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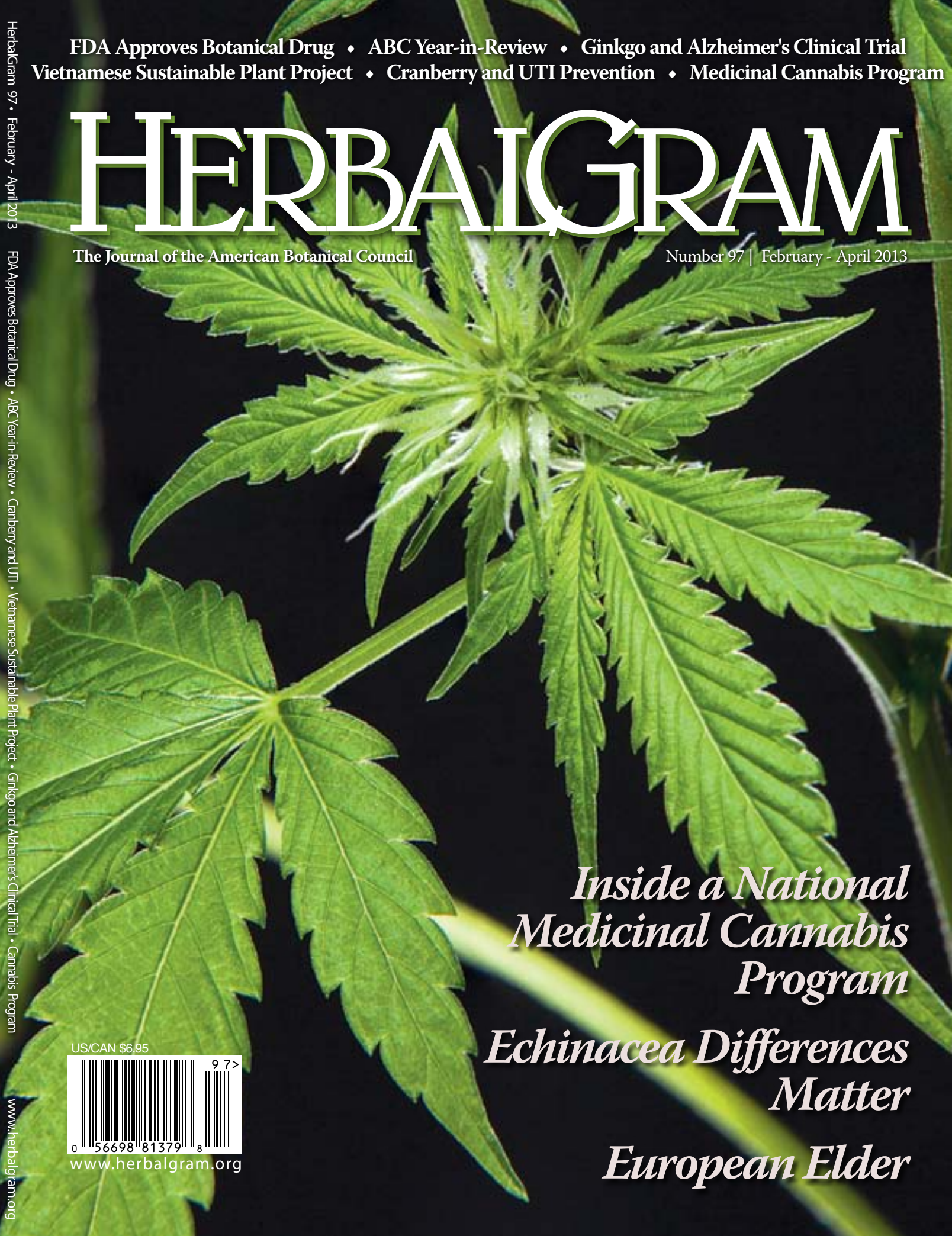

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HERB OF THE YEAR

European Elder

***Sambucus nigra*, L.**

Family: Caprifoliaceae

INTRODUCTION

European elder (*Sambucus nigra*, Caprifoliaceae), also known as black elder[1] and elderberry, is a deciduous tree that grows to 30 feet and is native to Europe, northern Africa, and western Asia.[2] It has flat-topped clusters of small, creamy-white flowers in early summer, followed by large, drooping bunches of purplish-black, juicy drupes (commonly referred to as berries) in late summer or early fall.[2,3]

Both the elder flower and berry are used medicinally. Most of the elder flower in commerce is collected from the wild, mainly from Albania,[4] Bosnia-Herzegovina, Bulgaria, Croatia, Romania,[5] Hungary, Macedonia,[6] Poland,[7] Russia,[8] Serbia, and Montenegro.[9] Elderberries also are wild-collected in the aforementioned countries, but there are several distinct cultivars grown in commercial orchards, particularly in Austria (*e.g.*, mainly the "Haschberg," "Rubin," and "Tattin" varieties), Denmark (*e.g.*, "Sambu," "Sampo," "Samdal," "Samyl," "Allesoe," and "Korsör"), and Germany (*e.g.*, "Haschberg," "Sambu," "Sampo," "Samyl," and "Haidegg 13"). Due to successful auto-vegetative propagation, regular yields, and high coloring matter content, "Haschberg" is the chief variety cultivated in both Austria and Germany.[10]

For the sake of convenience, European elder will be referred to as elder in this article, and the plant part under discussion will be specified.

HISTORY AND CULTURAL SIGNIFICANCE

The genus *Sambucus* contains more than 20 species, many with similar chemical constituents to *S. nigra*. One such species, American elder (*S. canadensis*), is a fast-growing, deciduous North American shrub that can reach up to 12 feet with flowers and berries similar to *S. nigra*.[1,3] While this species was used by Native American tribes and as a folk remedy in some of the same ways as *S. nigra*, it will not be discussed in this article for reasons set forth below in the Modern Research section.

The use of elder as a medicine dates back to antiquity, according to the writings of Hippocrates (ca. 470-410 BCE), Pliny the Elder (ca. 23-79 CE), and Dioscorides (ca. 40-90 CE).[11] The word elder is derived from the Anglo-Saxon word *ældl*, meaning "fire," because one could start a fire by blowing through its young, hollow branches.[12] Historically, medicinal uses for European elder could be found in Italian, Dutch, Portuguese, Croat-Slovak, German, Austrian, Swiss, and Hungarian pharmacopeias.[13]

Of interesting historical note, in *Anatomi Sambuci: The Anatomy of the Elder*, written in 1677, the physician Martin Blochwich described medicines made from the various parts of elder, including a berry tincture, extract (or essence), wine, spirits (fermentation), syrup, tragea (powdered elder-

European Elder *Sambucus nigra.* Photo ©2013 Steven Foster

berry kernels), and rob (a thickened juice made from the berries, either with or without sugar), as well as seed oil.[14] He also noted elder flower-derived preserves, syrup or honey, water and spirits, vinegar and oxymel (vinegar and honey), wine, and oil. Additionally, Blochwich elaborated upon powder, preserves, and syrup that could be made from the buds or sprouts of the plant, and also medicines that could be made with the leaves, middle bark, roots, pith, and fungus, including those in the form of water, syrup, oils, and liniments. Lastly, he chronicled making a "salt and its spirit" by reducing the entire plant to ashes over an open fire, pouring boiling water over it, and again reducing it over a low fire. This process produced the salt from which the spirit was then made. Blochwich then addressed the many ways in which these elder preparations were used alone (some of which might seem quite strange to the modern reader) and in combination with other "medicines" that are now known to be toxic. Common ailments these elder preparations were used to treat include headache, toothache, eye conditions, facial blemishes, mouth and throat conditions, cough, asthma, hoarseness, fever, smallpox, measles, stomach and intestinal conditions, stones, arthritis, menstrual complaints, inflammation, edema, and burns. Some of the more unusual conditions treated include deliria and affections (in combination with lily water, rose water, and opium); melancholy (by provoking vomiting); epilepsy (using an elder amulet worn over the heart); apoplexy and palsy (by vigorous rubbing of the extremities with elder spirit); protection from plague (by carrying and smelling an elder vinegar-soaked sponge in a hollow juniper-wood globe); and wound healing (by drinking wine that had elder leaves pounded into it, followed by a poultice of elder kernel oil, Venice turpentine, and verdigris [a poisonous green pigment caused by the action of acetic acid on copper]).

Traditionally, numerous ailments have been treated by elderberry including dysentery and diarrhea. It also was used to induce perspiration in order to remove toxins and increase resistance to illness.[13] Currently, elderberries are used to treat symptoms associated with colds, flu, and in feverish conditions as a diaphoretic (an agent that increases perspiration).[12,15,16] The expressed juice of the berries, as well as extracts and dried juice concentrates, are used as components of oral ingestion products like medicated syrups and tablets, as well as topical application products like lozenges and skincare products.[10] The fresh ripe berries are used in juices, jams, marmalades, liqueurs and dessert wines, and also as a coloring agent in beverages, foods, and textiles.[10]

Elder flowers are used as a diuretic, laxative, and diaphoretic.[12,17] Additionally, they are used as an astringent for the skin and in treating rheumatism, usually as an infusion (tea) or in a poultice.[18] The dried flowers of elder are used in European traditional herbal medicinal products mainly in the form of herbal teas, liquid extracts, and tinctures.[19] The German Commission E approved elder flower — administered as fluid extract, herbal tea, or tincture — for common cold symptoms in 1986.[20] In 1992, the British Herbal Medicine Association published an elder flower monograph in its *British Herbal Compendium*, specifying the forms of herbal tea infusion (drunk hot), liquid extract (1:1, 25% ethanol), and tincture (1:5, 25% ethanol) for treating feverish common cold conditions.[21] Elder flower water also has been used in eye and skin moisturizers, and flower extracts are used in perfumery.[18]

Both elderberry and elder flower extracts are used as flavorings in food products, alcoholic (bitters and vermouth) and nonalcoholic beverages, and confectionary items.[18]

CURRENT AUTHORIZED USES IN COSMETICS, FOODS, AND MEDICINES

In 2008, the European Medicines Agency (EMA) published a final labeling standards monograph on elder flower (as herbal tea for oral use, liquid extract [1:1, 25% V/V ethanol], or tincture [1:5, 25% V/V ethanol]), which superseded existing monographs of EU national authorities for the registration and marketing authorization of traditional herbal medicinal products that contain elder. The authorized therapeutic indication is "for the relief of early symptoms of common cold."[22]

One prerequisite of registration is that the quality of the herbal material complies with the corresponding quality standards monograph of the *European Pharmacopoeia* (Sambuci flos PhEur), which, for example, requires the dried flowers to contain a minimum of 0.80% flavonoids, expressed as isoquercitroside.[23] In European countries, elder flower also is found as an active ingredient of clinically tested polypreparations such as Sinupret® (Bionorica SE, Neumarkt, Germany), a licensed herbal medicinal product sold only in pharmacies and indicated for acute and chronic inflammation of the paranasal sinuses. (Sinupret also contains primrose [*Primula veris*, Primulaceae] flowers with calyx, common sorrel [*Rumex acetosa*, Polygonaceae] herb, European vervain [*Verbena officinalis*, Verbenaceae] herb, and gentian [*Gentiana lutea*, Gentianaceae] root.[24]) In the United Kingdom, aqueous liquid extract (1:1) of elder flower is an active ingredient of Cold and Flu Relief by Potter's Herbals (Wigan, UK; founded by Henry Potter in 1812), a registered traditional herbal medicinal product available without prescription from pharmacies and other retail outlets with the authorized therapeutic indication "used to relieve the symptoms of colds and flu, chills and sore throats."[25] (Potter's Cold and Flu Relief also contains ethanolic liquid extracts [1:1] of hemlock spruce [*Pinus canadensis*, Pinaceae] needle and bayberry [*Myrica cerifera*, Myricaceae] bark.)

In 2011, the EMA called for scientific data to be used by its Committee on Herbal Medicinal Products for assessment work toward the establishment of a community herbal monograph and/or community list entry for elderberries (Sambuci fructus).[26] Presently, there are also some elderberry-containing food supplement products in the European market, such as Wellion Diabasic® tablets (MED TRUST; Lichtenwörth, Austria), a dietetic food supplement labeled for special medical needs of diabetic patients with disease-related nutrient deficiencies.[27] Another example is the enzyme complex and herbal preparation Snorin® tablets (VitaBasix®; Maastricht, the Netherlands), labeled for chronic snoring whose cause is not determined to be anatomic after other causes (obesity, alcoholism, chronic tonsillitis, or sinusitis) have been excluded.[28]

Concerning use of elder in cosmetic products, the European Commission Health and Consumers Directorate lists "Sambucus Nigra Fruit Extract" for astringent (contracts the skin) function and "Sambucus Nigra Fruit Juice" for both astringent and skin-conditioning functions. "Sambucus Nigra Flower," "Sambucus Nigra Flower Juice" (juice expressed from the flower), and "Sambucus Nigra Flower Water" (aqueous solution of the steam distillate obtained from the flowers) are approved for use as skin-conditioning ingredients, while "Sambucus Nigra Flower Extract" is listed for refreshing (imparts a pleasant freshness to the skin), skin-conditioning, soothing (helps lightening discomfort of the skin or of the scalp), and tonic (produces an invigorating sensation on skin and hair) functions.[29]

In the United States, elder tree leaf is classified as a Generally Recognized as Safe (GRAS) natural flavoring substance, although its use is limited to only alcoholic beverages and not to exceed 25 ppm (parts per million) prussic acid in the natural flavor ingredient.[30] The essential oil or natural extractives (including distillates) of elder flower are GRAS flavoring agents in food products.[31] Elderberry and elder flower also are permitted as dietary supplement components in the United States, requiring Food and Drug Administration notification within 30 days of marketing a product (if a "structure-function" claim is made). In Canada, they are regulated as active ingredients of licensed natural health products (NHPs) requiring pre-market authorization from the Natural Health Products Directorate. As one example, Sambucol®* Original Lozenges (Healthcare Brands International Ltd., Surrey, UK), an elderberry preparation, is a licensed NHP indicated for reducing severity of flu symptoms (aches and pains, cough, congestion) and shortening duration of influenza A and B viruses.[32] Elder flower preparations, such as Gaia Garden Herbals Elder Flowers Tincture (Flora Manufacturing & Distributing Ltd.; Burnaby, Canada), are licensed NHPs with the authorized therapeutic indication "as a diaphoretic in conditions requiring fever management, including the common cold and influenza and for sinusitis and chronic nasal catarrh [inflammation of mucus membranes] with deafness."[33]

MODERN RESEARCH

Numerous *in vivo* and *in vitro* laboratory studies have assessed elder flowers and berries for antibacterial, anticancer, anti-inflammatory, antimicrobial, antiproliferative, antiviral, antioxidant, and immunomodulating activity, as well as chemopreventive and cytotoxic potential, cellular uptake, burn healing, insulin-simulating and insulin-releasing actions, anti-angiogenic (inhibiting the growth of blood vessels) activity, cardioprotective activity, and antihypertensive properties. Human clinical studies support the traditional use of and laboratory findings on elderberry and flower.

During the 2009 flu season, a short-term, randomized, double-blind, placebo-controlled pilot study was conducted on 64 volunteers suffering from three or more flu-like symptoms (coughing, fever, headache, muscle aches, and/or nasal congestion and mucosal discharge) for less than 24 hours.[34] The patients were randomized into two groups of 32 and administered four doses of 175 mg proprietary elderberry extract (HerbalScience Singapore Pte. Ltd.; standardized and enriched in phenolic acids, polyphenolics, and a broad diversity of other flavonoids)[35] or placebo daily for two days. After 48 hours, the elderberry group reported a significant reduction in symptoms with 28% of volunteers being symptom free. The symptoms of the patients in the placebo group were either unchanged or worse.

In 2004, a randomized, double-blind, placebo-controlled study (n=60) demonstrated the safety and efficacy of Sambucol in the treatment of influenza.[36] Patients with influenza type A or B received 15 ml Sambucol or placebo four times per day. Flu symptoms decreased significantly in the elder group by the third or fourth day versus seven-to-eight days in the placebo group. Treatment was initiated within 48 hours of symptom onset and the authors suggested that the elder preparation might have been even more effective with earlier intervention.

In a previous placebo-controlled, double-blind study conducted in 1995 on 27 patients with influenza symptoms

European Elder *Sambucus nigra*. Photo ©2013 Steven Foster

for 24 hours or less, patients received either Sambucol or placebo daily for three days (two tablespoons per day for children five-to-11 years of age and four tablespoons per day for adults 12 years and older).[37] Within two days, 93.3% of the elderberry group experienced a significant improvement in symptoms, and complete resolution was achieved by 90% of the group within two to three days. The placebo group did not experience similar improvement or resolution until day six.

A 2004 randomized, double-blind, placebo-controlled study investigated the effect of elderberry juice on cholesterol, triglyceride concentrations, and antioxidant status in young volunteers.[38] In the first arm of the study, 34 participants took three daily doses of 400 mg encapsulated spray-dried elderberry juice (Iprona; Lana, Italy; 10% anthocyanins, equal to 5 ml elderberry juice, processed first by ultra filtration after which the liquid extract is spray dried to a powder using maltodextrin as the carrier), or placebo for two weeks. A subgroup continued for another week to test for resistance to oxidation of low-density lipoprotein (LDL) cholesterol. There was a small, statistically insignificant change in cholesterol in the elderberry group (from 199 to 190 mg/dl) compared to placebo (from 192 to 196 mg/dl). Resistance to copper-induced oxidation of LDL did not change within the three weeks. In the second arm of the study, six participants took a single dose of 50 ml elderberry juice with a high-fat breakfast, and no significant post-meal triglyceride concentrations were observed. The authors stated that low-dose, spray-dried elderberry extract has a minor effect on serum lipids and antioxidative capacity, but that further studies employing higher, nutritionally relevant doses might affect significant postprandial serum lipids.

Based on evidence supporting the cardioprotective role of anthocyanins, a 2009 parallel-designed, randomized, placebo-controlled study was conducted to examine the effect of chronic anthocyanin consumption on biomarkers of cardiovascular disease (CVD) risk and kidney function.[39] Healthy postmenopausal volunteers (n=52) consumed 500 mg per day elderberry anthocyanins (Artemis International; Fort Wayne, IN; 125 mg cyanidin-3-glucoside, extraction method not stated) or placebo for 12 weeks. No significant change in biomarkers of CVD risk was observed and liver and kidney function remained within clinically acceptable ranges. The authors stated that while their findings are consistent with two previous studies that are not directly comparable (elderberry and cranberry [*Vaccinium macrocarpon*, Ericaceae] juices), their findings are inconsistent with two previous studies that showed reduction in CVD biomarkers (using Bing cherry [*Prunus avium*, Rosaceae] anthocyanins) and inflammatory markers (bilberries [*Vaccinium myrtillus*, Ericaceae] and blackcurrants [*Ribes nigrum*, Grossulariaceae]). They explained that differences in study design may explain the inconsistent results because the participants in their trial had lower levels of CVD risk than participants in the other study populations. They also suggested that the difference in inflammatory markers could be a result of this study's examination of high levels of anthocyanin intake over a short period of time rather than long-term intake of anthocyanin-rich foods.

Studies have been conducted on elder in combination with other plant materials investigating their usefulness in a variety of conditions. A 2009 monograph by the American Botanical Council on Sinupret concluded that the "scientific and clinical literature supported [its] pharmacological mechanisms of mucolytic, secretolytic, anti-inflammatory, antibacterial, antiviral, and immunological activity, some of which has been documented in open-label and randomized, controlled human clinical trials."[24]

A small, randomized, crossover, placebo-controlled, single-blinded study performed in 2010 evaluated the laxative efficacy of a combination product that has been available in Brazil since 1926.[40] The product contains fruits of anise (*Pimpenella anisum*, Apiaceae) and fennel (*Foeniculum vulgare*, Apiaceae), as well as flowers of elder and senna (*Cassia angustifolia*, Fabaceae) (Laboratórios Klein; Porto Alegre, Brazil; described only as a "homogeneous mixture of dried botanicals"). Each of the 20 patients with chronic constipation who participated in the study received the compound as a tea (15 g infused for five minutes in 1,500 ml boiling water) or placebo for five days. Following a washout period of nine days during which the patients were free to use other laxatives, the treatment was reversed in the two groups. The number of evacuations in the group receiving the combination tea increased during the use of the tea and significant differences were observed as of the second day of treatment. No adverse effects were observed.

In 2008, authors of an observational study sought to obtain information on the compounds in a food supplement sold as a weight reduction aid to determine its short-term effectiveness and safety as an initiator of lifestyle change.[41] While the name of the supplement was not stated, it consisted of elderberry juice supplemented with elder flower juice (concentrate based on 120 g fresh berries and extract of 3.9 g dried flowers), elder tablets (225 mg berry powder and 600 mg flower extract) three times per day, psyllium (*Plantago arenaria*, Plantaginaceae) two to three teaspoons each morning, and a dose of asparagus (*Asparagus officinalis*, Asparagaceae) tablets equivalent to 40.5 g dried asparagus per day. Participants (n=80) followed a 13-to-15 day protocol after which time their mean body mass index (BMI), weight, blood pressure, physical and emotional well-being, and quality of life had improved significantly. The authors stated that it remained to be established if any of the chemical constituents in the supplements contributed to the efficacy of the diet.

FUTURE OUTLOOK

For generations, European elder flower and elderberry preparations have been labeled and marketed as non-prescription herbal medicinal products available at most pharmacies and drugstores throughout Europe, as well as in countries where traditional European herbal medicines are licensed, listed, or registered (in particular, Australia, Canada, and New Zealand). In the United States, elder preparations are offered mainly as dietary supplements, although some, such as Sambucol Cold & Flu Relief, are listed homeopathic drug products. In recent years, new demand for elder is being driven, in part, by several alcoholic beverage brands offering certified organic elder flower and elderberry liqueurs, schnapps, spirits, and wines that have become trendy in both Europe and America. Moreover, non-alcoholic drinks — including the certified organic BIONADE® (Peter Bier, Ostheim vor der Rhön) Elderberry flavor (entered EU market in 1996) — are sold in conventional, natural, and organic grocery stores throughout Europe and are popular on the menus of cafes, clubs, and bars. The elderberries used in BIONADE products are organically grown in Germany's Rhön region (State of Hesse) and in Lower Franconia (State of Bavaria).

Elder (as elderberry) was the 18th top-selling herbal dietary supplement in the Food, Drug, and Mass Market channel in the United States for 2011.[42] A reported total of $797,915.00 in elderberry products was sold in that channel of trade, down almost 15 percent from 2010.

In a 2003 report, the estimated annual quantity of dried elder flowers wild-collected in Bosnia-Herzegovina was about 44 tons (five percent used domestically and 95 percent exported), and in Romania about 150 tons of elder flowers and 40 tons of elder fruits are wild-harvested annually.[5] A 2010 report by the European Herb Growers Association (Europam) states that elder flowers and fruits remain among the highest volume wild-collected medicinal plants in both Bulgaria and Romania for export trade as well as for domestic herbal tea and phyto-pharmaceutical production.[43] An International Trade Centre study on certified organic wild-collected plants estimated that, in 2005, about 472 tons of elderberries, 19 tons of elder flowers, and six tons of elder leaves were collected according to an organic wild-crop harvesting practice standard.[44] Demand for European elder flower and fruit with sustainability certifications (*e.g.*, Organic Wild and FairWild) appears to be increasing as evidenced by the fact that wild-collection firms are implementing ecological and social standards for elder harvesting in a number of countries, including Albania, Bosnia-Herzegovina, Hungary, Macedonia,[6] Croatia, and the Ukraine.[45] In Croatia, about 75 percent of the wild-harvested elder flowers are traded in the local and national markets, and about 25 percent are exported.[5]

European Elder *Sambucus nigra*. Photo ©2013 Steven Foster

* Sambucol was the initial trade name for the elderberry extract made by Razei Bar Industries in Jerusalem, Israel. Razei Bar was purchased by Health Brands International Ltd. (a private equity company based in the United Kingdom) in 2007. Health Brands International sold the Sambucol rights to PharmaCare Labortories, a Sydney, Australia company, which now markets the brand in the United States. HG

—Gayle Engels and Josef Brinckmann

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dear *reader*

ABC's Reporting on Marijuana, Medicinal Cannabis, Compassionate Use, Legalization, etc.

