assessments. So far, of the more than 25,000 species we have now documented as being published in pharmacopoeias, and of potentially 50-70,000 species used in medicine worldwide, only 500 medicinal plants

have been assessed according to the global IUCN Red List categories and criteria, and many of these assessments are inadequately documented and out of date. While we recognize that status assessment is only the first small step towards conservation action for those species that are threatened, without better data on current status and trends over time, we will not be in a position to understand whether the 2010 biodiversity target is or is not being achieved for medicinal plants."

Previous conservation work and the making of future conservation goals have not been completely in vain, however. A large, international, multi-organizational study presented at COP 10 reports that biodiversity would have eroded by an additional 20% without past conservation efforts.[11] Additionally, many COP 10 participants and observers have said that the tone of the meeting and its resulting decisions reflect a sense of urgency to not allow history to repeat itself in the form of unmet targets in 2020.[6]

—Lindsay Stafford

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Long-Term Study Confirms Anti-Carcinogenic Properties in Korean Red Ginseng

Reviewed: Kun YP, Kyung JC, Shan RC, et al. Non-organ-specific preventive effect of long-term administration of Korean red ginseng extract on incidence of human cancers. *J Med Food*. 2011;13(3):489-494.

The authors' goal in this trial was to accumulate evidence that supports cancer prevention through the use of natural therapies. To date, common cancer treatments include early detection, surgery, radiotherapy, chemotherapy, and gene therapy. The new strategy is moving toward preventative approaches aimed at reducing the incidence of all cancers. Due to the high incidence of stomach cancer in chronic atrophic gastritis patients over the duration of their disease, such patients present a beneficial population in which to study the anti-carcinogenic effects of Korean red ginseng (*Panax ginseng*, Araliaceae).*

Animal research on mice has confirmed the anti-carcinogenic properties of Korean ginseng.[1] Human studies, including a case-control study of 1810 participants, reported Korean ginseng reduced the risk of all types of cancer.[2] These results suggest that Korean ginseng exhibits a non-organ-specific preventative effect against cancer.

Ginsenosides in ginseng have been found to play an active role in cancer prevention and therapy. Rg3 and Rg5 reduced the incidence of benzo[a]pyrene-induced lung tumors.[3] Rg3 activated nuclear factor κB and extracellular signal-regulated kinase, inhibited cell proliferation, and induced apoptosis.[4] Further studies are needed to fully appreciate the constituents responsible for the effect of Korean ginseng on cancer cells. However, combined animal/human research and molecular mechanism studies give a good indication of benefit from the inclusion of Korean ginseng in cancer preventive treatment.

Chronic atrophic gastritis patients have a 5.73-fold higher development of stomach cancer than other individuals. This randomized, double-blind, placebo-controlled study sought to confirm the cancer-preventative effects of Korean ginseng with 643 male and female patients, recruited from 4 hospitals in China, aged 40-69 years, with this gastric disease. The duration of the study was 11 years: 3 years of supplementation with Korean ginseng, followed by 8 years of follow-up. The patients were randomly given 4 x 250 mg capsules per week for 3 years of 6-year-old ginseng root extract powder prepared by Korea Ginseng Corp (Seoul, Korea). The powdered extract was prepared by steaming fresh ("white") ginseng roots at 100°C for 2.5-3.0 hours. The roots were then dried. Once dry, the roots were boiled for 3 hours and centrifuged (600 g, 30 minutes), then concentrated until the water content reached 36%. The concentrated extract was dissolved in water, dried in a spray-dryer, and encapsulated as red ginseng extract powder.† The control group was given 4 x 250 mg capsules of a rice powder placebo per week for 3 years.

Relative risks (RRs) were calculated using Cox proportional hazards and logistic regression models. The RRs and confidence intervals (CIs) of the ginseng and placebo groups were adjusted for factors including sex, age, smoking, alcohol consumption, family history of cancer, and history of ginseng use. The results showed an RR of 0.54 for the ginseng group compared to the placebo group. The CI was 0.23-1.28, which was non-significant (P=0.13); for men only, the RR was 0.35 (CI 0.13-0.96), which was significant (P=0.03).

Twenty-four cancer cases occurred out of the 643 patients who participated over the 11-year study. The cumulative morbidity risk was much higher at 2.84-fold in the placebo group with 16 cancer cases compared to only 8 cancer cases from the ginseng group. Twenty-one cancer cases were in males.

Asian Ginseng *Panax ginseng*. Photo ©2011 Steven Foster

*The term Korean ginseng refers to *Panax ginseng* root grown in Korea. The term is synonymous in Western herbalism with Asian ginseng. The same species of *Panax,* when grown in China, is sometimes referred to as Chinese ginseng.

†Red ginseng is actually the fresh "white" ginseng which has been steamed according to a certain process, which has the effect of modifying the chemical composition.

There were only mild adverse side effects documented for the duration of the trial in the ginseng group, including headaches. The percentage of gastrointestinal symptoms between both groups was almost identical with 55.0% in the placebo group and 57.3% in the ginseng group. This symptom can be attributed to the patients' gastric disease.

The authors do not discuss their observation that the number of stomach cancer cases in the 2 groups was the same (3 cases per group). The study thus did not appear to have a chemopreventive impact on what would seem to be the disease for which atrophic gastritis patients are most at risk—stomach cancer. However, this is a small population for a chemoprevention study. No calculation of statistical power for the study or figures on projected incidence of stomach cancer is given.

The study's results suggest a non-organ-specific cancer preventative effect of Korean red ginseng and coincide with findings from other studies. One study reported that in 905 pairs of patients, various organ cancer risk decreased by half (RR=0.56) with the use of ginseng.[2] In an extended study with the same 905 pairs of patients included in a total of 1,987 pairs, Korean red ginseng reduced the cancer risk of all organs.[5] A similar study with 4,634 Korean subjects also found red ginseng to have a cancer preventative effect in all organ cancers.[6] Based on this research, Korean red ginseng root appears to be a promising adjunct to a healthy lifestyle and preventative therapy to reduce the occurrence of all cancer types.

—Erin Miner

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Ginkgo Extract EGb 761® Does Not Affect Blood Pressure in Elderly Subjects

Reviewed: Brinkley TE, Lovato JF, Arnold AM, et al. Effect of *Ginkgo biloba* on blood pressure and incidence of hypertension in elderly men and women. *Am J Hypertens.* 2010;23:528-533.

Ginkgo (*Ginkgo biloba*, Ginkgoaceae) is most often used for treating age-related cognitive decline and mild to moderate dementia. Some concerns regarding ginkgo extracts are that they might cause hypotension or lowering of blood pressure (BP) in some individuals.

This paper consists of a secondary analysis of data from the Ginkgo Evaluation of Memory (GEM) study which was initially published in 2008.[1] It was not a clinical trial designed to study BP effects of a ginkgo extract. The GEM study is a trial of 3,069 subjects (≥ 75 years old) without dementia who were recruited between September 2000 and June 2002 from 4 clinical centers: Johns Hopkins University (Baltimore, Maryland), University of California at Davis (Davis, California), University of Pittsburgh (Pittsburgh, Pennsylvania), and Wake Forest University (Winston-Salem, North Carolina). Subjects were excluded if they had congestive heart disease, or were taking warfarin, antipsychotic medications, or cholinesterase inhibitors. Subjects who were unwilling to reduce their vitamin E intake to 400 IU/day or stop taking ginkgo were excluded. Subjects received either 240 mg/day ginkgo extract (EGb 761®; Schwabe Pharmaceuticals; Karlsruhe, Germany) or placebo for 6-7 years.

Ginkgo *Ginkgo biloba*. Photo ©2011 Steven Foster

The authors of this article sought to evaluate the effect of ginkgo extract versus placebo on reduction of BP and pulse pressure (difference between the maximum and minimum BPs produced during one heartbeat) in elderly adults.

The primary outcomes were systolic blood pressure (SBP) and diastolic BP (DBP), pulse pressure, and incident hypertension. BP and the use of antihypertension drugs were monitored every 6 months for 6 years. As per the 7th Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7), subjects were classified as hypertensive if any of the following criteria were met: (1) self-reported hypertension and concomitant use of antihypertensive medications; (2) SBP ≥ 140 mm Hg; or (3) DBP ≥ 90 mm Hg. Subjects were classified as normotensive if they had a SBP < 120 mm Hg and a DBP < 80 mm Hg. Prehypertension was defined as a SBP of 120–139 mm Hg or a DBP of 80–89 mm Hg. Incident hypertension was defined as the start of antihypertensive medications or an increase in BP where the subject could be reclassified as hypertensive based on JNC-7 guidelines.

At baseline, 54% of the subjects were hypertensive, 28% were prehypertensive, and 17% were normotensive. Hypertensive subjects tended to be older, female, less educated, had a higher prevalence of diabetes and cardiovascular disease, a lower heart rate, and a higher body mass index. Baseline characteristics did not differ between treatment groups.

Combining the data from users and nonusers of antihypertensive medications at baseline revealed that both treatment groups had similar significant reductions in SBP and DBP. Pulse pressure significantly decreased from baseline in the entire ginkgo group ($P \leq 0.01$) but not the placebo group; nonetheless, the changes were not significantly different between treatment groups. Stratifying the subjects by baseline hypertension status revealed similar findings. Specifically in subjects with hypertension, the decline in SBP, DBP, and pulse pressure was significant for both groups but was not significantly different between treatment groups. In normotensive subjects, there were significant increases in SBP and pulse pressure that did not differ between treatment groups. In prehypertensive patients, there were no changes in the BP variables. The findings were similar when evaluating only the patients who were nonusers of antihypertensive medication.

Using logistic regression, the authors examined the association between treatment and antihypertensive medication use over time in subjects who were nonusers at baseline. Of those who were never users (n = 83), the odds ratio for being a never-user in the ginkgo group was not significantly different from being a nonuser in the placebo group. In other words, these patients never used antihypertensive medication, irrespective of whether they were treated with placebo or ginkgo. Also, there was no difference between treatment groups in the rate of incident hypertension or the number of subjects who went off antihypertensive medication over the course of the study.

The authors conclude that ginkgo extract EGb 761 had no effect on BP or pulse pressure in this population, and there was no evidence that ginkgo reduces the incidence of hypertension. The ginkgo extract EGb 761 has never been used to treat hypertension nor thought useful to do so. This secondary analysis supports this point.

—Heather S. Oliff, PhD

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Aged Garlic Extract™ Useful Adjunct Therapy to Conventional Medications in Uncontrolled Hypertension

Reviewed: Ried K, Frank OR, Stocks NP. Aged garlic extract lowers blood pressure in patients with treated but uncontrolled hypertension: a randomized controlled trial. *Maturitas.* 2010 Oct;67(2):144-150.

Garlic (*Allium sativum*, Alliaceae) supplements have been associated with a clinically significant blood pressure-lowering effect in patients with untreated hypertension (systolic blood pressure [SBP] ≥ 140 mm Hg or diastolic blood pressure [DBP] ≥ 90 mm Hg) similar to that achieved by first-line treatment with antihypertensive medication according to 2 systematic reviews and meta-analyses of randomized controlled clinical trials (RCTs) published in 2008.[1,2] A 2009 systematic review questioned the methodological quality of some of these RCTs.[3]

The antihypertensive properties of garlic have been linked to stimulation of intracellular nitric oxide (NO) and hydrogen sulfide (H_2S) production, as well as blockage of angiotensin II production, which promotes vasodilation and reduction in BP.

This double-blind, parallel, randomized, placebo-controlled clinical trial was conducted in Adelaide, South Australia, between March and September 2009 to investigate the effect, tolerability, and acceptability of Aged Garlic Extract™ (AGE) as an adjunct treatment to existing antihypertensive medication in patients with treated, uncontrolled hypertension. Fifty adult patients (mean age ± standard deviation [SD]: 66 ± 9 years) treated with conventional antihypertensive medications were randomly allocated to the treatment or placebo group for 12 weeks. Patients in the treatment group were assigned 4 capsules daily of Kyolic® AGE (Garlic High Potency Everyday Formula112, Wakunaga/Wagner®; Vitaco Health [NZ] Ltd; Auckland, New Zealand) containing 960 mg of AGE, equivalent to 2.4 mg SAC. Placebo capsules were matched to the active capsules in number, size, color, and odor. Comparison of baseline characteristics revealed no significant difference between placebo and treatment groups in most parameters and borderline significance in the mean number of BP medication classes prescribed.

Garlic *Allium sativum*. Photo ©2011 Steven Foster

Primary outcome measures were SBP and DBP at 4, 8, and 12 weeks compared with baseline. Tolerability of the trial medication was monitored by questionnaire at the 4 weekly appointments, while acceptability and willingness to continue the treatment long term were explored by an exit questionnaire using 5-point Likert-scales and open-ended questions. Statistical significance was set at $P < 0.05$. Differences between groups at baseline in continuous variables were assessed by Student's t-test, while categorical variables were assessed by chi-square test, and absolute CVD (cardiovascular disease) risk by Fisher's Exact test.

A significant treatment effect over 12 weeks was apparent between garlic and control groups in patients with uncontrolled hypertension at baseline (mean difference in SBP ± SD: –10.2 ± 4.3; $P = 0.0361$), while no significant differences were found in the subgroup of patients with controlled hypertension. Tolerability of trial capsules was generally high, with 24% of the garlic group reporting minor adverse effects including belching, reflux, and taste sensations ($P = 0.25$). Most of the participants found the treatment easy (93%) and acceptable (92%). Ninety-two percent (92%) of participants in the garlic group were willing to continue taking garlic supplements compared to two-thirds (66%) in the control group.

The authors conclude that AGE's effectiveness in lowering SBP in patients with uncontrolled, treated hypertension is significantly superior to placebo and similar to common antihypertensive medication. Further research is needed to determine the effectiveness of lower dosages of AGE that would have the benefit of improved tolerability and blinding, as well as reduced costs of treatment. Future larger trials are needed to investigate dose-response relationships and to examine the effect of AGE in association with different conventional BP medication classes.

—Silvia Giovanelli Ris

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Assessment of Clinical Data on Hepatotoxicity Associated with Kava Use

Reviewed: Teschke R. Kava hepatotoxicity. A clinical review. *Ann Hepatol*. 2010;9(3):251-265.

Hepatotoxicity (liver injury) caused by ingestion of herbal dietary supplements (or, as they are often regulated in many countries, herbal drugs) is considered comparatively rare. When hepatotoxicity does occur in someone using an herbal product, it is often difficult to determine if the herbal product contributed to or caused the injury. Determining causality can be further complicated by a lack of information about the processing and content of the product, poor ability to remember the duration and doses of the products consumed, lack of information about underlying diseases or other potentially confounding medical conditions, and the concomitant use of other herbs, conventional pharmaceutical drugs, or alcohol.

Kava *Piper methysticum*. Photo ©2011 Steven Foster

Many studies, reviews, and meta-analyses have demonstrated the efficacy of kava (*Piper methysticum*, Piperaceae) as a monotherapy for treating anxiety. Nonetheless, hepatotoxicity concerns have led to its withdrawal or restriction in numerous countries (including at least 3 nations in Europe: Germany, Switzerland, and the United Kingdom), with other countries following suit.* Kava hepatotoxicity is rare but it has been reportedly associated with ingestion of aqueous, ethanolic, and acetonic kava extracts.

The precise mechanism of kava hepatotoxicity is unknown, and many studies have evaluated different theories. These include the following: metabolic interactions with exogenous compounds at the hepatic microsomal cytochrome P450 level, alcohol abuse, genetic enzyme deficiencies, toxic constituents and metabolites derived from the kava extract including impurities and adulterations, cyclooxygenase inhibition, P-glycoprotein alterations, hepatic glutathione depletion, solvents and solubilizers of the extracts, and kava raw material of poor and/or non-officially approved quality (i.e., inclusion of non-rhizomatous [root] material, e.g., stems). The majority of patients with suspected kava hepatotoxicity co-medicated (with up to 5 different drugs). However, while conceivable, there is little clinical evidence for drug interactions with the main active compounds (kavalactones, aka kavapyrones) to be a contributing factor in hepatotoxic effects. Theoretically, if the metabolism of co-medicated drugs is altered by kava's interaction with liver cytochrome P450 enzymes, then even relatively benign compounds may exert hepatotoxic effects.

Beyond efforts to establish toxicological mechanisms, solvents used for extraction and kava quality have become key topics of investigation. Since toxicity has been demonstrated with kava formulations made with each of the 3 solvents (ethanol, water, acetone), the nature

* Sales of kava have been banned or otherwise curtailed in the following additional countries: France, Ireland, Japan, Australia (to some extent), Canada, New Zealand, Malaysia, and Singapore, with voluntary recalls in most European countries.

of the solvent does not appear to be the issue. Instead, the quality of the kava raw material probably plays an important role in the observed hepatotoxicity. There are 6 major kavalactones that comprise 96% of the lipophilic resin compounds of the plant: kavain, dihydrokavain, methysticin, dihydromethysticin, yangonin, and desmethoxyyangonin. They are used to define kava chemotypes and serve as markers of quality.

Good quality kava can be expected for kava cultivated varieties (cultivars) consumed traditionally for centuries by the people of the South Pacific Islands. These cultivars are named "noble" cultivars because they have a solid safety record, are commonly used in recreational quantities delivering up to 2500 mg kavalactones per day, and may be consumed on a daily, long-term basis. Aside from the cultivar, the quality of kava is based on the plant part used. The aerial, stump, stem, adventitious roots, bark, and rhizome all have different levels of kavalactones. The peeled rhizome is used traditionally. It has higher levels of kavalactones than other kava parts and contains no pipermethystine, an alkaloid which has come under increasing recent scrutiny as the putative source of the potential kava-associated hepatotoxicity.

The purpose of this review was to evaluate the clinical data of patients with suspected kava hepatotoxicity and to recommend ways to minimize the risk of hepatotoxicity associated with kava-containing products.

The author, Rolf Teschke, MD—a hepatologist at the Department of Internal Medicine at the Teaching Hospital of the Johann Wolfgang Goethe University of Frankfurt/Main, and author and co-author of several previous and recent reviews and evaluations of kava-associated hepatotoxicity[1-5]—states that all patients with suspected hepatotoxicity from drugs and dietary supplements (including herbs) should be assessed using specific diagnostic criteria. These criteria include elevated concentrations of certain liver enzymes and differentiation of the form of hepatotoxicity (hepatocellular, cholestatic, or mixed type). Causality should be assessed using rigorous scientific methods, as opposed to the ad hoc assessments made by regulatory agencies (including, but not limited to, Germany and Switzerland) following the initial reports of kava hepatotoxicity. The World Health Organization and Naranjo assessment scales, used by regulatory agencies for previous kava assessments, are nonspecific and should not be applied in cases of suspected hepatotoxicity from herbs and other dietary supplements, according to the author. The Council for International Organization of Medical Sciences (CIOMS) scale is a validated, structured, specific method for assessing hepatotoxicity, and the author notes that it is better suited for use by regulatory agencies.

This clinical review describes 31 cases of kava-associated hepatotoxicity for which there is sufficient information to assess causality. Causality for all 31 cases was assessed using the CIOMS scale. The 31 reports came from 26 regulatory cases originating in Germany and Switzerland and 5 case reports originating in Australia, New Caledonia, the United States, and Germany. In 14 of these cases, the causality was assessed as either highly probable, probable, or possible for kava, with or without involvement of other medicines. The following points summarize the findings from these 14 cases:

Patients ranged in age from 14 to 60 years, and 12 of the 14 patients were female.

Aqueous kava extracts were involved in 3 cases, ethanolic extracts in 5 cases, acetone extracts in 4 cases, and mixtures of kava with other herbs in 2 cases.

Daily intake of kavalactones (ranging from 45 to 2571 mg/day) exceeded manufacturers' and/or prescribers recommendations in 5 patients, the duration of use (ranging from 1 week to 12 months) exceeded recommendations in 2 patients, and daily dosage and duration of use exceeded recommendations in 3 cases.

Kava is contraindicated in depression, yet half of the patients using ethanolic- or acetone-based kava extracts were taking kava for depression.

Hepatotoxicity was reversed in 10 patients following discontinuation of kava. Four patients required a liver transplant, and 1 of those patients died after liver transplant.

A positive re-exposure test was reported in 1 patient; i.e., symptoms of hepatotoxicity re-occurred upon resumption of use of kava.

Causality for kava with or without co-medications (conventional pharmaceutical drugs, herbs, non-herbal dietary supplements) was assessed as highly probable in 1 patient, probable in 4 patients, and possible in 9 patients.

Additional case series, case reports, and spontaneous reports to regulatory agencies are available, but the quality of these reports is low because of lack of detailed clinical data, failure to report testing for hepatitis and other viral infections, failure to consider existing liver disease or co-medications, and other methodological problems.

The author concludes that kava hepatotoxicity was confirmed in a small number of patients, even though causality was assessed as only "possible" in the majority of the 14 cases reviewed. The lack of epidemiologic data makes it difficult to calculate the incidence of kava hepatotoxicity, but the incidence appears to be low. The author explains that risk factors for hepatotoxicity include combining kava with other medicines, exceeding the recommended dose of kava, exceeding the recommended duration of kava use, and using kava for unapproved conditions such as depression. Despite previous speculation, the type of solvent extraction could not be confirmed as a risk factor for hepatotoxicity, but poor quality of raw material may play a role.

The author recommends that certain measures be taken if kava is to return to the market in Europe. Providers and patients must adhere to the dose and duration recommendations, adhere to the recommended indications for use, and avoid the use of drugs, dietary supplements, and other herbs while using kava. In addition, quality standards must be implemented to reduce the risk of hepatotoxicity.

—Heather S. Oliff, PhD

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Asian Ginseng Extract G115® Improves Aspects of Working Memory and Self-Reported Calmness

Reviewed: Reay J, Scholey A, Kennedy DO. *Panax ginseng* (G115) improves aspects of working memory performance and subjective ratings of calmness in healthy young adults. *Hum Psychopharmacol Clin Exp*. 2010;25:462-471.

Numerous studies in humans have demonstrated that a single dose of a proprietary Asian ginseng (*Panax ginseng*, Araliaceae) extract, standardized to 4% total ginsenosides (specifically G115, aka Ginsana®; Pharmaton SA; Lugano, Switzerland) improves certain aspects of cognitive performance in healthy young subjects. In contrast, only 3 human clinical studies have evaluated the ability of multiple daily doses of Asian ginseng use to affect cognitive processes in this population. These studies have shown an improvement in working memory, speed of performing mental arithmetic, and faster reaction times. Only one of the 3 studies evaluated G115. Hence, the purpose of this randomized, placebo-controlled, double-blind, crossover study of 8 days daily dosing was to investigate G115's affect on working memory processes in more detail.

Asian ginseng *Panax ginseng*. Photo ©2011 Steven Foster

Thirty healthy men and women (mean age 23 years) participated in this study conducted at Northumbria University, Newcastle Upon Tyne, UK. All subjects were alcohol- and caffeine-free for 12 hours prior to baseline and abstained from these substances on testing days. Each morning, subjects ingested placebo, 200 mg G115, or 400 mg G115 for 8 days. There was a washout period of 6 days before the subjects were crossed over to another treatment. Subjects were tested on the first day and eighth day of each treatment period. Assessments were conducted 1, 2.5, and 4 hours post-dose. The battery of 4 cognitive assessments included: subjective mood (Bond-Lader visual analogue scales) and working memory (computerized Corsi block tapping task, N-back task, and random number generation task). Subjects were required to eat the same breakfast and lunch for the duration of the study period.

There was no significant multiple dose treatment-related effect over and above the acute effect for any outcome measure (i.e., for the sub-chronic, 8-day duration). In contrast, there were acute effects associated with treatment. The 200 mg treatment significantly improved self-reported ratings of calmness on day 1 at 2.5 hours ($P = 0.012$) and 4 hours ($P < 0.0001$) post-dose and on day 8 at 1 hour ($P = 0.029$) and 4 hours ($P = 0.015$) post-dose. The 400 mg treatment significantly improved self-reported ratings of calmness only on day 1 at 2.5 hours ($P = 0.007$) and 4 hours ($P < 0.0001$) post-dose. The Three Back Reaction Time Task revealed that, compared with placebo, the 400 mg dose resulted in significantly faster response times at 2.5 hours on day 1 ($P = 0.023$) and day 8 ($P = 0.001$). In contrast, the 200 mg dose led to significantly slower response times compared with placebo on day 1 at 1 hour ($P = 0.0004$), 2.5 hours ($P = 0.046$), and 4 hours ($P = 0.003$) post-dose, and on day 8 at 1 hour ($P = 0.004$) and 2.5 hours ($P = 0.0001$) post-dose. Similarly, on the Three Back Task Sensitivity Index, compared with placebo, the 400 mg dose resulted in a significantly improved sensitivity index on day 1 and day 8 at 1 hour ($P < 0.0001$), 2.5 hours ($P < 0.0001$), and 4 hours ($P < 0.0001$) post-dose. In contrast, the 200 mg dose led to significant impairment reflected in the sensitivity index, compared with placebo, on day 8 at 4 hours ($P = 0.02$) post-dose.