Perhaps the most groundbreaking news after the US elections last November was that citizens of the states of Colorado and Washington voted to legalize the use of recreational cannabis (*Cannabis* spp., Cannabaceae). Both states previously had legalized medicinal cannabis use, two of 18 total states, plus the District of Columbia.

As many American Botanical Council members and frequent *HerbalGram* readers likely have noticed, our journal has been devoting several pages in recent issues to the growing medicinal cannabis movement, in a new "Cannabis Update" section, home to a series written by associate editor Lindsay Stafford Mader. In this issue, Mader discusses the Israeli government's largely successful and non-controversial medicinal cannabis program, which currently enables almost 10,000 patients to access the herb. Her previous topics include sequencing the cannabis genome, the US government's monopoly on cannabis grown for scientific research, and the medicinal role of non-psychoactive cannabidiol (CBD).

ABC has not always featured such robust cannabis coverage. For many years, we chose not to publish articles on medicinal cannabis, even though we believed the topic was important, compelling, and worthwhile. During that time — in the late 1980s and early '90s — it was our editorial opinion that if we were to have done so, many people might have misinterpreted our mission as being "to legalize pot." And, because we were so passionate about ensuring coverage of many other medicinal plants — *e.g.*, chamomile, echinacea, garlic, ginger, ginkgo, ginseng, milk thistle, mint, turmeric, and hundreds of other traditionally used and scientifically researched plants — we did not want to be painted into the corner of being perceived merely as a marijuana legalization organization, which we are not.

In November 1992, *HerbalGram* published its first medicinal cannabis article ("Government Stops Legitimate Medical Use of Marijuana: Politics Becomes More Important than Science and Humanitarian Concerns") in Issue 26. It dealt with the decision of the administration of President George H.W. Bush to cease issuing new permits for the Compassionate Use program, which had enabled a few dozen very ill patients to have federally legal medicinal cannabis.

Since then, ABC has published approximately 29 *HerbalGram* articles and 97 HerbClips — many authored by longtime HerbClip writer Mariann Garner-Wizard — that discuss cannabis, marijuana, and/or hemp (a non-psychoactive variety of cannabis). The first cannabis-related HerbClip, published in January of 1996, discussed US federal regulators' concerns about a new Adidas shoe made with hemp. ABC's e-newsletter HerbalEGram also has published dozens of cannabis-related stories, featured book excerpts, and media news links.

The argument for legalization of medicinal cannabis, and even decriminalization of recreational use, has supporters in all areas of the political spectrum. This includes the late noted conservative William F. Buckley, and, later, retired libertarian Congressman and presidential candidate Ron Paul (a physician), among others. Retired liberal Massachusetts congressman Barney Frank joined with Paul to introduce a bill before Congress that sought to end federal cannabis prohibition so that states could make their own decisions regarding cannabis legalization, and comedian Bill Maher has been forthright about his cannabis use for years. As stated by Lieutenant Governor of California Gavin Newsome, a probable candidate for governor and a stated non-user who favors decriminalization, "These laws just don't make sense anymore. It's time for politicians to come out of the closet on this."

There is obvious growing social demand for and acceptance of medicinal cannabis, and for this, and other reasons, ABC has increased its cannabis coverage in recent years. Now, more than 20 years since our first cannabis story, we have decided to recognize this important plant with the first-ever *HerbalGram* cannabis cover, featuring a beautiful image by photographer Johnny Wiggs.

Other herb organizations also are dealing with cannabis. The American Herbal Pharmacopoiea is developing a Standards Monograph and Therapeutic Compendium — the first of its kind in North America — and the American Herbal Products Association's Cannabis Committee just released draft recommendations for regulators on the legal dispensation of medicinal cannabis.

As members of the medicinal cannabis community continue to work on quality standards, scientific research, and legal advocacy, ABC will maintain its medicinal cannabis coverage. From our perspective, cannabis is just another medicinal plant — one with a compelling history and an apparently promising future.

Mark Blumenthal

ABC Advisory Board

Each issue of *HerbalGram* is peer reviewed by members of the ABC Advisory Board and other qualified experts before publication.

HERBALGRAM

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Cannabis *Cannabis sativa*. Photo ©2013 Canndoc Ltd.

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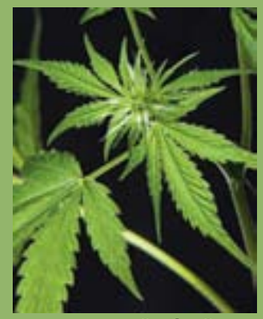

On the Cover
Cannabis *Cannabis sativa.*
Photo ©2013 Johnny Wiggs

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Employee Profile: Jenny Perez

Former Bastyr Herb Garden Manager Joins ABC as New Education Coordinator

Community herbalist and budding horticulturist Jenny Perez joined the American Botanical Council team in September 2012 as the organization's new education coordinator. A native Texan, Jenny is now back in Austin after living in Seattle, where she worked as Bastyr University's longtime herb garden manager and director of the holistic landscape design program, which she helped create. Although the climates of Texas and the Pacific Northwest are obviously dissimilar, Jenny remains in her element, surrounded by plants and educational opportunities.

"I'm a plant geek," she said. "I can't help but be passionate about what I've learned and be eager to share it. Plants [are] a practical aspect of human existence, really. Without plants, we don't have a whole lot."

Jenny, who grew up in San Antonio, was first exposed to natural medicine when she moved to Austin after high school and took a job as a receptionist at Austin Health Associates, a cooperative of natural healthcare providers that included herbalists, chiropractors, and massage therapists. It was through this organization that Jenny met her first herb teacher and became curious about the healing properties of plants.

"I became very interested with what [the herbalist] was doing with his clients," she said. "I noticed that he had people coming in with some serious health problems, but they were getting results through herbal therapies. My perception began to change in terms of healthcare. Before long, I just started to insert myself wherever people were working with plants … whether it was gardening or using them as medicine."

While working at the healthcare clinic in her early 20s, Jenny volunteered a couple of days each week at local institutions, including the Lady Bird Johnson Wildflower Center and the American Botanical Council.

"It was just a short period of time, where one day a week I was working with the [ABC] gardener and one day a week I was filing papers. It was when I was filing that I came across a flyer that read, 'Brand New at Bastyr: The Herbal Sciences Bachelor of Science Program,'" she explained.

Although she was planning to attend school in Arizona and was concerned about the state of herbalist certification programs in the United States — which does not allow herbalists to become licensed healthcare providers, as is the case in some other countries like the United Kingdom — the Bastyr program piqued her interest. "I knew I was going to take a leap of faith that could potentially lead to nowhere. My dad curiously questioned, 'What do you want to go study that for?' It's a private college with a big price tag, but I could not stop thinking about it. I re-enrolled in [Austin Community College], and got all of my basic sciences done and moved [to Seattle] to study," she said.

After completing Bastyr's herbal sciences undergraduate program, Jenny accepted a job as the herb garden manager, a position she held for seven years. While there, Jenny taught student interns in the federal work-study program and transformed the University's 5,000-square-foot herbal garden into a living laboratory.

"I taught them about horticulture, herb harvesting, herb drying, vegetable growing, and vegetable harvesting," she said. "Not only did I supervise the students, but I began to fill in the gaps that I observed there. We were able to slowly chip away at what herbs grew really well in our garden that we could gather as educational experiences, dry them, and then use them for students in their medicine-making labs. And not only was that an experience for them with local medicine, but we were saving money. So that was something I developed over time with the help of my supervisor."

ABC Special Projects Director Gayle Engels, who first met Jenny 15 years ago at Austin Health Associates, described her as very personable and organized. "Jenny has a real commitment to herbal education and an abiding love for people and plants and their connection," said Engels. "She has already proposed a number of ideas for improvements in ABC's internship program, the interns love working with her, and I have no doubt that she will continue to be an outstanding addition to the ABC family."

At ABC, Jenny continues to share her passion for plants with dietetic students from Texas State University and the University of Texas at Austin, and pharmacy students from the University of Texas at Austin. In December, she finished training her first rotation of ABC interns.

"I'm very fresh into that process, but it's fun and challenging in a whole different set of ways," she said. "I'm not teaching people that are already in the know, I'm teaching people who have never experienced herbal medicine before. It is exciting to introduce students to the many ways culinary herbs and medicinal plants can be used practically and therapeutically," she said. "What I often tell students is that I'm waiting for the scientific method to catch up with tradition. I can't say that I have converted anybody, but there was definitely some give in their perspective of where herbs fit in natural healthcare approaches."

Jenny, who came to ABC with a background in and passion for horticulture, in addition to plant medicine, is looking forward to providing a unique educational experience for student interns, volunteers, and visitors. "You can't have an herbal extract without a garden or without botany to properly identify it and know how to collect it," she said. "That's where I feel that my blending of herbal medicine and horticulture is a really strong match because you really can't have one without the other."

Just a few months into the job, Jenny is thankful for the opportunities that led her back to ABC. "I like plants and I want other people to create a relationship with plants, so I just try to be open and approachable," she said. "I'm excited about the realization that I have almost on a daily basis about how plants are changing my life and the lives of people I know. You can be 50 years old and have never had a feeling of what it is like to be doing something that you feel meant to do. And I feel lucky, because I think this is it." HG

—Tyler Smith

American Botanical Council Enters 25th Year

On November 1, 2012, the nonprofit American Botanical Council (ABC) entered its 25th year of education and research on the science-based health benefits of herbs, medicinal plants, and other beneficial plant-based ingredients. The independent research and education organization was established in 1988 by Founder and Executive Director Mark Blumenthal, along with noted ethnobotanist James A. Duke, PhD, and the renowned late pharmacognosist Professor Norman R. Farnsworth, PhD.

Remarking on the occasion, Dr. Duke said, "I am pleased and proud to see ABC approaching that monumental 25-year milestone. Nice work. It is so much bigger and better than I envisaged 24 years ago, thanks to Mark, of course, and the dedicated staff."

Blumenthal and Drs. Duke and Farnsworth came together to form ABC as a means of supporting *HerbalGram*, the seminal publication for which the nonprofit is most well-known. Since those first years of ABC, *HerbalGram* has grown from a grassroots newsletter into a full-fledged, peer-reviewed, quarterly scientific journal. ABC's 25th year will see *HerbalGram* celebrate 30 years of publication, with the 100th issue going to print in late 2013.

"ABC started as a means of supporting *HerbalGram*, which at that time was a newsletter for many people in the disparate herbal community," said Blumenthal. "Now in our 25th year, *HerbalGram* has not only surpassed all expectations in terms of quality, relevancy, and impact on the herbal community internationally, but its success has allowed ABC to branch out and create many new means of fulfilling our unique educational mission.

The number of ABC-produced publications continues to increase. One that also celebrated a major milestone is HerbClip™, which turns 20 in 2013. For two decades, HerbClip has offered summaries and critical reviews of seminal articles covering medicinal plant-related clinical research, regulations, marketing information, and conservation and sustainability. HerbalEGram, the monthly e-newsletter for ABC members, entered its tenth year in 2013, and with it came a new design. ABC's recently introduced weekly e-newsletter, Herbal News & Events, will commence a second year of keeping ABC members and supporters up-to-date on events, conferences, and news stories that are relevant to the herbal community.

In addition to using the written word to educate the public on the responsible use of herbal and other plant-based ingredients, ABC helps steward the next generation by offering internships for pharmacy, dietetic, botany, horticulture, journalism, and marketing students at its Austin, Texas headquarters. 2013 marks the 15th year that ABC has called the Case Mill Homestead "home." The 2.5-acre complex boasts 27 herbal theme gardens where medicinal plants are cultivated to help educate interns as well as the general public through tours and events like HerbDay. HerbDay is a coordinated series of independently produced public education events that celebrate the importance of herbs and herbalism. Each year, ABC opens its gardens for a full day of herb walks, lectures, children's activities, and plant and book sales. The 8th annual HerbDay will be held on May 4, 2013.

An increasingly digital world also has led ABC to expand its education methods online. The information-rich website, www.herbalgram.org, is constantly growing with new articles and information. ABC recently added a new database to its online resources: *The ABC Clinical Guide to Herbs*, ABC's highly praised reference book, is now available through ABC's website, allowing members to search through therapeutic monographs and clinical study details on 30 best-selling herbs. What barely could have been imagined when *HerbalGram* first began and ABC was founded is now a reality with the addition of a digital, flip-page version of the journal. The insightful articles and full-color photographs found in each physical edition of *HerbalGram* have been faithfully rendered online to create a seamless digital experience on a smartphone or tablet computer.

ABC's 25th year will feature the continued growth of two major research projects. In 2011, ABC collaborated with the American Herbal Pharmacopoeia (AHP) and the University of Mississippi's National Center for Natural Products Research (NCNPR) to address the accidental and intentional adulteration of botanical dietary ingredients. Dozens of underwriters and supporters have come together to sustain the program. To date, the ABC-AHP-NCNPR Botanical Adulterants program has published four articles on botanical adulteration, all of which appeared in *HerbalGram* and are available online. Four additional adulteration articles are slated for this year. In 2013, ABC also is planning to publish a book by Blumenthal and Jay Pierotti, PhD, on solvents used in the manufacture of botanical extracts, food flavors, and natural food ingredients.

Steven Foster, author, photographer, and chairman of ABC's Board of Trustees, said, "For nearly a quarter century, a time in which we've seen herbal product sales in the United States increase by an estimated ten-fold, and perhaps more scientific research on medicinal plants published than in the previous 200 years, the American Botanical Council has been at the international forefront of serving as the primary vehicle for bringing truthful information on the benefits and risks of herbs to the research community, health professionals, industry, the media, and consumers. Through its widely respected journal *HerbalGram*, HerbClip service, dozens of special publications, and media communiqués, ABC is the premier go-to source for cutting-edge knowledge in the modern herbal renaissance."

"It would be easy to look back at all we've accomplished so far and think, 'We're already doing so much for the herbal community,' and not push ourselves to do more," said Blumenthal. "But the drive to do more than the status quo is integral to the spirit of ABC. I look forward to everything we will do in our 25th year and beyond for the following decades." HG

—Sara O'Connor

2012: A Year of Progress and Growth at ABC

At its very core, the American Botanical Council's (ABC) mission centers on the enhancement of public wellbeing by improving the lives of people and the world through increasing the quality and quantity of information on the responsible uses of medicinal plants and related beneficial plant materials. In 2012, ABC continued to work toward that goal by promoting the use of herbs, essential oils, teas, and other beneficial botanicals for responsible healthcare and self-care on a global basis. ABC's approach is based on a unique, ever-improving, and expanding mix of educational services, including printed publications, a searchable website, online databases, public lectures, media education, consulting and research services, an online bookstore, herbal demonstration gardens, an internship program, and more.

These services reach a broad array of constituents — more than 3,000 ABC members and tens of thousands of additional consumers in 81 countries. They include the following areas of stakeholders: consumers, healthcare practitioners, researchers, educators, professionals from all segments of the natural products and health industry, government employees, and members of trade, local, and national media.

Below is a brief look at some of ABC's activities and accomplishments in 2012.

New Staff

ABC welcomed Jenny Perez, a former ABC volunteer, as the new education coordinator (see Employee Profile on page 14). Jenny came to Austin from Bastyr University, where she taught medicine-making classes to naturopathic students, as well as an undergraduate course called "Herbs and Food" and a series on "Medicinal and Edible Plants in the Landscape." Jenny also created and led the Holistic Landscape Design certificate program, which combined permaculture design, biodynamic agriculture, and landscaping.

In 2012, in an effort to increase services to and communication with our members, ABC added a communications and marketing position that was filled by Sara O'Connor. In addition to her degree in radio and television, Sara brings with her years of nonprofit experience and a gift for communicating through multiple channels, including video, the Internet, social media, and print.

Mary Ceallaigh joined ABC in late 2012 as the new executive assistant to ABC's Founder and Executive Director, Mark Blumenthal. Mary has a bachelor's degree in Human Development, is a certified yoga instructor, and has a passion for health and wellness.

Three New Benefits for ABC Members

In 2012, ABC put its highly respected reference book, *The ABC Clinical Guide to Herbs*, on its website at www.herbalgram.org, making it ABC's 8th searchable database available to ABC members. Used for years by educators, researchers, practitioners, industry members, and others, the content contained in *The ABC Clinical Guide to Herbs* database provides extensive therapeutic monographs and clinical study details on 30 popular herbs in the United States.

In response to demands for increased information about what's happening in the herbal community, ABC also created a new publication for its members in 2012. Published weekly, ABC's Herbal News & Events provides updates on conferences, symposia, webinars, and other educational opportunities, as well as links to recent herb-related media stories from around the world.

ABC also improved its highly acclaimed, peer-reviewed *HerbalGram* in 2012 by making the journal's content available online in a gorgeous, full-color, page-flip version or by PDF, which ABC members can access on their smartphones, tablets, and computers.

New Garden

ABC added a Sacred Seeds Garden to its more than 25 onsite herbal demonstration gardens. This garden is part of the international Sacred Seeds effort to conserve, through planting and harvesting, seeds that are historically important to a region. ABC's Sacred Seeds Garden focuses on medicinal plants used traditionally by Native Americans and early Mexican and European settlers in the Central Texas region. This garden is becoming an important part of ABC's educational services to dietetic and pharmacy interns, and many visitors including the general public, herbalists, and other health professionals.

Supply-Chain Integrity Programs

ABC continued making progress on its newest programs, including the American Botanical Council-American Herbal Pharmacopoeia-National Center for Natural Products Research (ABC-AHP-NCNPR) Botanical Adulterants Program, and the ABC Solvents Reference Book Project. Both of these educational efforts seek to improve the integrity of the global herb supply-chain in order to help ensure that consumers have access to clean, accurately identified, safe, and beneficial herbal products.

In 2012, the ABC-AHP-NCNPR Botanical Adulterants Program produced three extensively peer-reviewed articles focusing on the adulteration of bilberry (*Vaccinium myrtillus*, Ericaceae) extract, skullcap (*Scutellaria lateriflora*, Lamiaceae) herb, and so-called grapefruit seed extract. All are available for free on ABC's website.

ABC solicited and organized constructive comments from 25 international peer reviewers in academia, government, and industry, which have helped shape the development of an ABC Solvents Reference Book. The newest draft, which will undergo a second round of peer review in 2013, includes additional text and graphics to make the book more readable and engaging. ABC hopes to publish the book this year.

Ongoing ABC Educational Activities

Media education continues to be an important feature of ABC's educational mission. In 2012, ABC fielded approximately 50 media requests. Serving as a reliable third-party resource makes it possible for ABC to help the media better understand and interpret the scientific data surrounding herbs and other beneficial botanicals.

Blumenthal delivered 45 lectures on issues concerning the botanical and natural products industry. Traveling more than 60,000 miles, he visited 19 different cities, including Shanghai and Beijing, where he made presentations on quality control issues — particularly problems related to adulteration of botanical materials.

ABC's 2012 internship program trained 17 pharmacy and dietetic interns from sixth-year pharmacy school and graduate dietetic programs. At ABC, interns learn from knowledgeable professionals, conduct research on herbal topics, work with herbs in ABC's gardens, and prepare herbal teas, tinctures, salves, and other remedies. For many of these students, ABC's internship was their introduction to the traditional lore and science behind botanicals and herbal medicine.

New Awards for 2012

Blumenthal was honored to receive two awards in 2012. He was named one of the first Honorary Advisory Board Members of the Lloyd Library and Museum in Cincinnati, Ohio. Blumenthal also was named a Natural Legend by New Hope Natural Media for his significant contributions to the natural products community.

Each year, ABC presents awards recognizing excellence in the herbal community. In 2012, ABC created two categories for its James A. Duke Excellence in Botanical Literature Awards: Consumer/Popular and Reference/Technical. At the 7th annual ABC Celebration and Awards Ceremony in March 2012, Bharat Aggarwal, PhD, received the Consumer/Popular category award for his book *Healing Spices: How to Use 50 Everyday and Exotic Spices to Boost Health and Beat Disease*. Roy Upton received the Reference/Technical category award for the American Herbal Pharmacopoeia's *Botanical Pharmacognosy: Microscopic Characterization of Botanical Medicines*. In addition, Bioforce AG received the ABC Varro E. Tyler Commercial Investment in Phytomedicinal Research Award, and Professor Djaja Doel Soejarto, PhD, was awarded the ABC Norman R. Farnsworth Excellence in Botanical Research Award.

ABC Publications

Providing high-quality and reliable science-based information is an essential component of ABC's educational mission. In 2012, with the addition of its newest publication Herbal News & Events, ABC dramatically increased the number of publications and the amount of content available to ABC members. ABC published the following:

- Four issues of the quarterly publication *HerbalGram*. Topics covered include the following: numerous Research Reviews — including pelargonium (*Pelargonium sidoides*, Geraniaceae) use for acute bronchitis in children and the use of butterbur root (*Petasites hybridus*, Asteraceae) extract for migraines — medicinal cannabis (*Cannabis* spp., Cannabaceae) updates; articles on adulteration of bilberry, skullcap, and so-called "grapefruit seed extract;" a seminal article on herb regulation; an update on the controversial ingredient DMAA; and much more.
- 12 issues of the monthly publication HerbalEGram. This e-newsletter includes original articles by ABC editorial staff, updates on community news, links to current media stories and events, and a featured book section.
- 360 HerbClips. ABC publishes 15 HerbClips twice per month containing summaries and critical reviews of recent clinical trials and other publications relevant to the herbal community.
- 29 issues of ABC's newest publication, Herbal News & Events. In addition to providing media updates, this weekly e-publication provides information on upcoming conferences, webinars, seminars, and other events.

Anniversaries and Milestones

In 2012, ABC entered its 25th year of operation. Originally founded to support the publication of *HerbalGram*, ABC has grown tremendously over the years, both in terms of the quantity and quality of the educational services it provides and the number of individuals benefiting from those resources.

ABC is looking forward to continuing to provide high-quality, peer-reviewed information to the herbal community and invites its members and stakeholders to help it celebrate some exciting upcoming milestones in 2013:

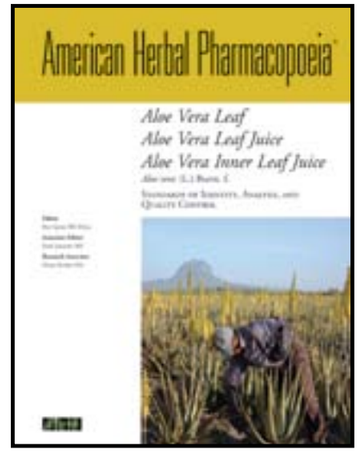
- ABC will move into its 26th year as it celebrates its official 25th birthday.
- ABC will publish the 100th issue of its acclaimed journal, *HerbalGram*.
- *HerbalGram* will celebrate its 30th birthday.
- HerbClip will turn 20.
- And, HerbalEGram, ABC's monthly e-newsletter, will observe its 10th anniversary.

More information on becoming an ABC member and supporting ABC's unique nonprofit educational mission is available by contacting ABC at 512-926-4900 or development@herbalgram.org. HG

—Denise Meikel

AHP Releases Quality Control Standards Monograph for Aloe Vera

The American Herbal Pharmacopoeia (AHP) has published its 34th monograph, which features quality control standards for aloe vera leaf, leaf juice, and inner leaf juice. The monograph focuses on commercially available *A. vera* plant materials, and also includes information on additional species in the genus *Aloe* (Xanthorrhoeaceae).



Each AHP monograph serves as an authoritative guide for verifying botanical purity and identification, and establishes quality and composition guidelines to be used for fulfilling Good Manufacturing Practice (GMP) requirements. Additionally, the monographs provide details on the historic uses of the herb, photographs and images for identification purposes, as well as information regarding physical and chemical analytical methods.