No other measures were significantly modulated by treatment. Safety was not assessed (presumably because numerous previous clinical trials on G115 have exhibited a high safety profile, as has common traditional use of various generic ginseng preparations over many centuries).

The authors conclude that G115 Asian ginseng extract had no effect following an 8-day dosing regimen. This is the first study to demonstrate a mood associated effect. The authors believe this effect may be due to the purported anxiolytic properties of ginseng. However, there have been no clinical studies assessing its anxiolytic properties in humans.

This study supports other reports that an acute dose of Asian G115 extract can affect cognitive function in young healthy subjects. However, this was the first study of G115 to include a comprehensive global assessment of working memory. The authors conclude that the 400 mg dose can modulate working memory performance. They note also that similar to their findings, other researchers have reported a decline in cognitive performance with the acute 200 mg dose (the average recommended daily dose). The authors do not have an explanation for this effect, particularly since the mechanism underlying the cognitive effects are unknown.

A limitation of the study is that 8-day dosing may not be long enough to see a chronic effect. Although the authors conclude that G115 can modulate working memory performance, as emphasized by the title, it is more accurate to say that G115 improves *aspects* of working memory.

—Heather S. Oliff, PhD

Soy Isoflavone Supplementation Improves Flow Mediated Dilation Based on a Meta-Analysis of Randomized Controlled Studies

Reviewed: Beavers DP, Beavers KM, Miller M, Stamey J, Messina MJ. Exposure to isoflavone-containing soy products and endothelial function: a Bayesian meta-analysis of randomized controlled trials. *Nutr Metab Cardiovasc Dis*. August 14, 2010; [epub ahead of print]. doi:10.1016/j.numecd.2010.05.007.

Impaired function of the endothelial cells lining the blood vessels and heart is an early marker of cardiovascular disease. Flow mediated dilation (FMD) of the brachial artery in the upper arm is a non-invasive method for evaluating endothelial physiology. Estrogen treatment improves endothelial function in postmenopausal women, and some studies have shown that soy-based phytoestrogens have vasodilating effects in men and women. Previous meta-analyses of randomized controlled trials (RCTs) testing the effects of soy products on endothelial function were limited by small sample sizes or inclusion of females only. The purpose of this research was to conduct a Bayesian* meta-analysis of RCTs to estimate the effects of isoflavone-containing soy products on endothelial function, as measured by FMD.

The researchers conducted a literature search of the PubMed database through August 21, 2009, to identify eligible RCTs. Search terms included soy, isoflavone, phytoestrogen, endothelial function, and flow mediated vasodilation. The researchers also searched the references cited in the articles and reviewed other sources to identify additional trials: trials that lasted at least 4 weeks; trials that tested dietary ingestion of soy foods, soy protein, or soy isoflavones; and trials that reported FMD as an outcome were included in the analysis. The primary outcome was the mean change in FMD attributed to soy product intervention.

Of the 42 trials identified by the search for possible inclusion in the analysis, 25 were excluded because of short duration, wrong product type, or unsuitable outcome measures. The remaining 17 trials included 1,281 participants from 6 countries. Some participants were healthy, whereas others had high blood cholesterol levels or other symptoms of cardiovascular disease. The average age of participants was 60 years, and 83% of participants were female. Duration of the intervention ranged from 4 weeks to 52 weeks. Six trials tested isoflavone-containing soy products, 7 isolated isoflavones, and 4 soy-based foods or foods fortified with isoflavones. Daily consumption of soy protein ranged from 25 to 40 grams and daily consumption of isoflavones from 33 mg to 120 mg.

The mean increase (improvement) in FMD following intervention with all tested soy products combined was 1.15%. The mean increase in FMD was 0.72% with soy protein intervention and 1.98% with soy isoflavone intervention. Only the soy isoflavone intervention represented a statistically significant improvement in FMD.

The authors discuss possible biological mechanisms for the effects of soy isoflavones on FMD. Impaired release of nitric oxide (NO) leads to endothelial dysfunction by constricting blood vessels and impeding flow. Estrogen appears to improve FMD by increasing the release of NO in endothelial cells, and soy isoflavones may act the same way. Laboratory and animal studies suggest that soy isoflavones increase NO production by increasing the level of nitric oxide synthase, the enzyme that produces NO. Other mechanisms may also be involved, such as reducing inflammation and inhibiting oxidation.

This review concludes that consumption of soy isoflavones modestly but significantly improves endothelial function as measured by FMD, and increasing consumption of soy isoflavones may have beneficial effects on vascular health. In this meta-analysis, soy protein and other soy foods containing isoflavones were associated with a smaller improvement in FMD than isolated soy isoflavones but a greater improvement than controls or placebos.

The authors discuss some limitations in interpreting the findings. The majority of participants evaluated in this meta-analysis were older women. Findings of this meta-analysis may not apply to other subgroups, such as younger people, men, and people with diabetes or other chronic health conditions. Also, FMD is only one method for measuring endothelial function, and other assessment methods may not yield the same results.

Finally, the authors state that additional, larger, randomized, controlled trials are warranted. They recommend that future trials directly compare soy protein with isolated isoflavones to better understand the effects of each on endothelial function. Future trials should also evaluate the dose-response relationship between soy isoflavones and changes in FMD.

—Heather S. Oliff, PhD

*Bayesian statistical analysis differs from classical meta-analyses in that the Bayesian analysis incorporates prior beliefs, does not use P values to measure statistical significance, and it allows calculation of probability (odds ratio).

The Safety of Bitter Orange (*Citrus aurantium*) and *p*-Synephrine

by Sidney J. Stohs, PhD, FACN, CNS, ATS, FASAHP
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Bitter Orange *Citrus aurantium*. Photo ©2011 Marilyn Barbone

Introduction

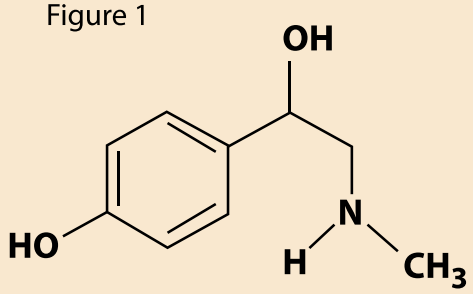
The extract of the fruit or peel of bitter orange (*Citrus aurantium,* Rutaceae) and its primary protoalkaloidal constituent, *p*-synephrine, are widely used in weight management as well as sports performance products, with many millions of doses having been consumed by possibly millions of individuals.[1] However, bitter orange has been listed by *Consumer Reports*[2] as being possibly unsafe and a dietary supplement "to avoid." The editors of *Consumer Reports* note that bitter orange has been "linked by clinical research or case reports to serious side effects," having arrived at this verdict based on conclusions found in the Natural Medicines Comprehensive Database. The article further states that bitter orange "contains synephrine, which is similar to ephedrine, banned by the FDA [US Food and Drug Administration] in 2004." No detailed information was provided to support these conclusions. The following information summarizes current research and knowledge regarding bitter orange extract and *p*-synephrine.

Chemistry

Like all botanical products, bitter orange peel contains a variety of naturally occurring compounds. In Traditional Chinese Medicine (TCM), the peel and/or whole, dried, immature fruit is used for a variety of clinical applications, including indigestion, diarrhea and dysentery, constipation, and as an expectorant.[3-5] According to TCM, *zhi shi* (immature bitter orange) "is one of the best herbs to treat gastrointestinal disorders characterized by stagnation and accumulation," and "is one of the best herbs to relieve distention and hardness of the epigastric area caused by cholecystitis."[5] Pharmacologically, this compendium[5] reports that *zhi shi* does not affect respiration or heart rate and has minimal toxicity. Bitter orange has also been used in South American folk medicine to treat insomnia, anxiety, and epilepsy.[4]

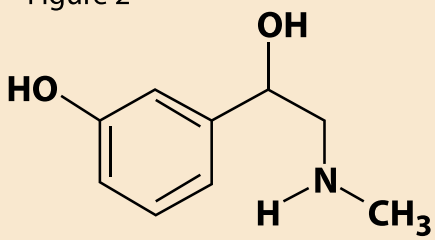
The primary pharmacologically active protoalkaloid (biogenic amine) in bitter orange peel and its extracts is *para*-synephrine.[6-13] *p*-Synephrine is a phenylethanolamine derivative with the hydroxy group in the *para* position on the benzene ring of the molecule (Figure 1). This is the form found in most bitter orange products (e.g., the patented bitter orange extract, Advantra Z® [Nutratech, Inc.,West Caldwell, NJ]). *p*-Synephrine comprises greater than 85% of the total protoalkaloids in bitter orange extract. Other minor protoalkaloidal constituents include octopamine, hordenine, tyramine, and N-methyltyramine.[6, 7, 12, 13] Much confusion exists in both scientific and lay literature because there is also *meta*-synephrine, known as phenylephrine (hydroxyl group in the *meta*-position on the benzene ring; Figure 2). The latter is an FDA-approved over-the-counter (OTC) drug ingredient typically found in nasal decongestants and sprays.

Figure 1



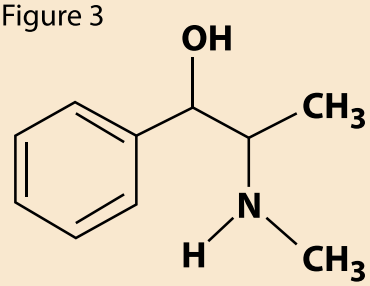
***p*-synephrine**

Figure 2



***m*-synephrine**

Figure 3



ephedrine

Contrary to some commentaries,[14,15] *m*-synephrine does not appear to be naturally occurring in bitter orange[6-13] and has not been shown to be present in some of the leading bitter orange extract products, such as Advantra Z.[16] No evidence exists that *m*-synephrine is a natural product. Furthermore, *m*-synephrine is not a constituent of—nor has it been identified in—standardized bitter orange reference materials prepared by the National Institute of Standards and Technology (NIST).[17] When *m*-synephrine has been reported in weight-loss products,[18] it is believed to be due to addition of the synthetic ingredient.[19] Trace amounts of *m*-synephrine have been reported in human plasma, although the source of this material is not known.[20]

Animal and Human Pharmacology

p-Synephrine is believed to act primarily as a beta-3 adrenergic receptor agonist, which results in increased thermogenesis and lipolysis (breakdown of fats).[11, 21-24] Ligand binding to alpha- as well as beta-1 and beta-2 adrenoreceptors results in cardiovascular effects including increased blood pressure and heart rate.[25,26,27] In general, binding to α-adrenergic receptors results in vasoconstriction, while increased cardiovascular contractility and heart rate occur in response to β1-adrenergic receptor binding, and bronchodilation occurs in response to β2-adrenergic receptor binding.[28] *m*-Synephrine is 100-fold and *p*-synephrine 40,000-fold *less potent* than nor-epinephrine with respect to binding to beta-1 and beta-2 adrenoreceptors in guinea pig atria and trachea.[25] *p*-Synephrine is approximately 50-fold *less potent* than *m*-synephrine in activating human alpha-1a adrenoreceptors, and has even lower binding affinity for human alpha-2a- and alpha-2c adrenoreceptor subtypes.[26]

The receptor binding activities of the *meta* and *para* isomers of synephrine as well as octopamine to rat aorta alpha-1 and rabbit saphenous vein alpha-2 adrenoreceptors have been studied.[27] The binding of *m*-synephrine was 6-fold less than nor-epinephrine to alpha-1 adrenoreceptors and 150-fold less to alpha-2-adrenoreceptors. Moreover, *p*-synephrine was 1000-fold less active than nor-epinephrine in binding to alpha-1 and alpha-2 adrenoreceptors. Finally, studies involving interactions for alpha-1 adrenoreceptor binding and activation have demonstrated that it is the *meta*-hydroxy of *m*-synephrine and not the *para*-hydroxy of *p*-synephrine that preferentially binds to the receptor, allowing receptor activation.[29] As a consequence, *p*-synephrine would be expected to have little or no effect on blood pressure relative to *m*-synephrine or nor-epinephrine.

The above receptor binding studies are in agreement with several human studies where *p*-synephrine exhibited little or no effect on blood pressure,[15,30-37] although an increase in heart rate was reported[33] that has not been observed or substantiated in various other human studies.[15, 30, 34-37] These receptor binding results are also in agreement with animal studies that have shown no adverse cardiovascular effects following oral administration of bitter orange extract or *p*-synephrine.[38, 39] The assumption that the 2 forms of synephrine have similar if not identical effects has lead to serious inaccuracies, and the inappropriate attribution of potentially adverse effects produced by *m*-synephrine to *p*-synephrine, which occurs in bitter orange.

Chemically, *p*-synephrine is structurally related to ephedrine (Figure 3). However, ephedrine is a phenylpropanolamine derivative, having a methyl group on the alpha carbon of the sidechain and no para-substituted hydroxy group, as compared to *p*-synephrine which is a phenylethanolamine derivative. These 2 chemical differences greatly impact the stereochemistry and alter the pharmacokinetic properties, particularly the ability of *p*-synephrine to cross the blood-brain barrier. The addition of the para hydroxy group on the *p*-synephrine molecule, as well as the lack of the additional methyl group, greatly decreases the lipid solubil-

ity of *p*-synephrine as compared to ephedrine, resulting in little transport into the central nervous system (CNS) as compared to ephedrine.[3,21,22] As a consequence, *p*-synephrine exhibits little or no CNS and cardiovascular stimulation. However, *p*-synephrine may act locally on the cardiovascular system. The existence of alpha- and beta-1 and beta-2 adrenoreceptors within the cardiovascular system is well known, while beta-3 adrenoreceptors have been recently identified in cardiovascular tissues,[40] and evidence suggests that their activation modulates sympathetic overstimulation through regulation of nitric oxide.[41] These observations may further explain the lack of cardiovascular stimulation by *p*-synephrine in addition to its low level of binding to alpha- as well as beta-1 and beta-2 adrenoreceptors.

Safety

A series of review articles regarding the safety and activity of bitter orange has been published over the past 8 years.[3,4,14,42-44] None of these reviews has reported any serious or significant adverse events that are directly attributable to bitter orange, nor does the research literature support the development of adverse cardiovascular or neurological events in humans or animals when administered orally.

The assumption that the 2 forms of synephrine have similar if not identical effects has lead to serious inaccuracies, and the inappropriate attribution of potentially adverse effects produced by *m*-synephrine to *p*-synephrine, which occurs in bitter orange.

During the past several years, a number of case studies have been reported for products containing bitter orange that involved adverse cardiovascular or other events where the authors suggested that the causative agent was synephrine or bitter orange.[45-54] However, in each case, the product in question contained 5 to 12 alkaloidal and protoalkaloidal ingredients, including bitter orange. It is not possible to ascribe the effects specifically to one of these constituents, and the effects may have been due to a combination of ingredients. High caffeine intake has been proposed as the most likely culprit responsible for cardiovascular adverse events when consuming dietary supplements containing multiple herbal ingredients.[55] In the majority of cases, other confounding factors were also noted. A number of the cases involved body builders or serious athletes,[4,46,50,52,54] and dehydration was involved in at least 2 of the cases.[46,50] There are questions as to whether individuals had also been using steroids, anabolic agents or other ergogenic or thermogenic agents, or various prescription and non-prescription drugs. Other factors may have contributed, including pre-existing conditions such as previously undetected heart disease[45] or hypertriglyceridemia,[48] sickle cell trait,[50] extensive use of tobacco products,[45,47,54] consumption of large amounts of caffeine daily,[45,53] or a history of substance abuse.[47] In addition, there is a high probability that the events were concurrent but random and unrelated, based on the fact that cardiovascular events occur in millions of people annually.

The historical and traditional use of extracts of bitter orange in TCM, as well as the extensive use of products containing bitter orange extract and *p*-synephrine aid in putting the safety issue into context. Two percent of respondents in a survey reported taking a dietary supplement containing bitter orange,[1] which, if extrapolated nationwide, would entail several million individuals. No serious adverse events have been directly attributable to bitter orange or *p*-synephrine.[3,4,14,42-44]

Furthermore, millions of people daily consume, without ill effect, various juices and food products such as marmalade from *Citrus* species including Seville orange, grapefruit, mandarin, and other orange-related species that contain *p*-synephrine.[3,7-10,56] A typical sweet orange contains about 6 mg *p*-synephrine.[10] A wide variety of citrus juices contain approximately 5 mg *p*-synephrine per 8-ounce glass,[3,7] while juice from mandarin oranges may contain more than 20 mg *p*-synephrine per 8-ounce glass.[3,56] These amounts of *p*-synephrine are similar to the amounts found in a vast range of dietary supplements. A US Department of Agriculture study of the *p*-synephrine content of mandarin orange juice from 10 different groves in California found that the *p*-synephrine content ranged from 73 to 158 mg per liter, with an overall mean of 93 mg per liter.[56]

A major contributor to the concerns regarding the safety of bitter orange and *p*-synephrine has been the US federal government. In 2004, the FDA supplied information to a major newspaper indicating that 85 adverse reactions and 7 deaths had been associated with bitter orange-containing dietary supplements. Subsequently, the purported number of adverse events increased to 169. A dissection of the FDA information by McGuffin,[57] obtained through the Freedom of Information Act and on which the reports were based, clearly indicated that no credible adverse events could be attributed to bitter orange. A recent review of FDA adverse events reports and published clinical case reports over the past 5 years has again concluded that no serious adverse events can be directly attributed to bitter orange or *p*-synephrine.[58] The FDA has acknowledged some "misstatements" about bitter orange.[59]

The possible dangers of bitter orange (fainting, heart-rhythm disorders, heart attack, stroke, death) listed in the *Consumer Reports* article[2] are clearly not supported by scientific and clinical literature. None of these adverse effects have been directly linked with bitter orange extract or *p*-synephrine. Unfortunately, this reality has not prevented many individuals from making statements that are not based on scientific fact or clinical data.

Bitter Orange *Citrus aurantium*. Woodville, William, 1752-1805. Medical botany: containing systematic and general descriptions, with plates of all the medicinal plants, indigenous and exotic, comprehended in the catalogues of the materia medica: as published by the Royal Colleges of Physicians of London and Edinburgh: accompanied with a circumstantial detail of their medicinal effects, and of the diseases in which they have been most successfully employed. London: Printed and sold for the author by J. Phillips, 1790-1793. Volume 3, plate 183.
Image courtesy of Lloyd Library and Museum, Cincinnati, Ohio www.lloydlibrary.org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Citrus Aurantium
Published by D.r Woodville. Jan.y 1. 1793.

Summary

In summary, based on current research as well as the extensive ingestion of bitter orange and *p*-synephrine in the form of dietary supplements as well as fruits, juices, and other citrus food products, the data demonstrate that bitter orange extract is safe for human consumption. No credible adverse events have been directly attributed to bitter orange, or its primary protoalkaloid, *p*-synephrine, in association with oral ingestion.

Conflict of Interest Disclosure

The authors have served as consultants for Nutratech, Inc., a company that markets bitter orange extracts.

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Bitter Orange *Citrus aurantium*. Photo ©2011 Steven Foster

The Genus *Ligusticum* in North America

An Ethnobotanical Review with Special Emphasis upon Species Commercially Known as 'Osha'

By Christina Turi, MSc and Susan J. Murch, PhD

Osha *Ligusticum porteri*. Photo ©2011 Steven Foster

Osha *Ligusticum porteri*. Photo ©2011 Daniel Gagnon

The genus *Ligusticum* consists of 40 to 60 perennial species found within boreal and mountainous regions of the world.[1,2] In Asia, native species of *Ligusticum* are held in great esteem for their therapeutic actions.[3] In North America, endemic species collectively known as osha* are also sought after by consumers within the dietary supplement and natural health products industry, in addition to being revered among indigenous groups.[4] Although research investigating the medicinal attributes of *Ligusticum* species commonly used within Traditional Chinese Medicine has been ongoing since the 1960s,[3] research into the medicinal efficacy of North American species is more recent. A literature search of "*Ligusticum*" in Web of Science™ on September 30, 2010, found a total of 257 articles in the scientific literature. Among these articles, approximately 85% pertained to species endemic to Asia (Figure 1).

In North America, First Nation's (i.e., Native Americans') uses of *Ligusticum* species include food, hunting, spirituality, and medicine[5] (Table 2). *Ligusticums* grow in North American regions ranging from north-eastern parts of Quebec, the Maritimes, and Ontario in Canada, to the Eastern United States as far south as Florida. *Ligusticum* species are also found in the Mexican Sierra Madre and through regions of New Mexico, Colorado, Wyoming, Montana, Alaska, British Columbia, and Western coastal States and Provinces[6] (Figure 2). Ecological zones where *Ligusticum* species known as osha are found in North America include montane to subalpine meadows,[7] spruce and aspen belts, windswept parks, oak and mature stands of conifers,[8] pine-oak forests of the Northern Sierra Madre Occidental and central to southern Rocky Mountains of the United States,[9] mountain ridges, within dry or moist slopes,[10] moist forests from the spruce-fir vegetation

*One of the major problems with commercial osha is the misidentification of species. Some suppliers, product manufactures, and some herbalists do not differentiate between species of *Ligusticum*, using osha interchangeably as a common name. A CITES report from 2000 suggests herbal companies often purchase unidentified species of *Ligusticum* from wildcrafters which they call '*L. porteri* or osha.' Consequently, *L. filicinum*, *L. canbyi*, and *L. tenuifolium* are species often found within the herbal market as osha or '*L. porteri*.' Moore's *Medicinal Plants of the Mountain West* (2003) refers to *L. filicinum*, *L. grayi*, *L. porteri*, *L. apifolium*, *L. californicum*, *L. canbyi*, *L. tenuifolium*, and *L. verticillatum* as osha but emphasizes the importance of *L. porteri* as 'True Osha.' Furthermore, Tilford's *Edible and Medicinal Plants of the West* (1997) places greater emphasis upon *L. canbyi* as osha, while also acknowledging other species of *Ligusticum* as osha including *L. porteri*. Finally, Cech's *Growing at-risk Medicinal Herbs* (2002) considers all species belonging to the family *Ligusticum* as osha. A major need for research is the development of an effective way to differentiate and identify dried root material to distinguish species but such methods are currently not available.

zone to foothills,[11] sagebrush meadows on rocky soils[4] and among subalpine zones and altitudes up to 10,000 feet.[12] *Ligusticum porteri* was also identified as a dominant species among Aspen communities in Gunnison County, Colorado (Figure 3).[13]

Botany and Taxonomy

Ligusticums belong to the family Apiaceae, otherwise known as the Umbelliferae, or the carrot family. In North America, there are 12 species of *Ligusticum*.[14] Among these, *L. porteri*, *L. canbyi*, *L. grayi*, *L. tenuifolium*, and *L. filicinum* are most commonly known as osha.[4,8*] Like other genera belonging to Apiaceae, *Ligusticums* are identified by their compound umbels, white or sometimes pinkish flowers, distinctly ribbed and narrowly winged fruits, taproot system, basal leaves, and ternate to pinnately compound or dissected leaves.[15,16] Though challenging at times, differentiation between species collectively known as osha is accomplished through examination of plant height, leaf morphology, and habitat (Table 1, Figure 2). Furthermore, species of osha can be mistaken with other members of the Apiaceae family, including the genera *Angelica*, *Conium,* and *Lomatium*.[4] This can be problematic, since *Ligusticum* species resemble toxic species such as water-hemlock (*Cicuta douglasii*, Apiaceae) and poison-hemlock (*Conium maculatum*, Apiaceae).[12] Differentiation of *Ligusticum* species from poison-hemlock is achieved through examining root morphology and scent. Typically, but not always, the roots of poison-hemlock are smooth, purplish, without leaf base remnants[15] and believed to have a "dead mouse like scent."[8] Roots from water-hemlock are said to be tuberous or fibrous, soft in texture, purplish, emerging from a thickened crown, and exuding a parsnip scent.[15] Root crowns of *Ligusticums*, on the other hand, have basal leaves,[16] and possess a distinctive celery-like odor similar to lovage (*Levisticum officinale*).[8,12]

Osha *Ligusticum porteri*. Photo ©2011 Daniel Gagnon

Table 1. Botanical Descriptors Used to Differentiate Several North American *Ligusticum* Species Commonly Known as Osha[4, 16]

Species	Leaves	Umbel	Plant Height	Fruit	Habitat
Ligusticum filicinum	Leaves dissected into numerous linear segments 1-3 mm wide. Basal leaves 10-25 cm wide.	Rays of main umbel generally 12-20.	Robust, 50-100 cm tall	5-7 mm	Open or wooded, moist to dry slopes and ridges in mountains.
Ligusticum tenuifolium	Leaves dissected, usually scapose or with 1 greatly reduced leaf. Basal are usually less then 10 cm wide.	Rays of umbel generally 5-13.	Small slender, 10-60 cm tall	3-5 mm	Marshes to wet or moist slopes
Ligusticum canbyi	Leaves less dissected, segments more or less toothed or cleft, leaflets generally 1-5 x 0.5-2cm	Rays of terminal umbel 15-40.	50-120 cm tall	Ribs of fruit narrowly winged.	Wet to moist or occasionally dryish soil.
Ligusticum grayi	Leaves less dissected, segments more or less toothed or cleft. Leaflets generally 1-5 x 0.5-2 cm. Usually scapose or with 1-2 reduced stem leaves.	Rays of terminal umbel 7-14.	20-60 cm tall	Ribs of fruit narrowly winged.	Moist to dry, open or wooded montane slopes and drier meadows.
Ligusticum porteri	Elliptic or lance-shaped 0.5-4 cm in width. Basal leaves 15-30 cm long.	Flat topped umbels.	50-100 cm tall	Oblong, ribbed fruits 5-8 mm in length.	Fertile ground in upland meadows and ravines.

Propagation

In China, growers are expected to follow Good Agricultural Practices (GAP). Currently, several GAP *Ligusticum chuanxiong* centers for cultivation are under development within the Dujiangyan County, Sichuan Province.[17] Traditionally, roots are collected in May and processed using a variety of methods, including stir-frying and sun- or oven-heating.[18] In North America, knowledge of the propagation and growth of *Ligusticum* species is limited and suggests osha is difficult to grow.[4,19,20] Renowned herbalist and author Michael Moore described cultivating osha as "[a]lmost impossible. Even in northern New Mexico (elevation averaging from 6,000 to 8,000 feet) where it is most widely used, the people are not able to cultivate it for their own consumption…If high-country curanderas and abuela can't grow *Ligusticum porteri*, who am I to try it?"[8]

Ligusticum porteri seeds can be sown in both garden and greenhouse environments during the fall, midwinter, or spring with an expected germination rate of 70%. Period of germination will vary, ranging between 6 to 12 weeks. However, it is not uncommon for seeds to remain dormant until the following growing season.[21] Stratifying seeds at 4.4 C for 12 weeks under moist, cold conditions before placing them on a mist propagation bench at 21.1 C can improve germination rates for unattached seeds. 6 weeks of stratification in a cold, moist environment followed by 12 weeks in a germination chamber is beneficial for attached seeds (although only 11% of attached and unattached seeds from umbels reportedly emerged).[20] Other research has shown that seed viability is improved by at least 10 weeks of stratification, exposure to GA_3, and by lightly covering seeds with soil before exposing them to light in a greenhouse.[22]

After 8 weeks, seedlings can be transplanted to a garden with an expected survival rate of 80% after 3 years.[22] Crown cuttings may be an effective alternate strategy for propagation of osha. It is believed that the branching cluster of root material associated with the taproot system of osha makes transplanting feasible.[21] This notion is reinforced, given that 90% of crown cuttings consisting of both root and stem material from *L. porteri* appeared to root successfully.[20]

Harvest and Processing

Ligusticum species known as osha are wild-harvested and sold within the herb and dietary supplement industry (known as the Natural Health Products industry in Canada). Market analysis reports that dried roots from *L. porteri* will fetch a price between 30 to 50 US dollars per pound.[22†] Given that success-

† In 1999, a group of scholars from the University of Maryland Program in Sustainable Development and Conservation Biology submitted a draft proposal to the US Fish & Wildlife Service Office of Scientific Authority. This document suggested that *L. porteri* be listed in Appendix II of the Convention on International Trade in Endangered Species of Wild Fauna and Flora (CITES).[4,81] Currently, no *Ligusticum* species known commercially as *osha* are CITES listed.[82]

Table 2. Ethnobotanical Uses of North American Species of *Ligusticum* per the University of Michigan's Native American Ethnobotany Index, Bye and Linares 1987,[9] and Henriette's Herbals Website (www.henriettesherbal.com/)

Uses	Species
Anti-convulsive, Analgesic, and Fever	*Ligusticum canbyi,*[37] *Ligusticum grayi,*[31] *Ligusticum porteri* (Bye 1985, Brambila 1976, Seiz de Lira, 1777, Bye 1986:115, Bye and Linares 1981-1986; Palmer n.d.)[9]
Anti-rheumatic	*Ligusticum porteri*[33,59] (Bye 1986, Bye and Linares 1981-1986, Palmer, n.d., Schulman and Smith 1962)[9]
Ceremonial Drug or Protection	*Ligusticum canbyi,*[24] *Ligusticum porteri*[25,33,34,39] (Bye 1985, Bye and Linares 1981-1986, Curtin 1965, Ford 1975, Schulman and Smith:1962, Kennedy 1978)[9]
Colds, Coughs, Sore Throat, Pulmonary or Respiratory aid (hemorrhages, tuberculosis, bronchitis, lung infections, sinus infection, congestion…etc.)	*Ligusticum apifolium,*[52,53] *Ligusticum canbyi,*[24,37] *Ligusticum filicinum,*[54-56,57,58] *Ligusticum grayi,*[31] *Ligusticum porteri*[33,59] (Bye 1981-1986; Bye and Linares 1981-1986; Curtin 1965; Ford 1975; Hrdlichka 1890; Moore 1979; Schulman and Smith 1962)[9]
Food	*Ligusticum californicum,*[49] *Ligusticum canadense,*[44-46] *Ligusticum grayi,*[31] *Ligusticum porteri*[39] (Bye and Linares 1987, Curtin 1965, Moore 1979),[9] *Ligusticum scoticum* (including *ssp. Hultenii* and *Scoticum)*[40-43,47,48]
Gastrointestinal (stomach upset, flatulence, colic...etc), Dietary aid (digestion, apperitif...etc)	*Ligusticum apifolium,*[51,52] *Ligusticum canadense,*[38] *Ligusticum grayi,*[31] *Ligusticum porteri*[59] (Bye 1985, 1986; Bye and Linares, 1981-1986, Curtin 1965; Ford 1975; Gonzalez 1984; Moore 1979; Pennington 1963, 1973, 1980; Schulman and Smith 1962, Robbins et al. 1916, Seiz de lira 1777, Esteyneffer 1978, Citolano de Escudero 1777, Villagra 1777)[9]
Heart Drug, Circulation Problems, Diabetes, Anemia	*Ligusticum apifolium,*[53] *Ligusticum canbyi,*[37] *Ligusticum porteri*[9]
Poison	*Ligusticum grayi,*[31] *Ligusticum porteri,*[32] (Pennington 1963, Brambila 1976),[9] *Ligusticum scoticum* (including *ssp. Hultenii* and *Scoticum)*[30]
Smoked or Incense	*Ligusticum canadense,*[38] *Ligusticum canbyi,*[37,24] *Ligusticum scoticum* (including *ssp. Hultenii* and *Scoticum*)[36]
Wounds, Skin and Ear Infections, Ticks, Lice, or Hair Rinse	*Ligusticum canbyi,*[24, 37] *Ligusticum porteri*[59] (Bye and Linare 1981-1986; Curtin 1965, Ford 1975; Hrdlicka 1890, Moore 1979, Schulman and Smith 1962, Falcon 1777)[9]

ful commercial cultivation is yet to be established, questions regarding sustainable harvesting practices have been raised.[4] Data collected over the last 10 years by the American Herbal Products Association (AHPA) indicates that wild collection and demand for *L. porteri* increased in the late 1990s and has remained constant for the last decade[23] (Figure 4). Roots are harvested during early spring before budding,[20] or during the months of August and September once the *Ligusticum*'s flowers have all died[8, 24] and its leaves have turned gold.[21] Typically, older plants are favoured for collection, usually those between 5 to 10 years of age[20] and possessing numerous flowering stalks with large rosettes. Seeds can be collected and detached once the umbel has reached maturity in the fall.[21] A variety of rituals have been associated with the collection of *Ligusticum* roots. For example, Turner et al. (1980) observed that the Okanagan-Colville people of southern British Columbia and northern Washington had a tradition of expressing gratitude before digging up the roots of *L. canbyi*.[24]

Once collected, roots from *Ligusticum* species should be cleared of soil and dried for approximately 2 to 3 weeks and stored away from moisture to ensure a long shelf life of osha products.[8,22,24] Alternatively, roots can be dried in a dehydrator and removed when easily broken apart.[21] Turner et al. (1980) found that the Okanagan-Colville would store the roots of *L. cambyi,* Canby's Lovage, in a medicine bag or tobacco pouch,[24] while Jordan (2008) recorded that the Plains Apache would store roots of *L. porteri* (also known as medicine fat) in "the family medicine bundle" and use its smoke to purify the bundles annually during spring rituals.[25]

Ethnobotany

(See Table 2)

Zoopharmacognosy

Kodiak bears (*Ursus arctos)* have been observed masticating the roots of *L. porteri*, sometimes known as bear root, and rubbing the salivated contents over their bodies, possibly to medicate infected topical wounds.[26] The Navajo believe that bear root's medicinal use was given to them by bears, which has led them to use its roots for treating ailments including skin abrasions.[27-29]

Poison and Hunting

According to Lantis (1959), the Eskimo considered mature plants from *L. scoticum* to be mildly poisonous,[30] while Garth (1953) observed that roots of *L. grayi* were used for hunting and poisoning fish among the Atsugewi of northern California.[31] Similarly, Campbell (1958) records that roots from *L. porteri* were used as a fish poison by the Tarahumar of northern Mexico.[9,32]

Spirituality, Protection, Smoke or Incense

Ceremonial uses for *L. porteri* and *L. canbyi* are documented for North American indigenous groups. Bye and

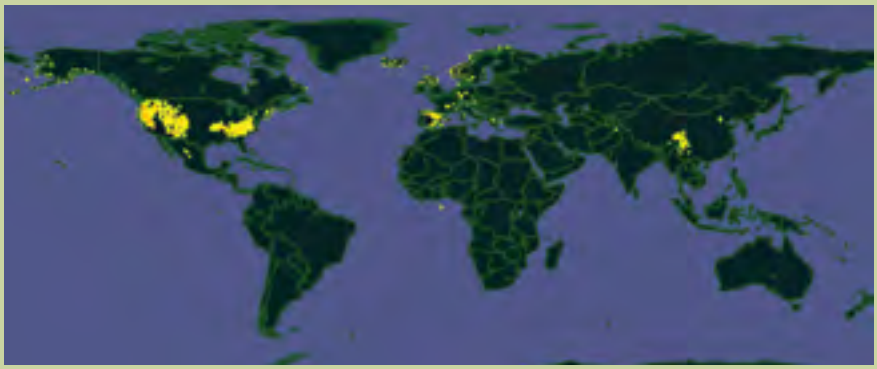


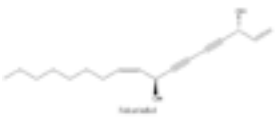
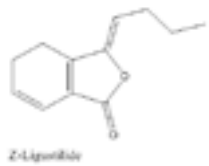
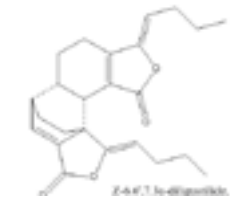
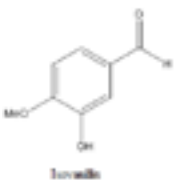
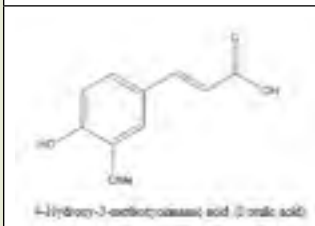
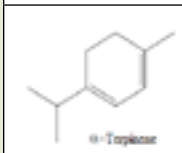
Figure 1. Distribution and Knowledge of *Ligusticum* Species Around the World
(a) Biodiversity occurrence data according to the Global Biodiversity Information Facility [6]
(b) Summary of reported literature indexed in Web of Science as of September 30, 2010.

Common Name	Species Name	Number of Articles	Endemic to
Szechwan Lovage	*Ligusticum chuanxiong* S.H. Qiu et al.	130	China
chuānxiōng	*Ligusticum wallichi* Franch	59	China
Gao ben	*Ligusticum sinensis* Oliv	5	China
Xi ye gao ben	*Ligusticum tenuissimum* (Nakai) Kittag	2	China
Duo guan gao ben	*Ligusticum multivittatum* Franch	1	China
Duo bao gao ben	*Ligusticum involucratum* Franch	1	China
	Ligusticum spp.	14	Asia
	Ligusticum marginatum C.B. Clarke	1	W. Pakistan through Himalayas
Gao shen gao ben	*Ligusticum elatum* C.B. Clarke	2	Nepal, India, Pakistan
Dong-Dang-Gui	*Ligusticum acutilobum* Siebold & Zucc.	2	Japan
True Osha	*Ligusticum porteri* Coult & Rose	17	Mexico, United States
Canby's Lovage	*Ligusticum canbyi* Coult & Rose	0	Canada, United States
Scottish Lovage and Hulten's Licorice	*Ligusticum scoticum* L (ssp. scoticum and ssp. hultenii [Fernald] Calder & Roy L. Taylor)	7	Canada, United States
Fern-leaf Licorice	*Ligusticum filicinum* S. Watson	1	Canada, United States
Idaho Licorice	*Ligusticum tenuifolium* S. Wats	1	United States
Gray's Lovage	*Ligusticum grayi* Coult & Rose	1	Canada, United States
	Ligusticum seguieri Koch	2	Europe
	Ligusticum pyrenaicum Gauan	1	Europe
Alpine Lovage	*Ligusticum mutellina* Crantz	3	Europe

Figure 2. Wild Collection of North American *Ligusticum* Species

A. A stand of *Ligusticum canbyi* in British Columbia, Canada
B. Umbel of *Ligusticum canbyi*
C. Leaves of *Ligusticum canbyi*
D. Roots of wild-harvested *Ligusticum canbyi*
E. Roots and powder sold commercially as osha

Table 3. Phytochemistry of North American *Ligusticum* Species

Compound	Species	Proven Medicinal Activity
	*L. porteri* [60]	Isolates taken from members belonging to the genus *Angelica* have shown analgesic, antiinflammatory, hepatoprotective, vasorelaxant, and anti-proliferative activity[66]
	*L. porteri* [60]	Anticancer, antibacterial, vasodilating, and antioxidant effects[67]
	*L. porteri* [60-63,64] *L. filicinum* [63] *L. tenuifolium* [63]	Smooth muscle relaxation, vasodilation, insecticidal, antibacterial, antifungal and anti-inflammation,[3] antihyperglycemic[78]
	*L. porteri* [62]	Antihyperglycemic[78]
	*L. porteri* [62]	Inhibits both aldehyde oxidase and mitochondrial aldehyde dehydrogenase[68]
	*L. porteri* [62]	Antioxidant, prevention against thrombosis and atherosclerosis, cholesterol lowering, antimicrobial, anti-inflammatory, anti-cancer[69]
	*L. porteri* [61,64] *L. filicinum* [63] *L. grayi* [65]	Antifungal,[70] insect repellent[72]
	*L. porteri* [61,64] *L. grayi* [65]	Antioxidant[71]

Linares (1981-1986), Curtin (1965), Schulman and Smith (1962), Kennedy (1978), and Ford (1975) observed the Tarahumara using infusions of *L. porteri* during ritual curing ceremonies or for protecting individuals against witches and rattlesnakes.[9] Similarly, Camazine and Bye (1980) report that both patient and medicine man in Zuni culture would chew on the root during healing rituals.[33] Jones (1992) describes the Arapahoe and Pawnee using the roots of *L. porteri* during sweat lodge ceremonies and purification rites.[34] While staying with the Tonkawa, Opler (1902) recounted that one must possess *L. porteri* in order to partake in the peyote ceremony:

> "The only way you could get in that ceremonial tent was to have long hair, your face painted to suit them, and an Indian shirt made of any colors you liked. And you had to have buckskin leggings or some kind of leggings such as the Indian used to wear. You had to have a long loin-cloth and you had to wear a sheet wrapped around you. You had to have different kinds of odorous herbs; you had to have Osha."[35]

Among the Plains Apache, Jordan (2008) reports that roots of *L. porteri* are thrown over fire to help console individuals during rituals associated with mourning.[25] Turner et al. (1980) found that aromatic smoke produced from roots of *L. canbyi* were used by the Okanagan-Colville to release individuals from trance, possession by spirits such as the "blujay spirit," or unconsciousness.[24] During the early 1900s, chewing the roots of *L. scoticum* was considered a substitute for tobacco.[36] Similarly, *L. canbyi* can be added to tobacco[37] and smoked in order to produce a menthol taste. It has been suggested

Osha *Ligusticum porteri*. Photo ©2011 Daniel Gagnon

that smoking its roots provides a relaxant effect, which most likely explains its common name "Indian marijuana." *Ligusticum canbyi* can be used as incense.[37] Exposure to excess amounts of smoke is believed to have a strong sedative effect upon children.[24] Furthermore, Sturtevant (1958) reports that members of the Cherokee would smoke the roots from *L. canadens*e in order to treat stomach problems.[38]

Food

Although it is likely that most species have been used for cooking or substituted with other species, *L. californium*, *L. canadense*, *L. grayi*, *L. porteri*, and *L. scoticum* are indicated for culinary use within the literature (Table 2). It is believed that *Ligusticums* produce a chervil-celery-parsley flavor;[8] and as a result, the leaves, seeds, and roots are used to season meats, beans, and chilis.[8,9, 39-43] *Ligusticums* can be eaten without preparation or by preparing leaves like greens through boiling or adding to salads.[31,44-46] Stalks can be used similar to celery,[47] while roots can be boiled, thrown into salads and soups, or eaten raw by peeling back the stem.[36,48,49]

Medicine

The use of osha to treat sickness and promote "well-being" has played an important role among North American indigenous cultures for centuries. In 1988, researchers in Utah discovered a medicine bundle containing *L. porteri*, thought to be 200 to 400 years old. After analyzing the contents of the package, it was suggested that these items were not simply "stash items," but rather of great significance.[50] Medicinal applications of *Ligusticum* species include the following: antirheumatic;[9] treat-

Table 3 (continued). Phytochemistry of North American *Ligusticum* Species

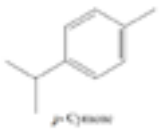
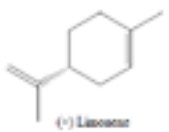
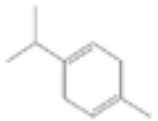
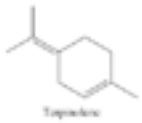
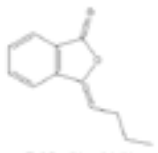
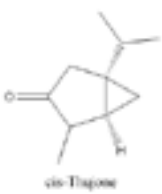
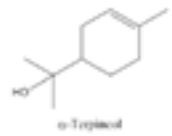
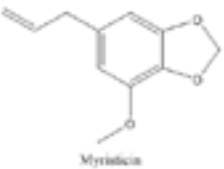
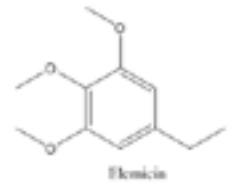
Compound	Species	Proven Medicinal Activity
	*L. porteri* [61,63,64] *L. grayi* [65]	Antifungal[70]
	*L. porteri* [61,63,64] *L. grayi* [65]	Antibacterial, enhances transdermal permeation of melatonin,[71] insect repellent[72]
	*L. porteri* [64] *L. grayi* [65]	Antioxidant[71]
	*L. grayi* [65]	Alpha is antioxidant,[71] insect repellent[72]
	*L. porteri* [61,64] *L. tenuifolium* [63]	Antianginal, antihypertensive, antispasmodic, vasodilation, serotonergic activity, and selectivity upon the central cholinergic neuronal system in rats,[3] antihyperglycemic[78]
	*L. porteri* [64] *L. grayi* [65]	Antibacterial[71]
	*L. porteri* [64] *L. grayi* [65]	Insect repellent[72]
	*L. porteri* [64]	Antinociceptive, insecticidal, and antihelmintic activity[73]

Table 3 (continued). Phytochemistry of North American *Ligusticum* Species

Compound	Species	Proven Medicinal Activity
	*L. porteri* [64]	Cancer suppression, vascular smooth muscle relaxant, antibacterial, antiallergenic[71]
	*L. porteri* [64]	Antibacterial,[70] insect repellent[72]
	*L. porteri* [64] *L. grayi* [65]	Hepatoprotective[71]
	*L. porteri* [64] *L. grayi* [65]	Antibacterial[74]

ment for hair, lice, ticks, wounds, and skin and ear infections;[9, 24, 37] as an anti-convulsive, analgesic, and fever treatment,[9,31,37] for gastrointestinal problems or dietary aid,[9,31,38,51] for colds, coughs, sore throats, and pulmonary or respiratory aid,[9,24,31,37,52-58] treatment for anaemia, diabetes, and circulation or heart problems[9,37,53] (Table 2). Personal preference towards a specific *Ligusticum* species varies throughout North America. The dispensatory of the United States indicated in 1918 that *L. filicinum* "is a highly prized expectorant" within Utah and the surrounding states.[56] Smith (1929) states that the Menomini describe 20 kinds of "osha root," the most powerful being the Mani'k (*L. filicinum*).[57] More recently, *L. porteri* was identified by Appelt (1985) as a commonly used herb in Hispanic communities of the San Luis Valley, Colorado.[59]

Medicinal Chemistry

Much of the research that exists investigating the molecular composition of *Ligusticum* species includes derivatives of coumarins and phthalides (such as Z-ligustilide and butylidenephthalide).[3,60] Over the last 50 years, Asian species of the genus *Ligusticum* have facilitated the discovery of many novel compounds. Approximately 40 phthalides have been isolated from *L. chuanxiong*, 20 from *L. officinale*, and 20 from *L. wallichi*.[3] Table 3 presents a summary of compounds identified from species commonly known as osha.[3,60-74] Although numerous compounds have been identified, Z-ligustilide and butylidenephthalide are most commonly purported to facilitate their therapeutic effects. Medicinally, Z-ligustilide is used for the following effects: smooth muscle relaxation, vasodilation, and as an insecticidal, antibacterial, antifungal, and anti-inflammatory. Further, antianginal, antihypertensive, antispasmodic, vasodilatory, and serotonergic activity—as well as selectivity upon the central cholinergic neuronal system in rats—have been associated with butylidenephthalide.[3]

Bioassay

Although a variety of therapeutic properties have been associated with *Ligusticums* found within Traditional Chinese Medicine, the exact

Figure 3. Distribution of Various *Ligusticum* Species in North America as Compiled by the Global Biodiversity Information Facility[6]

- ***Ligusticum porteri***
- ***Ligusticum filicinum***
- ***Ligusticum tenuifolium***
- ***Ligusticum canbyi***
- ***Ligusticum grayi***

mechanisms which underline these attributes are still unclear.[3] With respect to pharmacology, extracts of *L. porteri* have been shown to inhibit the infective capacity of several strains of bacteria.[75] On the other hand, essential oil and dichloromethane extracts did not exhibit significant antimicrobial activity against a norfloxacin-resistant strain of *Staphylococcus aureus,* but sensitivity to norfloxacin was restored.[64] Additionally, ethanol extracts taken from roots of *L. porteri* (0.05g/ml) have shown inhibitory activity against both *Bacilus subtilis* and *Pseudemonae syringae*.[76] In various model systems to test pain susceptibility, extracts of *L. porteri* have shown significant antinociceptive activity.[77] Orally administered extracts of *L. porteri* have shown antihyperglycymic effects in mice, with (*Z*)-6,6',7,3'a-Diligustilide, (*Z*)-ligustilide, and 3-(*Z*)-butylidenephthalide contributing to the observed effects.[78] In contrast, models of cancer metabolism did not find significant inhibition of proliferation of tumor cells or cytotoxic effects.[79] It is interesting to note that some toxicity has been determined in roots of *L. porteri* (LD_{50} = 1085 mg/kg in mice and CL_{50} = 777.98 µg/ml with Artemia salina lethality test [80]) suggesting further inquiry into safe dosage should be undertaken.

Conclusions

There is still much to learn about North American *Ligusticum* species with respect to their botanical diversity, growth, cultivation, phytochemistry, and potential therapeutic uses. These studies are especially timely since demand for North American *Ligusticum* species sold as osha has increased steadily and some collections may have reduced wild populations of certain species. Therefore, monitoring of wild populations and sustainable wild-crafting and cultivation will help ensure that sufficient osha germplasm is available for future generations of the natural health products and herbal dietary supplement industry.