According to the AHP monograph, released on December 18, 2012, "The plant genus *Aloe* has a history of economic and medicinal use that spans thousands of years and is the source of some of the oldest-known herbal medicines."[1] AHP addresses three parts of the aloe vera plant, sometimes referred to by its synonym *A. barbadensis*, including the leaf, leaf juice, and inner leaf juice. Over the past two decades, both aloe vera leaf juice and gel have become popular botanical materials.[2] The monograph will be of use for individuals and organizations that use aloe vera, including suppliers, manufacturers, researchers, regulators, and government agencies.

"I am ecstatic that AHP is the first pharmacopoeial standard developed for aloe vera leaf and inner leaf juice as these are important herbal products worldwide," said AHP Executive Director Roy Upton in the organization's press release.[2]

AHP received support for the monograph from the International Aloe Science Council (IASC), a nonprofit trade organization based in Silver Spring, Maryland. "AHP worked collaboratively with IASC to establish the standards as a way to establish a clear benchmark of quality and purity," said Upton (email, January 8, 2013). "AHP maintained complete editorial control over the entire process and content. The monograph was then subjected to peer review by IASC and industry experts, as well as a host of independent academic aloe experts."

The AHP aloe monograph provides much-needed information and guidance on the potential carcinogenicity of some orally ingested aloe vera material, which was brought into question by a 2011 report from the National Toxicity Program (NTP). In a two-year study, the NTP found a link between non-decolorized whole leaf extract and tumors of the large intestine in mice and rats.[3] However, the aloe vera material used in the study contained high amounts of the anthraquinone compound aloin.

"Some of these products averaged 6,300 ppm [parts per million] of aloin A and are completely different than many aloe vera juice products on the market that limit aloin to less than 5 ppm," Upton stated in the press release.[1] "I am happy that we can clarify the distinctions between the high-aloin-containing products for which safety concerns have been noted and help establish the standards for ensuring identity, purity, quality, and safety of aloe juice products."

The therapeutic compendium section for the AHP aloe monograph — a component which will contain pharmacological and clinical data on various types of aloe materials that usually is released with AHP quality standards monographs — is anticipated to be developed in the near future, according to the press release.

"We look forward to developing the therapeutic compendium, both because we like having a complete dossier for every herb we monograph but also because there are a number of studies showing the health benefits and establishing the safety of aloe vera juice that meet the AHP-IASC standards," Upton told the American Botanical Council in an email. "It would be good to get this information out there so consumers can make a clear distinction between products yielding high levels of anthraquinones and those that meet AHP-IASC standards and yield less than 10 ppm aloins."

The monograph for aloe vera leaf, leaf juice, and inner leaf juice is available through AHP's website at www.herbal-ahp.org. PDFs are available for $35.95, and printed four-color versions can be purchased for $44.95. HG

—Tyler Smith

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AHPA Launches New Botanical Authentication Wiki

The American Herbal Products Association (AHPA) announced in late October 2012 the launch of a new, collaborative, wiki-style website designed to provide information on botanical authentication techniques, including many industry-provided microscopy images and other identification tools.[1] The AHPA Botanical Authentication Wiki, currently in beta format, features authentication resources for more than 120 botanicals, a number that is expected to grow.[2] It is available at www.botanicalauthentication.org.

"The AHPA Botanical Authentication Wiki is a centralized source of information containing both examples and techniques [that] have been successfully applied to authenticate and qualify selected botanical materials," explained Merle Zimmermann, PhD, AHPA's information analyst (email, November 29, 2012). "These techniques are provided as a service to the trade and to further the production of high-quality botanical commodities."

In addition to providing a collaborative and expanding database of authentication tools, the move to a wiki-format allows for easier IT maintenance and a layout that is likely familiar to users, due to the worldwide popularity of the free online encyclopedia Wikipedia.

"The site is run using the same MediaWiki software which powers Wikipedia…. This reduces training requirements and effort needed for staff and editors when contributed material is added to the site," said Dr. Zimmermann. "This said, the site is not open for general editing, as Wikipedia is. There is a limited select group of editors with access to posting material on the site, including AHPA staff members and authentication volunteered to participate during the initial alpha site development."

As such, registered users are provided only with viewing access, but contributions from qualified individuals are encouraged. Contributor forms are available through the site, which allow users to submit their own information that is then reviewed by the expert advisory committee.

"The site is a technical reference tool directed towards botanical authentication experts, so the material discussed and presented in the entries are put forward for this particular type of user, who is already an expert, and who is using the site as part of a multifaceted toolkit of authentication resources," added Dr. Zimmermann. "It is not intended or directed towards the use of the general public, and presumes a certain level of experience in the authentication arena."

From the wiki's homepage, registered users can access a variety of authentication resources, such as macroscopy and microscopy images, data on high-performance thin-layer chromatography (HPTLC), practicals or white papers, and AHPA's Known Adulterants Guidance list, which the organization has been publishing since 1997.[3]

The Known Adulterants Guidance section includes herbs such as black cohosh (*Actaea racemosa,* Ranunculaceae) root and rhizome, *Ginkgo biloba* (Ginkgoaceae) leaf, hoodia (*Hoodia gordonii*, Apocynaceae) aerial parts, skullcap (*Scutellaria lateriflora*, Lamiaceae) flower, and bilberry (*Vaccinium myrtillus*, Ericaceae) fruit, among others. Each entry is linked to an expansive database of authentication tools, including botanical images from supporting industry organizations.

Just a few months old, the site already has been well received by many industry members. "User responses have been quite positive," said Dr. Zimmermann. "We've received a good amount of correspondence from our target audience of industry experts inquiring about access, as well as management members and small business owners who would use the tool along with their own or contracted specialists to improve efficiency and get more and better analysis done with the same amount of starting resources."

As more resources become available, AHPA's website will become an increasingly important authentication tool for industry members. "AHPA is to be congratulated for producing this important new quality control resource," said American Botanical Council Founder and Executive Director Mark Blumenthal. "The Botanical Authentication Wiki will someday become a widely used resource for companies in the herbal products industry, both in the United States and internationally, and will significantly help enhance industry efforts to ensure proper identity of botanical raw materials."

The AHPA Botanical Authentication Wiki currently is sponsored in part by Alkemists Laboratories and CAMAG Inc., both of which have provided authentication tools that are featured throughout the site. Such professional laboratory-sponsored images, techniques, and information are noted with a small logo in each section.[4]

As the site is still in its infancy, APHA continues to invite feedback. Specifically, the organization is welcoming ideas for the next botanicals it will feature on the site. For more information or to submit botanicals of interest, AHPA contact information can be found at www.ahpa.org/Default.aspx?tabid=62.

Dr. Zimmerman hopes the site will allow for quicker and improved access to authentication tools, a main goal of AHPA's Botanical Authentication Program. "The turnaround time between a cutting-edge botanical becoming important to the industry and authentication methods being developed and shared can … be reduced compared to a paper-and-ink publishing schedule," he said. "The site on its own [is] not, in this beta form, currently an exhaustive reference on all authentication topics, but it stands as a quick resource for consultation, allowing for savings and increased productivity for these experts." HG

—Tyler Smith

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James Simon Honored with Scientific Excellence Award from Presidentially Appointed BIFAD Council

About five times each year, James Simon, PhD, a professor of plant biology at Rutgers University, travels from New Jersey to Africa to implement projects that improve the lives of rural villagers through fruit, vegetable, and medicinal plant production. Since 1999, he has made more than 40 trips to Africa and taken about 30 additional flights to and from locations within the continent. His work training educators and scientists, non-governmental organizations, community growers, and associations of women farmers has helped to create hundreds of jobs and enabled communities to make higher profits on the plants they cultivate and process.

In September 2012, Dr. Simon — an American Botanical Council Advisory Board member — was honored for his work with the Award for Scientific Excellence in a US Agency for International Development (USAID) Collaborative Research Support Program (CRSP) from the Board for International Food and Agricultural Development (BIFAD).[1] An advisory group appointed by the President of the United States, BIFAD councils USAID, which President John F. Kennedy established in 1961 to provide foreign assistance that encourages economic prosperity, democracy, human rights, and other goals.[2]

Dr. Simon's excitement for the award — which he currently has hanging on his office wall — is balanced with a humility about his work; he credited the contributions of other individuals and groups, as well as the larger medicinal plant community.

"When you work in horticulture with aromatic and medicinal plants, versus the millions of acres in corn and soybeans, you just never anticipate getting any kind of national recognition along that line," said Dr. Simon, who is the director of Rutgers' Center for New Use Agriculture and Natural Plant Products (oral communication, November 26, 2012). "I was just so pleased that they considered me for this, and also because it reflects the reality that horticultural crops and aromatic and medicinal plants can truly lead to income generating activities, empower those involved, and such systems can be both scaled-up and replicated. I was very proud because it recognized my work, yet also realized that my work is dependent on all those people with whom I work, that I view it as an award for all those involved."

According to BIFAD, the awards committee chose Dr. Simon due to "his significant contributions to improving horticultural crops across the value-chain in several African countries," particularly for "his work [that] had an important impact upon thousands of small-holder farmers by connecting these farmers to higher-return markets, which led to over $25 million in trade to growers and processors during the five years of the project."[1]

Just one day after speaking with ABC about the BIFAD award and his career, Dr. Simon caught a plane to Zambia, where he held training sessions with small-sized community farmer associations on vegetable cultivation, production technologies and strategies, harvesting, post-harvest handling, and processing. He also met with partnering organization AgriBusiness and Sustainable Natural African Plant Products (ASNAPP), which he co-founded to focus on using a country's indigenous plants to economically develop impoverished villages.[3]

James Simon at a spice market in Sanniquellie, Liberia. Photo ©2013 Simon

Dr. Simon currently is leading or involved in four projects in Africa. One, in Ghana, has focused on higher-value forest commodities, spices, and medicinal and aromatic plants. In Zambia, Dr. Simon and partners have been introducing the production of fresh vegetables, often working with potential high-end buyers like hotels, as well as training disabled heads-of-household, such as blind farmers. Another project, in Zambia, engages communities to become involved in affordable post-harvest cooling systems, which consist of creative ways to preserve produce from spoiling, such as growing near markets, ensuring shade is used from the moment the product is harvested to where it is sold, using the natural cooling temperature of the earth in old-fashioned root cellars (where land and water tables permit), and — in concert with the Horticulture CRSP leadership — introducing low-cost coolers. The fourth project, which is led by Rutgers and Purdue University, focuses on indigenous African vegetables, including amaranth (*Amaranthus* spp., Amaranthaceae), nightshade (*Solanum* spp., Solanaceae), and spiderplants (*Chlorophytum comosum*, Asparagaceae), as well as hibiscus leaves and calyces (*Hibiscus* spp., Malvaceae) and moringa leaves (*Moringa oleifera*, Moringaceae).

All of these projects, Dr. Simon said, aim to help African farmers obtain improved production strategies, like reducing pests and drying herbs to increase shelf life, as well as providing access to higher-return markets, such as larger neighboring villages or supermarkets in sizeable towns, so that they can increase profits and thus create successful horticulture businesses. Most growers typically sell the same fruits, vegetables, and medicinal plants year-round and also sell their products to markets and small shops within their villages. Thus they often sell to customers who have as little money as they do, said Dr. Simon.

"We're trying to introduce concepts and approaches to have them view horticulture as a business and not just something they do to keep them busy," he said. "We use a market-first, science-driven model in our work and these models have taken years to develop and remain dynamic even today. Many farmers in Africa can't invest because they're just trying to survive. We're trying to work with them to develop their business skills and investment skills to get them out of that cycle of 'let's just plant more, even if we're not planning better.' The goal is at the end of the year, they made more money than last year, and they can send their children to school and increase their family earnings so they become both food secure, economically secure, and healthier through increased consumption of high-quality nutritious vegetables."

Dr. Simon first traveled to Africa when he was a faculty member at Purdue. During that time, he was awarded a Master Research License with the National Cancer Institute and began working on a cross-institutional project — which also included the Missouri Botanic Garden, and Professor Harry Fong, PhD, and the late Professor Norman Farnsworth, PhD, both of the College of Pharmacy at the University of Illinois at Chicago — to develop sustainable collection practices for *Ancistrocladus korupensis* (Ancistrocladaceae), a plant from the southwestern region of Cameroon that exhibited promising activity against the AIDS virus.

"It brought me to sub-Saharan Africa for the first time, and I fell in love with Cameroon and this type of project," he said.

Dr. Simon has been working on these projects in Africa since the early 1990s and has encountered many challenges along the way. These include identifying the right communities, organizations, and partners who are interested in working together on projects, as well as balancing different expectations and rewards, and developing strong working relationships.

"Ensuring and building trust and confidence between international partners and collaborators is always a massive challenge," said Dr. Simon. "It takes a long time to develop strong, true, productive working relationships."

And although he cited long-term resource support as an additional challenge, Dr. Simon has been commended on his ability to secure funding over these decades. "[Dr. Simon] works with stakeholders from farmers to university professors to help develop the industry of natural plant products for income generation for the benefit of Africans," said Roldolfo Juliani, PhD, a research associate in Rutgers plant biology department who has known and worked with Dr. Simon for over 10 years, adding that his colleague "is very talented at obtaining grants that can be used to achieve development goals" (oral communication, November 28, 2012).

"Jim is a real dynamo," said ABC Founder and Executive Director Mark Blumenthal. "He is one of the most active and prolific people dealing with medicinal and aromatic plants I have ever known in the academic community, and is a valuable member of the ABC Advisory Board. He is truly deserving of this prestigious award." HG

—Lindsay Stafford Mader

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CONSERVATION

TRAFFIC and Partners Pilot Sustainable Medicinal Plants Project in Vietnam

For nearly two years, TRAFFIC has been implementing a unique medicinal plant project in Vietnam — the conservation organization's first-ever initiative in this Southeast Asian country.[1] The project, which began in June 2011 and will conclude this May, seeks to implement sustainable harvesting of threatened medicinal plant species in the South Xuan Lac Species and Habitat Conservation Area, as well as to better the livelihoods of the local villagers who collect and sell these herbs. Partners in management and execution of the project include the Bac Kan Forest Protection Department and People Resources and Conservation Foundation (PRCF), with additional support and funding from the Critical Ecosystem Partnership Fund.

According to a 2006 Hanoi University of Pharmacy paper, Vietnam has "highly diverse climatic and geographical zones," giving the country "a very rich and diverse biodiversity, including a large number of medicinal plants, of which about 3,948 species are registered."[2] In addition to this natural botanical abundance, the Vietnamese people, especially those who live in mountainous regions like the location of TRAFFIC's project, also have a deep history of traditional medicine.

"Medicinal and aromatic plants play an important role in the day-to-day lives of many Vietnam communities, especially those in rural areas and villages," said Djaja Doel Soejarto, PhD, a professor of pharmacognosy and biology at the University of Illinois - Chicago (email, November 11, 2012). Dr. Soejarto has conducted ethnobotanical surveys in Vietnam with the aim of discovering bioactive compounds for pharmaceutical development. He noted that some groups use up to 400 different plant species in 200 traditional prescriptions — available in local markets and through village healers — and dozens of plant species also are used in some hospitals and healthcare institutions.

This widespread medicinal plant usage and growing commercial trade demand, particularly from China, has led to decreases in some Vietnamese plant populations due to unsustainable harvesting.[1] TRAFFIC and its partners chose to implement its project in the South Xuan Lac Species and Habitat Conservation Area in northern Vietnam because it has experienced such biodiversity loss. According to PRCF, "Limited law enforcement activities, coupled with the protected area being considered by local communities as an open access resource, have resulted in highly unsustainable and deleterious forest usage practices."[3]

The project's first goal was to introduce a successful sustainable harvesting program based on the FairWild Standard, a set of principles and criteria that address ecological, social, and economic requirements for sustainable wild collection from the FairWild Foundation. (TRAFFIC has implemented similar FairWild medicinal plant projects with success in several countries, including Cambodia and Nepal.)

"The connection with FairWild is a promising one," said Uwe Schippmann, head of the Department for Plant Conservation at Germany's Federal Agency for Nature Conservation (email, December 10, 2012). "FairWild-certified products are now finding their way to the shelves of the shops, *e.g.* through Pukka Herbs in Britain and Traditional Medicinals in North America. The use of medicinal plants in Vietnam is not only important for local communities with respect to their income and healthcare situation, [Vietnam] is also a significant exporter of medicinal plants."

After holding community meetings with villagers and local authorities, TRAFFIC and its partners selected four medicinal plant species from the ginger family (Zingiberaceae) —*Amomum villosum* and *A. xanthioides,* which are used as antipyretics and diuretics, and *Alpiniamalaccensis* and *A. latilabris*, which are used for stomach conditions — to assess for growth-rate and regeneration capacity, as well as market-trade chains and increased market access opportunities for local harvesters.

"A resources assessment was produced which has provided critical information for local harvesters as to where they can sustainably harvest these species as well as local measures they will need to enact in order to protect the ecological areas buffering these population centers," said Nguyen Thi Mai, forest trade officer of TRAFFIC's Southeast Asia-Greater Mekong Programme (email, November 8-December 17, 2012).

Then, in order to train the villagers on sustainable harvesting techniques, TRAFFIC held several workshops discussing medicinal and aromatic plant (MAP) biodiversity, including an introduction to endangered MAP species in the project area, threats to these resources, how to identify the target species, and value-addition processing practices for target species. Through these training sessions, 51 collectors were able to obtain certification from the local government in order to legally wild-harvest the medicinal plants.[4]

"Before these trainings," said Nguyen, "many of the local collectors were unaware that they were harvesting MAP species illegally and the impact they were doing to the environment in the process. Additionally, with legal licenses, the project remains eligible for FairWild certification, which if attained, will allow harvesters to sell their product to a much wider global market."

TRAFFIC also provided the communities with five dryers for drying fresh herbs in order to improve product quality. It and partner groups also are working to establish a cooperative of harvesters from seven local villages, which will help to perpetuate the coordination of harvesting activities and ensure that harvesters from one village are not selling their products at prices substantially lower than other villages. Nguyen said this initiative has been particularly challenging.

"As local harvesters in this area have been accustomed to

Group discussion at the medicinal and aromatic plant species training at the Xuan Lac commune. Photo ©2013 Mai Nguyen/TRAFFIC

A local collector demonstrates how to cut *Alpinia malaccensis* in order to wild-harvest sustainably. Photo ©2013 Mai Nguyen/TRAFFIC

working independently and sometimes in competition with others," she said, "it has taken a while for the participating villages to understand the usefulness of working together and collective bargaining. Though there have been substantial improvements in coordination and cooperation, there still remains work to be done to create a lasting and productive local MAP cooperative."

These efforts by TRAFFIC, its partners, and the local communities already have had an impact on the villages and their members. According to Nguyen, TRAFFIC believes that if local collectors continue to use sustainable harvesting techniques, populations of these at-risk medicinal plants in the South Xuan Lac Species and Habitat Conservation Area will be able to recover and increase. Also, she noted, the four medicinal plants species have been yielding higher quantities and thus higher profits than in previous harvesting seasons.

"Before being trained, local collectors used to harvest unripe *Alpinia* and *Amomum* species' fruits, which led them to get unqualified product and low product quantity," said Nguyen. "After attending the training provided by TRAFFIC, they know the techniques to harvest sustainably. Collectors shared that they were able to harvest a greater volume of raw product, *i.e.* seed from fruit, if they were able to harvest later in the season when fruit were mature rather than at an earlier seasonal stage. This comparison provides a compelling argument for collectors to harvest at the end of the season when fruit is mature and seed is larger."

During the project's next several months, TRAFFIC will continue working with local collectors and authorities to better manage the conservation area, establish the inter-village cooperative, create business connections among local harvesters and international traditional medicine companies, and eventually attain FairWild certification for the project's products. And, Nguyen noted, TRAFFIC is applying for additional funding to extend the project for another three years and to expand it into other areas of Vietnam.

"As the conservation of MAP species is not given a huge priority by many national governments," said Nguyen, "it is important that greater spotlight is given to the importance of these plants for rural people's economic and health security." HG

—Lindsay Stafford Mader

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Group discussion among training participants in the Xuan Lac commune to identify medicinal and aromatic plants occurring in the South Xuan Lac Species and Habitat Conservation Area. Photo ©2013 Mai Nguyen/TRAFFIC

Lavender Oil Aromatherapy Reduces Falls in Elderly Nursing Home Residents in Long-Term Trial

Reviewed: Sakamoto Y, Ebihara S, Ebihara T, *et al*. Fall prevention using olfactory stimulation with lavender odor in elderly nursing home residents: a randomized controlled trial. *J Am Geriatr Soc*. 2012;60(6):1005-1011.

Falls are a major health problem for the elderly, as they are linked to increased morbidity and mortality. Risk factors for falls include physical weakness, gait and balance instability, sedating and psychotropic medications, and cognitive impairment. The latter is a strong factor due to the multiple behavioral and psychological symptoms of dementia (BPSD), such as pacing, wandering, aggression, anxiety, and agitation. The essential oil of lavender (*Lavandula angustifolia*, Lamiaceae) is used in aromatherapy to treat anxiety, nervousness, insomnia, and melancholy. Studies have shown that aromatherapy using lavender can improve balance and gait performance and reduce anxiety in elderly people. The purpose of this randomized, placebo-controlled, double-blind study was to evaluate the effect of continuous lavender olfactory stimulation on the incidence and risk of falls in elderly nursing home residents.

The study was conducted in three nursing homes in Aomori, Japan. It included 175 subjects, aged 65 years or more, who had the ability to move independently — with or without assistive devices. Subjects with pica disorder (appetite for non-nutritive substances such as dirt or paper) were excluded. Lavender olfactory stimulation was provided using a commercially available 1 cm by 2 cm paper patch (Aromaseal Lavender, Hakujuji Co.; Tokyo, Japan). The placebo was an identical unscented Aromaseal paper patch. The Aromaseal lavender patch originally was developed to help busy and stressed people relax by providing continuous olfactory exposure to lavender for 24 hours. The odor is so faint that it can be sensed only by the person wearing the patch. (Note: No information was provided on the lavender raw material source [*i.e.*, the herb from which the lavender oil was distilled], oil concentration or other chemical features of the oil, or the patch production). The head nurse prepared the patches and distributed them to the nursing home staff who affixed one patch inside each subject's clothing near the neck. The staff replaced the patch daily for 360 days.

The primary outcome measure was the number of falls. A fall was determined in accordance with the World Health Organization's definition: "an event which results in a person coming to rest inadvertently on the ground or floor or other lower level." The nursing home staff was trained to identify and record daily falls according to this definition. Behavioral measurements included the Cohen-Mansfield Agitation Inventory to quantify behavioral and psychological symptoms, the Barthel Index to assess level of functional ability, the mini-mental state exam (MMSE) to assess cognitive function, and the Vitality Index to assess activity of daily living (ADL)-related vitality. The groups did not significantly differ in age or risk factors for falls.

There were a total of 62 falls reported over the course of one year, with subjects in the lavender group falling 0-5 times and subjects in the placebo group falling 0-7 times (only 2 falls resulted in injury; one in each group). In the lavender group, 35.6% of subjects fell at least once, and 50% of the placebo group fell at least once. In the placebo group, 47% had recurrent falls, while only 24% in the lavender group had more than one fall (P=0.08). The total number of falls in the placebo group was 88 compared to 46 falls in the lavender group. The incidence rate ratio (IRR) for the lavender group was significantly lower than for the placebo group (P<0.04). After adjusting for confounding variables (such as age, sex, fall history, MMSE, tranquilizer use, etc.), the IRR significance was even greater (P<0.02).

There were no between-group differences in behavioral and cognitive measurements at baseline. At 12 months, the lavender group had a significant decrease from baseline in agitated status (P=0.04); in contrast, the placebo group did not. There was no significant difference between groups in the number of subjects who were given newly prescribed tranquilizers. However, the frequency of tranquilizer use was lower in this trial compared to other studies — a difference the authors attributed to the use of Yokukansan, a traditional Asian medicine commonly prescribed for BPSD. Yokukansan contains toki or Japanese dong quai (*Angelica acutiloba*, Apiaceae), cang-zhu atractylodes (*Atractylodes lancea*, Asteraceae), Chinese thoroughwax (*Bupleurum chinense*, Apiaceae), poria (*Wolfiporia cocos* syn. *Poria cocos*, Polyporaceae), Chinese licorice (*Glycyrrhiza uralensis*, Fabaceae), marsh parsley (*Ligusticum ibukiense* syn. *Cnidium officinale*, Apiaceae), and gambir (*Uncaria rhynchophylla*, Rubiaceae). No adverse events were reported.