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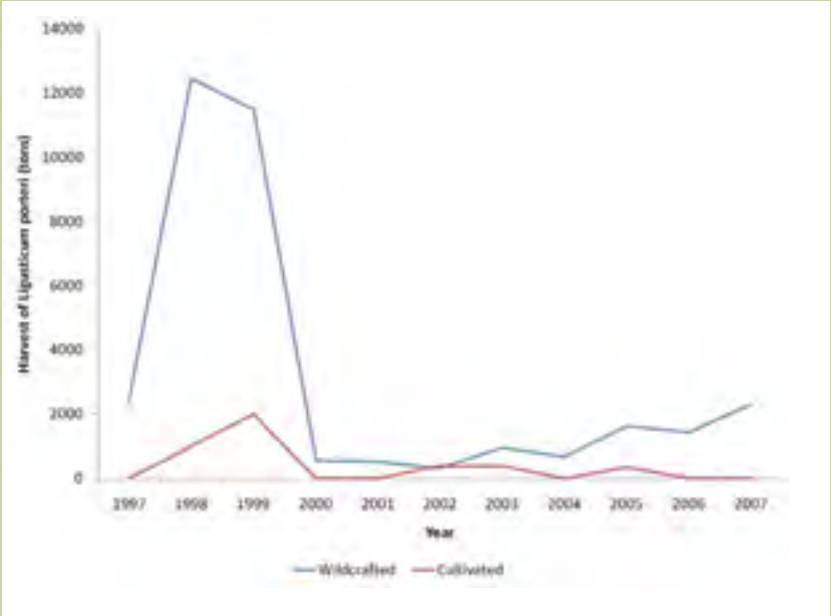
Figure 4. Harvest and Sales of *Ligusticum porteri* as Osha [23]



Osha *Ligusticum porteri.* Photo ©2011 Steven Foster

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Osha *Ligusticum porteri*. Photo ©2011 Daniel Gagnon

Regulating Herbal Products: An Historical Canadian Perspective

By Dennis V. C. Awang, PhD, FCIC

This is a revised version of the author's presentation to the Canadian Herbalist's Association of British Columbia, Vancouver, June 13, 2010.

Several years before the Natural Products Section, of which I was the head, was canceled in 1993, and prior to elimination of the entire Bureau of Drug Research of Health & Welfare Canada (HWC), I circulated a discussion paper titled "A Drug Identification Number (DIN) Ought to Mean Something" and proposed that natural products should not be granted DINs but rather TMNs (Traditional Medicine Numbers)—unless there were acceptable clinical trials in support of specific therapeutic claims for marketed product forms.

At the time, I successfully promoted the granting of the first such DIN to feverfew (*Tanacetum parthenium*, Asteraceae)* whole leaf for prevention of migraine attacks. Then all other DINs for herbal products had been granted based on acceptance of the claims of traditional medicine; however, few of these products bore much resemblance to products prepared by traditional methods, which are mostly whole plant material or water extracts. Nevertheless, the regulatory authority granted DINs to a variety of preparations, including combination products, with no assurance of botanical identity or consistent method of preparation.

Several instances of adverse reactions were observed during that period, resulting from adulteration and/or substitution. The adverse effects were relatively mild, despite the occasional need for hospitalization in more serious cases, such as contamination by tropane alkaloid-containing plant material—likely belladonna (*Atropa belladonna,* Solanaceae), also known as deadly nightshade, which was indicated in 5 different plants resulting in hallucination, CNS and respiratory depression. A widely publicized case of botanical substitution, popularly described as "The Hairy Baby Case," resulted from Chinese silk vine (*Periploca sepium*, Asclepiadaceae) being consumed by a pregnant nurse in Toronto, instead of the apparently innocuous intended eleuthero (*Eleutherococcus senticosus,* Araliaceae), labeled "Siberian ginseng."

In 1990, in Belgium, the formula of an established slimming regimen was modified by inclusion of extracts of 2 Chinese herbs imported from Hong Kong, where there was no legal regulation of Traditional Chinese Medicine (TCM). One of the intended herbs was *han fang ji* (*Stephania tetrandra,* Menispermaceae), but the herb supplied—either by accident or possibly due to the unfortunate belief that a substitution was appropriate—was *guang fang ji (Aristolochia fangchi*, Aristolochiaceae), which contains the nephrotoxic aristolochic acid, known to be mutagenic and carcinogenic in laboratory animals. Prolonged ingestion of the slimming treatment, administered by doctors untrained in herbal medicine, led to more than 100 cases of kidney failure in women in Belgium and France.[1-4]

The foregoing examples, as well as more recent occurrences of adverse health effects (AHEs), including *reports* of serious adverse reactions to purported black cohosh (*Actaea racemosa* syn. *Cimicifuga racemosa*, Ranunculaceae) products, popular for treatment of menopausal complaints, reveal some unfortunately related aspects of herbal regulation. Notably, almost invariably, occasions of adulteration/substitution are revealed by observation of AHEs reported via the medical community. For example, in the case of 4 serious adverse effects reported in Canada and attributed to a specific black cohosh product, a subsequent analytical investigation resulted in recall of such products from at least 7 companies supplied with the wrong plant species, probably the Asian species *A. cimicifuga,* but possibly *A. podocarpa*.[5]

Identity and Quality

The underlying situation responsible for all these observed AHEs is the failure of the various regulatory systems to ensure proper botanical identity and quality of marketed plant products. Simple declarations of manufacturers on license application forms and elaborate product labels *cannot assure identity and quality.*

In the current climate, judicious consumer choice can be advanced only by education regarding medicinal effects, their relation to the type of preparation, and, arguably most importantly, knowledge of the experience and scientific competence of manufacturers.

Quality assurance (QA) is aided by promotion of Good Manufacturing Practices (GMPs) which, if effectively enforced, should address most purity issues, including contaminants such as pesticides and pollutants, toxic metals (e.g., arsenic, cadmium, lead, and mercury), bacteria, molds and mycotoxins, processing impurities and solvent residues, as well as adulteration with undeclared pharmaceuticals. Quality issues may also involve botanical identity and the use of incorrect plant parts.

Identity

At present, the predominant methods for botanical identity testing rely on the plant's morphological features or phytochemical profiles. Historically, morphological identification could be reliably accomplished by macroscopic examination of whole plants and/or plant parts, essentially intact after harvest, by an experienced botanist or trained herbalist. However, a botanist at the herbarium of the University of Texas at Austin wrongly identified a voucher specimen as German chamomile (*Matricaria recutita,* Asteraceae), purportedly of Argentinian origin and containing 7.3% of anthecotulid—a noxious, highly allergenic sesquiterpene lactone.

Examination of the specimen by German researchers revealed the plant material to be, in fact, derived from dog's chamomile

* The author notes his reluctant adherence to the ABC/*HerbalGram* style convention for scientific notation of botanicals in which the accepted and/or preferred Latin binomial is employed with the family name, but without the attribution of the botanical authority, as was formerly the ABC/*HG* style. The author hereby notes his preference for the latter, despite ABC's decision to discontinue the use of authorities, as is still employed elsewhere, e.g., in professional botanical journals. —DVCA

(*Anthemis cotula*, Asteraceae). *M. recutita* contains variable, but much lower levels of anthecotulid.†[6] Commercial raw material can be available in various forms, from cut and powdered, otherwise untreated plant parts, to extracts using a variety of solvents. Definitive species diagnosis from solid plant material is often elusive by macroscopic and/or microscopic means, making identification increasingly reliant on phytochemical procedures, mainly of the chromatographic and spectroscopic/spectrometric varieties. Largely reliable, well-established chemical separation techniques can provide distinctive profiles without necessarily identifying individual phytochemical compounds. However, complete reliance on chemical profiles for botanical identification is problematic since marker compounds may exhibit wide variation in concentration of the naturally occurring chemical constituents of plants. Definitive comparative data on plant-to-plant, population-to-population, and species-to-species are prerequisite to reliable taxonomic diagnoses. Also, the preponderance of processed botanical material in the herbal supply chain precludes the broader reliable application of macroscopic and microscopic morphology-based identity testing, and by default the herbal community relies largely on phytochemical measurements to ascertain sample identity.‡

DNA

DNA-based approaches appear to be particularly useful for deconstructing plant mixtures to confirm the identity of components in blended herbal products.[7] Nucleotide-based methodology has been used to overcome many of the shortcomings associated with morphological and chemical identification techniques, including identification of both single herb and mixed plant preparations: St. John's wort (*Hypericum perforatum*, Clusiaceae) has been effectively differentiated from morphologically and chemically similar species, as have other species such as Korean/Chinese or Asian ginseng (*Panax ginseng*, Araliaceae) from American ginseng (*P. quinquefolius*), and Chinese star anise (*Illicium verum*, Illiciaceae) from Japanese star anise (*I. anisatum*). Further, the time and cost surrounding DNA-based analytical techniques have steadily decreased over the last 20 years: Data collection which once required days or weeks can now be completed in a matter of hours, with service pricing in the neighborhood of morphological and phytochemical methods.

A Prescription for Improved Regulation

After a decade of virtual dormancy of HWC herbal regulatory programs, the promulgation of the Natural Health Products Regulations in 2003 and the staffing-up of the Natural Health Products Directorate (NHPD) as part of a renovated Health Canada (HC) to administer these regulations created a regulatory framework and process to replace herbal DINs with Natural Product Numbers (NPNs). A website developed since publishes plant species monographs (webprod.hc-sc.gc.ca/nhpid-bdipsn/monosReq.do?lang=eng) and also elaborates extensive specifications required for licensing finished products. However, a seminal—and critical—deficiency of NHPD's regulatory process is the lack of a confirmatory aspect, respecting both botanical identity and chemical analysis.

Low Dog *et al.*[8] acknowledge that both Canada and the United States require manufacturers of herbal products to report to their respective "appropriate government agencies" "serious adverse effect reports," and regard the Canadian system as superior to that of the US because the former requires market authorization of each NHP before it can be legally sold. However, the Canadian judgment of safety, efficacy, and "high quality" is based solely on consideration of an application form—and "on the basis of evidence of compliance with current GMPs."

† Anthecotulid is responsible for the commonly observed primary irritant contact dermatitis specific *A. cotula,* is absent from bisabolol chemotypes of German chamomile flowers; its low yield in the bisabolol oxide -B chemotype does not induce primary irritations, although specific hypersensitivity might rarely be induced by that and other known chemotypes.

‡ Recent advances in metabolomics and chemometrics for medicinal plants involve applying multivariate statistical treatments (e.g., Principal Components Analysis, Hierarchical Cluster Analysis, or Partial Least Squares and its extensions such as Orthogonal PLS) to the "fingerprint" results obtained from phytochemical analyses. The data may come from simple broad-spectrum extracts, e.g., from deuterate solvents (single or mixed) subjected directly to nuclear magnetic resonance (NMR) spectroscopic analysis, or from any of the wide variety of chromatographic separation techniques (e.g., HPLC, GC) combined with detection and analysis by mass spectrometry, NMR, diode-array UV, etc. The advantages of the metabolomic/chemometric approach are that it allows one to work with complex extracts rather than a limited number of marker compounds that may or may not be relevant to the medicinal properties of the plant, and one has systematic, objective, reproducible conclusions on the similarity of samples with a reference standard, revealing the degree of natural variability in the species compared to significant differences from other species. Applications of medicinal plant metabolic fingerprinting with chemometrics for both quality control and bioactivity assessment have been reviewed recently by Verpoorte *et al.* [9,10]

Suggested Initiatives

A Registry of Certified Growers (obedient to Good Agricultural and Collection Practices [GACP])/Suppliers, based on established competence in Botanical Authentication of Raw Material, who can be identified at all subsequent stages of supply and processing.

Certification of analytical laboratories qualified to conduct chemical testing of both raw material and finished products. (The most recent refinements of analytical methodology should be provided in a timely manner to prospective license applicants.)

A schedule of rotational random manufacturer product testing should be established (such as operated biannually in France); product candidates ought to be prioritized for selection, as in the earlier Natural Products program, on the basis, mainly, of sales volume, severity of associated health conditions, and recognition of past incidences of adulteration/substitution.

Development of a database of DNA analytical profiles, as an aid to characterizing herbal products, especially the components of blended finished products.

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US Dietary Supplement cGMPs and Ingredient Supplier Qualification

By Andrew Shao, PhD

Editor's Note: In 2006, a group of dietary supplement industry trade associations formed the SIDI (Standardized Information on Dietary Ingredients) Working Group to help streamline communications among suppliers and customers. The efforts of the Working Group have since expanded to address the broader issue of supplier qualification, a requirement in the dietary supplement current Good Manufacturing Practices (cGMPs) regulation and a potentially critical element for the prevention of supply chain failures. We invited Andrew Shao, PhD, of the Council for Responsible Nutrition, a leading industry trade association, to explain this initiative and its current status.

Published by the US Food and Drug Administration (FDA) in June, 2007, cGMPs for dietary supplements (21 CFR Part 111) are now mandatory for all firms that manufacture, package, label, or hold dietary supplements for sale in the US, including foreign manufacturers who ship product to the US. Ingredient supplier qualification remains one of the most critical, yet least understood, aspects of the regulation. The increasing global supply chain and multiple instances of supply chain failures that have led to adverse consequences have elevated the need for proper supplier qualification across all FDA-regulated industries. Although defined in the regulation, its interpretation and FDA's future enforcement of dietary supplement supplier qualification remain unclear, and there is little agreement on what constitutes industry best practices. Following the precedent set by other FDA-regulated industries, several responsible parties in the dietary supplement industry have formed a consortium to address the knowledge and practice gaps regarding supplier qualification.

The group has developed a series of voluntary guidelines to assist ingredient suppliers and dietary supplement manufacturers with the qualification process. These guidelines, some of which are still under development, are intended to serve as tools or templates on which a firm's own qualification program or standard operating procedure(s) can be based. Those developing the initiative hope that these guidelines will serve as the basis for future FDA guidance or rulemaking, should the need arise.

Failures in the Global Supply Chain

In the past decade there have been numerous incidents and outbreaks in various FDA-regulated industries related to contamination or adulteration of material along the supply chain. The drug industry has experienced contaminated heparin,[1] and glycerin contaminated with diethylene glycol in cough syrup[2] and toothpaste;[3] the food industry has experienced intentional adulteration with melamine[4] and unintentional contamination by salmonella,[5] all of which were linked to numerous deaths. While the dietary supplements industry has yet to be the source of a widespread outbreak associated with deaths, the US industry has historically suffered its share of accidental supply chain failures, ranging from contaminated tryptophan[6] to contamination of plantain *(Plantago ovata*, Plantiginaceae) leaf with leaf of yellow foxglove (*Digitalis lanata*, Scrophulariaceae)[7] to numerous reports of weight loss, bodybuilding, and male sexual enhancement products intentionally adulterated with active pharmaceutical ingredients (APIs) or analogs thereof.[8,9,10,11] FDA leadership has stated repeatedly that the pharmaceutical spiking of products marketed as dietary supplements is the agency's single greatest concern regarding dietary supplements.[12] The aforementioned incidents all stemmed from supply chain failures. Somewhere in the process a vendor, supplier, or distributor was not properly qualified and/or failed to properly qualify the material being sourced.

US Dietary Supplement cGMPs Part 111.75

For dietary supplements, the requirement for supplier qualification is isolated to a small section of the GMP regulation. Subpart E, § 111.75(a)(ii)(A) states that before a dietary supplement manufacturer uses a component (and after verifying the identity of all dietary ingredients), the manufacturer may rely on an ingredient supplier's certificate of analysis (CoA) to determine that all established specifications have been met, provided that:

> [The "you" in the following list refers to the manufacturer]
> "(A) You first qualify the supplier by establishing the reliability of the supplier's certificate of analysis through confirmation of the results of the supplier's tests or examinations;
> (B) The certificate of analysis includes a description of the test or examination method(s) used, limits of the test or examinations, and actual results of the tests or examinations;
> (C) You maintain documentation of how you qualified the supplier;
> (D) You periodically re-confirm the supplier's certificate of analysis; and
> (E) Your quality control personnel review and approve the documentation setting forth the basis for qualification (and re-qualification) of any supplier."[13]

Comprehensive raw material testing can pose a substantial cost burden, and this provision is aimed at providing the basis to support reduced testing of incoming ingredients or components. Some may interpret the language in the cGMPs to mean that if reduced testing is *not* desired and that full testing (i.e., testing for all specifications) will be conducted of all incoming lots of raw material, then supplier qualification is not necessary. This may not be an appropriate interpretation, because testing alone may not be adequate to assure the quality of incoming ingredients. As pointed out in recent comments to the FDA, one cannot test for adulterants, economically motivated or otherwise, that one does not know exist, or for which no "scientifically valid" method(s) of testing exist. While a robust supplier qualification program cannot guarantee protection against adulterated ingredients or supply chain failures, when combined with a risk-based approach to ingredient testing, it can help minimize the likelihood and occurrence of problems. Indeed, in a recent letter addressed to the dietary supplement industry on the issue of products intentionally adulterated with APIs, FDA Commissioner Margaret Hamburg stressed the importance of supplier qualification, stating, "A strong program of qualifying your suppliers, testing incoming ingredients, and verifying the contents of finished products—all of which are required

Table 1. General Criteria* for Determining Ingredient/Ingredient Supplier Risk

Criteria	*Lower risk*	*Higher risk*
Complexity/novelty of the raw material or ingredient	Commodity ingredient (e.g., ascorbic acid or granulated sugar)	Complex botanical extract, prone to economically-motivated adulteration
Country of origin (i.e., level of regulatory oversight)	USA, Australia	China, India
History of supplier	Strong customer service history; little/no regulatory enforcement actions	No customer service history; history of enforcement actions (e.g., warning letters, 483s†)
Stability/Sustainability	Stable and sustainable raw material supply	Less certainty around sustainability
Intended use	Processing aid that does not figure in the final product specifications	Prominent active ingredient, e.g., basis of label claim

* These represent general examples that firms might use to assess risk of suppliers; the list is not intended to be comprehensive.
† 483s refers to GMP inspection reports by FDA field officers of dietary supplement manufacturing facilities.

by the cGMP regulations—can help minimize those risks."[14] Such programs can be used to assess both the risks posed by a supplier and/or component and serve as the basis for supplier management (e.g., supply agreements, continuous improvement, etc.).[15]

FDA has yet to issue any guidance related to maintenance of dietary supplement supply chain integrity. However, since 2009, Center for Food Safety and Applied Nutrition (CFSAN) officials at the FDA have been communicating the agency's expectations to the supplement industry regarding dietary supplement ingredient supplier qualification at various trade shows and conferences. Officials have stressed the need for complete documentation of the process, involvement of quality control, and the need for the industry to be innovative in order to deal with the challenges of a global supply chain.[16]

As FDA implements the dietary supplement cGMPs, industry members are beginning to see agency inspectors focus on manufacturing firms' supplier qualification programs, or lack thereof. Agency inspectors are now beginning to note the failure of Quality Control (QC) personnel to review and approve documentation serving as the basis for supplier qualification.[16] While to date only about 100 large (500 or more employees) and medium (20 or more employees) companies have been inspected, the ensuing inspections of smaller firms (less than 20 employees) are expected to expose substantial deficiencies in supplier qualification.

Defining Supplier Qualification

Following the precedent set by the excipients (www.ipecamericas.org) and pharmaceutical (www.rx-360.org) industries, 3 dietary supplement industry trade associations* are in the process of creating a series of voluntary guideline documents aimed at helping US firms with supplier qualification (see www.crnusa.org/SIDI). The guidelines stress the principles of risk management based on International Conference on Harmonization (ICH) guidelines,[17] as different ingredient suppliers and ingredients or components pose different levels of risk; this, in turn, drives the resource allocation dedicated to the qualification process. Risk may take different forms: It can include safety risks to the consumer and liability, financial, and/or supply disruption risks to the manufacturer. Table 1 provides examples of some general criteria or factors that may be used to assess risk. This list is not intended to be comprehensive, but merely illustrative of what criteria might be considered, and an individual firm's experience may vary greatly. FDA's diminished ability to inspect foreign manufacturers due to resource constraints renders these raw materials a higher risk. How manufacturing firms deal with or mitigate that risk depends on a combination of regulatory requirements, best practices, and business interests.

Qualification of botanical suppliers and/or ingredients poses some unique challenges. Many suppliers of botanical ingredients are located overseas, and botanical extracts can be difficult to qualify due to a lack of general familiarity with many of the materials, a lack of characterization and availability of reference standards, and appropriate and/or otherwise validated analytical methods. Furthermore, these extracts can be particularly prone to economically motivated adulteration through spiking with APIs, the addition of dyes (or other colorants used to foil colorimetric analytical methods), or substitution with cheaper species.[18]

The basic and most important aspects of supplier qualification appear in Table 2. The dietary supplement industry is diverse, with foreign and domestic ingredient suppliers, distributors, and contract manufacturers ranging in size from a handful of full-time employees to several thousand. The nature of ingredients and components varies greatly as well, from commodity vitamins and minerals, to excipients, to chemically complex botanical extracts. The resources available for regulatory compliance efforts, including supplier qualification, also vary greatly, as do business practices. Therefore, flexibility is a key factor in the development of these guidelines. The available and in-process voluntary guidelines are summarized in Table 3.

The most important considerations for supplier qualification

* The Joint SIDI Working Group is comprised of representatives from the Consumer Healthcare Products Association (www.chpa-info.org), the Council for Responsible Nutrition (www.crnusa.org), and the United Natural Products Alliance (www.unpa.com), and member company representatives from each trade group, respectively. To inquire about the Working Group contact Andrew Shao at ashao@crnusa.org.

Table 2. Key Elements for Dietary Supplement Component Supplier Qualification

Element	*Description*	*Relevance*
Supplier capability/ audit assessment	Assessment of supplier quality management systems and adherence to applicable GMP requirements	Component suppliers must adhere to food cGMPs at a minimum (21 CFR Part 110); assessment of the QMS is an important aspect of verifying the reliability of the supplier CoA
Certificate of analysis (CoA) recommendations	Establishment of appropriate specifications based on the nature of the component and intended use, including limits on contaminants; agreement on relevant and required information to be included on the CoA	Central focus of 21 CFR Part 111.75
Certificate of analysis (CoA) verification	Pre-commercial and commercial phases involving testing of component batches to verify the accuracy of the CoA; extent of testing proportionate to component/supplier risk	Central focus of 21 CFR Part 111.75; sets the basis for reliance on supplier CoA for all specifications (except identity)
Requalification / Disqualification	Periodic reverification of the accuracy and reliability of the CoA; involves testing, auditing, and disposition decision	Requirement according to 111.75 (a)(2)(ii)(D)
Supplier management recommendations	Covers important aspects of the supplier-manufacturer relationship, including supply/quality agreements, change management, continuous improvement, and claims substantiation	Not specifically required for reliance on the supplier CoA, but still may be necessary to maintain supply chain integrity and minimize risk and liability
Best business practice recommendations	Covers additional aspects of risk to supplier sustainability, including business continuity and capability, accountability/financial stability, environmental stewardship, labor and safety, crisis management, recall capability, and liability coverage	Not specifically required for reliance on the supplier CoA, but still may be necessary to maintain supply chain integrity and minimize risk and liability

Table 3. Voluntary Guidelines Developed by the Dietary Supplement Industry* for Supplier Qualification

Guideline	*Description*	*Status*
Dietary Supplement Component Supplier Qualification Guideline	Guideline based on risk management principles to assist manufacturers and suppliers with the development of their supplier qualification programs to satisfy compliance requirements of Dietary Supplement Current Good Manufacturing Practices (21 CFR Part 111)	In-process
SIDI™ protocol†	Outline representing the type and scope of information that an ingredient supplier typically needs to provide to a manufacturer; provides standards for voluntary use in the exchange of relevant and required information between ingredient suppliers and finished product manufacturers	Launched in 2006, updated in 2008
Certificates of Analysis (CoA) Guideline†	Guideline for the preparation by suppliers and appropriate use by their customers of a Certificate of Analysis (CoA) for dietary supplement components; standardizes the content and format of CoAs for dietary supplement components to help meet the dietary supplement cGMP requirements	Launched in April 2010

* Developed and maintained by the Joint SIDI™ Working Group. Documents and other information on the working group are accessible at www.crnusa.org/SIDI.

† Based on similar guidelines developed by IPEC Americas.

fall under 4 primary areas: Supplier Capability/Audit Assessment, Certificate of Analysis Recommendations, Certificate of Analysis Verification, and Requalification and Disqualification (Table 2), as these pertain directly to the requirement listed in 21 CFR Section §111.75. The initial phase of qualification involves gathering and reviewing information, primarily in the form of documents. Typically, this pre-assessment is executed through the use of vendor questionnaires or paper audits, which are intended to probe, at a general level, a supplier's manufacturing and quality systems and its adherence to applicable laws and regulations.