The authors concluded that daily olfactory stimulation with lavender may prevent falls in elderly nursing home residents. Although the mechanism is unknown, the results of this study support lavender's traditional use to soothe anxiety and agitation, which may play a role in reducing falls. Lavender's previously demonstrated stabilizing effects on balance also may be a factor. Additionally, the authors suggested that the relationship between lavender stimulation, tranquilizers, and Yokukansan warrants further investigation.

In the final analysis, only two of the 145 subjects incurred injurious falls; this study was not large enough to detect clinically relevant reductions in injurious falls. The study also is limited by its potential lack of adequate blinding, which could have resulted in reporting biases. The nurses applied the patches to the patients, and there is the chance they could not remember which patient received which patch. Also, the possibility exists that some subjects could not detect the odor (olfactory functioning was not tested). The results cannot be generalized because people in nursing homes are subjected to different, and possibly fewer, environmental risks than the elderly dwelling outside of nursing homes. Although no adverse events were reported, the authors did not rigorously evaluate safety of long-term use. HG

—Heather S. Oliff, PhD

Cochrane Collaboration Revises 2008 Conclusions on Cranberry for UTI Prevention

Experts, researchers clarify results from recent meta-analysis

Reviewed: Jepson RG, Williams G, Craig JC. Cranberries for preventing urinary tract infections (review). *The Cochrane Library*; 2012:10.

Urinary tract infections (UTI) are among the most common type of infection in adults and result in more than 8 million visits to healthcare providers annually. UTIs — which are 50 times more likely to occur in women — can arise in any part of the urinary tract, including the kidneys, bladder, or urethra, and are most frequently caused by bacteria such as *E. coli*. Currently, antibiotics are considered the most effective treatment for the infection, and some women who experience frequent UTIs are prescribed low-dose antibiotics as a preventative measure.[1] With antibiotic resistance a growing concern in recent years, however, researchers are studying plant-based UTI prevention strategies, including formulations of American cranberry (*Vaccinium macrocarpon*, Ericaceae).

Cranberry has been a popular prophylactic for urinary tract infections for decades and has been used by indigenous North American peoples for centuries to treat certain urinary conditions.[2] Since 1998, cranberry has been the focus of four major reviews from the Cochrane Collaboration, an independent research organization that advocates evidence-based decision-making in healthcare.[3,4] Its popularity as a urinary tract health supplement, in part, helped make cranberry the best-selling single-herb supplement in the US Food, Drug, and Mass Market retail channel in 2011, commanding sales of more than $40 million.[5]

A 2008 Cochrane Review, which analyzed 10 studies of cranberry for the prevention of UTIs, concluded that cranberry products — such as juices or capsules — significantly reduced the occurrence of UTIs at 12 months, particularly in women with recurrent infections.[6] An update of the review, published in October 2012, however, found that "there was a small [but insignificant] trend towards fewer UTIs in people taking cranberry products compared to placebo or no treatment." Although the authors noted a number of potential weaknesses in the reviewed studies, they concluded that "until there are more studies of products containing enough of *the active ingredient* [emphasis added], measured in a standardised way, cranberry products cannot be recommended for preventing UTIs."[4]

Unusually high dropout rates and methodological issues with many of the studies included in the 2012 review — such as failure to quantify the main active ingredient for UTI prevention in cranberry and small sample sizes — have led some to question the validity of the Cochrane group's findings.

"It is essential that cranberry continue to be regarded and researched as an important area of study to help address the public health challenge that urinary tract infections and their treatment presents to antibiotic resistance," said Amy Howell, PhD, an associate research scientist at Rutgers University's Marucci Center for Blueberry and Cranberry Research (email, November 27, 2012). "UTIs are a significant public health challenge with more than 15 million cases in the US each year, and their treatment accounting for 15 percent of all community-prescribed antibiotics. I think that cranberry has great potential to help slow the pace of resistance development in an era when consumers are concerned with having to rely on pharmaceuticals to prevent and treat disease. "

Cranberries as a Preventative Measure

Fresh cranberries are composed of roughly 90 percent water and are known for their elevated concentration in total polyphenols, such as anthocyanins, tannins, flavonoids (flavonols and flavan-3-ols), and, most notably, proanthocyanidins (PACs). The amount of polyphenols in cranberry, however, comprises just a small percentage of the fruit's total organic constituents. Previously, scientists believed that organic acid in cranberry acidified the urine, which acted as an antimicrobial agent. Current hypotheses revolve around a specific type of PACs — those with type-A linkages — that are thought to be responsible for the fruit's ability to inhibit bacteria from sticking to the urinary tract lining, thus preventing infection. According to authors of an unrelated 2012 review of cranberries for lower UTI prevention, PACs "function as a natural plant defense system against microbes."[7] This well-studied *in vitro* effect did not translate to a measurable effect in the populations analyzed by the Cochrane group.

Dr. Howell, who has been researching cranberries for two decades, did not agree with the Cochrane group's essential dismissal of cranberries — particularly cranberry juice — for the prevention of UTIs. "I was disappointed by the authors' conclusions given that, as a cranberry researcher, my lab has consistently found that cranberries effectively help prevent bacterial adhesion to bladder cells, the first step in the initiation of a UTI," she said. "If the bacteria are prevented from adhering, they will not be able to grow and cause an infection. They are washed out of the body in the urine stream."

Methodological Issues

Ruth Jepson, PhD, of the Department of Nursing and Midwifery at the University of Sterling, in Scotland, and lead author of the 2012, 2008, and other previous Cochrane Reviews of cranberry, mentioned in an email a number of possible weaknesses in the chosen studies. In total, the latest analysis included 24 studies — 14 more than the 2008 review — totaling 4,473 participants. The 14 new studies were published after the group's original literature search in January 2007. To meet inclusion criteria, all studies had to be randomized controlled trials (RCTs) or quasi-RCTs of cranberry products for UTI prevention. Even with this criteria, studies varied greatly in terms of cranberry product used, type of placebo or control, and study design.

Funding for the 2012 Cochrane Review came from the UK National Health Service's National Institute for Health Research, a government initiative. Importantly, Dr. Jepson noted that the authors of the review did not receive any funding from cranberry product manufacturers or drug companies.

As noted in the review, of the 24 studies included, 11 used a cranberry juice product, nine evaluated cranberry tablets or capsules, two used a liquid cranberry concentrate or syrup, one compared juice and tablets, and one compared capsules and tablets. Of the studies that examined the effectiveness of cranberry tablets or capsules, only one reported the amount of PACs in the product. Without prior analysis, the precise amount of PACs in cranberry juice products — which are often not marketed as dietary supplements — is impossible to determine.

Dr. Jepson said that the lack of active ingredient quantities for products in many of the studies might have had an impact on the review's outcome. "I think there are two reasons for why we did not see [the *in vitro* effects] translate to a living population, both related to which cranberry product is being consumed," she said (email, November 9 and December 6, 2012). "Firstly, the effects of the PACs only last for about 10 hours. So to get maximum benefit, someone would have to drink two glasses of juice a day every day.… Indeed many people dropped out of the studies, possibly because it was difficult to drink these amounts." However, Dr. Howell pointed out that the 10-hour effect is from *in vitro* data and that previous clinical work has shown that cranberry juice can be effective if a single serving is consumed only once per day.

Dropout or withdrawal rates ranged from 3 to 55% in studies where the data were available. The Cochrane group noted that adherence was varied, with several studies reporting "participants withdrawing because of the unpalatable or intolerable nature of the cranberry product."[4] The resulting large number of dropouts is one reason why there has been an increased interest in cranberry tablets and capsules, which may be more suitable to consume on a daily basis as a preventative measure.

Dr. Jepson noted that future studies should focus on cranberry tablets or capsules, where amounts of PACs can be more accurately determined. "We know now that a specific process is needed to make sure that the PACs remain active in the dried preparations," she said. "However, many of the studies did not specify whether this process was undertaken, or indeed how much of the active ingredient was in the preparations (if any)."

Room for Improvement

Similarly, Dr. Howell sees room for improvement in many of the studies' designs. "Cranberry researchers use different dosages and product types which in many cases were not standardized to the active anti-adhesion compounds (proanthocyanidins) and may not have had sufficient amounts to achieve efficacy. I agree that this has been a problem in past studies and has most likely led to the results showing little

Cranberry *Vaccinium macrocarpon*. Photo ©2013 Steven Foster

effect, but I strongly believe that this is a very good reason to continue with clinical research and do it the right way, using well-characterized products and protocols," she said.

Gunter Haesaerts, founder and CEO of Pharmatoka — which manufactures Ellura®, a cranberry capsule with a significantly high standardized amount of PACs[8] — also takes umbrage with the Cochrane Review's apparent dismissal of cranberry juice products.

"Cochrane's jumping to the conclusion that it would be a waste of time to conduct more juice studies is a little bit unfair [to] the juice industry (led by Ocean Spray). But that same juice industry should realize once and for all that either they conduct and finance serious trials or they abstain from further inadequate clinical trials that can only irritate scientists and regulators," said Haesaerts (email, November 30, 2012). "On the other hand, the 'capsules and tablets' industry, to which Pharmatoka belongs, is explicitly encouraged by Cochrane to conduct more clinical studies on [the] condition that they use efficacious products."

Specifically, Haesaerts mentioned three prerequisites for the inclusion of cranberry capsules or tablets to achieve measurable results, two of which were mentioned in the Cochrane Review. "To ensure potency in cranberry powders, levels of PACs must be quantified properly; and the 4-dimethylaminocinnamaldehyde [DMAC] method is currently the most validated standard method," Jepson wrote. One peer reviewer of this article, however, noted that the DMAC method might not adequately account for larger molecules in cranberry, including some PACs. Further, the Cochrane Review noted that a recent study "found that to achieve a bacterial anti-adhesion effect in urine, 36 mg of cranberry PAC equivalents per day is effective, but 72 mg may offer better protection in some cases."

In order to maximize bioactivity, Haesaerts also suggested that bioactive PACs should be extracted from the juice, not from the cranberry presscake — the remaining material after juice extraction that includes seeds and skin — that also contains PACs but shows little bioactivity.[9]

"The mechanism of anti-adhesion of cranberry PAC is quite well known, even though certain aspects of the mechanism are still under study," he added. "Therefore, you cannot say that cranberry does not work. It does work. But to prove it's working *clinically* is another issue, and an immense challenge for the juice producers."

Looking Beyond the Cochrane Analysis

Dr. Howell urges consumers to be skeptical when dealing with meta-analyses that attempt to find answers to complicated questions. Whenever large amounts of data are involved, there is usually room for varying interpretations.

"The recent review on cranberry needs to be put into perspective and weighed against the other positive clinical trials over the past couple of decades in which cranberry was effective in maintaining urinary tract health.… There is a wealth of evidence from independent research institutions globally that has demonstrated that regular consumption of cranberry products helps to promote urinary tract health," she said. "Much of the recent prevention research is actually quite positive. Those studies that came out negatively all had issues with the products used, or design flaws in the methodologies that resulted in poor outcomes. Consumers need to be aware of these issues, especially when it comes to clinical trial results on functional foods. Just because a study does not yield significant results, it does not necessarily mean that the food is ineffective."

In particular, Dr. Howell noted the outcome of a recent analysis by Wang *et al*. published in *The Archives of Internal Medicine*, which included 13 clinical trials with a total of 1,616 participants. According to Risa Schulman, PhD, author of a research review of Wang's paper that appeared in *HerbalGram* 96, "Cranberry juice was shown to be more effective than capsules or tablets, which may be because it provides better hydration or because there are other substances in the juice that contribute to efficacy," she wrote. "On the other hand, juice has the potential drawbacks that it is high in sugar and may cause gastrointestinal or other adverse side effects."[10] Importantly, Wang noted that the results of his analysis should be treated with caution due to heterogeneity among the studies.[11]

Additionally, a 2012 paper in the *Open Access Journal of Clinical Trials* by Uberos *et al*. compared the efficacy of cranberry syrup against trimethoprim, a common antibiotic, for the prevention of UTIs in children aged one month to 13 years. "Our study confirms that cranberry syrup is a safe treatment for the pediatric population," Uberos wrote. The author also noted that, due to limits imposed on studies of children by the Declaration of Helsinki, no placebos were given, resulting in a simple "test of equivalence or non-inferiority." Therefore, the author concluded that "cranberry prophylaxis is not equivalent to trimethoprim, but it is shown to be non-inferior versus trimethoprim in recurrent UTI."[12]

Future Trials

Despite the negative conclusions of the 2012 Cochrane Review of cranberry for UTI prevention, many experts agree that more and better research is needed. Dr. Jepson noted that certain aspects of the included studies — such as the lack of quantified, standardized PACs — were cause for some concern. "[That] was why we recommended further studies using [a] standardised amount. It was difficult to say whether we were looking at a true estimate of effectiveness or not. If the underlying hypothesis is correct I would expect that new studies would show it," she said. "It is very possible, that if studies were undertaken using a standardised product which we were sure of the active ingredient, an effect would be seen."

Dr. Howell espouses a similar belief and urges consumers not to change their habits based solely on the recent meta-analysis. "I have been doing research at Rutgers University for the past 20 years and have found that cranberry consumption prevents bacterial adhesion to cells from the urinary tract — the initial step in the urinary tract infection process," she said. "If women are currently consuming cranberry products, the results of this one review do not provide a reason for them to change their current practices."

Haesaerts of Pharmatoka believes cranberry's fate now lies in the hands of researchers conducting clinical trials. With better study designs, he hopes future results will more accurately reflect cranberry's potential to provide urinary tract health benefits. "We are walking a very dangerous path. No new families of [conventional pharmaceutical] antibiotics are in sight. Cranberry as a prophylactic treatment of recurrent UTI is going to be dearly needed in the future because of the fast-growing resistance of uropathogens against existing antibiotics," he said. "Let highly respected experts like Cochrane continue their critical work, but give them study results that match their criteria and expectations. Cranberries deserve no less." HG

—Tyler Smith

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Ginkgo and Alzheimer's Disease Prevention

Researchers, herbal experts interpret results of the five-year GuidAge clinical trial

Reviewed: Vellas B, Coley N, Ousset PJ, et al. Long-term use of standardized Ginkgo biloba extract for the prevention of Alzheimer's disease (GuidAge): a randomized placebo-controlled trial. *The Lancet Neurology.* 2012;11(10):851-859.

Alzheimer's disease (AD) is the sixth leading cause of death in the United States and is the most common form of dementia in older adults.[1] The National Institute on Aging estimates that as many as 5.1 million Americans currently have AD, and experts predict the prevalence of the disease will quadruple by 2050.[2,3] In September 2012, a group of French scientists published the final results of a long-term, placebo-controlled clinical trial assessing the effects of a standardized ginkgo (*Ginkgo biloba*, Ginkgoaceae) extract for the prevention of Alzheimer's disease in older, healthy adults.

The GuidAge study, as it is known, was one of the largest and longest trials on *Ginkgo biloba* and AD prevention to date, and is the first of its kind to be performed outside the United States. Researchers found that the standardized *Ginkgo biloba* extract did not reduce the participants' risk of developing Alzheimer's disease, and some major media outlets erroneously reported that there is no benefit to taking the supplement, failing to take into account several shortcomings of the study.[3]

"After the results of GuidAge were published, some comments pointed out that this study provides further proof that ginkgo is ineffective in treatment of dementia. Those people are probably confusing prevention and treatment," said Wolfgang Weber, PhD, a pharmacist with Dr. Willmar Schwabe GmbH & Co. in Karlsruhe, Germany, which developed the EGb 761® ginkgo extract used in the trial (email, October 19, 2012). Notably, EGb 761 is marketed in many countries around the world for the *treatment* of dementia symptoms.

"The GuidAge trial was an Alzheimer's dementia *prevention* trial; EGb 761 is approved for *treatment* of dementia. This is definitely not comparable," said Dr. Weber. "Today there is no compound which has an effect in prevention of AD, though there are many trials available in which different compounds (acetylcholinesterase inhibitors [AChE-I, *e.g.,* donepezil], vitamins, statins, [nonsteroidal anti-inflammatory drugs, etc.]) were tested for that purpose. All of them failed."

Ginkgo biloba and Alzheimer's Disease

Alzheimer's disease is a progressive brain disease that affects behavior and personality in addition to cognitive processes such as thinking, judgment, and memory. The exact cause of the disease is not known, but it is thought to involve buildup in the brain of certain protein fragments known as beta-almyloid (βA), which can form clumps or plaques that disrupt normal brain function and cause cell death.[4]

Ginkgo *Ginkgo biloba.* Photo ©2013 Steven Foster

Among the primary active ingredients in ginkgo are specific flavone glycosides (*e.g.*, rutin, quercetin, kaempferol) and unique terpene lactones (ginkgolides, bilobalides), which contribute to the neuroprotective and antioxidant properties of the extract. In animal models, the extract or components of it have been shown to increase neurogenesis and enhance neuroplasticity.[5,6] Furthermore, it can inhibit βA aggregation[7] and βA-induced pathological behavior.[8] EGb 761, which has been used in numerous clinical trials including the 2008 US-based Ginkgo for the Evaluation of Memory (GEM) study, is standardized to 24% ginkgo flavone glycosides and 6% terpene lactones.[9]

In a guest comment published in the same issue of *The Lancet Neurology* as the recent GuidAge trial results, Lon S. Schneider, MD, director of the University of Southern California's (USC) Alzheimer's Disease Research and Clinical Center, wrote that EGb 761 "had a typical preclinical pharmacological profile for a modern Alzheimer's disease drug."[10]

Despite the promising pharmacological profile of ginkgo extract, the findings of the GuidAge trial were not as robust as expected. Researchers initially enrolled 2,854 healthy individuals who had reported memory problems to their primary care physicians. According to the study's authors, "Subjective memory complaints in elderly individuals, especially if spontaneously expressed to a doctor, are associated with an increased risk of dementia, and have been linked to brain atrophy and amyloid-β deposition … and could thus be a target population for interventions aimed at prevention of Alzheimer's disease." After five years, 61 of the 1,406 individuals taking 240 mg ginkgo extract daily and 73 of the 1,414 participants taking a placebo equal in taste and appearance had been diagnosed with probable Alzheimer's disease — a statistically insignificant difference.[3]

Potential Issues with the GuidAge Trial

In Schwabe's "Facts and Interpretations" sheet for the GuidAge trial sent to the American Botanical Council, the company's scientific team noted that choosing an appropriate study population for such large-scale prevention trials is problematic in itself. "Finding representative probands [*i.e.*, study subjects with relevant genetic backgrounds] for an Alzheimer's prevention study is extremely challenging. Even with today's technical possibilities in analyzing genetic information, it is practically impossible to predict the probability of Alzheimer's disease developing in a healthy individual within a

defined period of time. This is also true for people already complaining about memory impairment."

Jerry Cott, PhD — a pharmacologist and toxicologist at the US Food and Drug Administration's Center for Drug Evaluation and Research, chair of the Center's Dietary Supplement Subcommittee, and an ABC advisory board member — speaking on behalf of himself, acknowledged the importance of positive preclinical data for *Ginkgo biloba* extracts, but said he was not surprised by the results of the trial.

"The reason why this is important is that the preclinical data would suggest that there might be a preventative effect with ginkgo," said Dr. Cott (oral communication, November 5, 2012). "This is very different from the data on cholinesterase inhibitors, which are for treating symptoms. You're boosting the effect of what little acetylcholine is left, but you wouldn't expect that to have a neuroprotective effect. While it's disappointing, it's not surprising that a preventative effect was not found in this study. No preventative effect has *ever* been shown for [an Alzheimer's] treatment, including the best-selling pharmaceuticals."

Importantly, the expected rate of AD development in the GuidAge trial — a number that must be reached to ensure ideal statistical significance — was not met. Although researchers expected the cumulative incidence rate of AD to be 13.8%, only 4.8% of trial participants were diagnosed with AD by the end of the study. According to the trial authors, the "main limitation of [the] study was that the number of dementia events was much lower than expected, leading to a lack of statistical power to detect effects."

However, of 13 planned subgroup analyses, three groups showed a significant reduction in progression to AD: participants who stayed in the trial for at least four years, men, and those who consumed alcohol.[3]

According to Schwabe's "Facts and Interpretations" document, participants in the group that took the supplement for at least four years had a 47% reduced incidence rate of AD compared to placebo. "During the first four years of treatment, the difference between EGb 761 and placebo was not significant. However, after four years, the incidence of AD for the placebo group (3.01) almost doubled compared to the rates observed in the EGb 761 group (1.51)," wrote the Schwabe scientists. "Even though the authors recommended treating these results with caution, this is a clear trend towards a possible preventative effect of EGb 761."

USC's Dr. Schneider, in his guest comment, offered a different explanation for the particular subgroups' positive analysis. "The hypothesis that an individual has to take *Ginkgo biloba* for 4 years before it can protect against Alzheimer's disease is essentially a proposition for a filtering or survival effect according to which — assuming participants are able to comply or survive with four years of *Ginkgo biloba* use and avoid discontinuing it, becoming lost to follow-up, becoming ill, becoming demented, or dying (30% of the trial participants had any of these events) — continued use into a fifth year will decrease risk for dementia," he wrote.[10]

Keith Laws, PhD, a professor of cognitive neuropsychology at the University of Hertfordshire in the United Kingdom and author of a September 2012 meta-analysis of randomized, controlled clinical trials examining the effects of ginkgo on cognitive enhancement in healthy individuals, failed to detect any significant benefits in measures of memory, executive function, or attention. The 28 studies included in the analysis —which ranged in duration from five days to four months — included only individuals without dementia.[11]

According to Dr. Cott, making any strong conclusions from meta-analyses can be problematic. "A meta-analysis can show anything you want to show. Junk in, junk out," he said. "The bias of the investigator can really be present in a meta-analysis."

Dr. Laws, though, said he was impressed by the quality of the studies included in his meta-analysis. "Any meta-analysis is limited by the studies that are published, *i.e.*, the number and quality of studies," he said (email, October 19, 2012). "We found really high-quality studies — all were randomized, controlled trials with double blinding."

The GuidAge study, according to Dr. Laws, also was well-crafted. "The Vellas *et al*. study seems very sound — it … quite clearly found *Ginkgo biloba* made no difference to rates of transition to Alzheimer's," he said (email, October 19, 2012). "I am of the opinion that those who market *Ginkgo biloba* as a substance that sustains, enhances, or maintains memory need to provide evidence of that claim; our data suggest it is a claim with little or no foundation, and I would prefer to see such claims removed from packaging when they are unwarranted and unsupported."

However, the meta-analysis differed from the GuidAge clinical trial in that it examined studies specifically for cognitive enhancement, not AD prevention. The 28 trials included in the meta-analysis featured different doses of various ginkgo extracts such as Li 1370 (Lichtwer Pharma AG; Berlin, Germany) and Blackmores (Warriewood, Australia), in addition to EGb 761. Although the marketing materials and/or labels of many ginkgo formulations claim to have cognitive enhancing properties (*e.g.*, for improving mental sharpness, memory, and concentration[12]) in healthy populations, EGb 761 is marketed in numerous countries as a licensed or registered medicinal agent specifically for the treatment of dementia. The target group of EGb 761, according to Schwabe's website, "includes patients with demential syndrome in primary degenerative dementia, vascular dementia, and mixed forms of both," not healthy individuals hoping to prevent Alzheimer's disease.[13]

Dr. Laws acknowledged that ginkgo extract might have an impact in people already suffering from dementia. "*Ginkgo biloba* may have a quite different role in Alzheimer's. Meta-analyses (*e.g.* Weinmann *et al*. 2010)[14] do indicate that *Ginkgo biloba* may have some beneficial effects on the cognition of those who already have Alzheimer's disease," he explained. "So [it] may not prevent transition to Alzheimer's disease, but does appear to benefit patient cognitive abilities once people have actually developed the

disease. The issue then becomes … for how long and to what degree, and these questions require further investigation."

Future Research and Ginkgo Safety

Kelly Harrison, PhD, an instructor in the Department of Psychology at Virginia Tech University, noted a number of such dementia treatment studies. "Wang *et al.* (2010)[15] performed a meta-analysis on the use of ginkgo in the treatment of dementia in which subjects took the preparation for six months and found a significant difference in favor of ginkgo," she said (email, October 26, 2012). "Once again, this was a study looking for improvement in those already diagnosed with dementia, not 'healthy populations.' Similar results were found by Yang *et al.* (2011).[16] I would suggest that the modest improvements found in some clinical trials are as frequent in the literature as are those that find no significant change. Such is the nature of scientific inquiry."

According to Dr. Bruno Vellas, the lead author of the GuidAge trial, more research needs to be conducted before the effects of *Ginkgo biloba* on AD prevention can be stated with any certainty. "We think that the ginkgo hypothesis is still open and more studies have to be done," he said (email, October 22, 2012).

Dr. Harrison noted that researchers should account for conventional pharmaceutical medications taken by participants, many of whom are elderly, through blood draws and analyses to help determine the blood levels of ginkgo's primary active ingredients. "One in three of the elderly uses five or more prescription medications regularly, and about half use over-the-counter medications and dietary supplements," she said. "Thus each person could actually be receiving an individualized dosage based on the number of drugs they are taking that interfere with ginkgo's conversion. This may account for a lot of the variability in the herb's performance and certainly deserves consideration before writing the drug off as a wash."

Bill Gurley, PhD, a professor of pharmaceutical sciences at the University of Arkansas for Medical Science's College of Pharmacy, agreed that adding blood work to such long-term clinical trials would be beneficial. "Having blood data to confirm compliance would certainly have been helpful, but the samples have to be taken at the appropriate times," he said (email, November 5, 2012). "Too many clinical studies fail to measure phytochemical levels to confirm compliance at best and efficacy at least."

Dr. Weber, too, sees room for improvement in future clinical trials. "In my opinion the failure of EGb 761 to show an effect in prevention trials for dementia might not so much be a problem of EGb 761 but rather a problem of dementia prevention trials," he said. "Compliance is very difficult to achieve over a period of four or five years."

Dr. Vellas, in the GuidAge paper's conclusion, suggested that future trials "should use new methods, such as less burdensome cognitive assessments or home visits to reduce the number of non-completers, and should include new biomarker and imaging surrogate outcomes when these have been developed and validated."[3]

Although various pharmaceutical drugs have been developed in recent years to combat AD, unpleasant side effects and limited effectiveness have prompted the investigation of alternatives such as ginkgo extract. And, despite differing interpretations of the GuidAge trial, the safety of EGb 761 has not been questioned. Researchers found no significant differences between ginkgo extract and placebo in terms of reported adverse events.[3]

"Our products are tested extensively and EGb 761 is in fact [one of the] best researched herbal extracts worldwide," said Dr. Weber. "From numerous clinical and preclinical trials and also by the sheer number of users we know for sure that it is a very safe product."

Dr. Cott says that despite the conventional medications or supplements one is taking, safety and tolerability should be a primary concern. "One should *always* do this risk/benefit analysis when considering a medication," he said. "In a situation where one weighs the potential benefits against the known side effects and/or harms, ginkgo is a strong contender." HG

—Tyler Smith

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Cannabis *Cannabis sativa*. Photo ©2013 Johnny Wiggs

THE QUIET GIANT

Israel's Discreet and Successful Medicinal Cannabis Program

By Lindsay Stafford Mader

DESPITE ITS STATUS AS ONE OF THE WORLD'S LEADING NATIONS for medical research and innovation, the United States has a remarkably restrictive system in place to regulate medicinal cannabis research. Even when the US Food and Drug Administration (FDA) approves medicinal cannabis studies, the researcher or institution must then obtain approval from the Public Health Service (PHS), as well as procure cannabis material from the National Institute on Drug Abuse (NIDA), which has a monopoly on the supply of cannabis that can be used for research throughout the entire country.[1] Cannabis (*Cannabis* spp. Cannabaceae) is the only scheduled substance for which PHS approval is required, and those wishing to study the plant often have been rejected by the agency — effectively quelling this important area of science. An increasing number of US states have taken matters into their own hands by legalizing medicinal cannabis for residents with certain health conditions. But the federal government continues to raid and shut down state-based medicinal cannabis operations, even sending some of these business owners to prison. Although the US situation is largely based on the discrepancy between state and federal law, Americans and citizens of other countries that ban medicinal cannabis could learn just how successfully, compassionately — and non-controversially — such a program can be handled by looking at the unique national medicinal cannabis program in Israel.

Path to Medicinal Access

The Israeli government always has classified cannabis as dangerous and illegal, and it remains a crime to use the herb recreationally and without a license from an approved physician. Unlike US state-based medicinal cannabis initiatives, the nationwide program in Israel has won growing support from government officials, inciting relatively little controversy among Israeli citizens, public officials, and religious leaders.[2]

In 1995, the Israeli Parliament Drug Committee formed a subcommittee to examine the legal status of cannabis, which recommended that the government continue to categorize cannabis as illegal, but also that it allow and regulate access to medicinal cannabis for severely sick patients.[2,3]

"The second recommendation was of course extremely positive and important," said Boaz Wachtel, a medicinal cannabis activist in Israel who served as one of two public representatives on the committee (email, November 29, 2012).[3] "For the first time a Parliament-nominated committee acknowledged the medical use of cannabis and created an opening to advance the subject."

Wachtel noted other important factors behind the committee's recommendations, including the US Food and Drug Administration's 1985 approval of the synthetic THC-containing drug Marinol®, as well as input from Raphael Mechoulam, MD, who also served on the committee. Dr. Mechoulam, a Bulgarian-born Israeli scientist, isolated tetrahydrocannabinol (THC) in 1964.[2] In 1992, Dr. Mechoulam and colleagues Lumír Ondřej Hanuš and William Anthony Devane isolated and described anandamide, a endogenous cannabinoid neurotransmitter in the human brain.[4]

Cannabis plants as part of a rotation growing method that entails planting every two weeks to ensure constant supplies, at the Canndoc Ltd. growing facility in 2010. Photo ©2013 Boaz Wachtel.

Mature cannabis plants ready for harvest at the Canndoc Ltd. growing facility in 2010. Photo ©2013 Boaz Wachtel.

A small kiosk for patients who visit the MECHKAR distribution and training center. Photo ©2013 Moish Yarel

"I assume that the successful cannabis research in Israel has had some impact on the decision by the Ministry of Health to proceed with a carefully regulated medical marijuana program," said Dr. Mechoulam (email, December 6, 2012). "The committee I chaired in 1995 consisted mostly of government officials. Their overall attitude was quite liberal. We tried to minimize criminalization and to find ways to legalize medical use. Our report was never discussed or approved, but I am under the impression that it affected the attitude of the police and the Attorney General."

Several societal and political forces also were at play before and during the Israeli government's cautious but genuine interest in medicinal cannabis, said Rick Doblin, PhD, executive director of the California-based Multidisciplinary Association for Psychedelic Studies (MAPS), who has collaborated with the Israelis on medicinal cannabis and MDMA (also known as ecstasy) research. For one, Israel's most important ally, the United States, is opposed to medicinal cannabis and Israel did not want to compromise that relationship. On the other hand, there is the deep, fundamental Jewish principle to ease suffering, which many saw cannabis as doing.

"Also the fact that Mechoulam is from Israel and they had this tradition in being world leaders in cannabinoid research, they put their toe in the water," said Dr. Doblin (oral communication, December 4, 2012). "They did see that there is an awful lot of suffering that marijuana can help reduce at a very low cost."

When considering a national program, the Israeli Ministry of Health (MOH) consulted with Dr. Doblin and MAPS and a few additional medicinal cannabis groups on programs in other countries. Israel strived to comply with international drug treaties, particularly the 1961 United Nations Single Convention on Narcotics, which "aims to combat drug abuse by coordinated international action" and limits narcotic drugs to medical and scientific use.[5] Among several provisions on medical usage in the 44-page document, the Single Convention calls for limiting "the cultivation, production, manufacture, and use of drugs to an adequate amount required for medical and scientific purposes, to ensure their availability for such purposes and to prevent illicit cultivation, production and manufacture of, and illicit trafficking in and use of, drugs." (Interestingly, this is the very same treaty that the United States has used to argue in favor of its stifling monopoly on cannabis research supply.[1])

"The Israelis have been quite aware of the obligations of the Single Convention and the different ways it has been interpreted around the world," said Dr. Doblin. "They could see that even though the US wasn't willing to go that far on a federal basis, that there were states that were going this far and also other countries, like the Netherlands and Canada. That helped them to feel more comfortable because what we were able to show them is that the International Narcotics Control Board — which evaluates compliance with international treaties, particularly the Single Convention — had never censured any of the countries or spoke out against them."

Despite Israel's initial concerns for compromising its strong relationship with the United States, Dr. Doblin noted that he has seen no evidence of such backlash. "None at all," he said.

To satisfy an important Single Convention requirement for one specific agency to oversee certain functions related to the medicinal use of prohibited drugs, Israel appointed its MOH to lead the country's medicinal cannabis program.[3] Still, implementation was slow and measured. In 1996, Wachtel met with an MOH official to discuss the implementation of the cannabis subcommittee's recommendations, and he also submitted a request to supply an HIV patient with medicinal cannabis.

"He said, 'You have opened an important but controversial door — find a way to implement the program that would not cost the Ministry any money,'" said Wachtel, recounting the official's response. "Supplies were a problem. The police [were] not willing to provide the cannabis confiscated from the black market. The patients need a few strains of standardized, organic product that will not damage their weakened immune systems. The MOH did not have an answer at this point."

About two years later, the MOH permitted several patients to grow a few cannabis plants in their own homes, but most became too sick to attend to the plants and an accusation arose that the HIV patient was selling cannabis to minors.[3] As a result of these initial roadblocks, the MOH did not issue any additional medicinal cannabis prescriptions for two years. It considered importing cannabis, but due to concerns regarding cost and Single Convention limitations, officials eventually decided to allow a young Crohn's Disease patient to grow cannabis for himself and the other six patients who were licensed at the time. He also became too sick to grow. With the MOH still unsure of exactly how to implement large-scale production of medicinal cannabis, the program experienced several years of little action.

"The breakthrough occurred when the MOH appointed Dr. Baruch as the new Deputy Director specifically to deal [with] the issue of medical cannabis," said Wachtel. "The final decision to approve requests from patients and move the program forward was in his hands."

Modern Evolution of Israel's Medicinal Cannabis Program

Israel's medicinal cannabis program has evolved ever so slowly with each passing year. During its first decade, the government issued only 62 prescriptions. Now about 9,000 medicinal cannabis prescriptions are currently active, said Yehuda Baruch, MD, the former head of the program (email, December 4-16, 2012).

"The vision [has been] to help those in need when there is no other viable option [at] an affordable price and with as little bureaucracy as can be," said Dr. Baruch, who is also a psychiatrist and director of the Abarbanel Mental Health Center in Bat Yam. The widespread relief medicinal cannabis can provide to many patients does not come without the paradoxical negative, from Dr. Baruch's perspective, that the same patients also achieve a recreational high. "The increasing number [of permits] is both a point of concern because the main source today for recreational use is medical cannabis, but also a blessing because it is one more medi-

"Cannabis is one more medicine in the pharmacopeia that can be used when all else has failed, and since it works by a different mechanism of action, it may prove successful."

cine in the pharmacopeia that can be used when all else has failed, and since it works by a different mechanism of action, it may prove successful."

Dr. Baruch led Israel's medicinal cannabis program for a decade, from 2002 until December 2012. (Although his replacement has not been publicly announced, sources for this article have indicated it is Yuval Lanshaft, a former high-ranking Internal Security officer.) For several years Dr. Baruch was the only physician in the entire country allowed to issue patient licenses, and he also was in charge of organizing and leading the program along with the Ministry of Agriculture, Homeland Security, and the customs office.

"I personally lectured in every academic or medical meeting that was possible, even if it was a very small one," said Dr. Baruch, "and gave my private phone number and an invitation to call on anything. I also worked closely with relevant politicians and discussed the subject in the Israeli parliament various times. All in all, a lot of leg work."

In 2010, the MOH decided to allow additional physicians in five hospitals to provide medicinal cannabis licenses to patients, lifting the heavy responsibility from Dr. Baruch and enabling somewhat faster and easier patient access to the herb.[6] Currently, nine physicians are permitted to share this load. Dr. Baruch noted that while all senior physicians in the country can *request* a license for any number of their patients who might benefit from medicinal cannabis, only these nine MOH-appointed physicians are allowed to *approve* and *issue* permits. Because cannabis can be prescribed only as a "last resort" medicine, patients usually are told about it while they are in emergency rooms and oncology and pain wards, and the requesting physician must state that all drug treatment used thus far has been unsuccessful.[7]

While the increase to nine physicians was an improvement, Dr. Doblin noted that having this few prescribing doctors might impose burdensome limits on a nation of patients (news reports have referenced a MOH study that found 40,000 Israelis could benefit from cannabis[8]).

"I think that right now [Israel's program] is a tremendous success," said Dr. Doblin. "It's too limited, I would say, because there are a lot more people that could benefit. The Ministry is keeping a fairly solid control over the growth of the program. But in the Israeli context, I think that prevented a backlash, so maybe that was the right approach at the time. Still, it's not the best approach since patients are not currently permitted access for [post-traumatic stress disorder] and other conditions."

Initially, patients could obtain medicinal cannabis licenses only for asthma, and years later additional conditions were accepted, including AIDS wasting syndrome, vomiting and pain associated with chemotherapy for cancer, and all other applications were considered on a case-by-case basis, said Dr. Baruch. Now patients with the following conditions are considered for prescriptions:

- Chronic pain due to a proven organic etiology
- Orphan diseases (*i.e.*, diseases and conditions that affect only a small percentage of the population and for which few, if any, pharmaceutical drugs are developed)
- HIV patients with significant loss of body weight or a CD4 cell count below 400
- Inflammatory bowel disease (but *not* Irritable Bowel Syndrome)
- Multiple sclerosis
- Parkinson's disease
- Malignant cancerous tumor in various stages.[9]

As of 2011, most patients using cannabis had chronic pain, closely followed by cancer-related conditions.[9]

For many years, the MOH struggled to achieve a cultivation and distribution system that satisfied government officials as well as patients. In 2007, Dr. Baruch licensed one individual in Israel to grow about 50 cannabis plants to provide material to patients free-of-charge.[3] The man, Tsachi Cohen, did so in his parents' house in northern Israel. The garden was attended and cared for by his mother, a former biology teacher. Eventually, Dr. Baruch licensed several other growers, none of whom were allowed to sell the cannabis for a profit. Many sources interviewed for this article indicated that the initial nonprofit model contributed to the program's success and acceptance.

"The first feel that the public got was that these are people acting in the public interest and not for personal gain," said Dr. Doblin.

This small-scale operation by the Cohen family eventually grew into the country's first, and currently the largest, production center, called Tikun Olam (the Hebrew term based on the Jewish principle that all people should try to repair the broken fabric of the universe through acts of kindness, compassion, healing, and justice). Ultimately, all of the growers' nonprofit model — which relied mainly on donations — could not be sustained due to the increasing number of licensed patients and the intensive and expensive process required for cultivating high-quality cannabis on a large scale. So the government began requiring licensed growers to charge patients a monthly fee of 360 Israeli New Sheqels (approximately $100 USD) for up to 100 grams per month. The initially prescribed monthly dosage is 20 grams, with 42 grams being the average amount, and every patient is charged the same fee every month, regardless of how much cannabis they receive.[8] The price is relatively inexpensive when compared to cannabis in other countries, and several large Israeli medical insurance companies, the Holocaust Survivors fund, and the Ministry of Defense (for some patients with post-traumatic stress disorder) partially cover the cost of medicinal cannabis.

"The most important [milestone] was the transition from nonprofit to for-profit," said Dr. Doblin, whose MAPS organization had donated about $85,000 to support the nonprofit facilities. "You could say it was a transition from a non-sustainable model to a sustainable model. Another point that makes Israel so astonishingly successful as a model is that some of their health insurance companies cover marijuana. That's the kind of information that really needs to get out in America. That for whatever reason, we have insurance companies deciding it is a smart investment to cover medical marijuana. Israel is the only place I know of where that happens."

There are currently seven licensed growing centers that distribute medicinal cannabis on-site, through home deliveries, in small dispensaries in a limited number of urban locations and hospitals, or at one of the larger distribution centers.[9] The central distribution center, named MECHKAR, a Hebrew acronym meaning research, represents an important aspect of the Israeli program. At MECHKAR, patients not only obtain cannabis, but also are welcomed to be trained and counseled on topics such as which strains and dosage forms might be best for their particular condition and lifestyle; levels and location of pain and any other health conditions; and emotional or religious concerns and experiences.[10] Staff also closely supervise patients

Various cannabis products at the MECHKAR distribution and training center available to Israeli medicinal cannabis patients. From top, a cannabis tincture, baked cannabis cookies, cannabis salve, and cannabis cigarettes rolled with organic paper.
Photo ©2013 Moish Yarel

Store at the MECHKAR distribution and training center, offering various cannabis accessories including a Volcano Vaporizer. Photo ©2013 Moish Yarel

throughout the first few months with feedback forms and meetings in order to optimize dosages, reduce any unwanted side effects, and discuss potential drug interactions.

"We may be the only government on earth right now where patients are sent to use marijuana who have absolutely no desire to use it," said Mimi Peleg, the director of large-scale training at MECHKAR (email, November 29, 2012). "They do have a strong desire to stop suffering, of course. My first job as a trainer is to relax them enough to even consider the idea that it is okay to use this medication. Working with patients who receive cannabis has taught me that the quality of education that is shared at the beginning of the treatment is an important factor in leading to an optimal control of symptoms."

From time to time, the MOH discusses the possibility of importing medicinal cannabis from the Netherlands, and it is currently in the process of setting up a large, multi-institutional ministerial Medicinal Cannabis Agency to handle all aspects of medicinal cannabis production, dispensing, testing, and licensing.[3] The government also has been discussing pharmacy distribution to begin sometime in 2013, but it is unclear if this initiative will actually be implemented on time.[6] If this step is taken, it is anticipated that the large government agency will purchase all cannabis material from growers, store it in government-controlled warehouses, and then distribute it though pharmacies.[9]

"As a cannabis trainer, this shift will impact my current role," said Peleg. "By and large, I think it is a positive move in the right direction. I [still] see the need for some distribution centers where patients can go for further training and strain adjustments. Treating people with cannabis requires much more than just purchasing medicine at a pharmacy."[10]

Cannabis is available to patients in a variety of forms such as baked goods, ready-made cigarettes, oils, and tinctures.[10] Patients with a medicinal cannabis license also are allowed to ingest cannabis through Volcano® Vaporizers, a device typically costing $500-600 USD retail that heats the cannabis without burning it so that no smoke and reduced amounts of combustion byproducts are produced. Several Israeli health insurance companies and patient care groups also cover some of the price of purchasing or renting a Volcano, which has been licensed by the MOH and approved by the Israel Standards Institute, and several devices donated by Volcano Medic in Israel are available in four public hospitals for patients who cannot afford their own.

"All this has been a huge cooperative effort," said Peleg. "They put four Volcanos in major hospitals and patients with licenses can request private mouth pieces and balloons or take their own Volcanos in. I did when I was healing from cancer and thereby avoided needing morphine in recovery! It was wonderful to have the choice."

For all the bold measures taken with medicinal cannabis in Israel, it remains a largely non-controversial situation. The diverse range of patients helped by the herb includes former soldiers, police officers, settlers, Arab Israelis, and elderly Holocaust survivors. Dr. Doblin mentioned that religious leaders have declared cannabis kosher, and Peleg noted a religious, political, gender, and age diversity among the hundreds of patients she has trained over the years.

"A month after her initial training, Hanna* came back in with [her husband] Hiem*, and as is often the case, I barely recognized them," said Peleg of a Holocaust survivor whom she trained to use medicinal cannabis for pain.[10] "There was an undeniable intimacy between them that had been absent in their prior visit — clearly they had been doing some communicating. Instead of being happy, Hanna was livid and for all the right reasons. She wanted to know who to blame for the fact that she hadn't been given this medication years ago if it had been known and available. Again, who could blame her? Her pain was gone, she had an appetite, she was communicating with loved ones — cannabis was doing its job. Israel is a very small country. We are only 8 million citizens. Word spreads fast and the pressure on the system is extremely high due to stories like Hanna's that highlight efficacy."

Cannabis activist Wachtel also noted the late-1980s discovery of ancient cannabis material in a burial tomb in Israel, which researchers postulated was likely given to a 14-year-old girl, also found in the tomb, to "facilitate the birth process" of her unborn child.[11] "Cannabis," said Wachtel, "is therefore viewed here as an indigenous medicinal plant, one that was out of use for a while but is now back in its natural place in the modern pharmacopoeia to alleviate a great number of medical symptoms."

Even with relatively little controversy, Israeli police allege that cannabis fields attract criminals who steal plants to sell on the black market.[12] But Wachtel noted that very little diversion is taking place because the growing operations are typically secured by cameras and armed guards.

Supporters of medicinal cannabis in Israel also see areas where the program can be improved upon. Peleg noted the need for a national strain bank, retrospective assessments of medicines used concurrently with cannabis, a broadened list of diseases, and a more comprehensive training program for medical professionals and patients. Additionally, the process of requesting cannabis and obtaining a physician recommendation and official patient license, while sometimes quick, also can be very lengthy.[13]

"The system is bursting at the seams," said Peleg. "If 10 more people worked in the MOH just on cannabis, we couldn't do all the work that needs to be done."

Dr. Doblin stressed the need for Israel to produce official medical-grade cannabis supported by Good Manufacturing Practices, thorough documentation, and product standardizations. Even though several Israeli health insurance companies already cover cannabis without it having been through the formal drug-approval process, he noted the possibility of importing medical-grade cannabis from Israel into the United States to support scientific research. (Dr. Doblin's FDA-approved research that seeks to develop the plant into an approved prescription medicine has been rejected by the PHS/NIDA process.[1])

That Israel's government is generally far more accepting of the herb's potential as a medicine has enabled a much freer cannabis research community. Dr. Mechoulam, for example, has been obtaining hashish (a preparation made from compressed THC-rich resinous material) from the Israeli police for more than 40 years, with MOH approval.

"Research in Israel is highly respected and neither the police nor the Ministry of Health have ever raised any major problems," said Dr. Mechoulam. "They have been, and still are, very helpful. This is true for both basic and clinical research."

"The benefit of a program like Israel's is that the government takes a role in ensuring quality and safety of the product, and supports research to further the understanding of the plant's medical benefits, said Amanda Reiman, PhD, California policy manager for the Drug Policy Alliance (email, December 1, 2012). "In the US, the government has actively prevented research from taking place, and has threatened municipalities that attempt to regulate the quality and safety of the product with criminal prosecution." HG

* Names have been changed to protect patients' privacy.

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Echinacea *Echinacea angustifolia*. Photo ©2013 Steven Foster

ECHINACEA
DIFFERENCES MATTER:
Traditional Uses of *Echinacea angustifolia* Root Extracts vs. Modern Clinical Trials with *Echinacea purpurea* Fresh Plant Extracts

By Francis Brinker, ND

Editor's note: This article is based on a prior version published in the International Journal of Naturopathic Medicine*, Vol. 5, Issue 1, 2012. This version has been enhanced with additional text and table notes, modified for* HerbalGram *style, and peer-reviewed by experts in the field.*

Introduction

Circa 1900, the reputation of echinacea among Eclectic physicians* was built on the common use of high-alcohol extracts of *Echinacea angustifolia* (Asteraceae) roots applied topically for wounds, infections, and poisonous bites and stings, and administered internally for acute infections now known to be bacterial. Beginning in the mid-20th century, European clinical research on plant preparations of fresh aerial *E. purpurea* plant juice, preserved with 22% ethanol or the whole plant extracted with 65% ethanol, established its usefulness in treating the common cold. Thus, the perception of *Echinacea* spp. root extracts was transformed based on their generic relationship. The proclivity of modern botanical use for evidence-associated applications has led to widespread confusion regarding the differences between these distinct botanical species and their preparations.