The dietary supplement industry has developed a voluntary guideline aimed at assisting ingredient or component suppliers with the compilation of this basic information for presentation to their customers in a clear, concise manner. Launched in 2006 and revised in 2008, the Standardized Information on Dietary Ingredients (SIDI™) protocol[19] outlines the type and scope of information an ingredient supplier should provide to a dietary supplement manufacturer regarding its ingredient(s) to help fulfill the documentation needs of the manufacturer. The 41-page guideline includes sections that separately address botanical and non-botanical ingredients. By relying on the SIDI protocol to develop ingredient information packages or dossiers on a proactive basis, suppliers can provide the same basic information requested on questionnaires. Manufacturers frequently require that their own unique questionnaire be filled out, and each questionnaire can run from 50 to 100 pages in length. Some suppliers have teams of technical service representatives whose sole purpose is to fill out questionnaires, while manufacturers spend needless resources tracking down missing or incorrect information on returned questionnaires. Furthermore, the information provided in a vendor questionnaire is typically not subject to change control, so the accuracy of the information at any given time may be equivocal. Eliminating questionnaires and using SIDI-based dossiers in their place can result in significant cost savings for both suppliers and manufacturers. Some manufacturers have experienced a reduction in the time it takes to obtain this critical information from suppliers, from weeks using the questionnaire-based approach down to as low as a few hours using the SIDI protocol.[20]

The main elements of Supplier Capability/Audit Assessment include review of the suppliers' quality management system and their compliance with applicable GMPs. An actual GMP audit of the suppliers' facilities is necessary to provide a true sense of risk assessment, to determine the degree of GMP compliance, and the ability to meet customers' needs. However, FDA CFSAN has stated only vaguely that it expects audits to be conducted and that it expects a full audit report to be on file (as opposed to a summary letter or statement from the auditor).[17] Whether FDA will ultimately require actual audit information on *all* dietary supplement component suppliers used by a given dietary supplement manufacturer—and, if so, with what frequency—remains to be seen. Regardless of the specific requirements FDA may (or may not) impose, the approach should be consistent with the principles of risk management, with the higher-risk materials and suppliers receiving onsite audits more frequently.

Reputable, independent, third-party certifiers and auditors can effectively assist firms in assessing suppliers' GMP compliance and thus in assessing (or mitigating) risk. In the US, the United States Pharmacopeia (USP; www.usp.org), NSF International (www.nsf.org), and the Natural Products Association (NPA; www.npainfo.org) all maintain well-recognized third-party certification programs that certify facilities and/or products, including suppliers and their ingredients. Independent third-party auditors can obtain audit information on an ingredient supplier's facility at a fraction of the cost that a firm can incur in maintaining its own internal audit team. Collectively, third-party certifiers and auditors can help in risk assessment (GMP certified facilities from one of the aforementioned programs present lower risk) or risk mitigation (GMP deficiencies identified by a third-party auditor can lead to corrective actions) processes.

The CoA represents the official interface between the ingredient or component supplier and finished product manufacturer. According to FDA, at a minimum, "The certificate of analysis includes a description of the test or examination method(s) used, limits of the test or examinations, and actual results of the tests or examinations."[21] Adequate CoAs are needed to assure specifications are being met for all components as well as for contaminants, and confirmation of the test results and reliability of the CoA are specifically stated as supplier qualification requirements in the cGMP. However, the quality and content of ingredient CoAs vary greatly across the industry. To assist suppliers with the development of consistent CoAs containing the required and relevant information, a voluntary CoA Guideline was created.[22] The purpose of the guideline is to provide recommendations for the preparation by suppliers, and appropriate use by their customers, of a CoA for dietary supplement components. Accompanying the guideline are example CoA templates for both botanical and non-botanical ingredients, given some of the unique specifications for botanicals. The goal is to standardize the content and format of CoAs for dietary supplement components, and to clearly define the roles and responsibilities for component suppliers, distributors, dietary supplement manufacturers, and other users who need to meet the dietary supplement cGMPs.

CoA verification is a requirement in the cGMP for those manufacturers who choose to rely on the CoA for all specifications except identity in lieu of full testing (i.e., testing each lot of incoming ingredients for all established specifications). This is a complex process that requires close communication between suppliers and manufacturers and can generally be divided into at least 2 phases: Pre-commercial and Commercial. Pre-commercial involves initial examination of the supplier's CoA, with testing to confirm its general reliability. Commercial testing typically occurs after the manufacturer and supplier have agreed on or established specifications for the ingredient that meets the needs of the manufacturer for the ingredient's intended use. Supplier-manufacturer communication may be necessary to establish the appropriate analytical methods that will ultimately be used in the Commercial phase of verification. The amount and scope of actual testing (i.e., number of lots tested, frequency of reverification, etc.) will depend on the risk assessment of the supplier (and ingredient) along with the performance of the supplier over the course of the relationship.

How, and with what frequency, suppliers are requalified should also be given ample consideration. The frequency of onsite facility audits, CoA reverification, and reevaluation of documentation are also highly correlated with the risk of the supplier and its past performance. It follows that the manner in which a given supplier manages change, or change control, becomes a critical aspect of the requalification process. Poor change control and change notification—particularly changes related to the manufacturing process

or formulation—on the part of a supplier, can expose customers to unnecessary and burdensome enforcement actions and other liabilities. It is inevitable that some suppliers and ingredients will pose too high a risk to warrant inclusion in the dietary supplement product. Whether to cut ties with the supplier or consider some type or form of risk mitigation (i.e., working with the supplier to address deficiencies) is ultimately a business decision for the manufacturer. This decision requires ongoing collaboration among the firm's different departments, including quality control, regulatory affairs, manufacturing/operations, procurement, and sales/marketing.

There are other considerations for supplier qualification that may not be required for cGMP compliance or assessing risk, but are still important for the ongoing supplier-manufacturer relationship. Also listed in Table 2, some of these considerations—or supplier management recommendations—include establishing appropriate supply and quality agreements, keeping thorough documentation and records, and striving for continuous improvement related to process and cost controls. Finally, there are best business practices to consider, although these are less likely to have a direct impact on the supplier performance or risk of the ingredient(s) under consideration. The business capabilities, financial stability, environmental stewardship, and labor and safety conditions of the supplier and its facilities can have an impact on its ability to perform and provide consistent, sustainable raw material. How well a supplier manages crises (e.g., if an important manufacturing facility is destroyed in a fire) can determine the continuity of its business. These are less critical, yet still important criteria to evaluate as they help assess the risk and reliability of the supplier.

Summary and Conclusion

The global supply chain has become more complex, with major outbreaks and adverse events resulting from breakdowns in the supply chain prompting the US government to propose new legislation concerning food and drug safety and importation. Some FDA-regulated industries have responded by developing recommendations or voluntary guidelines for supplier qualification. Some responsible elements of the US dietary supplement industry have begun the development and implementation of some voluntary supplier qualification initiatives. They should continue to address and implement minimum requirements, not wait for potential catastrophic failures in the supply chain that may prompt additional regulation from FDA or legislation from Congress—which would likely not be science- and risk-based, and possibly overly burdensome. For its part, these elements in the industry would welcome more open dialog and communication of its expectations for supplier qualification, continuing to be receptive to the exchange of ideas and information on approaches to supply chain qualification. In the end, consumers and policymakers will hold both FDA and industry accountable for supply chain failures.

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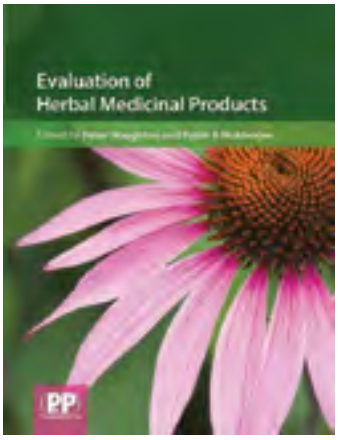
Evaluation of Herbal Medicinal Products by Peter Houghton and Pulok K Mukherjee (eds). London: Pharmaceutical Press; 2009. Hardcover; 520 pages. ISBN 978-0-85369-751-0. Price $199.99.

The enormous growth in the market for herbal medicinal products over the last 25 years has been one of the most remarkable aspects of healthcare in the developed and developing world. The (re)discovery and widespread use of natural substances with therapeutic uses has created a demand by both regulators and the general public for measures to be implemented to assure safe and efficacious herbal medicinal products. In response to this demand, regulators in the European Union have introduced the Traditional Herbal Medicinal Products Directive (THMPD), which, while harmonizing the regulatory standards throughout the EU, addresses one of the key issues of herbal medicinal products. Although they may have hundreds of years of documented traditional use in a certain indication, the mechanisms of action of many of these THMPs may still be poorly researched and their efficacy not clinically proven. The THMPD outlines a scheme for registering medicinal herbal products based on their traditional use only. While the requirements for documenting the safety and quality of the product as part of the registration process are similar to those for conventional medicines, proof of efficacy (derived from clinical trials) is replaced with adequate documentation of traditional use.



This book contributes to a better understanding and utilization of these regulations, as it brings together articles on current thinking and practices regarding quality, plus pharmacological, clinical, and safety assessments of herbal medicinal products. *Evaluation of Herbal Medicinal Products* also highlights up-to-date research that should facilitate improvements of the topics under consideration. The book seeks to provide a state-of-the-art review, informing and guiding those who are involved in the development, manufacturing, and marketing of HMPs. It extends coverage beyond herbs used in rational phytotherapy to those employed in other traditional healing paradigms such as Traditional Chinese Medicine, Ayurveda, and others. Challenges in understanding and explaining the activity of herbal products, and thus, of the development of standardized phytomedicines, are also discussed. Beyond the general overview, the publication covers approaches for pharmacological evaluation in some key therapeutic areas, such as gastrointestinal, cardiovascular, respiratory, memory and cognitive disorders, etc. It also elaborates on common hurdles in product development, such as stability of herbal products, and also provides perspectives on the evaluation of quality and safety.

The editors, Peter Houghton, emeritus professor in pharmacognosy at King's College London, UK, and Pulok K Mukherjee, director of the School of Natural Product Studies, Jadavpur University, Kolkata, India, have compiled 77 highly informative and valuable contributions from a wide range of sources. All contributions are well-represented, well-structured, and extensively referenced. The book opens with a glossary of key terminology, guidelines, and regulations, and is complemented with an impressive 20-page index. In summary, this book is a timely, highly valuable, and potentially indispensible resource for researchers in both academia and industry.

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Goddesses, Elixirs, and Witches: Plants and Sexuality throughout Human History by John M. Riddle. New York, NY: Palgrave Macmillan; 2011. Hardcover, 213 pages. ISBN: 978-0-230-61064-4. $88.00.

All too infrequently do students and scholars researching the history of pharmacology begin when our written sources in the West begin: with the cuneiform scripts of the earliest ancient Near Eastern cultures. Even more rarely do academics deign to admit that basic drive of human existence—sex. And when such research and examination of the cuneiform and later sources combine to ask how and why medical botany and phytochemistry have, from the earliest times, an essential function in the always excruciatingly tangled and raveling coils that detail sexual activity—whether to enhance blunt satisfaction of raw lust through the act of copulation or for presumably reliable aids in making babies, or oppositely to expel the unwanted product of coition—such research is not only more honest than is normal about the emotional and hormonal upheavals of human behavior, but also unmasks the not-so-subtle rituals and taboos that almost always enwreathe sex and the common links to religion.

Some scholars may wrangle about "codes" and their hidden meanings, others may bedeck their essays and books with the jargons of an always-faddish sociology or the opaque vocabularies characteristic of one or another "school" of cultural anthropology, while still others make our ancient predecessors into ignorant copies of our arrogantly modern selves. But not John Riddle. As usual, what he has to say rests on 2 basic foundations: the sources themselves as perused in the original languages, and, an assumption that one can indeed comprehend "what plants do as drugs" by means of what we loosely term *pharmacognosy*.

Goddesses, Elixirs, and Witches follows in the wake of his earlier and curiously controversial books on contraception and abortion,[1] volumes that irritated establishment members of the medical profession as much as they did some traditionalists and feminists among classical scholars.[2] Riddle's insistence that one must know the texts *first*—and in their original tongues—before drawing conclusions from them, sets him apart from the large majority of those who publish in both the History of Medicine and Pharmacy, since all too often what is touted as "original research" is founded on secondary, or even in some cases, tertiary, sources.

Even within the few numbers of scholars who can decipher cuneiform tablets and their often barely legible signs, there is fierce debate regarding the forms and intended use of botanical and animal drugs.[3] This healthy and continuous argument among specialists about the texts ensures our better understanding of these earliest documents of a Western pharmacology, similar to the necessary and ongoing controversies among phytochemists as

they discuss the multiple effects of botanicals.[4] In almost all his books and articles, Riddle attempts answers to that simple and most direct and difficult of questions posed by students in any of our classes: "Do the drugs actually *work*?" Thus, once the reasonably assured identity of the plant or animal product is established, the next step consists of analyses of the phytochemical properties paired with survivals in modern folk medical traditions, in turn linked with laboratory findings that demonstrate (or do not demonstrate) the claims made for the "natural drug" in question.

Goddesses takes up specific and occasionally detailed consideration of sources in the cuneiform languages (e.g., Akkadian and its 2 dialects, Assyrian and Babylonian, as well as Hittite and Sumerian), Hebrew, Greek, and Latin that attest to the potency as sex drugs of the pomegranate (*Punica granatum*, Punicaceae), mandrake (among 6 species, either *Mandragora autumnalis* or *M. officinarum,* Solanaceae), wormwoods (among some 400 species, most often *Artemisia absinthium*, *A. abrotanum*, *A. pontica*, and also likely *A. vulgaris*, Asteraceae, the so-called mugwort), and the chaste tree or monk's pepper tree (*Vitex agnus castus*, Verbenaceae). Not surprisingly, folk medical traditions in the Near East and North Africa still value all 4 genera in treatments of various ailments, ranging from use as antihelmintics, infertility and sexual unresponsiveness (in females), as emmenagogues (often prescribed for their abortive properties) and uterine relaxants, to the expected employment to dampen down sexual proclivities, and conditions and/or diseases of the sex organs.[5]

The tricky part now comes as one attempts to determine the phytochemical actions of the "natural" substance—always with myriad constituents present in nature, and until harvested, always to be understood in 4 dimensions, since the phytochemical constituents are rarely static in the living plant. At this stage of our historical analysis, one can refute such arguments as those advanced by Helen King and others, quite simply since one cannot reproduce *exactly* the "natural product" in the laboratory, any more than the rough equivalents can be *exactly* replicated from tablet to tablet, as provided in the cuneiform measures that accompany the texts of Assyrian or Babylonian pharmacology. *Do these particular genera produce physiological changes in our bodies*? And almost as importantly, *can an experienced medical professional of whatever era predict such effects*? Riddle's list is short, the botanical-phytochemistries of all four are fairly well-known, and what pharmacists like to term "active ingredients" can thereby be recorded with reasonable assurance.

Regarding pomegranates, Riddle begins at the beginning, with the book of Genesis fused with what we know from Sumerian tablets about the fruits of Eden, forbidden and otherwise. Arguing carefully from the texts, he can indicate that *P granatum* was widely known as a fertility drug *and* contraceptive from earliest times in Mesopotamia, through the Old Testament Hebrew kingdoms, and thence on into the future as shown in Greek myth and history, the list of contraceptives given in Soranus's *Gynecology* (dated to ca. 130 CE) and on into the Middle Ages. And if one augments from references not used in *Goddesses*, Riddle's case becomes even stronger.

Estrone (estrol; folliculin) is prominent in the seeds of *P. granatum*, with notable estrogenic activity;[6] the dried bark of the stem and root contain ca. 0.04-0.09% of alkaloidal pelletierine tannates deemed dangerous for pregnancies,[7] and in the words of a recent article on the phytochemical properties of the pomegranate, "Ethnomedical explorations have shown that pomegranate hull and/or root extract has been used orally and intravaginally to prevent both fertility and abortion and to treat various gynecological conditions, predicting the presence of compounds with hormonal activity... traditional knowledge of medicinal properties of plants predicts modern analyses."[8]

The literature on pharmacological biochemistry of plants, as it applies to human physiology and drug actions, more than confirms Riddle's conclusions regarding the Mesopotamian and later use of the pomegranate: In fact, human-centered research documents the probability of such use more thoroughly than do the studies cited by Riddle that give results of experimental studies on laboratory animals. Certainly similar literature on mandrake, wormwoods, and the monk's pepper tree, would also confirm the not-so-controversial assembly of evidence in *Goddesses* documenting the shrewd and often prescient knowledge of our most ancient ancestors in the use and understanding of love potions, fertility aids, contraceptives, and abortifacients.

If humanity loses its interest in sex, a rather obvious preoccupation by almost everyone since our origins somewhere near the Olduvai Gorge,[9] it may well be that *Homo sapiens* is destined to disappear. *Goddesses* tells us that we not only want to know about sex, but that methods of procreation and the deep histories of sexual pleasures long predate what we snootily like to label pornography. *Goddesses* should be issued in paperback, so ordinary readers without a fat bank account can own this treasure, a literate retelling of what we likely knew all along.

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Endnotes

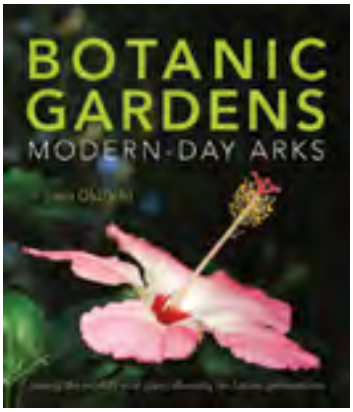
1. E.g. esp. *Contraception and Abortion from the Ancient World to the Renaissance.* Cambridge, MA and London: Harvard University Press; 1992, and *Eve's Herbs: A History of Contraception and Abortion in the West.* Cambridge, MA and London: Harvard University Press; 1997). Anticipating much of the controversy is the perceptive and positive review by Paul T. Keyser of *Ancient World to the Renaissance* in *Bryn Mawr Classical Review* (04.04.08 [1992: online]). Keyser rightly cites Riddle's "Oral Contraceptives and Early Term Abortifacients during Classical Antiquity and the Middle Ages" (*Past and Present.* 1991;[no. 132]:3-32), as a "...valuable article..." that "focusses on one aspect of [Dioscorides'] drug lore," that broached the topic of contraceptives. One could also cite Riddle's "Ancient and Medieval Chemotherapy for Cancer" (*Isis.* 1985;76:319-330) as indicative of further thinking on phytochemical substances, amply suggested by Riddle's truly pioneering monograph, *Dioscorides on Pharmacy and Medicine* (Austin: University of Texas Press; 1985).
2. Representative among many is Helen King,

Hippocrates' Woman. London and New York: Routledge; 1998. Esp. ch. 7, "Reading the Past Through the Present: Drugs and Contraception in Hippocratic Medicine" (pp. 132-156). Taking particular issue with Riddle's use of modern laboratory studies that employed rats and other animals to 'test' the abortifacient efficacy of botanical substances that include estrogenic properties among several ingredients, King writes that "The use of these plants in traditional medicine cannot possibly replicate this purity and concentration" (p. 147). In all fairness, King does cite those fellow-scholars who support Riddle's conclusions (pp. 132-133), but King's "Reading the Past" is a detailed refutation that *actual* phytochemical substances had any role whatsoever in contraceptive or abortion techniques in classical antiquity. Others, of course, begged to disagree, e.g. Lesley A. Dean-Jones in a review of King's *Hippocrates' Woman* in *Bulletin of the History of Medicine*, 74 (2000): 812-813. King doubts that *any* "natural" substance used as a drug was in the least effective, an opinion that includes anesthetics. Helen King, "The Early History of Anodynes: Pain in the Ancient World," in Ronald D. Mann, ed., *History of the Management of Pain.* Carnforth, England and Park Ridge, NJ: Parthenon; 1988: 51-62.

3. Recently, Markham J. Geller—a most talented physician-rabbi now professor of Semitic languages at University College London—has concluded that many of the pharmaceutical recipes in cuneiform consist of a "kind" frequently reproduced in tablet after tablet. See esp. "Therapeutic Prescriptions as Genre" in *Ancient Babylonian Medicine.* Oxford and Malden, MA: Wiley-Blackwell; 2011: 97-108. Of importance are also the following "Poetry within Therapeutic Prescriptions" and "The Babylonian Background to Greco-Roman Pharmacology" (pp. 108-117).
4. Salutary are the occasional commentaries in the monographs incorporated in Max Wichtl, ed. *Herbal Drugs and Phytopharmaceuticals*, 3rd ed., trans. from the 4th German ed. by Josef A. Brinckmann and Michael P. Lindenmaier. Stuttgart and Boca Raton: Medpharm and CRC; 2004. E.g. (on the *Valerianae radix*), "...the general opinion in the practice of phytotherapy today is that the efficacy of valerian depends upon an interplay between the constituents groups rather than on individual substances" (p. 631, col. 3). The debate will continue....
5. E.g. Loutfy Boulos. *Medicinal Plants of North Africa.* Algonac, MI: Reference Publications; 1983: 148-150 (pomegranate), 167 (mandrake), 54-57 (wormwoods), and 193 (chaste tree). Interestingly, *Vitex agnus castus* is a drug for weight gain by women, as is *Mandragora autumnalis*.
6. Jeffrey B. Harborne, *et al.*, eds. *Phytochemical Dictionary*, 2nd ed. London and Philadelphia: Taylor & Francis; 1999: 779 [no. 2694].
7. James E. F. Reynolds and Anne B. Prasad, eds. *Martindale The Extra Pharmacopoeia*, 28th ed. London: The Pharmaceutical Press; 1982: 104, col. 2, 804-b, and 102, col. 3, 797-r. *Cf.* Kathleen Parfitt, ed. *Martindale: The Complete Drug Reference*, 32nd ed. London and Taunton, MA: The Pharmaceutical Press and World Color Book Services; 1999: 108, col. 2, 804-b: the abortifacient properties have been omitted. Notably, Maryadele J. O'Neil, *et al.*, eds., *The Merck Index*, 13th ed. (Whitehouse Station, New Jersey: Merck and Co., 2001: 1267-1268 [No. 7143: pelletierine]) lists this isolated constituent gained from the rootbark of the pomegranate tree as used only as a vermifuge against cestodes. Among some German naturopaths, *Granatapfelbaum* (i.e., apparently all parts of the plant) is considered too poisonous to be useful: Ingrid and Peter Schönfelder. *Das neue Handbuch der Heilpflanzen.* Stuttgart: Franckh-Kosmos; 2004: 370.
8. Diane M. Harris, *et al.*:"Assessment of Estrogenicity of Pomegranate in an *in vitro* Bioassay." In: Navindra P. Seeram, *et al.*, eds. *Pomegranates: Ancient Roots to Modern Medicine.* Boca Raton, London, and New York: CRC/Taylor and Francis; 2006: 143-155 at 143-144.
9. One of the most important prehistoric sites known, also known as Aldupai Gorge, a steep-sided gorge in Eastern Africa in northern Tanzania in the Great Rift Valley where archaeological evidence, much of it studied by the famed Leakey family, shows that hominid species and early humans have lived for over 2,000,000 years.

Botanic Gardens: Modern-Day Arks by Sara Oldfield. Cambridge, MA: MIT Press; 2011. Hardcover; 240 pages. ISBN: 978-0262015165. $29.95.

Botanic Gardens: Modern-Day Arks provides a captivating overview of the plant conservation work going on at major botanic gardens around the world, providing a glimpse into the innovative works, collaborations, and successes of people and gardens dedicated to protecting plants.



The need to steward our once-abundant plant diversity is urgent. The reasons are many—continuous population growth, rapid economic development, loss of wild pollinators, and environmental degradation caused by a host of factors. The traditional concept of botanic gardens as collectors of plant oddities for display is taking a backseat to this more critical role in documenting, preserving, researching, reintroducing, and restoring the world's flora. One of the most interesting aspects of this book is learning how, through botanic gardens, different countries, regions, and networks have pulled together to deal with the complexities of plant conservation. There are some amazing success stories of plant reintroduction into the wild, ecological restoration, creative partnerships, and conservation resource-sharing that demonstrate how and why botanic gardens are the modern day arks.

For example, the work at National Tropical Botanical Garden, in Hawaii, is especially interesting given that over 90% of their flora is unique, with roughly 1,200 native plants growing nowhere else in the world. Approximately one-half of these species are threatened with extinction as a result of deforestation, grazing by introduced livestock, invasive plants, introduced insects and diseases, fire, and climate change. Hawaii's Plant Extinction Prevention Program has defined strict protocols for the rescue of some of the rarest plants in the world. In collecting seed and cuttings of these rare plants, these guidelines are followed to ensure that a representative sampling of genetic diversity is collected, meticulous records are kept, and the plants are given a safe haven until they can be reintroduced and then monitored in the wild. The garden's nursery is overflowing with native Hawaiian plants effectively being used in it's major reintroduction and restoration work. When possible, seed is stored to ensure long-term *ex situ* conservation of highly threatened species. The garden's Conservation Director, Dr. David Burney, has coined the term "*inter situ*" for the introduction of native plants into new areas near the locations where they have grown previously. He looks at ancient records, such as fossil remains, to help determine restoration plans for degraded areas.

Over 160 botanic gardens exist in China, and most are run and supported by the Chinese government, which has directed that cities should create botanic gardens in

order to conserve local biodiversity. The country's economic growth has created an urgent need for the protection of natural habitats and an appreciation of China's natural plant wealth. As an example, China's huge array of medicinal plants is of primary importance for healthcare throughout the country. About one third of their medicinal plants are well established in cultivation, yet wild harvesting continues to be a major threat to wild plant diversity. Given that medicinal plants are expected to form a part of China's bioeconomy, their conservation and cultivation are critical.