Original Eclectic Preparations and Official Recognition

Dr. H.F.C. Meyer of Nebraska was the first to produce a commercial extract of echinacea. Although usually combined with about one-eighth part each of hops (*Humulus lupulus*, Cannabaceae) and wormwood (*Artemisia* spp., Asteraceae) — plant parts not specified — in his Meyer's Blood Purifier for internal use, he used the tincture of *E. angustifolia* root for local applications (either externally or internally to mucosa in the nose, mouth, and rectum).[1,2] In 1887, Meyer and Dr. John King[2] described Meyer's use of the root for 16 years as an "alterative"† and antiseptic in the *Eclectic Medical Journal*, claiming that the tincture was effective internally and externally for treatment of boils, carbuncles, ulcers of the throat and extremities, hemorrhoids, and wasp and bee stings. In 613 cases of rattlesnake venom poisoning treated in humans and animals, most recoveries occurred in two to 12 hours.

By 1900, most Eclectic physicians were using Lloyd Brothers Pharmacists' *E. angustifolia* extracts, following years of study by J.U. Lloyd.[1] After privately supplying a tincture of *E. angustifolia* root to Eclectic investigators beginning in 1890, in 1894 the Lloyd brothers introduced their commercial Specific Medicine Echinacea to the medical profession.[3,4] J.U. Lloyd determined that the characteristic acrid principles of the dried root that produced a tingling and numbness of the tongue required a high-alcohol concentration for extraction.[1] By 1906, the use of echinacea as an external and internal remedy had extended to conventionally trained physicians. It also was being used by them for the treatment of infected wounds, septicemia, and poisonous insect bites and stings.[5]

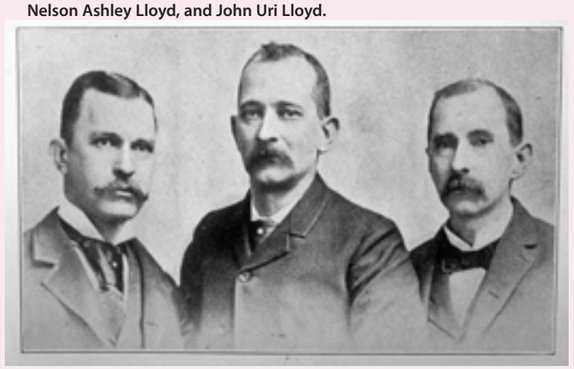
The Lloyd Brothers Pharmacists manufactured various *E. angustifolia* preparations. Their Specific Medicine Echinacea with 65% alcohol (ethanol) had the same drug strength as a fluid extract (1:1), but its production involved a proprietary process.[6] Other Lloyd brothers preparations included Echafolta, a refined preparation free of sugars and coloring matter and made with 92% alcohol. Considered equivalent to Specific Medicine Echinacea, Echafolta was the preferred choice in surgical cases, where greater cleanliness was desired.[1,6] By 1922, a small quantity of iodine tincture had been added to Echafolta, causing it to be reserved for external use only.[7] Echafolta Cream provided the active principles in a bland petrolatum base.[8] It was used locally as a soothing dressing and as an adjunct to internal medication and surgical measures.[1,6] A nonalcoholic extract of *E. angustifolia* for hypodermic use was given the trade name Subculoyd Echinacea.[4] While occasionally specifying the specific type of preparation, most physician reports of *E. angustifolia* root extracts refer to whatever preparation was used simply as "echinacea."

The Lloyd brothers emphasized the quality of their product as follows:

> *Echinacea* is made from the carefully selected, prime, dried, cured, and assayed root of *E. angustifolia*. The quality of but few drugs is more influenced by conditions prevailing in different localities and by treatment during drying, than is *Echinacea*…. Prime drug from favored geographic regions may be ruined by careless or faulty manipulation…. The famous Lloyd process permits the extraction of delicate and complex botanical therapeutic principles without harm.[8]

The Lloyd brothers' ongoing laboratory research led to their 1923 statement that "the therapeutic importance of the acrid constituent emphasized in our former litera-

The Lloyd brothers in 1879 from left to right — Curtis Gates Lloyd, Nelson Ashley Lloyd, and John Uri Lloyd.



*Eclectic physicians were American reform physicians from the mid-19th to the mid-20th centuries who defied current medical conventions and incorporated in their practice any measures believed at the time to be clinically effective, especially by developing the application of native medicinal plants and their pharmaceutical preparations.

† The term alterative refers to an agent that "causes a favorable change or alteration in the processes of nutrition and repair, probably through some unknown way improving metabolism"[7] or "medicinal materials that reestablish healthy function in various systems of the body."[32]

ture constitutes but a part of its qualities, being most pronouncedly supported by less sensible constituents."[3]

American Medical Association Condemnation Despite Acceptance by Physicians and the *National Formulary*

In 1909, a report by the Council on Pharmacy and Chemistry in the *Journal of the American Medical Association* condemned Dr. Meyer's "absurd" claims and those "made on no better basis than that of clinical trials by unknown men who have not otherwise achieved any general reputation as acute, discriminating and reliable observers."[9] The report declared that "*Echinacea* is deemed unworthy of further consideration until more reliable evidence is presented in its favor."[9]

Dr. Finley Ellingwood, the Eclectic *materia medica* professor at Bennett Medical College in Chicago, Illinois, responded to the Council on Pharmacy and Chemistry with the following:

> Not a single member was engaged in active medical practice or was in a position to observe the action of drugs in the influence they exercise in the cure of disease…. In view of the fact that 20,000 physicians of the United States are using this remedy with success; and in view of the fact that there is a perfect agreement concerning the observations made by these reliable and trustworthy practitioners, … it seems strange indeed that this half dozen or more men should say that because of the scrutiny (or lack of scrutiny) that had been made, the remedy is deemed unworthy of further consideration.[10]

Clinicians remained enthusiastic about the usefulness and efficacy of echinacea after the condemnation published in the *Journal of the American Medical Association*. A survey was sent by the Lloyd brothers to more than 30,000 physicians who graduated from an array of medical schools, asking them to indicate which botanical drugs they used in their practices. More than 10,000 responded, and *Echinacea* ranked eleventh (listed by 5,065 physicians) in importance among all botanical drugs, as published in 1912 in the *Journal of the American Pharmaceutical Association*.[11]

In 1916, the fourth edition of the *National Formulary*,[12] published by the United States Pharmacopeia, established *E. angustifolia* dried roots and its fluid extract as official remedies. In testing the manufacture of a standard echinacea fluid extract in 1911 for inclusion in the *National Formulary*, it was concluded that menstruums with less than 67% ethanol did not adequately extract from the dried root those pungent principles responsible for the tingling sensation in the mouth (now known as alkamides).[13]

Early Scientific Assessments of *E. angustifolia* Root Extracts

The first major clinical research performed with *E. angustifolia* was conducted from 1913 to 1916 by Dr. V. von Unruh, a United States Army lieutenant. He used the nonalcoholic injectable medications Subculoyd Echinacea and Inula Compound (1.0 and 1.33 mL, respectively, intramuscularly or intravenously; Inula Compound also contained an extract of the root of elecampane [*Inula helenium*, Asteraceae]) in the treatment of patients with tuberculosis. Among 150 patients, he described 100% recovery in those with incipient pulmonary disease, 50% arrest in those with moderately advanced disease, but no success in those with advanced disease.[14,15] In microscopic research involving more than 500 differential and cell counts carried out over more than four years, he found that injected *Echinacea* extract raised the opsonic index (making bacteria more susceptible to phagocytosis), increased the phagocytic power of leucocytes (allowing white blood cells to more readily engulf bacteria), improved leukopenia and hyperleukocytosis (helping normalize insufficient and excessive numbers of white blood cells), and normalized the percentage of mature neutrophils (balancing the number of the primary phagocytes for infections).[15]

Couch and Giltner subsequently tested the major echinacea products in animals.[16] Performing injections in relatively small numbers of guinea pigs, they used bacterial toxins to experimentally induce tetanus and botulism, rattlesnake venom to simulate snakebites, and live bacteria to cause tuberculosis, dourine (a type of chronic venereal disease in animals), anthrax, and septicemia. Control animals were untreated or were administered the same alcohol content as in the extracts. Echinacea preparations (Specific Medicine Echinacea, Subculoyd Inula and Echinacea, or Echinacea fluid extract [*National Formulary,* 4th ed.]) were administered orally or parenterally before and/or after the pathologic injections. The induced diseases were interpreted as essentially the same in the control and treated animals. The authors concluded that the echinacea preparations were not of value in the treatment of diseases produced by microorganisms or biologic toxins.[17,18]

A 1921 editorial review of these findings published in the *Journal of the American Medical Association* noted:

> "Of course, it will be retorted that the negative results on laboratory animals need not necessarily apply to sick human beings, and that subtle potent effects are not always discovered by research workers… Scientific medicine of today, however, asks for evidence that can be demonstrated by the pharmacologist or can be appreciated and accepted by the critical clinician as well as the quack."[16]

The authors argued that the Echinacea fluid extract used in the experiment should be removed from the *National Formulary*.[16]

The same year, James Beal[19] — director of pharmaceutical research at the University of Illinois, Urbana, and former editor of the *Journal of the American Pharmaceutical Association* — published a critical response to the laboratory research. He noted that the experiments were too few to be conclusive and that the results were not interpreted from a clinical perspective. Three times the minimum fatal dose of tetanus was administered to 19 animals receiving Specific Medicine Echinacea; 10 times the minimum fatal dose of botulinus was administered. The septicemia and dourine produced by *Bacillus bovisepticus* and *Trypanosoma equiperdum*, respectively, were species that were unassociated with human pathologic conditions. He further noted that, in the tuberculosis experiments, the mean weight loss in control

Echinacea *Echinacea purpurea*. Photo ©2013 Steven Foster

animals was 129% that of the treated animals, which survived 36% longer. Of the animals injected with rattlesnake venom, the three controls died, while one of the six echinacea-treated guinea pigs survived.[19]

Responses of Clinical Empiricists

The Lloyd brothers, as a courtesy to Couch and Giltner and in fairness to all concerned, publicized their experimental results and suspended advertisements of echinacea preparations for one year, despite the fact that echinacea products were their best-selling botanicals from 1885 to 1921.[17,18] Following publication of the 1921 negative laboratory research, the Lloyd brothers recorded their best sales of echinacea extracts by even larger margins over other botanicals. In 1922, echinacea sales increased again, almost 25 percent above the previous year's sales and more than three times more than sales of the second-ranked plant drug, fringe tree (*Chionanthus virginicus*, Oleaceae), among their 239 different plant remedies.[3]

In another attempt to assess the value of echinacea, the Lloyd brothers sent a postcard questionnaire to physicians concerning the use of echinacea preparations in their clinical practice in 1921. They asked for the physicians' prominent indications and uses of echinacea, providing one line for the response and two additional lines for remarks. Physicians were asked to consider whether they would be willing to use a synthetic or other substitute to replace echinacea. In 1923, the responses were published.[3] This unparalleled document provides ardent empirical consensus to support prior clinical claims.

In comments received from 701 physicians who used *E. angustifolia* preparations in their practices, 70.3% (493 respondents) advocated its general use in septic conditions, 22.1% (155 respondents) specified its effectiveness in cases of septicemia or blood poisoning, and 14.3% (100 respondents) noted its efficacy for treatment of typhoid fever (Table 1). Use in cases of blood "dyscrasias" — a morbid imbalance of component elements; as used by Eclectics (see footnote 'd' in Table 1), this is considered descriptive of blood disorders, blood perversions, blood trouble, blood diseases, vitiated blood, morbid blood, etc. — by 21.4% (150 respondents), and as an alterative by 11.3% (79 respondents) were cited as other major indications. J.U. Lloyd[3] noted that neither tetanus nor botulism was mentioned in any of the survey responses, nor had treatment with echinacea been recommended for these conditions in major Eclectic texts, challenging the pertinence of the findings by Couch and Giltner.[17,18] However, a striking feature of the survey results was that most indications mentioned by physicians for *E. angustifolia* root preparations were for bacterial infections while few mentioned viral or fungal infections.[3]

In the survey results, 31.5% stated explicitly (88 respondents) or implicitly (133 respondents) that no substitute for echinacea would be acceptable, while

Table 1. continued.

Acne, anthrax, atonic mucosa, bronchitis (moist), canker, chronic appendicitis, colds, conjunctivitis, epilepsy, epithelioma, felons, gonorrhea, intertrigo, Ludwig angina, meningitis, osteonecrosis, ovarian neuralgia, pelvic inflammation, after escharotics, ptomaine poisoning, pyelitis, ringworm, scrofula, septic vomiting, sinusitis, spotted fever, surface hemorrhage, tetanus, thrush, tumors, uterine cancer, vaccinations	1
Numerous others	19
Effects	
Alterative** (blood purifier)	79
Antiseptic (used for sepsis)	75
Tonic	12
Increase leucocytosis, stimulant	4
Antizymotic, sedative	3
Antispasmodic, phagocytotic, uterine tonic, vitalizer	1
Applications	
Internal	169
Local	115
External	87
Hypodermic	5
Intravenous	1
Preparations	
Specific Medicine Echinacea	113
Echafolta	40
Combinations	24
Subculoyd Echinacea	7
Echinacea fluid extract	5
Echafolta Cream	2
Green tincture	2
Homemade tincture	2
Ointment	1
Tolerability	
Safe	7
Use for infants or children	7
May upset digestion	2
Repulsive taste	1
Too pungent for children	1

[a] Based on survey results by Lloyd.[3] In the context of clinical experience, the mean duration of prescribing *Echinacea angustifolia*, as reported by 15 of the physicians, was about 27 years
[b] Includes antiseptic, septic conditions, septic indications, septic infections, infections
[c] Includes blood poisoning, bacteremia, blood sepsis, systemic sepsis
[d] Includes blood disorders, blood perversions, blood trouble, blood diseases, vitiated blood, morbid blood, etc.
[e] Includes impure blood, auto-intoxication, toxic blood, internal toxic conditions
[f] Includes low vitality, run down, broken down, depletion, depraved condition, impoverished system, low resistance

1.5% of respondents indicated that they would use a substitute if it was shown to be equally as effective.[3] The most preferred preparations were Specific Medicine Echinacea internally or locally by 16.1% (113 respondents), Echafolta Cream by 5.7% (40 respondents), injectable Subculoyd Echinacea by 1.0% (seven respondents), and the Echinacea fluid extract by 0.7% (five respondents). Internal use was specified by 24.1% (169 respondents), local use by 16.4% (115 respondents), and external use by 12.4% (87 respondents). The most common local conditions treated topically or internally were poisonous snakebites (10.6%, 74 respondents), insect or spider bites and stings (9.6%, 67 respondents), and wounds (7.7%, 54 respondents). In the published survey, a list of the responding physicians' names was provided. They hailed from 41 of 48 states, plus Canada, Mexico, and New Zealand.

Clinicians were enthusiastic about echinacea (see "Representative Remarks by 100 Physicians About Liquid Extracts of *Echinacea angustifolia* Root From Survey Results by Lloyd," available online at: http://cms.herbalgram.org/herbalgram/issue97/hg97-feat-echinacea.html). In 1924, sales of echinacea products were seven times greater than those of any other product made by the Lloyd Brothers Pharmacists.[20] To keep the use of echinacea in context, the Lloyd brothers described the therapeutic rationale for its application as follows: "Echinacea is a useful aid in the treatment of infection and sepsis, local or systemic… It is employed as an aid where there is a necessity for agents that possess general antibacterial properties."[8]

Medical Use of *E. angustifolia* Root Extracts for Respiratory Infections

Notably, when *E. angustifolia* was first introduced to clinical medicine in the late 19th century, scant mention was made of its use in treating simple upper respiratory tract infections. In 1898, Felter and Lloyd[1] noted that *E. angustifolia* hydroalcoholic extract contributed much to the cure of catarrh of the nose, nasopharynx, and respiratory tract. In a 1919 summary by the Lloyd brothers[21] of reports from 1,000 physicians asked to cite the most important flu remedy following the recent influenza pandemic, echinacea was not listed among the nine most useful remedies for influenza or pneumonia, or among the nine best external applications for either of these conditions. Echinacea was noted in passing by some physicians who listed it when certain remedies were most indicated, for example, "where sepsis is marked, Echafolta or Echinacea becomes most important."[21]

That same year (1919), when *E. angustifolia* extracts were recommended by Ellingwood[22] for catarrhal conditions, it was cited both as an internal and as a local medication. In the survey responses from 701 physicians published by J.U. Lloyd[3] in 1923, 10 respondents mentioned influenza as a prominent indication for use of echinacea, while only two specified its use for catarrh and one specified it for colds.

The use of echinacea extracts for treating influenza was discussed in 1929 by H.T. Cox,[23] who believed (as is

the general consensus today) that early application of "good-sized doses" from the first day until the body temperature reached normal was the best means of using this remedy. However, even after several days of influenza, echinacea in "large enough dosage" still was used persistently. In patients with purulent expectoration, the dosing continued until the sputum cleared. *Echinacea angustifolia* was prescribed along with appropriate cough preparations until the pulmonary congestion was entirely resolved. Large doses (the author again referred to "good-sized doses") were administered to patients with influenza until the cough subsided.

Eclectic Human Research and Decline

Preliminary human research was attempted in 1934, when students at the Eclectic Medical College in Cincinnati, Ohio, volunteered as subjects to study the effects of echinacea by taking therapeutic doses for four days. Specific Medicine Echinacea was administered in water in doses of two-to-15 minims, derived from two-to-15 grains (130-975 mg) of the dried root. Blood samples were drawn at baseline and again after each day of use. Increases in total leukocyte counts were apparent, peaking in two-thirds of the subjects after 24 hours and in the remaining one-third after 48 hours.[24] The leukocyte increase was mostly neutrophils after 24 hours and mostly lymphocytes after 48 hours. Total and differential counts were normal after 72 hours. These uncontrolled results, crude by modern standards, suggest that echinacea combats infectious agents acutely, briefly, and indirectly through the blood.

Echinacea angustifolia use diminished after the decline of Eclectic medicine in the late 1930s. This was indicated by the dropping of Echinacea fluid extract from the eighth edition of the *National Formulary*[25] in 1946, although the dried roots entry appeared in this official text that year for the last time. In 1950, in an attempt to identify direct antibacterial activity, German researchers isolated the caffeic acid derivative echinacoside from the root, which demonstrated weak inhibition of streptococcal and *Staphylococcus aureus* gram-positive bacteria.[26]

Adoption by Naturopathic Physicians

Echinacea angustifolia was prescribed by early naturopathic physicians for local and internal use in accord with the indications established by the Eclectics. Echinacea was considered one of naturopathy's most valuable herbs. In 1936, Specific Medicine Echinacea was recommended by naturopathic physicians as an alterative for septic conditions.[27] In such cases, 20 drops of Specific Medicine Echinacea in a little water every four hours was suggested for treatment of recurring boils, carbuncles, ulcerations, and lymphangitis (inflamed lymphatic vessels). Septic fevers, typhoid fever, and acute nephritis were treated with 20 drops every two hours until the crisis passed. This preparation was to be administered internally and applied locally as a wet dressing for snakebites, cuts, wounds, and insect stings.

Twenty years later, the Echinacea fluid extract was advocated again in a naturopathic journal as a treatment for septicemia, as an antiseptic for boils, and as a local application for swelling.[28] A tincture of the fresh root (one teaspoonful every two-to-four hours) was recommended in patients with diphtheria and puerpural septicemia. It was often combined with other appropriate remedies.[28,29]

In 1953, the *Naturae Medicina and Naturopathic Dispensatory* recommended hydroalcoholic extracts of the dried root of *E. angustifolia*, along with its water-based decoction, as "one of Naturopathy's most faithful antibiotics and alteratives."[29] Internal use of the tincture or Specific Medicine Echinacea, together with its external application, was emphasized again for insect stings, boils, carbuncles, and certain septicemias. The tincture or decoction was used as a gargle for buccal ulcerations, ulcerative stomatitis, gingivitis, tonsillitis, pharyngitis, and as a retention colonic for ulcerative colitis. In a mixture with glycerin, it was applied on a tampon for eroded cervix and nonspecific vaginitis with leucorrhea.[29]

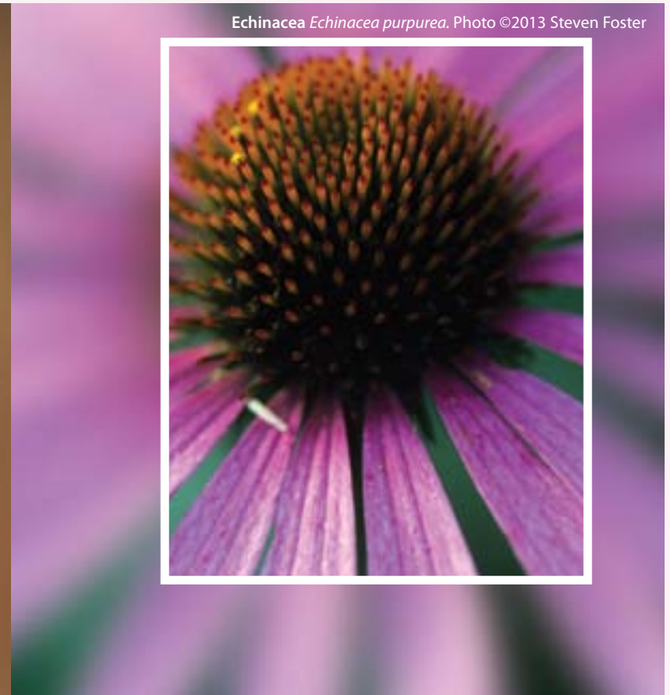
Notable natural medicines excluded from this compendium[29] were opiates and antibiotics. The absence of antibiotics is particularly noteworthy because their use had been addressed positively by John Bastyr, the renowned naturopathic physician, in an article in the *Journal of the American Naturopathic Association* in 1950.[30] He discussed in detail the use of penicillin, streptomycin, aureomycin, bacitracin, polymyxin, neomycin, terramycin, and others. These products were considered by Dr. Bastyr to be appropriate for use on a selective basis, being derived from lower plant life forms according to the taxonomic classifications of that time.

Naturopathic physicians treated many infectious diseases without modern antibiotic medicines. This was primarily due to the disruptive effects that these powerful medicines had on symbiotic bacteria in the intestines. Natural methods of destroying germs and stimulating natural immunity were used preferentially.[31] Dr. Bastyr[30] specifically noted the antibacterial efficacy of allicin from garlic (*Allium sativum*, Liliaceae) and extracts of sagebrush (*Artemisia tridentata*, Asteraceae), juniper (*Juniperus communis*, Cupressaceae), and buttercups (*Ranunculus* spp., Ranunculaceae), when prescription antibiotics were inappropriate or if a change of therapy was required.

Echinacea *Echinacea angustifolia*. Photo ©2013 Steven Foster

Dr. Bastyr also used *E. angustifolia* root tincture internally for the treatment of septicemia, pyuria (pus in the urine), and gangrene.[32] He administered it to treat coughs and colds, and to boost deficient immune function in many infections. For the treatment of infections, echinacea was used frequently in combination with other immune-enhancing and antimicrobial botanicals. A fundamental formula used by Dr. Bastyr combined four parts *E. angustifolia* root extract, four parts goldenseal (*Hydrastis canadensis*, Ranunculaceae) rhizome extract, and one part poke (*Phytolacca americana*, Phytolaccaceae) root extract. He also spoke highly of adding wild indigo (*Baptisia tinctoria*, Fabaceae) root to this formula. He often would combine five parts echinacea with one part wild indigo for infections, and administer 60 drops three times daily. He used diluted echinacea extract topically to treat decubitus ulcers as well.