Africa has a strong network of botanic gardens that play a vital role in protecting Africa's rich natural heritage. Many of the gardens are working to meet the needs of local communities, to educate and demonstrate food and economic plant production, as well as helping secure conservation and protection of medicinal plants. While there are some excellent examples of international collaborations, community action is recognized as the key to lasting conservation success.

One of the strongest examples of international collaborations described in *Botanic Gardens* is between the Missouri Botanical Garden and conservation groups in Madagascar. With much of the African island's flora highly threatened and irreplaceable, the garden staff have helped to conduct botanical inventories, helped train local botanists and conservationists, as well as collaborated in community-based conservation.

Scientists in Australia are looking for ways to both conserve and utilize the native flora. Clearance of the native flora for agriculture is a major threat to fragile species in parts of Australia. In some cases, healthy ecological conditions for restoration no longer exist due to salinization, agricultural chemicals, rabbits, or invasive weeds, resulting in the need for assisted migration or restoration at nearby sites. Material from seed banks is often used in supporting ecological restoration. Mining in Australia has also impacted some of the continent's rare and endangered plants; however, there have been successful efforts to work with the mining industry in recovery and restoration work.

Botanic Gardens: Modern-Day Arks is a valuable reference guide because the conservation potential for botanic gardens is just being realized. Serving as a portal into the successes of gardens throughout the world, this book both informs and inspires the reader to place more resources, energy, and effort into activating gardens/organizations to move forward. As humankind faces the challenges of global climate change and ecological uncertainty, it is incumbent upon everyone to be responsible leaders in plant conservation. These success stories can lead to improved education and knowledge as each garden's role evolves in this direction. Both *in situ* and *ex situ* plant conservation work is valuable. While *in situ* is considered best for the long-term protection of the plants, *ex situ* collections play a vital role in conserving plant diversity, not only as an insurance policy for the future, but also as the basis for restoration, reintroduction, and educational programs. Gardens need to ensure that their collections are increasingly representative of the genetic diversity of wild populations. Botanic gardens are learning that sharing expertise in areas such as population genetics, plant taxonomy, horticultural management, environmental education techniques, and project management can help develop the tools to make successful collaborations, especially with local communities, which provide the lasting answer to the successful protection of the world's flora.

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Pharmacy and Drug Lore in Antiquity: Greece, Rome, Byzantium by John Scarborough. Variorum Collected Studies. Farnham, VT: Ashgate Variorum; c. 2011. Pp. xxviii + Hardcover; 354 pages. ISBN: 978-0-7546-5954-9. $144.95.

John Scarborough is a leading historian of early medicine, especially pharmacy, whose many articles have beenare published in an impressively wide range of journals and collections, from *Clinics in Plastic Surgery* to *Les écoles médicales à Rome.* Such diversity of publication outlets effectively means that those interested in historical herbal lore are unlikely to have savored the full range of Scarborough's scholarly insights, especially with those pieces written before the advent of online databases. Happily, some of his most important publications are collectively reprinted in *Pharmacy and Drug Lore in Antiquity*, a tome that all who have a serious interest in herbs historically and even presently should have on their bookshelves and in their brain's databases.

The first study on the pharmacology of sacred medicinal plants is well-chosen as the lead article. The Greek epoch-setting trend towards rational medicine exclusive of religious-magic causation is off-set by the acceptance of "magicolegendary and empiricial-practical ways." On one hand, there is the 5th century (BCE) Greek philosopher Empedocles' straight-forward statement: "You will learn drugs (*pharmaca*) for ailments and for help against old age." On the other, Scarborough argues that Greek inquiry "applied levels from pure 'magic' to utter rationalism." His evidence derives from a lucid discussions about the historic usages of opium poppy (*Papaver somniferum*, Papaveraceae; presenting a strong case identification of the plant called *moly* as poppy, at least in Homer), pennyroyal (*Mentha pulegium*, Lamiaceae), chaste tree (*Vitex agnus- castus,* VerbenaceaeL.), purple orchid (*Orchis mascula,* OrchidaceaeL), and deadly carrot (*Thapsia garganica,* Apiaceae L.), among other examples. Extending his evidence back to Mesopotamian and Egyptian medicine, he demonstrates a pharmacy that blended folk lore, magical allusions, and keen rational observations. Scarborough's reflections on magical papyri appropriately summarize Greek pharmacy as combining "vividly the ordinary and sophisticated command of drug compounding by the common people." Drugs may be from the hands of the gods, but people learned and applied them as reasonable therapeutic addresses. Through deftly applied scholarship, Scarborough proves—and I use this word advisedly—that Greek medicine's attitude towards rational medicine was a monumental, historical achievement.

Other studies deal with specific ailments (burn treatments), drugs (e.g., opium, cantharidin), drug trade (between Rome and East Asia and Africa), pharmacy writers (Hippocratic writers, Theophrastus, Nicander, Criton, and Galen), early Byzantine pharmacology,

and herbs connected to Byzantine gardens. The last study on Byzantine gardens was delivered by Scarborough in a symposium at Dumbarton Oaks. In his paper, Scarborough focused on a 12th century "dream-garden" manual from which he concluded that Byzantine "doctors, pharmacologists, herbalists, *and* farmers not only were by interested (and literate)," but they extended their skills to cultivated and wild plants. The Byzantines' harvesting and preparations were "well balanced by city and countryside" applied knowledge.

Aloe (*Aloe* spp., Liliaceae) drug trade indicates Roman reliance on Eastern drugs and the importance of the Indian Ocean island of Socotra as a depot. Scarborough describes Theophrastus, a successor to Aristotle as Head of the Lyceum, as a leading conveyor of drug lore; another study shows that Pliny the Elder, a Roman, considered "drugs … are to be understood as an integral part of the lore of food." Pliny, Scarborough said, had an "enthusiastic, breathless mood" for his "tumbling of facts, tales, stories told for amusement, anecdotes, [and] legends" about plants as foods and medicines. Scarborough makes a case for Criton, whose medical works are lost, to be the same author who wrote a history of Trajan's Dacian Wars. Known only through quotations ascribed to him by later authors, Scarborough calls Criton "…an astute pharmacologist who employed the best written sources of his time, and who was careful with his patients and shrewd in his preparations of drug recipes."

Scarborough directs the reader's attention to animal and mineral drugs as well as the field of toxicology with a thorough overview of Nicander's works (*Theriaca* and *Alexipharmaca*) on poisons from snakes, vipers, plants, spiders, scorpions, insects, and myriapods. Spiders not only had a poisonous bite but also, if properly used, were medicinal agentses.

Modern writers on medicinal herbs often include a near-obligatory paragraph or two on the plant's history, all too often culled from superficial secondary sources, such as Maude Grieve's *A Modern Herbal*. Much better— and useful!—information can come from publications by this excellent historian of pharmacy. Because of the diversity of wide-ranging studies, it is difficult to convey the importance of John Scarborough to the history of drugs. The salient point is that Scarborough's meticulous attention to detail, combined with a thorough command of ancient languages, mastery of biographical data, and lively, charming writing style, deserve the attention of all people who are interested in herbal medicine, whether concentrating on present science or not. This volume begins with an insightful introduction by the author, and concludes with a long, rich, complete, and impressive list of his publications, together with a full index.

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African Natural Plant Products: New Discoveries and Challenges in Chemistry and Quality by H. Rodolfo Juliani, James Simon, and Chi-Tang Ho (eds). Washington, DC: American Chemical Society; 2009. Hardcover; 595 pages. ISBN 978-0-8412-6987-3. $195.00. Available in ABC's online catalog #570.

A wide range of indigenous plant-derived health and nutritional products are utilized across the length and breadth of the African continent to improve human and animal health, and yet natural, plant-derived products from Africa presently have a disproportionately small market share of the global trade in such products. The dearth of up-to-date and authoritative sources of information is at least one of manifold reasons for this inequity.

The purpose of this book is to provide a comprehensive overview of recent scientific, technical, and economic developments across a broad range of African nutritional, medicinal and aromatic plants (MAPs), and plant-derived products. This useful reference book achieves its purpose, making a significant contribution to the scientific literature on useful African plants and plant-derived products. *African Natural Plant Products* is an information-dense volume that explores the current contributions that African plants make to local health and wellness within Africa, and identifies plants with economic importance on international markets. The reader is afforded an early glimpse of the emerging science on plants with promising economic and health potential, as the book includes some of the latest basic and clinical research supporting the plants' uses in self-care and healthcare. There are 29 scientific articles and reviews contributed by more than 80 authors, organized into 5 sections.

The section "Overview" includes a foreword by Mark Blumenthal, founder and executive director of the American Botanical Council, and a paper on the economic value of African plant-derived products.

"Traditional Medicines from Africa" consists of papers on the folk-uses and commercial applications of a wide range of African plants, and includes useful comprehensive reviews on baobab (*Adansonia digitata*, Malvaceae) and tamarind (*Tamarindus indica*, Fabaceae).

The section "Pharmacognosy and Validation of Traditional Medicines" provides recent advances in the scientific validation of indigenous therapeutic uses, and includes papers on plants as possible treatments for the prevalent diseases malaria, sickle-cell anemia, and diabetes. The review on the South African medicinal plant, *Pelargonium sidoides* (Geraniaceae) serves as a model for product development for African medicinal plants for the international market, and includes summaries of an impressive range of clinical trials, including "gold-standard" randomized, double-blind, placebo-controlled studies on a proprietary product from this plant.

"Quality Control of African Natural Plant Products" focuses on the development of quality standards and provides practical information on quality issues for a wide range of African plants and products, and includes general reviews as well as proposed quality standards for the seeds of *Voacanga africana* (Apocynaceae) and *Griffonia simplicifolia* (Fabaceae).

The section "Applications and Commercialization of African Natural Plant Products" includes reviews on moringa (*Moringa oleifera*, Moringaceae) as well as papers on the uses and composition of essential oils from Madagascar and Kenya.

The book closes with a paper dealing with models for equitable benefit-sharing, an essential consideration for all those dealing with the research and commercialization of indigenous plants that have established local uses.

In a few of the contributed papers there are some omissions of—or insufficient emphasis on—important information. With the prevalence of malaria in Africa and the importance to local communities of the clinical validation of local antimalarial treatments, a complete description of published clinical studies (such as Dr. Marian Addy's "Cryptolepis: An African Traditional Medicine that Provides Hope for Malaria Victims" in 2003's *HerbalGram* #60 [available at: http://cms.herbalgram.org/herbalgram/issue60/article2597.html]) on infusions of *Cryptolepis sanguinolenta* (Asclepiadaceae) roots would have strengthened the review article on this plant. The growing use of moringa leaf as an apparently immune-supporting nutritional supplement by rural African people living with HIV is not mentioned. For baobab, an important omission is the European Commission Decision 2008/575/EC of 27 June, 2008, which authorizes the placing on the market of baobab dried fruit pulp as a novel food ingredient under Regulation (EC) No 258/97 of the European Parliament and of the Council. This decision is the key to establishing markets in Europe for this quintessential African functional food. The granting of GRAS (generally recognized as safe) status to baobab dried fruit pulp in the USA in 2009 may have been too late for inclusion in the review.

The editors are acclaimed academics in their field. H. Rodolfo Juliani, PhD, is a plant biologist working as a research associate at the Plant Biology and Pathology department at Rutgers University in New Jersey. He serves as the quality assurance and quality control coordinator for international development programs, and as the associate director of the New Use Agriculture and Natural Plant Products Program at Rutgers, a program which seeks to identify new crop opportunities, new applications of bioactive and nutritious plant compounds, and new products from fruits, vegetables and herbs including nutraceutical, bioactive, and cosmetic ingredients. James E. Simon, PhD, is a professor in the department of Plant Biology and Plant Pathology, and serves as the director of the New Use Agriculture and Natural Plant Products Program. Chi-Tang Ho, PhD, is professor in the department of Food Science, Rutgers University. He has published over 450 scientific articles, and is an editorial board member for a number of publications, including the *Journal of Agricultural and Food Chemistry*.

The editors have spent many years working on the ground with local African MAPs scientists and producers under the auspices of ASNAPP (Agribusiness in Sustainable African Natural Plant Products), an organization dedicated to improving the production, quality, and marketing of African plant-derived, beneficiated, raw materials and products. Many of the contributing authors are African, a testament to the contribution African scientists are making to the growing body of scientific research on African edible, medicinal, and aromatic plants.

I recommend this book as a valuable reference to a broad audience including scientists, clinicians, product developers, policy-makers, and development agencies. It is an important recent contribution to the steadily growing literature on African ethnobotany, plant chemistry, pharmacology, clinical research, and raw material production and quality control.

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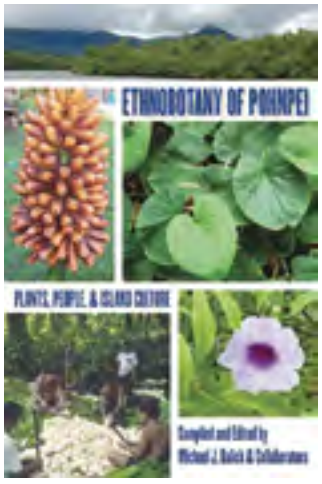
Ethnobotany of Pohnpei: Plants, People, and Island Culture by Michael J. Balick and collaborators. Honolulu, HI: University of Hawaii Press; 2009. Softcover; 583 pages. ISBN 978-0-8248-3293-3. $28.00.



In their overview, noted ethnobotanist Michael Balick and co-authors David Lorence, Dana Lee Ling, and Wayne Law introduce rather concisely the culture, geography, people, and terrain, major crops and vegetation types of Pohnpei, a Micronesian island of some 30,000 plant-friendly inhabitants. One might say that many of these inhabitants, like *Ethnobotany of Pohnpei*'s multiple authors, are all ethnobotanists, interested in the various uses for plants.

The authors, acknowledging that they are simply messengers, repeat that the data they present are the products of "thousands of Pohnpeian 'scientists' that [sic] preceded" them. In cataloguing many classes of banana (*Musa* spp., Musaceae), Lois Englberger, Adelino Lorens, Amy Lavendusky, and Jeff Daniells single out one of the banana cultivars (called '*Karat*') as about 100 times richer in beta-carotene than most commercial bananas marketed in the United States and the United Kingdom. But they tabulate data on the '*Utin Iap*' cultivar with 1250 mcg/100g, the richest tabulated for beta-carotene. It is also one of the more productive bananas (some bunches weighing around 100 pounds).

Bill Raynor, Lorens, and Jackson Phillip, in a well-illustrated chapter, elaborate on yams (*Dioscorea* spp., Dioscoreaceae) and their traditional culture, seasonality, their importance to the citizenry, and even tabulate 179 varieties, in addition to discussing trellis alternatives and providing a summary of diseases that yams are prescribed to treat.

In another nicely illustrated and interesting chapter, Englberger, Kiped Albert, Lorens, and Amy Levendusky, address the "taro" (spanning 4 genera in the Araceae).

I was very interested in Balick and Roberta Lee's chapter on *sakau* or kava kava (*Piper methysticum*, Piperaceae) especially since a friendly physician was against my taking kava for peripheral neuropathy and concomitant depression. (I suspect the physician read and believed some of the poorly documented reports of kava-associated hepatotoxicity.) Balick and integrative physician Lee do mention the real but reversible kava dermopathy which has been recognized since the days of Captain Cook's second voyage: "The skin dries up and exfoliates in little scales." Between 1990 and 2006, over 80 cases of kava-related hepatotoxicity were reported, says the book, but only 5 of these were clearly causally related, according to an expert in hepatotoxicity. The authors' conclusion of the kava chapter spans from its divine origin and revered status in Pohnpeian traditional culture to its modern-day use in sacred ritual and recreational activity. "[S]akau is without doubt the most important plant on Pohnpei." Then Lee solos on a short chapter, "Traditional Medicine, Pohnpei, and Its Integration."

Then follows a multi-authored chapter: "Local Uses of Plants and Fungi on Pohnpei." Yes, this was the chapter that this

compulsive compiler was most anxious to see. I am always tempted, as a chronic compiler, to dig in and see what any beautifully illustrated ethnoflora could add to my formatted text on 3,000 medicinal plants. Alphabetically, first is *Abelmoschus moschatus* (Malvaceae), the musk okra, for which I already had about 130 colloquial names from around the world. I was pleasantly surprised to find that the turmeric (*Curcuma longa*, Zingiberaceae) account alone adds 9 common names and a couple of indications, when I already had more than 250.

I get the despairing and eerie feeling that when I finish (one does not finish studying medicinal plants, thank goodness), all plants will have been reportedly used for at least one ailment. But all plant species have hundreds of phytochemicals already known to your genes, and some already have 5,000 phytochemicals, almost all with many biological activities. But 3 species seemed to have the most medicinal information in this great book, and they are the sacred sakau, the famous noni (*Morinda citrifolia*, Rubiaceae), and the more obscure *Premna serratifolia* (Verbenaceae). Hundreds of medicinal uses were mentioned, among food plants and crops, spices, and plants important in craftsmanship, ornament, and other utilities.

The traditional Pohnpei diet was once comprised mainly of cooked starchy staples, such as breadfruit (*Artocarpus* spp., Moraceae), banana, and taro (*Colocasia* spp, Araceae) (why not yam?) with fish and other seafood. Other fruits and sugarcane are eaten as occasional snacks. Diabetes and hypertension were once unusual on the island, but after World War II, imported foods gradually rose to about three-quarters of the diet, and statistics on cancer, cardiopathy, diabetes, and obesity worsened rapidly. Almost all my ethnobotanical friends can recount similar episodes from their lifetime of observation: native diets lost to an American-like processed diet, and native health lost to diseases related to diet-induced obesity and diabetes and ultimately cardiopathy.

Perhaps uniquely, this book is truly a community ethnobotanical effort, guided by Traditional Leaders. People in each of the 5 kingdoms on Pohnpei participated in the inventories. The project focused on 3 objectives: (1) Cataloguing the agrobiodiversity information on traditional and currently grown cultivars. Yes—cultivar diversity is diminishing, with only a handful of cultivars persisting today with traditional cultivation methods, some still utilized, others forgotten; (2) Of even greater interest to me was the well-rounded ethnobotanical inventory of plants used for food, medicine, construction of homes, boats, smaller artifacts, and in rituals and spiritual belief systems. Much of this was gathered by the Pohnpeian team, who are all recognized as coauthors of the book; and (3) A provisional checklist of the flora of Pohnpei, the first in contemporary times, that contains information on species status as endemic, introduced, invasive, etc. These goals were well met.

Significantly, this great book is copyrighted by the Mwoalen Wahu Ileilehn Pohnpei, the Pohnpei Council of Traditional Leaders. This publication then at once documents proof of prior art and prior knowledge, thus helping to protect the intellectual property rights of the Pohnpeian people. We have been artfully apprized of the utility of plant species to Pohnpeian people. Let us hope it will stimulate the preservation of this great society and their flora and fauna and culture.

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The H.E.R.B.A.L. Guide: Dietary Supplement Resources for the Clinician by Robert A. Bonakdar (ed). Philadelphia, PA: Lippincott Williams & Wilkins; 2010. Paperback; 401 pages. ISBN-13: 978-0-7817-8268-5. $59.95.

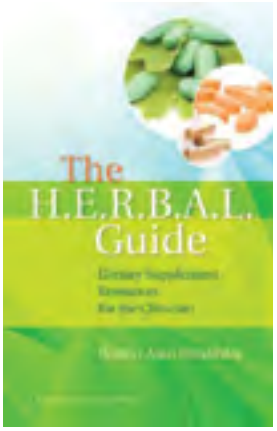
Navigating the arena of dietary supplements can be a daunting task, even for those who work in the industry, much less those in the healthcare professions. Because a large segment of the population uses dietary supplements as part of its daily healthcare routine, it is important for clinicians to be knowledgeable in this area in order to guide patients toward making more informed decisions. Fortunately, Robert Alan Bonakdar, MD—a physician and Director of Pain Management at the Scripps Center for Integrative Medicine in La Jolla, CA and, for 10 years, the co-director of Scripps' annual conference on evidence-based dietary supplements—has compiled an excellent resource for clinicians to guide patients who are integrating dietary supplements into their lifestyles, and to answer common questions that a patient may have. The book, *The H.E.R.B.A.L. Guide: Dietary Supplement Resources for the Clinician*, offers a comprehensive overview of the supplement arena, including clinical management, efficacy, regulation, safety, adverse event reporting, resources and education, and case studies. The book also provides a reference guide that lists dosages for conditions that have been clinically studied. The goal of the book is to provide a framework for the discussion of evidence-based dietary supplements and a foundation of knowledge and resources to facilitate discussion with a patient.

Dr. Bonakdar assembled this book in response to the discomfort he felt from lack of information available when responding to patient concerns regarding dietary supplements. The guiding principal of the book and important steps in patient care are summarized in Section 1 by the mnemonic acronym "H.E.R.B.A.L.", which stands for: (1) Hear the patient out, (2) Educate the patient, (3) Record, (4) Be aware of reactions/interactions, (5) Agree to discuss, and (6) Learn. In general, doctor-patient communication regarding supplements is often poor from the viewpoints of both the physician and his or her patients. The H.E.R.B.A.L. acronym was developed to capture and reinforce the key steps in a discussion on dietary supplements. It is a starting point to systematically put the pieces of the dietary supplement puzzle together.

The successive sections provide information on how to implement the "H.E.R.B.A.L" concept in the clinic. Section 2 ("Understanding Dietary Supplements") describes what constitutes a dietary supplement, prevalence of use, and the legal implications of prescribing supplements. Section 3 supplies an overview of regulation of supplements implemented by the US Food and Drug Administration (FDA), including the Dietary and Supplement Health and Education Act (DSHEA), Nutrition Labeling and Education Act (NLEA), Good Manufacturing Practices (GMPs), and adverse event reporting. This section is important because consumers and physicians tend to be misinformed regarding the extent of supplement regulation and how it differs from that of over-the-counter and prescription medications. In addition, this section covers—from an international perspective—the regulation

of dietary supplements and the role of trade associations and the industry in general to improve standards for dietary supplements.

Section 4 discusses how to address safety with regards to adverse effects, reactions, and interactions of supplements. The safety aspect is often misunderstood and mishandled in the clinic due to the lack of information available on this topic. Given the recent implementation of FDA regulations regarding reporting of serious adverse events, one important chapter of this section proffers guidance on how to report these events. In order for adverse event reporting to be useful, clinicians need to be provided with reporting guidelines so that they capture all relevant information that can be used to determine the safety of dietary supplements.



Section 5 provides guidance on how to evaluate clinical studies using dietary supplements, which is an important skill for surveying the literature for efficacy of these products. Section 6, titled "Clinical Management," outlines the role of various healthcare providers with regard to supplements, including physicians, pharmacists, dietitians, nurses, naturopathic physicians, and Traditional Chinese Medicine practitioners. Section 7 then summarizes available resources to help clinicians best address their patients' needs. It also suggests educational programs to prepare the clinicians of tomorrow to address the areas of dietary supplement discussion, education, and management.

Section 8 provides case studies that demonstrate how to apply guided care with dietary supplements and how they can be practically incorporated into sometimes complex patient scenarios. The book closes with Section 9, a guide that includes a brief sampling of the most typical initial choices for dietary supplements based on available level of efficacy and safety. This section provides formulation, dosing, and brand names utilized in clinical trials. It is designed to be a quick reference for the busy clinician who has a patient with a particular condition in need of additional options. Unfortunately, several of the clinically studied proprietary extracts that are listed in this book, such as those produced by Zeller AG, Lichtwer Pharma, Alk Abello, or Schwabe, may be difficult to obtain in certain markets given that some of these products appear to be available only in Europe. For example, the homepage for the allergy supplement Grazax® (www.grazax.com), supplied by Alk Abello, indicates that this product is only offered in European countries.

Included in *The H.E.R.B.A.L. Guide: Dietary Supplement Resources for the Clinician* is a password that allows access to an online version of the full text of this book and a list of links to important resources (www.herbalguideforclinicians.com). This provides a convenient way to access resources compiled in the book. Although Bonakdar targets his information toward clinicians, anyone interested in learning more about dietary supplements stands to gain from reading this guide. Other references may discuss many of these topics in more detail. However, Dr. Bonakdar arranges them into one easily understood reference that can serve as a starting point.

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A Practical Guide to Licensing Herbal Medicinal Products by Thomas Brendler, L. Denzel Phillips, Stefan Spiess, Ann Godsell, and Birgit Wobst. London and Chicago: Pharmaceutical Press; 2009. Hardcover; 770 pages. ISBN 978-0853697848. $330.00

European Union markets for herbal products are currently undergoing dramatic changes. The industry is facing major problems with the authorization of health claims on food supplements with herbal ingredients by the European Food Safety Authority (EFSA). With the future of the botanicals in potential jeopardy, the members of the herb industry have started considering the possibility of using a process to re-categorize food supplements* with herbal ingredients into licensed drugs. One way of achieving this goal was been implemented into the EU drug legislation in 2004 in the form of the so-called "Traditional Herbal Medicinal Product Directive" (2004/24/EC), which has been included into the general drug legislation 2001/83/EC. The Traditional Herbal Medical Product Directive, or THMPD, allows for a simplified access to drug registration for traditionally used herbs and herbal ingredients, without the need of submission of clinical and preclinical data to support safety and efficacy, under certain conditions.