A modern *E. angustifolia* fresh root (1:1) 65% ethanol extract (Specific Echinacea Extract, Eclectic Institute, Inc.; Sandy, Oregon [manufactured using the Lloyd extractor]) administered orally to six male rats in their drinking water for six weeks recently was shown to increase the initial antigen-specific day 0 induction of immunoglobulin G (IgG) antibody response after seven days and subsequent day 10 antigen inductions of IgG on days 14, 21, 24, and 27, in a statistically significant manner compared with four control rats (range, P=0.04 to P=0.002).[33] Non-significant IgG increases also occurred on days 10, 18, and 32, but not after the third antigen challenge on day 35. Although increases in antigen-specific immunoglobulin M occurred on all of the aforementioned days, as well as on days 35 and 39, none of these increases were significant compared with control animals. These results suggest that this fresh root extract may enhance subacute immune responses by increasing antigen-specific antibody production.



Echinacea *Echinacea purpurea*. Photo ©2013 Steven Foster

Introduction of *Echinacea purpurea*

Other *Echinacea* species (*e.g.*, *E. pallida* root in the fourth [1916] and eighth [1946] editions of the *National Formulary*[12,25]) sometimes were used as substitutes for *E. angustifolia*.[28] *Echinacea purpurea* was mentioned by Dr. John King in his Eclectic *American Dispensatory* (1853) as a remedy deserving "a full and thorough investigation from the profession;"[1] at that time, *E. purpurea* also was known by the synonym *Rudbeckia purpurea* and occasionally was confused with *E. angustifolia*, although rarely used by the Eclectics.[1]

Echinacea angustifolia had been introduced into homeopathic practice in Europe in the late 19th century. Because of a severe shortage of this drug in Europe in the 1930s, the German phytopharmaceutical manufacturer Gerhard Madaus went to the United States to obtain seeds of *E. angustifolia*; however, he mistakenly bought *E. purpurea* seeds.[34,35] Consequently, Madaus decided to extract the juice from the aboveground (aerial) part of the blooming *E. purpurea* plant.[35] Preserved with 22% alcohol, *E. purpurea* plant juice with cichoric acid and water-soluble arabinoxylan and arabinogalactan polysaccharides is distinct from *E. angustifolia* root extracts in greater than 50% ethanol with echinacoside and is distinguishable from lipophilic alkamides.[36] Because *E. purpurea* juice previously had not been used clinically, Madaus experimented with its use. Since then, much European research on *Echinacea* has used this preparation (Echinacin®, Madaus AG; Koln, Germany) or similar preparations internally and externally.[34-36]

In the 1950s, the Swiss naturopath Alfred Vogel[37] traveled to America and learned the native uses of *E. angustifolia* from Native Americans of the Lakota (Sioux) tribe in South Dakota. Finding that the related species *E. purpurea* was effective and easier to harvest, he returned with seeds of this species to cultivate in the Swiss "lowlands" at 4,500 feet above sea level (ca. 1,600 m). After 10 years, when these plants had acclimated sufficiently to produce flowers, he began using the tincture of the whole fresh plant to strengthen the immune response to infectious conditions. Vogel's *E. purpurea* extract combines 95% aerial plant with 5% roots in 65% ethanol (Echinaforce®, Bioforce AG; Roggwil, Switzerland).

In 1989, the German Commission E officially approved the fresh-flowering *E. purpurea* aboveground plant and its preparations for "supportive treatment" of colds and chronic infections of the respiratory and lower urinary tracts, and, externally, for poor wound healing. In 1992, *E. pallida* fresh or dried root was recognized officially by the Commission E as supportive therapy in influenza-like infections, particularly the 50% alcoholic tincture. However, the roots of *E. purpurea* and *E. angustifolia* were not approved, due to lack of adequate clinical data available at the time.[38] *Echinacea purpurea*, *E. angustifolia*, and *E. pallida* roots are phytochemically distinctive (Table 2).[36] Surprisingly, although water extracts of *E. purpurea* roots were potent against influenza virus, and although ethanolic fractions and alkamides of *E. angustifolia* root inhibited rhinovirus *in vitro*, the *E. pallida* root water and ethanolic fractions were ineffective against both.[39] European experience and clinical research with the

cultivated *E. purpurea* plant led to its popularization in the current American marketplace.

Randomized and Controlled Therapeutic and Prevention Trials With *Echinacea* Extracts for Upper Respiratory Tract Viral Infections

Recent clinical trials of commercial *E. purpurea* fresh plant liquid preparations and extracts have been well publicized and consistently demonstrate efficacy against acute upper respiratory tract viral infections. A 2007 meta-analysis[40] of 14 studies among various *Echinacea* products evaluated randomized, controlled trials that studied a total of 1,356 patients for incidence and 1,630 patients for duration of the common cold. It showed that the use of these preparations decreased the chance of developing a cold by 58% and reduced the duration by a mean of 1.4 days. The 14 preparations in the meta-analysis included seven from *E. purpurea*, four from a combination of *E. purpurea* and *E. angustifolia*, one from *E. angustifolia* only, one from *E. pallida*, and one from an unidentified species. Significant reductions in occurrence and duration of the common cold were observed based on a subgroup analysis limited to five *E. purpurea* aerial plant juice investigations.

A 2006 systematic review[41] of 16 randomized, controlled trials for the common cold was performed for heterogeneous *Echinacea* preparations**.** In two prevention trials, 411 subjects received *Echinacea* products, while five trials involved self-treatment (1,064 subjects), and nine trials studied clinically treated upper respiratory tract viral infections (1,126 subjects). This review identified no preparation with evidence of benefits for prevention but concluded that preparations based on *E. purpurea* aerial parts may be effective for early treatment of colds. Because other preparations were not phytochemically comparable, variations in the studies provided no clear evidence of their efficacy.

The single, randomized, placebo-controlled, double-blind study[42] of *E. angustifolia* performed using three noncommercial extracts of two-year-old fresh roots to prevent or treat colds induced by rhinovirus type 39 in 399 volunteers was possibly the most publicized investigation; this study was funded by the US National Institutes of Health (NIH), and results were published in the *New England Journal of Medicine*. These extracts, made with supercritical carbon dioxide, 60% ethanol, or 20% ethanol, produced no tendency toward improvement when used for one week after virus exposure. For volunteers treated one week before and one week after exposure, clinical colds developed in 50% of participants receiving the 20% ethanol extract, in 57% receiving the 60% ethanol extract, in 62% receiving the supercritical carbon dioxide extract, and in 66% receiving placebo. The mean total symptom score was 12.1 for patients receiving the 20% extract, 13.2 for those receiving the 60% ethanol extract, 15.5 for those receiving the supercritical carbon dioxide extract, and 15.1 for those receiving placebo. However, none of the differences were statistically significant compared with placebo.

This study[42] has been criticized for insufficient dosage (900 mg of root extractives vs. recommendations of a daily dose of 3 g by the World Health Organization and the Canadian Natural Health Product Directorate), inadequate validation of species identity, and limitation to one of more than 100 subtypes of rhinovirus.[43] However, the daily dose in an *E. pallida* study[44] of 160 patients with flu-like infections was extracted from 900 mg of root, which significantly reduced the illness duration, symptom scores, and clinical scores compared with placebo.

Although two authors of the NIH study[42] had previously acknowledged that the geographic location of growing *E. angustifolia* and the time of its harvest affect the chemical composition,[45] neither of these factors was described in the 2005 study[42] in characterizing the roots obtained from a German company (presumably cultivated in Europe). While the supercritical carbon dioxide extract contained 74% alkamides and no polysaccharides or caffeic acid derivatives, the 60% ethanol extract had an uncharacteristically high 49% total polysaccharides, 2.3% alkamides, and 0.16% cynarin.[42] The 20% ethanolic extract with 42% polysaccharides and 0.1% alkamides contained no caffeic acid derivatives. The polysaccharide content was not profiled on the basis of molecular weight but only on relative monosaccharide content, which is of no real value.

The high polysaccharide content of the 60% ethanol extract and the low or 0% content of caffeic acid derivatives (especially echinacoside) in all three extracts suggest that the roots used were not equivalent to "wild-crafted" roots traditionally favored and now used in some commercial echinacea products sold in North America. However, whether or not the lack of efficacy of these experimental *E. angustifolia* root extracts against a single rhinovirus subtype is accepted as legitimate evidence of its clinical effect on the common cold, this application is not representative of the traditional empirical use of this species.

On the other hand, success for prevention of the common cold was shown over a four-month period in a large randomized, double-blind, placebo-controlled study published in 2012. A total of 355 patients took a liquid 57% ethanolic extract of the fresh *E. purpurea* aerial plant (95%) and root (5%) (Echinaforce®, Bioforce; Roggwil, Switzerland) versus 362 taking a placebo. A dose of 0.9 ml, three times daily (from 2,400 mg herb/day) was used, except during acute stage of colds that developed when the dose was increased to five times daily (4,000 mg/day). The extract was diluted in water and held in the mouth for 10 seconds before swallowing. Though the extract group had a history of significantly greater susceptibility to cold infections, it had significantly fewer cold episodes and episode days (each 26% less). Recurrent infections were significantly decreased with echinacea extract (59% less), while use of concurrent pain medications aspirin, acetaminophen, and ibuprofen were also significantly fewer with the extract (52% less). There were no significant differences between adverse effects or tolerability between the two groups over the four-month period, indicating safe long-term use.[46]

Table 2. Some Phytochemical Distinctions Among Popular *Echinacea* Crude Herb Parts[36]

Major Phytochemical	*Echinacea purpurea* Aerial Plant	*Echinacea purpurea* Root	*Echinacea angustifolia* Root	*Echinacea pallida* Root
Hydrophilic				
Polysaccharides	Present (*e.g.*, arabinoxylans, arabinogalactans)	Present (*e.g.*, fructosans, arabinogalactans)	Present (*e.g.*, 5.9% inulin)	Present
Glycoproteins	…	Present	Present	Present
Caffeic acid derivatives	Present (*e.g.*, 1.2%-3.1% cichoric acid in flowers)	Present, 0.6%-2.1% (*e.g.*, cichoric acid)	Present (*e.g.*, 0.3%-1.8% echinacoside, cynarin)	Present (*e.g.*, 0.7%-1.0% echinacoside
Flavonoids	Present, 0.48% (*e.g.*, quercetin and kaempferol)	…	…	…
Lipophilic				
Alkamides	Present, 0.001%-0.04%[A] [0.02%-0.39% [B]]	Present, 0.001%-0.04%[A] [0.12%-1.21% [B]]	Present, 0.01%-0.15%[A]	
Ketoalkynes, ketoalkenes	…	…	…	Present
Essential oils	Present, 0.08%-0.32%	Present, ≤0.2%	Present, <0.1%	Present, 0.2%-2.0%

[A] Results from Bauer and Remiger (1989) indicate these percentages describe the major dodeca-2E, 4E, 8Z, 10E/Z-tetraenoic acid isobutylamide content only, as for *E. purpurea* aerial parts (0.001-0.03%) and roots (0.004-0.039%).[60]
[B] Results from Stuart and Wills (1999) analysis of total alkamide contents of 62 commercial samples of *E. purpurea* from Australia.[61]

Echinacea *Echinacea purpurea*. Photo ©2013 Steven Foster

Contraindications and Potential for Drug Interactions

The German Commission E monographs[38] for the approved *E. purpur*ea herb and *E. pallida* root and for the unapproved *E. purpurea* root, *E. pallida* herb, and *E. angustifolia* herb and root, speculate that risks warrant avoidance of use in cases of systemic diseases such as tuberculosis, multiple sclerosis, leukosis, collagenosis, AIDS or HIV infection, and autoimmune diseases. These contraindications remain controversial, as they are theoretical and not based on any actual clinical data. Reactions may occur in allergic individuals, especially when aerial parts are used.[47]

Legitimate concerns about combining *Echinacea* species preparations with pharmaceutical drugs are also largely speculative and are based on *in vitro* research. For example, as a precaution, patients undergoing organ transplantation who take immunosuppressive drugs, such as cyclosporine, should avoid the use of *Echinacea* preparations or should consider short-term use.[46] *Echinacea purpurea* root extract (oral dose of 1.6 g/day) for eight days increased the clearance and reduced the bioavailability of intravenous midazolam when this cytochrome P450 (CYP) 3A4 substrate was

administered to 12 subjects; the same dose of *E. purpurea* root extract did not alter oral midazolam clearance, suggesting that some extract components inhibit intestinal CYP3A, while other absorbed components induce liver CYP3A.[48] In a 15-day open-label trial with 15 HIV patients receiving antiretroviral treatment with darunavir/ritonavir, 500 mg of *E. purpurea* root extract (Arkocapsulas Echinacea, Arkopharma; Madrid, Spain) given every six hours for 14 days was well tolerated and did not significantly affect the drug pharmacokinetics.[49] *Echinacea angustifolia* root tincture is a potent CYP3A4 inhibitor *in vitro*, more so than tincture of *E. purpurea* roots,[50] but this has not been verified in human studies.

When an *E. purpurea* whole plant extract was given orally in a 1.6 gram daily dose to 12 healthy humans for 28 days, no significant effect on oral sedative midazolam was detected.[51‡] An 8:1 extract of the whole fresh plant (Echinamide, Natural Factors Nutritional Products, Inc.; Everett, WA) was given in doses of 750 mg daily for 28 days to 16 healthy humans who were taking the antiretroviral combination drug lopinavir-ritonavir for 15 days prior and then 14 days with the extract. After the 14 combination days, there was no change in lopinavir bioavailability. After the extract had been administered for 28 days, single doses of fexofenadine and midazolam were administered; the midazolam bioavailability was significantly reduced, but fexofenadine pharmacokinetics were not significantly altered. This extract was shown to have a modest inducing effect on CYP3A as shown with midazolam, but not enough to counter the CYP3A inhibiting effect of ritonavir. It had no impact on P-glycoprotein efflux of fexofenadine.[52]

Most conventional pharmaceutical drugs, including the macrolide antibiotics clarithromycin and erythromycin, are metabolized by CYP3A4. A theoretical interaction between CYP3A4 substrates and *E. angustifolia* root tinctures is limited to *in vitro* data, while human research on the effects of *E. purpurea* root and whole plant extracts on this enzyme is equivocal; due to variations in preparations and outcomes, the current body of human research is too limited to predict pharmacokinetic or pharmacodynamic interaction outcomes with certainty, and little evidence exists to support significant clinical interactions with medications.[53]

Endangerment and Cultivation

The issue of sustainable harvest of wild-crafted *E. angustifolia* has been raised,[54] yet it remains abundant in central Kansas, despite more than 100 years of commercial harvesting and digging booms.[55] Because seeding in November yields the highest emergence for *E. angustifolia* plants in Nebraska,[56] harvesting in the autumn and reseeding holes with the dry flower heads is a way to diminish loss from wildcrafting.

Echinacea angustifolia still grows over much of its historical range. Its global conservation status is ranked G4, *i.e.*, "apparently secure." In Kansas, where several generations of the same families have dug this species since the early 1900s, tagging pick-holes showed a regrowth potential of 36%, and measuring harvest density confirmed that the stands were not significantly diminished; areas that lay fallow for two-to-three years after harvesting allow more growth of the small roots and regrowth from remnants of larger harvested roots.[57]

Cultivation of *Echinacea* has increased rapidly because of the demand and its great value. Growth of the three major medicinal species, *E. angustifolia*, *E. pallida*, and *E. purpurea*, has been the most studied.[58,59] *Echinacea purpurea* is easy to grow compared to the other two commercial species.[59]

Conclusions

The traditional clinical applications of *E. angustifolia* root hydroalcoholic extracts demonstrate their empirical usefulness. Simultaneous internal and local use was believed to increase efficacy. The historical use of *E. angustifolia* extracts to treat serious infectious diseases suggests that an advantage could be gained if they were given to complement conventional antibiotics. Clinical studies to investigate this possibility appear warranted, given the increasing incidence of antibiotic resistance.

However, positive evidence from clinical research on *E. purpurea* fresh plant liquid extracts for the treatment, and recently for the prevention, of upper respiratory tract viral infections has focused most attention in regard to commercial *Echinacea* species on this important use. *Echinacea angustifolia* also has been combined with *E. purpurea* in effective preparations for treating colds. Consequently, the recognition of *E. angustifolia* use for other infectious conditions has diminished, as conventional medicine inexorably depends on antibiotics.

Although sharing some similarities, selective use of *Echinacea* species, parts, and their preparations seems most appropriate for conditions established through empirical tradition (*e.g.*, *E. angustifolia* root high-ethanol extracts internally and locally for treating sepsis, wounds, and bites) or through modern clinical research (*e.g.*, fresh *E. purpurea* plant products for prevention and/or treatment of upper respiratory tract infections). The safety of *Echinacea* products is a major advantage, with few theoretical contraindications or individual allergic sensitivities. *Echinacea* popularity has resulted in regional overharvesting of wild *E. angustifolia*. Nonetheless, commercial cultivation of *E. purpurea* and conscientious wildcrafting can continue to provide a sustainable supply of these important botanical medicines. HG

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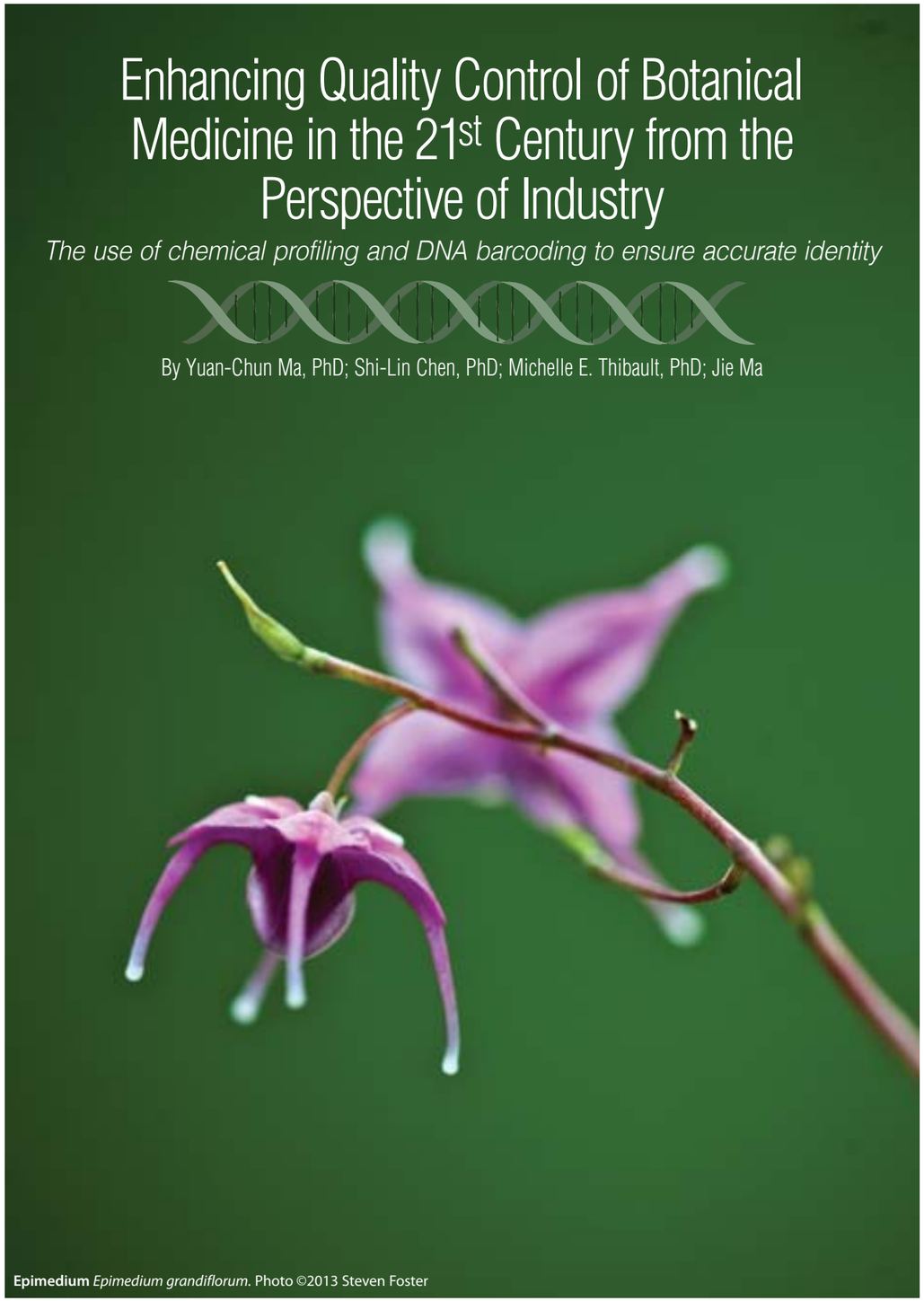
‡ Characterization is obscure; on page 431 it states it was purchased from Wild Oats Markets, Inc. (Boulder, CO). There was no standardization claim. On page 435, it specifies the *E. purpurea* product is a whole plant extract.

Enhancing Quality Control of Botanical Medicine in the 21st Century from the Perspective of Industry

The use of chemical profiling and DNA barcoding to ensure accurate identity

By Yuan-Chun Ma, PhD; Shi-Lin Chen, PhD; Michelle E. Thibault, PhD; Jie Ma



Epimedium *Epimedium grandiflorum*. Photo ©2013 Steven Foster

Introduction

Herbal products are growing increasingly popular in North America, including those derived from North American and European herbal traditions, Traditional Chinese Medicine, and Ayurveda. However, there are problems with many products on the market today. Misidentification of plant species, adulteration with counterfeit ingredients, insufficient quantities of the known primary active ingredients, and spiking with marker compounds commonly occur.

Manufacturers of many consumer products that include medicinal plant ingredients have an obligation to ensure that the products they sell are genuine and safe; marketers of food products containing so-called "medicinal botanicals," including dietary supplements in the United States, usually have no regulatory requirements to ensure that their products are effective (unless certain limited health-related claims are made).

Adulteration via species substitution may occur accidentally or intentionally using closely related or completely unrelated species. Thus, the first step in quality control must be proper identification of each ingredient. Botanical medicinal materials are identified by their organoleptic (color, taste, fragrance, etc.), morphological (shape), microscopic, and/or chemical chromatographic characteristics, *e.g.*, by the use of thin-layer chromatography (TLC) and/or other chromatographic methods. Someone who is not sufficiently knowledgeable of the plants in question will not be able to accurately identify botanical ingredients. Many closely related species share morphological features and/or common names, which can lead to potential confusion and accidental adulteration. Furthermore, most herbs are sold partially processed — dried, cut into pieces, shredded, or even powdered — such that macroscopic morphological identification of the plant part (flowers, leaves, roots, etc.) is no longer possible, although microscopic and chromatographic identification can still be performed.*

Reliable analytical methods are needed to supplement these typical protocols for identification of botanical medicinal materials. Chemical profiling using TLC, high-performance TLC (HPTLC), gas chromatography (GC), and high-performance liquid chromatography (HPLC) is common, and such profiles are documented in herbal monographs found in resources such as the *American Herbal Pharmacopoeia*, the *United States Pharmacopeia*, the *Pharmacopoeia of the People's Republic of China*, and the *Journal of the Association of Official Analytical Chemists*. In addition, techniques such as near-infrared (NIR) and nuclear magnetic resonance (NMR) spectroscopy are becoming more common in the scientific community. However, it must be considered that the chemical profile of an herb may vary due to factors such as growth stage, plant part, geography, and post-harvest processing and storage, which is why multiple reference materials must be used to statistically overcome such variations.†

DNA barcoding is growing in popularity as a means of species identification.[1] In October 2011, the US Food and Drug Administration (FDA) formally approved the use of DNA barcoding for the identification of seafood in order to counteract the widespread practice of substituting and mislabeling cheaper or undesirable species of fish and seafood as more expensive species.[2] Simultaneous with this announcement, FDA released a validated laboratory method for the DNA barcoding of fish species for the purposes of regulatory compliance.[3] We propose that DNA barcoding be added in the future to the quality control toolbox for medicinal botanical identification, alongside organoleptic, microscopic, and chemical profiling.