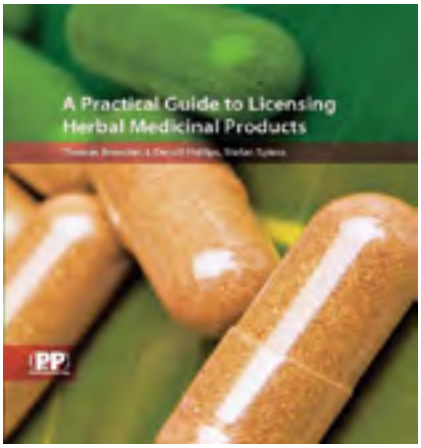
The EU botanicals industry has not fully risen to the occasion, and the transition deadline of April 30, 2011, is drawing closer—with potential consequences for the existing markets. Whereas EU member states such as the United Kingdom have already announced forthcoming regulation of unlicensed botanicals, other EU states (e.g., Italy, Portugal) do not seem to care about the upcoming deadline. This is also reflected in the numbers of granted licenses, which vary between none granted to date in many EU member states (and no applications pending) and at least 27 different herbs in at least 166 products approved in the UK.

To date, the THMPD cannot be considered as a success. Due to the restrictions in the registration process and the high financial burdens for the manufacturers in developing the required analytical standards, many manufacturers prefer to remain in the sector of food supplements and to undergo health claim applications with the EFSA as the less costly and apparently simpler access to markets. It remains to be seen what will happen after the end of the transition period. However, with a realistic timeframe from bench to registration of 3 years, it would now be too late to change the course for the already-existing botanicals in supplements.

The apparent apathy of both many members of industry and regulators may change in view of the *de facto* higher requirements on proof of efficacy for food supplements claimed by the EFSA as compared to traditional herbal medicinal product registration. This situation is likely to trigger a higher interest in the registration proce-

*The operative legal term is *food supplement* in Europe; the term *dietary supplement* was initially an American term, initiated with the passage of the the Dietary Supplement Health and Education Act of 1994.

dure, but the manufacturers coming from the food sector frequently feel helpless when it comes to the practicalities of herbal medicinal drug registration—even in the simplified form as traditional herbal medicinal products (THMP). The recently published *Practical Guide to Licensing Herbal Medicinal Products* may thus become a useful tool for companies considering the switch from the category of food supplement to registered medicinal product. In the following, the contents of the guide will be critically assessed from the point of view of an expert dealing with the practical application of herbal medicinal product licensing on a daily basis. The authors are highly knowledgeable in their respective fields, and the information given is accurate.



The Guide is organized into 8 chapters giving information on product eligibility, herbal raw material and herbal product quality, and the contents and internal organization of the Common Technical Document (CTD), that is, the dossier required for licensing.

The Guide starts with an introduction giving background information on why the THMPD was deemed necessary. It explains why the THMPD was introduced for simplified and less demanding access to the drug market. The requirement for such a regulation was mainly seen as a contribution to consumer protection. Marketing of herbal medicinal products under drug status involves stringent quality testing and should therefore avoid many of the adulterations and contaminations observed in the uncontrolled supplement sector.

Registration as a THMP has its restrictions: A tradition of 30 years of use must be demonstrated (15 of which must be within the EU), and the regulation is confined to herbs only (with the possibility to use ancillary quantities of vitamins or minerals). However, not even all herbs would be eligible, as they have to be compatible with oral or topical nonprescription drug use, i.e., without medical supervision. Moreover, when a given herb is well-researched, a registration as a THMP might not be granted, as in such cases the applicant would have to go through the regular marketing authorization process.

Chapter 1 ("Classification of Herbal Medicinal Products") gives a valuable overview of potential herbal product classifications and provides a decision-tree allowing a quick check on which approach might be taken for a specific product, with a strong emphasis to the situation encountered in the UK. The reader must be aware that THMPs are purely national registrations; thus, the situation is almost completely different in other EU member states. Still, the basic differentiation between drugs, foods, and cosmetics is a more global one and applicable to other EU member states as well.

Chapter 2 ("Proof of Tradition") gives information on how to find or use data on traditional application of herbal medicinal preparations. The references to overseas EU territories are highly interesting and open doors for unusual traditions. The chapter also provides ample reference to monographs which can be used for proofs of tradition. Unfortunately, the current practice of THMP licensing shows that the mere reference to such sources does not seem to be sufficient, as they merely provide information on the former existence of a given preparation, but not on the scope of actual use or availability on the market. The concept of proof of tradition is therefore still wide open to discussion.

Highly important is the reference to the

New Book Profiles

Anatomia Sambuci: The Anatomy of the Elder: Revised Edition 2010. Martin Blochwich. Appenzell, Switzerland:BerryPharmaAG 2010. Hardcover, 113 pages. ISBN: 978-3-9523693-0-2. $124.95.

This small 31-chapter book is a revamped edition of a 17th century physician's volume about the many therapeutic uses of elder (*Sambucus* spp., Caprifoliaceae), produced for its historic relevance. This more easily understood publication paints an important historical picture of health and wellness, and is divided into sections by ailment as well as treatments using specific parts of the elder. A glossary has been amended at the end to help retain some of the historic language throughout the book.

Phytotherapy Essentials: Healthy Children: Optimising Children's Health with Herbs. Rob Santich and Kerry Bone. Warwick, Queensland, Australia: Phytotherapy Press; 2008. Paperback, 218 pages. ISBN: 978-0-646-48616-1. $45.00

This book addresses a multitude of possible childhood health problems, such as fever, infections, allergies, as well as digestion, respiratory, central nervous system, urinary tract, skin, and endocrine disorders. The book discusses herbs used for infant to school-age children, and includes safety information and dosing. Actual case reports with the prescribed formulations are also included to help the reader differentiate among common disorders and how they are treated.

Drugs of Natural Origin: A Treatise of Pharmacognosy, 6th Revised Edition. Gunnar Samuelsson and Lars Bohlin. Sweden: Swedish Pharmaceutical Press; 2009. Hardcover, 776 pages. ISBN: 978-91-976510-5-9. $149.95.

This 6th edition textbook further expands on the previous edition, the leading text on pharmacognosy used in Scandanavia, which has been available in English since the second edition. Like earlier versions, this edition covers developments of drugs from plants and other natural materials, including new research on "genomics, proteomics and metabolomics," while also expanding on previous information that has now been updated. The subjects are arranged by biosynthetic processes and highlight many important vitamins, herbs, drugs, and disease states. The mechanistic approach gives a step-by-step depiction of metabolism, intermediate constituents, and how the formations of final medicinal products are constructed.

The Healthy Gut Workbook: Whole-body Healing for Heartburn, Ulcers,

work of the European Medicines Agency's (EMA) Herbal Medicinal Product Committee and the so-called Community Monographs. These monographs will tremendously facilitate the proof of tradition, as the burden of proof will no longer be with the applicant. The *Guide* makes reference to 22 adopted monographs — fortunately for the potential applicant, there has been a further increase in published monographs since the *Guide* appeared (89 published, 74 of which were adopted on December 6, 2010). The downside, however, is that the list in the *Guide* does not differentiate between eligible and non-eligible plants.

A potential applicant should always check with the most recent list of monographs published on the website of the EMA (www.ema.europa.eu).

Chapter 3 ("Common Technical Document") describes the contents and structure of the registration dossier. For those who do not already know the registration process, the information is not detailed enough to understand the underlying concept, and those who are familiar with the process will recognize that this chapter is an almost verbatim replication of existing official guidelines on the application of the "Common Technical Document" (CTD) format, without additional information. Even the expert will have to countercheck with the most recent version of this guideline published on the EMA's website—a simple reprint of a potentially older version is therefore not useful. A more practical approach with explanations of the pitfalls with practical examples would have been more suitable.

Chapter 4 ("Good Agricultural and Collection Practice") gives a good description of the backgrounds of herbal raw material quality required for drug registration—a topic that many companies selling herbal preparations apparently have never considered. Experience shows that information on the traceability of the herbal raw material and the quality issues related with the treatment of the plant from seeding to processing are more and more in the focus of regulatory authorities. This is with good reason, as the quality of herbal medicinal products is largely defined by the selection of a suitable source ensuring the absence of contaminants and adulterations, as well as sufficient levels of relevant analytical marker substances.

Chapter 5 ("Quality Requirements for Traditional Herbal Medicinal Products") starts by giving details on legal definitions and guidelines. These guidelines, listed in Appendix 2, must not be considered as complete, as the EMA is constantly producing new guidelines, notes for guidance and Question and Answer papers on specific topics. In fact, the new EMA website provides a tool for the quick identification of the relevant regulations.

The quality requirements provided in this chapter are generic: They do not only refer to the special case of THMPs, but to herbal medicinal products in general. Basically, there is no difference in quality requirements between traditional and well-established herbs—which is also one of the reasons why so few applications have been filed. Going through the process of quality assurance is rather expensive, and in the case of combination products containing multiple herbal ingredients—for many traditional preparations, this is the rule rather than the exception—may become prohibitively costly. Still, the chapter is extremely important as it provides the background, information, and explanation the reader is missing in Chapter 3.

Chapter 6 ("Safety and Pharmacovigilance") describes the data required for the compilation of safety data in the non-clinical and clinical parts of the CTD documentation. As the requirement for genotoxicity data has been introduced only after the implementation of the THMPD, the chapter on pre-clinical data puts special emphasis on genotoxicity testing. Again, the regulatory development is by now way past the point described by the *Guide,* which is based on EMA guidelines of 2007. Meanwhile EU regulatory authorities not only call for product-specific genotoxicity testing, regardless of data derived

Constipation, IBS, Diverticulosis & More. Victor Sierpina, MD. Oakland, CA: New Harbinger Publications, Inc.; 2010. Paperback, 184 pages. ISBN: 978-1-57224-844-1. $21.95.

This book functions as an owner's manual to a healthier gastrointestinal tract. Its interactive approach helps the reader take charge and track health progress by journaling through it. It is divided into 2 parts—the first addressing the gut, and the second, discussing helpful gut treatments. It covers prevention as well as treatment for a healthier GI tract, while also defining natural treatments for acute and chronic GI complaints.

Microgreens: How to Grow Nature's Own Superfood. Fionna Hill. Buffalo, NY: Firefly Books; 2010. Paperback, 107 pages. ISBN: 978-1-55407-769-4. $17.95.

This colorful book will make any reader hungry as it guides through the description of microgreens—edible greens and herbs that have "produced at least two 'true' leaves after the cotyledons appear"—and ends with mouthwatering recipes. It explains how to cultivate microgreens and provides individual descriptions and pictures of many popular crops. Even the most skilled growers can experience problems with their crops, so there is a chapter in the book to help with planting troubles. There is even a chapter for children who are interested in growing microgreens themselves.

Principles & Practices of Naturopathic Botanical Medicine, Volume I: Botanical Medicine Monographs. Anthony Godfrey and Paul Richard Saunders, with Kerry Barlow, Cyndi Gilbert, Matthew Gowan, and Fraser Smith. Toronto, Ontario, Canada: CCNM Press Inc; 2010. Hardcover, 568 pages. ISBN: 978-1-897025-26-0. $119.95.

This book provides an in-depth look at botanical medicine laid out in 3 different parts: Introduction to Naturopathic Botanical Medicine, Botanical Medicine Monographs, and Course in Naturopathic Botanical Medicine. The book's detailed botanical monographs are organized by relevance to different body systems (e.g., respiratory, cardiovascular, immune), allowing for ease of navigation. A color photograph accompanies each plant and fungus. Monograph information includes TCM and historical indications in addition to constituents, pharmacology, actions, toxicity, and contraindications. Sample cases and recommendations close the book, challenging the reader to apply knowledge gleaned from the book to hypotherical situations.

from bibliographic sources, but also call for a detailed justification of the observation of negative test results (whereas products with positive test results would stand little chance of being registered). Herbs are now generally considered as genotoxic, and if the testing does not confirm this, the applicant will have to explain why the test results did not confirm the suspected genotoxicity.

The *Guide*'s parts on pharmacovigilance shortly describe the requirements for periodic safety update reports (PSURs) post-registration—a task of which many potential applicants originally coming from the food sector are not aware. In fact, it appears important to strengthen the part on pharmacovigilance in future editions of the *Guide*. Pharmacovigilance does not only imply the collection of safety-related information and the periodic filing of such data, it also implies the creation of an infrastructure within the company to conduct such a process and to act on it when needed. Manufacturers coming from the food supplement sector may not be aware that a "Qualified Person responsible for Pharmacovigilance" (QPPV) is mandatory for every pharmaceutical company, and that the company needs to establish a "Pharmacovigilance System" with standard operation procedures (SOPs) in place, documented according to rules related to Good Manufacturing Practices (GMPs). These tasks go along with regular literature searches for newly published safety data, and the obligation to analyze and report potential cases within given time frames. Unfortunately, this topic is not presented in the *Guide*.

Chapter 7 ("Labelling") describes the parts relating to the administrative information of Module 1 of a CTD for drug registration. These requirements are specific for every single EU member state. They are described in the *Guide* from the UK perspective. Some parts of the description are directly applicable to other EU member states as well, but adaptations must be made. The focus on UK regulations is also clear by the claim that all information in the package labeling and in the readability user test needs to be made in English. Of course, the information needs to be in the language of the EU member state, in some cases even in more than one language. This focus on the UK situation is found throughout the whole guide and makes the title *A Practical Guide to Licensing Herbal Medicinal Products* somewhat misleading, as the words "in the UK" are missing.

Chapter 8 ("Submission of THMP registration Applications – Frequently Asked Questions") is again entirely focused on the submission in the UK. It briefly describes the possibility of obtaining scientific advice by the regulatory authorities, and quickly touches on questions related to manufacturers or distributers/importers licensing. It also provides a short introduction to electronic submission of parts of the licensing application. Similar regulations are in place in other EU member states, but it is highly advisable to check with the websites of the corresponding regulatory authorities before a submission is made—this also applies to the UK, as the details may change.

In conclusion, the *Practical Guide to Licensing Herbal Medicinal Products* provides valuable information for the background and practical problems of THMP licensing. From experience with non-EU companies trying to find their way into the European system, the information might still not sufficiently cover the main questions and problems the companies are facing. The *Guide* should also provide some ideas regarding realistic time schedules—many applicants are not aware that registration takes years until reaching a point where a product can be marketed, years during which the applicant has only expenses, but no return on investment.

The *Guide* is written from the perspective of experts familiar with the drug registration process, which explains why many questions regularly asked by non-experienced companies are not covered. For example, it would be preferable to more closely explain the key steps in product development, especially regarding the analytical processes and the galenical development, including validations. The information is there, but the key points deserve a more detailed explanation with a focus on typical traditional preparations, i.e. simple plant powder preparations or the specific problems with combinations of herbs for which there is no monograph.

The idea behind the *Guide* is good—but the *oeuvre* still needs updating, opening to the conditions in other EU member states, and to take into account the perspective of an unknowledgeable applicant completely overwhelmed by the regulations.

Who needs this book? Probably not those who are already familiar with drug licensing in Europe, especially in the sector of well-established herbs. For manufacturers unfamiliar with drug regulatory affairs it represents a useful introduction into the topic.

And, yet, there is one minor (or possibly major) drawback to this otherwise excellent resource: For some inexplicable reason, the publisher has issued this item in a 2-ring binder format. With the weight of about 6 pounds, the 2 binders simply cannot hold the pages together, and the pages pull the ring apparatus from the binder. Given the fairly significant price for this "book," it is mystifying why the publishers would produce it in a format that would create inevitable problems and frustration for the intended buyer.

—Mathias Schmidt, PhD
Director, HerbResearch Germany
Tussenhausen-Mattsies, Germany

Hortence Robinson 1923–2010

Esteemed midwife and natural healer Hortence* Robinson passed away at her daughter's home in Ladyville, Belize, on November 7, 2010. She suffered from strokes for 7 years before ceding her life—with a smile on her face—at age 87.

Miss Hortence, as she was respectfully and affectionately called, was descended from midwives on both maternal and paternal sides. While her father worked in the chicle camps of Cozumel, Mexico, she forwent school to assist her family with household chores, and to spend time gathering healing plants. Hortence noted that she was interested in herbs from her earliest days—treating her mother for a headache at age 3.

She told Channel 5 Belize that the Q'eqchi' Indians were some of her first traditional medicine teachers: "I was a child that if you said, 'Let's go collect herbs,' we go with the people collecting herbs and to each herb they collected I was 'What you want it for? What will you do with it? What you use it for?' And they keep telling me; they weren't selfish."[1]

At just 9 years of age, Robinson was aiding her mother and grandmother in midwifery. She independently delivered her first infant at 13, while she was in the hospital recovering from a near-lethal asthma attack. According to her friend and colleague, Rosita Arvigo, DN, Robinson was walking down a hospital corridor when 2 men brought in a stretcher. "On the stretcher was a woman in final stages of labor," Dr. Arvigo recounted in her eulogy for Robinson, "[The woman] looked over at Hortence and pleaded, 'Come here child and catch this baby.' Hortence knew just what to do. She delivered the infant on her own, waited for the placenta to pass, then wrapped the baby and placenta in her own hospital nightgown and went to find the nurse."

Such behavior was typical of Miss Hortence, who always put the wellbeing of others before her own comfort. Robinson moved to Belize as a teenager, and in time she had a tiny blue house perpetually teeming with people, both family and not. "Some sat under the shade of her great mango tree waiting to be healed; others came just to bask in her warmth and hospitality," said Dr. Arvigo in her eulogy. "Children passed right though her living room and kitchen taking a shortcut on their way to and from school twice daily. She knew them all by name and had delivered most of them."

Robinson was a proud mother as well as a midwife. Altogether she had 23 children—9 biological and 14 adopted sons and daughters—whom she singly raised.

Though she did not learn to read or write as a child, Robinson became a compelling public speaker. She was invited to lecture at a number of institutions and conferences, including Carnegie-Mellon University, the Women's Herbal Conference, the International Herbal Conference, the National Cancer Institute, the New York Botanical Garden, and 5 Traditional Healers Conferences in Belize.

Miss Hortence also played a key role in a project to inventory the plant diversity of Belize and gathered information about the uses—medicinal and otherwise—for these species. "She made an extraordinary contribution to the Belize Ethnobotany Project," said Michael Balick, PhD, "and her contributions to recording the traditional knowledge of the plants of her country are to be found in the many hundreds of plant specimens she helped gather during dozens of scientific expeditions, as well as in a forthcoming guide to the useful plants of Belize. Her work also supported the effort by the National Cancer Institute of the US National Institutes of Health to evaluate the medicinal potential of local plants. It was her desire that the Belizean tradition of using plants for healing not be lost, but continue to serve future generations. She felt strongly that such new discoveries could help the people of the world" (e-mail, January 19, 2011).

Because of the breadth of her knowledge and experience with medicinal plants—particularly their active ingredients—Robinson came to be known as *Mil Secretos* (a thousand secrets). She is said to have had a spiritual relationship with plants, and her healing preparations included idiosyncratic steps such as cutting bark only from the south side of a tree for use in a diabetes treatment, and utilizing only the ants that were crawling upward on cockspur trees (*Acacia cornigera*, Fabaceae) in her catarrh remedy.

When asked at an Art of Birthing conference if she performed episiotomies, Robinson puffed up her chest, looked right out into the waiting audience and declared, "*Well, I never did have a lady who tore!*" The crowd of medical professionals went wild, offering her a standing ovation, after which Robinson explained her secrets to preventing tearing during childbirth.

Robinson's greatest contribution to women's health may be her uterine massage techniques. Abdominal massage is a traditional component of Maya female reproductive-system treatment, and according to Dr. Arvigo, Robinson originated "a very useful formula for smaller uterine fibroids known as Hortence's Formula." Arvigo added that one must be able to locate Hortence's Point—"a miniscule area on the ischial ramus…that brings great relief to many female complaints when palpated according to her instructions"—in order to be certified by the Maya Abdominal Therapy Association.

"May her beloved memory be a blessing to all who knew her," said Mark Blumenthal, ABC Founder and Executive Director, "and to those who continue to receive her invaluable teachings."

—Ashley Lindstrom and Rosita Arvigo, DN

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*Alternately spelled "Hortense"

Robert Crayhon
1961–2010

Robert Crayhon, a nutritionist, author, and commentator who was full of humor and passion for the science of food and dietary supplements, died September 4, 2010, from colon cancer.[1] He was 49 years old.

Born in Mt. Vernon, New York, on April 30, 1961, Crayon grew up in Pelham, New York, and attended Iona Preparatory School and then Colgate University. He later graduated from Oberlin College with a degree in classical piano. But his deepest love was for nutrition. This led him to earn a master's of science degree in nutrition at State University of New York (SUNY). As a certified clinical nutritionist, Crayhon lived and taught in Boulder, Colorado, where he founded and ran the Boulderfest Integrative Medicine Conference.[1] A modern renaissance man of many talents, Crayhon was also an exceptional jazz pianist, a talented lyricist and composer, an accomplished stand-up comic, and a boxer.

Crayhon had the ability to grasp the "take-home" message when reading technical scientific papers and could distill the information in a way that others could understand and derive benefit. As such, he was a gifted teacher, as well as a capable writer and author of 4 books, including *Nutrition Made Simple* and *The Carnitine Miracle*. His passion to understand the health benefits of carnitine, a substance produced by the body from amino acids, was complemented by his passion to study nutrition, brain function, and performance.

"In my opinion," said Esther Blum, a holistic nutritionist and author in New York, "his greatest achievement was making clinical nutrition and biochemistry hysterically funny. Robert catered to a wide variety of audiences—MDs, PhDs, RDs, fitness professionals, and patients—and was able to break down incredibly complex concepts in order to reach everyone. His humor was an incredible gift he bestowed to those around him" (e-mail, December 29, 2010).

Crayhon went on to help found the dietary supplements company, Designs for Health, his stake of which he sold in 2005. He then founded Crayhon Research in Reno, Nevada, and recorded numerous interviews with leaders in the field of nutrition, such as Harvard Medical School instructor and Robert Wood Foundation Fellow John Abramson, MD. These recordings were inculcated into his company's serial, *Nutritional Medicine Update With Robert Crayhon, M.S., C.N.*, which will continue to be available though Complimentary Prescriptions has since taken over the company. (Complementary Prescriptions will also continue to hold Boulderfest each year.)

Mark Schauss, who worked at Crayhon Research, said Crayhon was "a gifted writer, communicator, and—most of all—a teacher" (oral communication, December 20, 2010). "He so wanted to impart his knowledge to others that he spent hours and hours learning so that he could share what was out there in the world of nutrition with as many people as possible. His greatest achievement was the number of people he inspired to help others."

"Robert would always be straightforward with you," Mark Schauss continued. But more important, "He always tried to help others, especially those less fortunate than him. He would allow people to show up at his seminars for free, or even pay for part of their transportation and lodging if they needed it. He'd give you the shirt off his back. Robert almost always thought of others first. When I asked him what I could do for him the day before his surgery to remove a tumor in his colon, he asked that I go get a colonoscopy (which I did)."

Crayhon also spent time as a frequent guest commentator on various radio and television programs, including Fox News and CNN. He hosted his own national radio show for 3 years and a national television program on health and wellness for two, and was a regular columnist for *Townsend Letter, the Examiner of Alternative Medicine*. What many didn't know about Crayhon were the hours he spent in soup kitchens in New York, as well as his support of many other charities. Anyone who had the opportunity to know him will never forget his boundless energy, immense passion for nutrition, and desire to urge others to make healthy choices. His generosity, talents, and attributes, combined with a wonderful sense of humor made him someone very special, never to be forgotten.

"Robert was one of the most brilliant minds I've ever met," Blum continued. "He was a rare breed in that he truly used both the right and left sides of his brain and I don't think I'll ever meet another gifted soul like him in my lifetime. The challenge lies within all of us to honor Robert through the continual quest for knowledge, sharing that knowledge with the public, and to fearlessly seek out the truth. Robert is irreplaceable, yet together we each hold a piece of him that we can share with the world."

During his last months, Crayhon was surrounded by friends, particularly Jonathan and Linda Lizotte, who co-founded Designs for Health. Crayhon is survived by his sister and parents.

—Lindsay Stafford and Alexander G. Schauss, PhD, FACN, president and CEO of AIBMR Life Sciences, Inc.

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Beatrice Waight 1948–2010

Beatrice Waight, a traditional Maya healer who spread the medicinal customs of her family and ancestors around the world, died on October 3, 2010, at the age of 62.

Originating from a small village in the Cayo District of western Belize, Waight was a multiple-generation healer who obtained her skills and knowledge from observing her father, who was a traditional Maya healer, from her upbringing in a traditional Maya home, and through training with her grandmother, who was a midwife.[1] She was also trained through dream visions, a common occurrence among Yucateca Maya healers. Going back in time as far as her family can remember, the women were midwives and herbalists and the men were healers, shamans, snake doctors, herbalists, and Maya acupuncturists, said friend and student Katherine Silva (e-mail, December 4, 2010).

"Miss Beatrice impacted her patients and students with her deep faith in her Maya spirituality and way of life, the plants, prayers, and ceremonies, and her wonderful sense of humor and warm heart," said Silva. "During her life, she carried forth her father's role of ceremony leader, herbalist, and spiritual healer, combined with her grandmother's role of carrying the women's wisdom and women's wellness the Maya way to people in her village and all over the world," said Silva.

Among the extraordinary aspects of the vast Mayan civilization, which inhabited Belize, Guatemala, and southern Mexico for almost 2,000 years,[2] was its traditional medicine. This holistic system considers bodily ills in conjunction with the affects of the spirit, such as attitudes and emotions.[3] Based on 6 main ideas, one of the fundamentals of Maya healing is the concept of "life energy," a force that connects all things and resides in every person, animal, and plant, as well as non-living things like homes and rivers and mountains. Additional beliefs include the importance of developing a relationship with medicinal plants that will be used for healing; the importance placed on using prayer in the healing process; the use of pulse reading to determine types of imbalances and the direction of the treatment; and the belief in hot and cold foods, drinks, plants, and diseases.

Just as Waight learned from her elders, Maya medicine survived by being passed down orally through generations. Now it is practiced by descendants like Waight, though it differs somewhat from the original Maya medicine due to influences from Spanish tradition and Catholicism.

Waight spent the majority of her life treating fellow villagers and others abroad with traditional Maya medicine practices, while also educating people around the world on this system of healing. From the time when her first children were small, she treated or offered healings to neighbors and family in her home, and about a decade ago, she began seeing patients, teaching workshops, and conducting ceremonies in a "healer's hut." A small clinic in a traditional, round Maya building, the healers' hut was built using funds donated from noted herbalist and author Rosemary Gladstar and a group of students.

Though she received midwifery training from her mother and grandmother, Waight felt more drawn to the other components of Maya healing. "She felt that her calling was not to be a midwife but to be a traditional Maya healer using massage, herbs, ceremonies, and Maya spiritual healing to ease people's physical and emotional suffering," said Silva. Additional techniques Waight used in her healing sessions included prayer, egg cleansings (a practice in which an egg is run over a patient's body to remove negative energy), herbal baths, plant brushings, application of plant allies to the pulses, Maya hydrotherapy, dietary suggestions, humor, counseling, and group and individual ceremonies, Silva added.

Perhaps the most important of these were herbs. "Herbs were the center of Miss Beatrice's life," said Silva. "Plants were dear friends to her and she used them every day. For her, herbs were vital in the role of medicine because they were effective, available, affordable, and healing, both physically and spiritually."

Waight had training from the Ministry of Health on how to perform basic nursing tasks, but she generally did not use these skills in her healing treatments. Waight taught at many workshops led by Rosita Arvigo, an herbalist and naprapathic physician who also practices Maya healing techniques, and also held her own workshops at her home in Belize and in the United States, England, and Mexico.

"She taught so that her tradition would remain alive and accessible," said Silva.

In addition to her healing and educational activities, Waight advised the Belize Ethnobotany Project at the New York Botanical Garden, as well as the Student Rainforest Fund in Pennsylvania. According to Silva, Waight spent her life helping others, "because her heart was huge and she was very compassionate, and because her father asked her to take his place in a dream so she promised him she would and she kept her promise."

Waight is survived by her children Edilberto Leonel, Nary Junior, Abimeal, Thelma, Marlyn, Berta, Judy, Jeanette, and Zena. In memory of Waight, who used her income from teaching to send 8 of her 9 children through college, an educational fund has been set up for Zena, her youngest daughter, so that she may attend a university in Belize. More information on this, as well as details on Waight's upcoming posthumous book, *Fire Heart*, is available at www.missbeatricewaight.com/About-Us.html.

—Lindsay Stafford

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Leonardo L. Co
1953–2010

Leonardo L. Co, a Filipino botanist and taxonomist who was respected worldwide and dearly loved by the people of his country, died November 15, 2010, from gunshot wounds.[1] He was 57 years old.

Co was collecting seeds from endangered trees in a forested area in Kananga, Leyte, Philippines, when he and 2 others in his 5-man team were shot and killed. He had been hired by Energy Development Corporation (EDC), a Philippine developer of renewable energy, to conduct a study on the area's tree biodiversity and potential for a reforestation project. Co died alongside Sofronio G. Cortez, a forest guard of EDC's environmental management division, and Julius Borromeo, a member of the Tongonan Farmers Association (ToFA).

The nature of these deaths has been and continues to be very controversial and remains somewhat unsolved. Soldiers of the Filipino army originally claimed that the men were killed in crossfire between the military and armed rebels of the Philippine Communist Party's New People's Army (NPA). This depiction of events, however, was disputed from the start. An EDC spokesperson told the media that the company informed the military of the group's plans and received a security clearance before proceeding, and that NPA rebels did not have any nearby camps.[2] Additionally, eyewitness accounts from the survivors on Co's team and a recent multi-organizational fact-finding mission reported that there was no crossfire and the gunshots came only from the direction of where the military was located.[3] As of press time, more than 2 months since the killings, the army has not commented on these findings and the official Department of Justice report is pending.

A noted botanist, ethnobotanist, and taxonomist, Co spent his life with plants and the people who use them. He discovered several new plant species native to the Philippines, including *Vaccinium oscarlopezianum* (Ericaceae). The plants *Rafflesia leonardi* (Rafflesiaceae) and *Mycaranthes leonardoi* (Orchidaceae) were both named after him and a new species of pitcher plant (Nepenthaceae), discovered in the Philippines in November, is also to be named after him.[4] Co authored *The Forest Trees of Palanan, Philippines: A Study in Population Ecology* in 2006, and served as president of the Philippine Native Plants Conservation Society (PNPSC), curator of the Jose Vera Santos Herbarium, and museum researcher at the University of the Philippines (UP) Institute of Biology.[1] He received his bachelor's degree in botany from UP Diliman.

"Working with him was stimulating because Leonardo was full of ideas regarding many things, not only about plants," said Elena M. Ragragio, an assistant professor in UP Manila's Department of Biology, who knew Co for 30 years (e-mail, December 18, 2010). "He knew about constellations, played the national anthem of different countries on his harmonica, was able to talk and read [the] Chinese, English, and Filipino languages. He was also very funny and found humor in many things. [When] we were young, many of our ideas were really ambitious about how to change the world, our society, etc."

A large part of Co's career was focused on medicinal plants. Working with Community Health Education, Services and Training in the Cordillera Region (CHESTCORE) in the 1980s, Co helped to list 122 Filipino medicinal plants.[1] He also worked in the Cordilleras region to help local communities systematize their traditional medicine knowledge so that they could employ it in their own primary healthcare. As part of this work, he wrote and distributed the book *Common Medicinal Plants in the Cordillera Region: A Trainer's Manual for Community-Based Health Programs*.

Additionally, Co set up community-based health systems in poverty-stricken indigenous villages around the country. According to colleagues quoted in local newspapers, he did all of this not "for his own personal career or economic advancement, but instead offered it back for the benefit and use of the communities."[5] For these efforts, Co is credited with helping to prevent biopiracy, as well as loss of traditional practices as a result of globalization. He is now widely remembered as a "scientist of the people."

"[Leonardo] was specially involved in the various struggles of the marginalized sectors in our country who live in poverty in spite of the richness of natural resources in the country," said Ragragio. "Leonardo was well aware of the inequalities in our society, so his work on medicinal plants here in the Philippines was his way of contributing to alleviation of this poverty since medicines in our country are beyond the reach of majority of the people. He lived and believed that botanical knowledge is for the people and should not be confined within the walls of the university."

Reflecting the international scope of respect for Co's work, S. H. Sohmer, PhD, president and director of the Botanical Research Institute of Texas, called Co's death "a keen loss for Philippine botany" (e-mail, December 16, 2010). "There are so few botanists of his caliber in the Philippines," said Dr. Sohmer, who initiated and organized the Philippine Flora project in the 1980s and also did field work there. "He was competent, positive, and very collaborative. It will be a loss that will affect Philippine botany significantly." USAID-Philippines wrote in a letter to Co's wife, which was posted on Facebook: "We admire your husband's unparalleled dedication and deep commitment to his work, particularly in conserving the forests, and helping families and communities who are dependent on these forest resources. Your husband and other people like him who lost their lives in doing conservation work are true patriots. USAID will continue to support conservation work

in the Philippines so that their sacrifices are not left in vain. His passing away is truly a great loss to the country and to the global community."

CHESTCORE recently released a statement, documented in various news reports, noting that it is not uncommon for health workers carrying out projects in remote communities to be accused of helping or being a part of NPA.[5,6] A separate news editorial on Co states that community-based health programs continue to be harassed by the military, and that the location where he was shot is controlled by a part of the army that is known for alleged crossfire-related citizen deaths.[7]

Co is survived by his parents, Lian Sing and Emelina Co, his wife, Glenda Flores Co, and his daughter, Linnaea Marie, named after 18th century botanist and father of taxonomy Carl Linnaeus. "His work is very significant since there are only a handful of botanists in the country, most of whom are specialists on only one family of plant," said Ragragio. "However, Leonardo's plant knowledge encompasses all divisions, from ferns, to angiosperms, including the particular species' ecology. Leonardo has no equal. Some botanists can perhaps work on Leonard's latest collections, which are housed in the UP Diliman Herbarium. However, I am not so optimistic about who will continue Leonardo's work."

Co's colleagues, students, friends, and family are heartbroken over the loss and remain determined to uncover the events surrounding his death. A Facebook page titled, "Leonardo L CO: In Memoriam," for example, has more than 1,200 followers and numerous wall posts informing people of the latest developments with the Justice for Leonardo Co movement. As he wished, a third of Co's ashes were scattered on a blackboard (or dita) tree (*Alstonia scholaris,* Apocynaceae) growing on UP Diliman's campus and another third will soon be scattered in Palanan forest's 16-hectare forest dynamics plot. The remaining ashes were given to his family. A Leonardo L. Co Justice Fund has been established to help pay for the costs of prosecuting his killers. More information is available at: www.facebook.com/note.php?note_id=182359148446942&id=162637747108520.

—Lindsay Stafford

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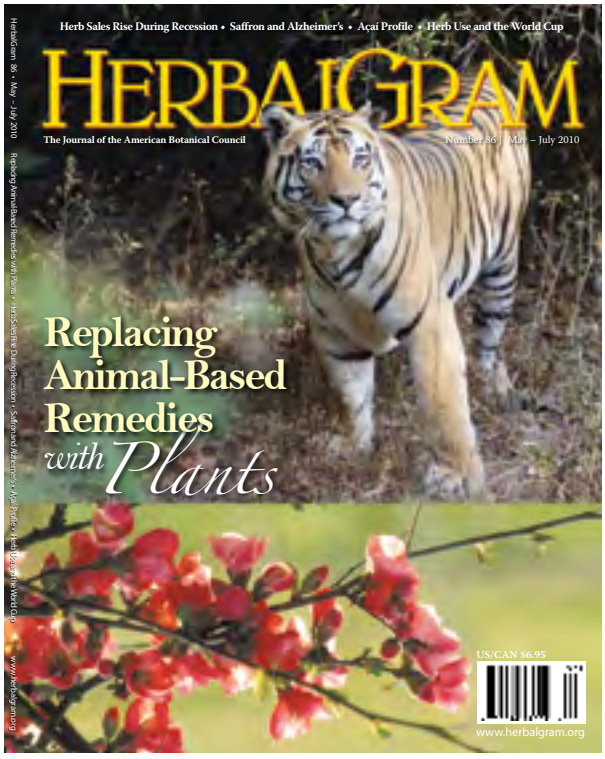
Re: **Replacing Animal-based Remedies with Plants**

Dear Editor,

I read your article on zootherapy, which was well-researched and beautifully presented. All the same, I still see a problem with your approach.

It is good that you mention the dearth of scientific studies confirming the claims of animal-based medicine, and even better that you note: "many remedies appear to be primarily based on folklore and superstition." This statement, however, raises the question, "Which remedies?" And the answer, unfortunately, is right on the cover: tiger-based remedies—"tiger medicine"—based on folklore and superstition. This being the case, you might not have begun your article by stating that "animal-based remedies are important therapeutic resources within many cultures," and by affirming that "the medicinal use of animal species has led to the development of pharmaceuticals for global markets." Because then you are compelled to cite the medicinal use of snake venom as an overall justification for the "many remedies based on superstition"—namely, for the massive killing and ultimate extinction of the tiger.



A less gentle approach to the subject, but one more helpful to the wild tiger, would have been to state on the cover that "Ginseng works—tiger medicine does not!" And then, in the article, to identify phony animal medicines, or at least to call for scientific tests to confirm their incredible claims. But instead you chose the polite path of advocating alternative plant-based medicines. "Polite to whom?" you might ask. To the Chinese, of course.

Your approach is the same as that adopted by the World Wildlife Fund and other animal-conservation organizations back in 1993. For 17 years the WWF has been gently and politely trying to persuade "Practitioners of Traditional Chinese Medicine (TCM)," as it titles the criminals who support the illegal tiger trade, to seek "equally effective alternatives to tiger-based medicines." In some instances they have succeeded in making a change, but overall their program has disastrously failed. The Chinese aren't listening. The demand is increasing. The population of wild tigers has plummeted, and the species is sliding into extinction. The March 2010 Conference of Parties in Qatar, to which you refer positively, was a signal defeat for tiger conservationists. The Chinese government would not budge, would not allow outside inspections of trade from Asian tiger farms. Thus tiger conservation, based on soft-pedaling TCM, came to a dead end.

It is understandable that in *HerbalGram* you should seek to propose well-researched plant medicines as substitutes for unresearched (and imaginary) animal medicines. You might also have recommended rice protein powder and calcium tablets as a substitute for tiger bone, which has protein and calcium (plus imagination) as its active ingredients. Similarly, Viagra® can be proposed as a substitute for tiger-penis soup, which you neglected to mention. But from the point of view of tiger conservation, it is far too late for such games.

You can do the math yourself, using the figures from your own article. There are 1.4 billion people in the People's Republic of China (PRC). You cite a 2007 survey in which 43% of PRC respondents admitted to consuming products with tiger "derivatives." So let's say, just to be conservative, that 10% of China's population consumes tiger products in the next 10 years. That's 140 million people served by 3,000 wild tigers, plus perhaps 10,000 farmed tigers. That's roughly 1 tiger for every 10,000 Chinese consumers, plus all the hungry consumers of tigers outside of China—in Taiwan, South Korea, Thailand, etc. The population of tigers is falling; the population of tiger-eaters is rising.

The South China tiger is extinct. No one has seen any of the supposed 50 animals you mention for many years. The Sumatran tiger will be extinct within a few years. India has about 1000 tigers left, but the reserves are going silent one by one. Indian expert Valmik Thapar, after 30 years in tiger conservation, says that his life has been a failure. So it's too late for ginseng, and besides, ginseng is often mixed with tiger potions anyway.

In such a circumstance, the only chance to save the wild tiger is to state the truth openly: that tiger medicine is a primitive superstition and the cause of the tiger's destruction. The need is to stop the demand, and the only way I can see is to discredit it, to show that it is based on magical thinking—the belief that by consuming the great cat or any of its parts one can obtain its power and vitality. TCM should not be revered: It should be open to criticism and scientific testing, the same as medicine in the rest of the world.

Having said this, I am glad that you demonstrate very precisely that there is a specific herbal alternative to every animal medicine that endangers a major species. This part of the argument is therefore nailed down. I have written a long article on the plight of the tiger and plan to add citations to your work, but the effort to save the wild tiger now strikes me as so futile that it is difficult to keep going. It is time for screaming and shouting, not gentle diplomacy, which makes your delicate and beautiful piece so distressing.

—Gary Kern
Author, critic
Las Cruces, NM

February 10-21: 53rd Congress of the International Hop Growers Convention. Hobart, Tasmania. Taking place in Australia, the largest producer of hops in the Southern Hemisphere, this congress features committee meetings; tours of hop fields, farms, and processing factories; technical discussions; and fun trips to local breweries and a wildlife park. An optional 10-day extension takes attendees to New Zealand, where specialized hop growing discussions will take place. More information is available at: www.hmelj-giz.si/ihgc/act.htm.

February 16-19: BioFach 2011. Nuremberg, Germany. Each year more than 43,000 people attend this international trade show in which 2,500 exhibitors display their organic and natural products and services, which range from produce, to green finance, to natural remedies. A concurrent congress, known as the largest organic conference in the world, attracts 8,000 participants. This year's congress will feature discussions on the topics of German organic trade, fair and ethical trade, catering, textiles, natural cosmetics, and wine. With the overall theme of how to sustainably feed the world on organic and natural foods, BioFach 2011 provides an international platform for professional discussion on how to devote combined efforts to joint projects. More information is available at: www.biofach.de/en/.

March 4-6: Integrative Healthcare Symposium. New York, NY. This event gathers persons involved with the integrative healthcare community and features more than 40 sessions with nationally recognized practitioners and experts in the fields of women's health, environmental health, Ayurveda and Traditional Chinese Medicine, functional medicine, homeopathy, and more. The 2011 conference takes the following focus topics: nutrition, integrative oncology, endocrinology, brain and mind health; and leadership and policy. Featured speakers include Mark Hyman, MD, Tieraona Low Dog, MD, Robert Rountree, MD, and John Weeks, among others. The symposium aims to give attendees the practical and inspirational knowledge to boost their own professional practices. Continuing education credits will be offered to acupuncturists and practitioners of traditional oriental medicine, dietitians, chiropractors, naturopathic physicians, and nurses. More information is available at: www.ihsymposium.com.

March 10-13: Natural Products Expo West/SupplyExpo 2011. Anaheim, CA. These two main events, also held in conjunction with Nutracon, Healthy Baking Seminar, and Fresh Ideas Organic Marketplace, come together to create the world's largest natural, organic, and healthy products trade show. Nearly 56,000 professionals and customers gather to attend, and more than 3,000 booths showcase the newest and most popular products from the areas of health and beauty, natural and specialty foods, natural living, organics, pet products, and supplements. Additionally, educational activities, such as expert speakers, leading manufacturer seminars, and a retail store tour, aim to help attendees learn about industry trends, as well as strategies for improving business and increasing knowledge. More information is available at www.expowest.com and www.supplyexpo.com.

March 15-17: 8th International Conference "Functional Foods for Chronic Diseases: Science and Practice." Las Vegas, NV. Experts in the fields of medicine, biology, and food gather at this yearly event to discuss the use of functional foods in chronic disease prevention and management. The conference focuses on the relationship between functional foods and 5 main topics: diabetes, obesity, cardiovascular diseases, cancer, and general health and disease. Twenty-four credit hours of continuing education units (CEUs) are available for attending doctors, nurses, dietitians, and nutritionists. More information is available at: www.functionalfoodscenter.net/Conference_2011.html.

April 2-3: Southwest Conference on Botanical Medicine. Tempe, AZ. Held at the Southwest College of Naturopathic Medicine, this event focuses on botanical therapies that treat chronic health conditions. Fifteen expert speakers, including Paul Bergner, Cascade Anderson Geller, and Christopher Hobbs, will discuss topics ranging from bitter mints, parasites, and medicinal mushrooms. A great variety of additional subjects will also be discussed. Two herb walks through the desert will be offered, as well as a pre-conference intensive on the neuro-endocrine-digestive connection given by Mary Bove, ND. CEU credits are also available for attendees. More information is available at: www.botanicalmedicine.org/conferences/sw2011/sw2011info.htm.

April 6-7: Shea 2011: Sustainable Solutions. Accra, Ghana. Just 6 months after the first private sector alliance was established to better the global industry for shea (*Vitellaria paradoxa*, Sapotaceae), this event gathers industry stakeholders from around the world. Attendees include shea producers, traders, international buyers, retailers, associated logistical support organizations, financiers, certifiers, transporters, packaging suppliers, and researchers. Many of these individuals and groups will present on promoting shea in international markets, forming an international shea alliance, sustainable sourcing of shea nuts and butter, and improving supply chain transparency. More information is available at: www.globalshea.com.

April 11-15: 10th Annual Oxford International Conference on the Science of Botanicals. Oxford, MS. This event aims to gather those from the natural products research community to review, discuss, and explore current research topics related to natural products chemistry, pharmacognosy, and botanicals. Specific topics of focus include: assuring quality; assessing authenticity, identity, and purity; modern technology approaches to establishing safety, efficacy, and quality; and international regulatory approaches for safety assessments and adverse event reporting. Expert speakers from industry, academia, nonprofit organizations, trade associations, and government will open and lead each session. More information is available at: www.oxfordicsb.org.

More calendar listings at
www.HerbalGram.org
See "News" Tab

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.

DietandCancerReport.org, a website containing the expert report, *Food, Nutrition, Physical Activity and the Prevention of Cancer: a Global Perspective,* has been recently updated. Organized by the World Cancer Research Fund and the American Institute for Cancer Research, this website also features a companion report titled *Policy and Action for Cancer Prevention,* as well as related resource materials. The new material featured in this update includes information on recent progress with breast, bowel, prostate, and pancreatic cancer research; cancer protocols; and a full report and summary on updated breast cancer research. Additional new features include new executive summaries of the policy report, availability of this report in Portuguese and Spanish, and listings of conferences and other events where these expert reports have been presented and discussed. Available at: www.dietandcancerreport.org.

The Pill Identifier, a new online tool from WebMD, aims to assist those who are having trouble identifying a medicine or dietary supplement. Pills are sometimes misplaced or separated from their original containers, making it difficult to identify them with an untrained eye. The Pill Identifier allows users to enter into an online form the basic characteristics of the pill, such as shape, color, and any visible imprint. Example images of shape and color are provided in a drop-down menu, enabling easier visualization. The tool will then display detailed images of all possible prescription and over-the-counter (OTC) drugs, as well as some dietary and herbal supplements, and users can then match the mystery pill with a name. Once the pill's name is decided upon, users can read that specific medicine's patient education handout, which discuss uses, side effects, interactions, warnings, and dosing. The tool also provides information on and images of commonly abused drugs, popular pill imprint number and letter combinations, and educational information on prescription drug abuse. Available at: www.webmd.com/pill-identification.

Herbaria@Home is a new project that uses a creative approach to digitize archives of the United Kingdom's herbarium collections held in various museums, universities, and other institutions. Because most aspects of herbarium digitization are very costly, Herbaria@Home encourages the everyday person to spend 30 minutes each week to document the United Kingdom's biodiversity. After obtaining a photograph of a herbarium specimen and data sheet, volunteers can proceed to enter the plant's taxon, collector, collection date, herbarium, site, and any additional notes into an online database. Volunteers need no prior botanical knowledge as they receive an online tutorial and a small portion of the data is sent to multiple participants for crosschecking. Additionally, all users can check submitted records and correct any changes, a technique similar to the online, user-generated encyclopedia, Wikipedia. Once the records are documented and digitized, they are immediately available online. Herbaria@Home is sponsored by the Botanical Collections Managers Group, a specialist group of the Linnean Society of London, and currently has digitized herbarium collections from Birmingham University, Bolton Museum, and Charterhouse School. Available at: www.herbariaunited.org/atHome/.

New Earth BioMed is a new tax-exempt nonprofit organization whose mission is to discover synergistic mixtures, compounds, and doses of natural products (e.g., phytochemicals) that produce the greatest inhibition of cancer at the highest level of safety. Unlike the majority of drug discovery companies, New Earth BioMed is completely nonprofit and focuses on mixtures and compounds as opposed to single molecule drugs. Also, their research strives to produce large mixtures of compounds in which the concentrations of all compounds are relatively low in order to reduce potential adverse effects as much as possible, while also increasing synergistic activity. The first project of the organization's research program currently has scientists working toward developing advanced laser analytical technologies, complex cell culture systems, and sophisticated mathematical models to help analyze the cancer-fighting potential of natural compound mixtures found in vegetables, fruits, spices, and medicinal herbs. Once completed, this will be used as a core technology in a large-scale mixture-screening program. The organization's founder, John Boik, has published books documenting plants and plant-derived compounds with anti-cancer activity. Available at: www.newearthbiomed.org.

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) 488-8839, or stop by the College campus located at 5940 SW Hood Ave., Portland OR 97239.

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Plant Lovers Journey to the Patagonia. Join Rosemary Gladstar and Dr. Richard Liebmann March 1-12, 2011. Summer herbal adventure in Argentina and Chile. Email richardliebmann@gmail.com.

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Herbal Teleclasses for Children (Ages 8-100). First Thursday of each month at 8 pm EST. $5.00 per child. Parent attends free! Visit www.herbal-educator.com for details.

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