What Is DNA Barcoding?

DNA barcoding is the use of a short region of DNA to identify species.[4] The first step to obtaining a DNA

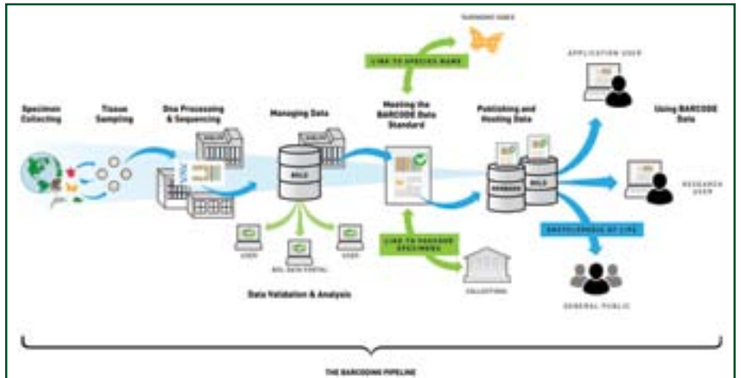


Figure 1: DNA barcoding (graphic from www.barcodeoflife.org/content/about/what-dna-barcoding). Reprinted with permission from the Consortium for the Barcode of Life.

* Responsible companies should require their qualified suppliers to carry out suitable identification tests, including appropriate macroscopic examination, prior to particle size reduction and also require their supplier's quality control unit to retain samples of the whole, uncut starting material so that the companies can trace back and re-test such material at a future date in the event of a problem requiring rapid investigation, for example, a quality problem (adulteration, contamination, etc.) or, in a worst-case scenario, a product recall.

†This may seem self-evident. In the context of pharmacopoeias mentioned in the previous sentence, these factors are accounted for in the establishment of a monograph. If a material does not test in conformance with all of the qualitative and quantitative limits in the monograph, then a company producing botanical products with the intention that they should provide a therapeutic or other health benefit likely should reject the material as it would be indicative of one or more problems at source, such as having been harvested at the wrong growing stage (*e.g.*, immature) or wrong plant part (*e.g.*, should be all leaf but contains a high percentage of stems), or having been grown in the wrong climate such that secondary metabolites never developed due to lack of stress conditions.

A great deal of work is still needed before DNA barcoding of plants can be considered sufficiently reliable for widespread practical application.

barcode is the extraction of DNA from a small sample of the specimen. Second, the selected barcode region undergoes polymerase chain reaction (PCR) amplification, or copying. Third, the PCR-amplified product is purified and sequenced (the order of nucleotides read). Finally, the DNA sequence is compared to the sequences in a library to identify the species in question. Figure 1 illustrates the DNA barcoding process.

PCR amplification entails multiple cycles of a three-phase process. The double-stranded DNA is denatured (separated into its individual strands) at a high temperature. Next, the temperature is lowered and sequence-specific primers (short sequences of 20 or so nucleotides) attach to sites neighboring the target sequence. Primers are required as the DNA polymerase can only add new nucleotides to an existing piece of double-stranded DNA. Finally, the DNA polymerase uses the single strand of DNA as a template to extend the sequence from the primers. This new product then becomes the template for the next cycle. The cycles are repeated 20 to 30 times, generating thousands to millions of copies of the target DNA sequence.

Table 1. Databases containing plant DNA sequences

Database	Web Address
GenBank	www.ncbi.nlm.nih.gov/genbank
Barcode of Life Database (BOLD)	www.boldsystems.org
IdIt-ITS2	http://its2-plantidit.dnsalias.org
IdIt-PsbA-TrnH-IGS (PTIGS)	http://psba-trnh-plantidit.dnsalias.org
Medicinal Materials DNA Barcode Database (MMDBD)	www.cuhk.edu.hk/icm/mmdbd.htm
DNA QR Code	http://qrfordna.dnsalias.org

Standardization, minimalism, and scalability are key factors in the application of DNA barcoding. Practically speaking, this means that one or a few standard regions of a limited number of DNA base pairs (usually 200 to 1,000) must be chosen so that they can be sequenced readily in a large and varied sample set, enabling comparison of the data and allowing for species identification.[5] As a corollary, the inter-species variation in the DNA sequence should be much larger than the intra-species variation. In animals, a fragment of the cytochrome *c* oxidase 1 (CO1) gene has been accepted as the standard DNA barcode. In plants, however, no single region has been found that meets all of the criteria of universality (ease of sequencing in all land plants), sequence quality, and species discrimination. The Consortium for the Barcode of Life (CBOL) has proposed the combination of the *matK* and *rbcL* genes as the core plant barcode, though it recognizes that *matK* + *rbcL* may at times need to be supplemented with other markers.[6] Specifically, *matK* cannot always be amplified and sequenced, though its species discrimination is high, while *rbcL* is easy to amplify and sequence, but its species discrimination is low. The internal transcribed spacers of nuclear ribosomal DNA (nr ITS/ITS2) and the chloroplast intergenic spacer *psbA-trnH* have been proposed as alternates to *matK* + *rbcL*,[5] and, in fact, the China Plant Barcode of Life group has suggested the addition of ITS, or ITS2 when ITS cannot be successfully sequenced, to the core plant barcode of *matK* + *rbcL*.[7]

The biggest challenge thus far in DNA barcoding of plants has been that good, universal primers for plant marker barcodes can be difficult to design. Amplification and/or sequencing of a given marker may be possible only in certain families of plants. For a particular marker, genetic gaps between species may be large in some groups of plants, but not in others.[8] For these reasons, it appears that several markers, alone or in combination, will be required for the DNA barcoding of plants, rather than the single CO1 marker prevalent in the DNA barcode analysis of animals.

A further problem with DNA barcoding of plants is that many plants lack barcodes altogether, and there is not yet a universal database of plant barcodes.[9] However, as a major use of DNA barcoding is the identification of unknown specimens, non-chemistry specialists such as customs officers, producers of traditional medicines, pharmaceutical manufacturers, and forensics investigators may welcome a relatively rapid and simple — albeit still imperfect — method for the identification of botanical products.[10] Nevertheless, a great deal of work is still needed before DNA barcoding of plants can be considered sufficiently reliable for widespread practical application.

GenBank is a database of all publicly available DNA sequences and is part of the International Nucleotide Sequence Database Collaboration, which also includes the DNA DataBank of Japan and the European Molecular Biology Laboratory. These three organizations exchange data on a daily basis. Databases specific to DNA barcodes include the Barcode of Life Database,[11] which is based on the *matK* + *rbcL* combination, as well as the IdIt-ITS2 and PTIGS (IdIt-*psbA-trnH*-IGS) databases, which are based on ITS2 and *psbA-trnH*, respectively.[12,13]

Of particular interest and use to those in industries or markets that utilize medicinal plants as ingredients is the Medicinal Materials DNA Barcode Database (MMDBD).[14] At the time of its 2010 publication, the database contained more than 18,000 sequences from 1,259 species, representing 66.5% and 84.5% of the medicinal materials listed in the 2005 *Pharmacopoeia of the People's Republic of China* and the *American Herbal Pharmacopoeia*, respectively. As of May 2012, the MMDBD featured more than 31,000 barcode sequences from more than 1,650 indexed species. Core and supplementary DNA barcodes for medicinal materials listed in the above pharmacopeias and other sources are included, as well as information on adulterants and substitutes, photographs of the medicinal materials, PCR conditions, and literature references. The database can be searched by keyword or sequence similarity, and researchers can upload their DNA barcode sequences to help expand the database.‡

Finally, Liu *et al*. have established a web application that will convert a DNA barcode into a two-dimensional Quick Response (QR) Code for use in practical applications — in essence, barcoding the barcode.[15] The user can retrieve the DNA sequence and QR code for a species of interest, convert a sequence to a QR code and vice-versa, or search the database using a QR code to identify a sample. This leads one to envision a system in which an herbal material is labelled with its QR DNA barcode as a means of inventory tracking.

Undoubtedly, DNA barcoding of plants will improve with advances in PCR amplification and DNA sequencing technology. Identification of plants will be enhanced with better access to authenticated botanical DNA libraries that contain more species and more samples of each species.

DNA Barcoding of Botanical Medicines

According to surveys in China, medicinal plants comprise more than 11,000 species in 2,300 genera and nearly 400 families. Quick and accurate authentication of these plants and their adulterants can be difficult on an international trade scale. Shi-Lin Chen, PhD, an author of this article, and colleagues at the Institute of Medicinal Plant Development in Beijing have been dominant in the field of DNA barcode analysis of botanical medicines. Chen *et al*. investigated different DNA regions for the purpose of barcoding plants found in the traditional Chinese *Materia Medica*, both in terms of PCR efficiency and species identification.[10] The PCR efficiency for both ITS2 and *psbA-trnH* was greater than 90 percent. Furthermore, *psbA-trnH* was more successful for some plants such as ferns. The identification rate of ITS2 was 92.7% and 99.8% at the species and genus levels, respectively, for 6,685 samples from 4,800 species in 753 genera of 193 families. In contrast, *psbA-trnH* correctly identified only about 70 percent of the species, though it was more than 95 percent accurate at the genus level for 2,108 samples from 1,433 species in 551 genera of 135 families. They proposed the use of ITS2, supplemented by *psbA-trnH*, as the standard barcode for international trade and safe use of medicinal plants.

In an additional study, Yao *et al*. evaluated the ITS2 sequences of 50,790 plant samples available in GenBank. Species identification rates ranged from 67 percent to 88 percent.[12] A recent review article by Chen *et al*. summarized their work on the families Rosaceae, Fabaceae, Asteraceae, Rutaceae, Euphorbiaceae, Polygonaceae, and the genera *Paris* (Melanthiaceae), *Lonicera* (Caprifoliaceae), *Dendrobium* (Orchidaceae), *Cistanche* (Orobanchaceae), *Panax* (Araliaceae), and *Datura* (Solanaceae), as well as medicinal pteridophytes and cortex herbs (medicinal materials from the bark of stems or roots).[16]

The *Journal of Systematics and Evolution* recently published a special issue on plant DNA barcoding in China.[17] In particular, Li *et al*. reviewed more than 125 studies on the application of DNA barcodes to the identification of more than 75 different Chinese herbal medicinal materials.[18] They concluded that DNA barcoding of medicinal plants is still a work in progress, but that it holds great promise for future applications in taxonomy, biodiversity, conservation, the pharmaceutical industry, and foren-

Eleuthero *Eleutherococcus senticosus*. Photo ©2013 Steven Foster

‡The PPRC 2010 has 2,165 botanical monographs including Chinese *Materia Medica* crude drugs, crude drug preparations, prepared slices, patent Chinese traditional medicines, oils and extracts. So far the AHP has published 33 monographs.

DNA barcoding is an excellent solution for identifying raw or dried plant products.

sics; the authors proposed that future work should focus on reliable species identification and barcoding multiple samples of each species to help build the reference database for Chinese medicinal plants. The Chinese Pharmacopoeia Commission, recognizing the value of DNA barcoding for the authentication of medicinal materials, has included protocols and DNA barcodes for some animal-derived traditional Chinese medicines in the 2010 edition of the *Pharmacopoeia of the People's Republic of China*, such as *Wushaoshe* (Chinese rat snake; *Zaocys dhumnades*, Colubridae) and *Qishe* (Chinese moccasin; *Agkistrodon acutus*, Viperidae).[18,19] Work is underway on drafting guidelines for the identification of Chinese herbal medicines using DNA barcodes, potentially to be included in the 2015 edition (Hui Yao email to M. Thibault, September 5, 2012).

An Explanation of Chemical Profiling

DNA barcoding is an excellent solution for identifying raw or dried plant products. However, many botanical products are sold as liquid or powder extracts. The alcohol and heat used during the extraction process filters out or eliminates most cellular data and denatures proteins and DNA, rendering DNA barcoding unfeasible. Consequently, chemical identification of marker compounds must be utilized.

Raw herbs and extracts possess a characteristic botanical profile of phytochemicals. Initially, one or two of these phytochemicals were used as marker compounds for the purpose of qualitative and quantitative quality control, which led to spiking with low-quality or fraudulent botanical extracts containing the marker compounds by unscrupulous producers. With the technological advances of the last 20 years, simultaneous analysis for multiple chemical constituents is possible. Thus, many herbs and botanical extracts are now analyzed for several marker compounds as a means of circumventing potential spiking issues. For example, *Rhodiola rosea* (Crassulaceae) root extracts were formerly standardized only for salidroside. After the discovery of widespread substitution of other *Rhodiola* species for *R. rosea*, the latter extracts are now standardized for salidroside and rosavins. Rosavins are unique to *R. rosea*, whereas salidroside is found across the *Rhodiola* genus and in some plants outside the genus.[20]

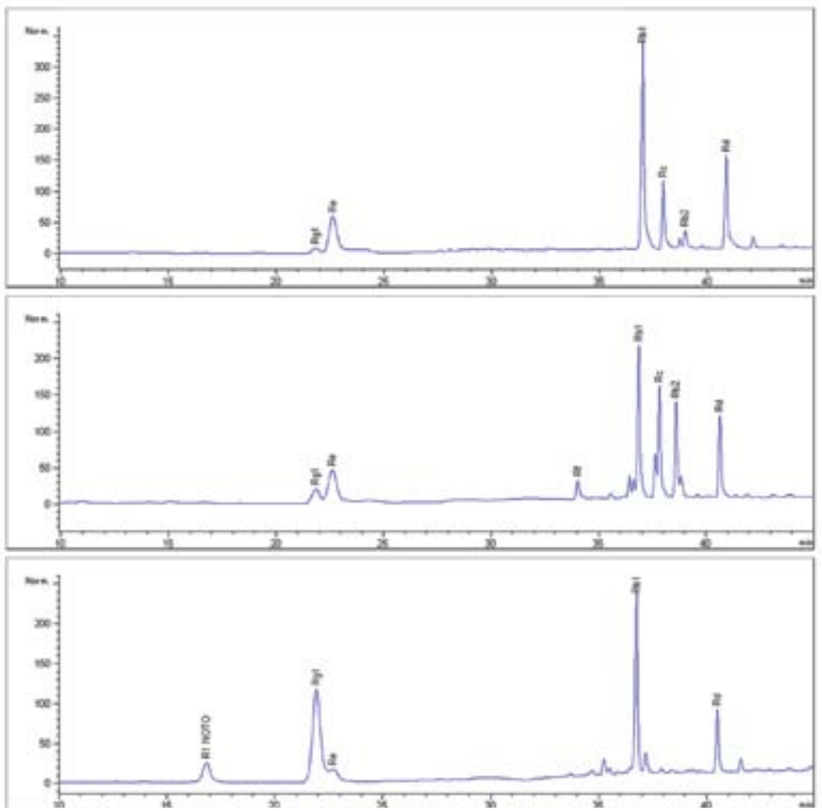


Figure 2. HPLC profiles for American ginseng roots (top), Asian ginseng roots (middle), and notoginseng roots (bottom). These methods take 45 minutes to run.

HPTLC is a simple, rapid, economical, and qualitative method of identification. It allows for the natural variability within a plant and can be used even when many chemical components of the sample are unknown. Reference compounds, plant samples, and adulterants can be compared in a parallel, high-throughput fashion. In addition, the multiple chemical components of an herb are often present in a consistent ratio to one another. HPLC commonly is used to separate and quantify these constituents, which results in a characteristic profile, or fingerprint, of the herb or extract. Manufacturers can use these profiles to help optimize their extraction procedures, such that the resultant extract has the same profile as the initial raw herb. This is beneficial to herbalists, naturopaths, integrative physicians, and other traditional medicine practitioners who have a holistic view of herbs and healing.

Over the last 20 years, there have been thousands of publications discussing the HPLC profile of popular herbs. As mentioned earlier, many pharmacopoeias include HPLC methods and profiles for quality control in the botanical industry. The Canadian Phytopharmaceuticals Corporation has established a proprietary database of HPLC profiles for more than 100 North American, South American, European, Ayurvedic, and traditional Chinese botanicals and extracts. Shown in Figure 2 are the HPLC profiles developed by this *HerbalGram* article's co-author, Ma, and colleagues in the 1990s for American ginseng (*Panax quinquefolius*, Araliaceae), Asian ginseng (*P. ginseng*), and notoginseng (*P. notoginseng*).[21,22] Each of these species has a characteristic ratio of ginsenosides that distinguish one from the other.

With advances in technology — such as the development of Ultra High-Performance Liquid Chromatography (UHPLC, also commonly referred to as UPLC), gradient elution, multi-wavelength detectors, and other types of detectors — analytical methods have become much more powerful and simple. UHPLC offers significant time and cost savings over conventional HPLC, due to its shorter run times and concomitant reduced solvent usage. Thus, returning to the example of the three *Panax* species, the UHPLC profiles developed in the 2010s are completed in half the time but maintain the same appearance as the earlier HPLC profiles (Figure 3). In a further development, a method recently was established in which the three *Panax* species, alone or in combination with *Epimedium* leaves (Berberidaceae), could be quantified in just four minutes as compared to the 45 minutes required by the HPLC method.[23]

Remedies developed by traditional Chinese and other herbal medicine practitioners often involve combinations of herbs. Method development for the HPLC fingerprinting

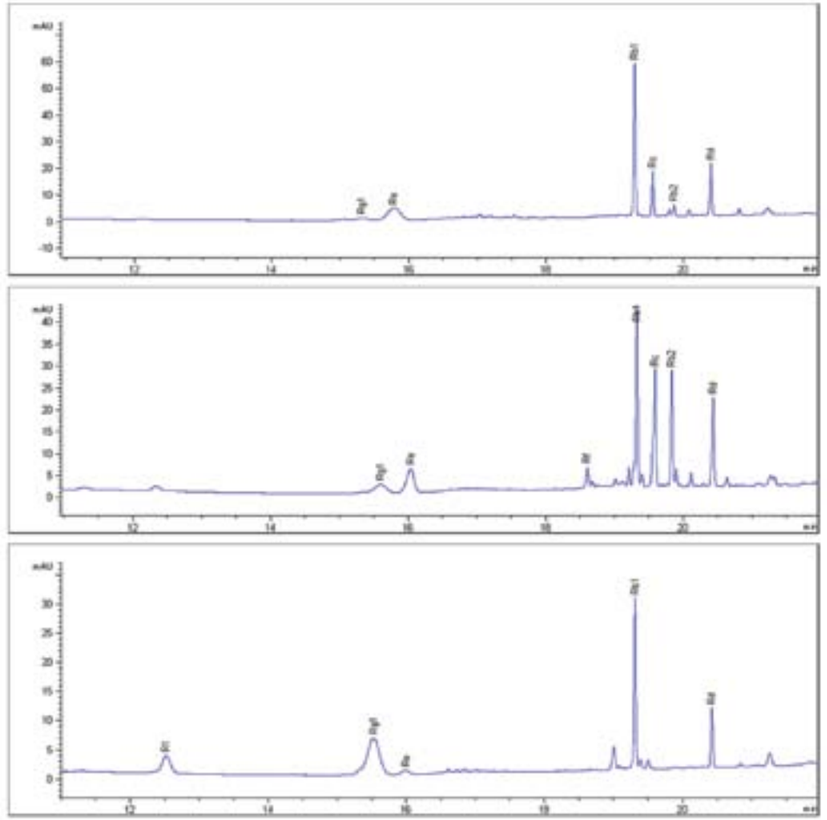


Figure 3. UHPLC profiles for American ginseng roots (top), Asian ginseng roots (middle), and notoginseng roots (bottom). These methods take only 22 minutes to run. Chromatograms are from the Canadian Phytopharmaceuticals Corporation's research database.

of formulated or combination products represents a breakthrough in the quality control of botanical products. Individual herbs may have been analyzed by different methods, using different HPLC columns, solvent gradients, or detection wavelengths. Their profiles may overlap; hence, new methods must be developed that will distinguish the profile for each herb, yet still allow for analysis within a reasonable timeframe. The complexity of this task necessarily increases with the number of herbs present in the combination product.

As an example, consider a formulated product consisting of American ginseng roots, *Epimedium koreanum* (Berberidaceae) leaves, eleuthero (*Eleutherococcus senticosus*, Araliaceae) rhizomes, and *R. rosea* roots. Such a combination may be used as a Western-style "Energy Formula." UHPLC profiles for the latter three herbs are shown in Figure 4, with relevant marker compounds labeled. Run times range from four minutes for *Epimedium* to eight minutes for *R. rosea*[24] and eleuthero.[25] The UHPLC profile for the combination product (Figure 5), while complicated, clearly shows the unique fingerprint of each herb, and the quantification of more than 20 compounds is complete in only 22 minutes in a single run.

Shuang-Huang-Lian (SHL) is a traditional Chinese formula comprised of *Flos Lonicerae* (Japanese honeysuckle; *Lonicera japonica*, Caprifoliaceae), *Radix Scutellariae* (Chinese skullcap; *Scutellaria baicalensis*, Lamiaceae), and *Fructus Forsythiae* (forsythia; *Forsythia suspensa*, Oleaceae). It is used commonly to treat upper respiratory illnesses. Ma *et al*. developed a UHPLC profile for SHL that is complete in seven minutes (Figure 6),[26] and extended the study to an "East-meets-West" SHL-*Echinacea* combination (*E. angustifolia* and *E. purpurea*, Asteraceae).[27]

Technological and analytical methodology development makes possible the qualitative and quantitative analysis of multiple marker compounds in formulated products, guaranteeing the quality of these products. Very few manufacturers currently analyze combination products. Those that do are in a position to be leaders in the marketplace.

Conclusion

The current industry standards can and will change and improve according to market demands. Industry must take the lead and set the benchmark for the quality control of botanical extracts and Traditional Chinese Medicine, to counteract the erroneous belief that herbal medicines are unregulated, untested, and ineffective. Combining the applicable, reliable, and practical complementary techniques of DNA barcoding and chemical profiling for the quality control of herbal products — from raw herb to

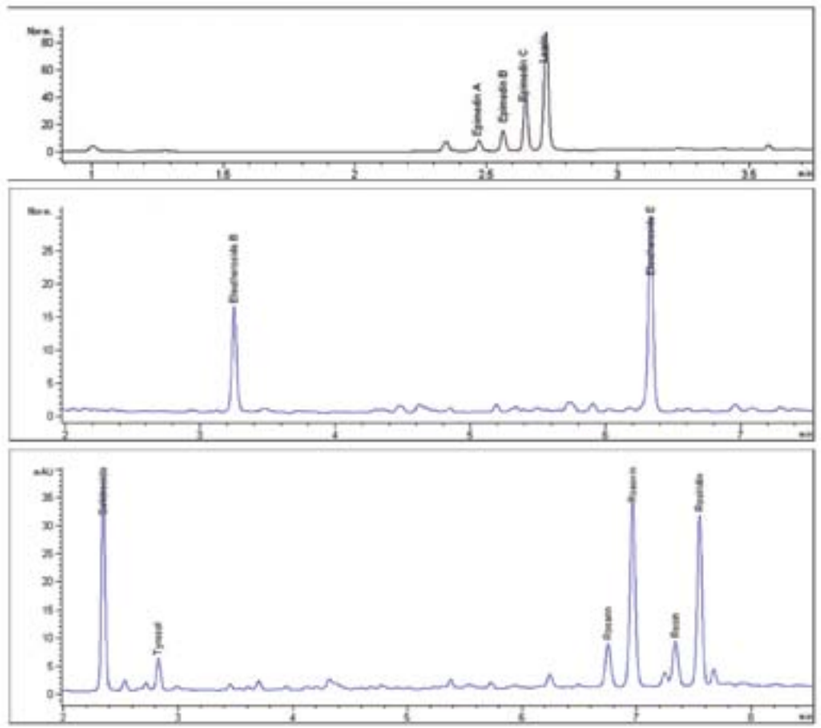


Figure 4. UHPLC profiles for *Epimedium* leaves (top), eleuthero roots (middle), and *Rhodiola rosea* roots (bottom).

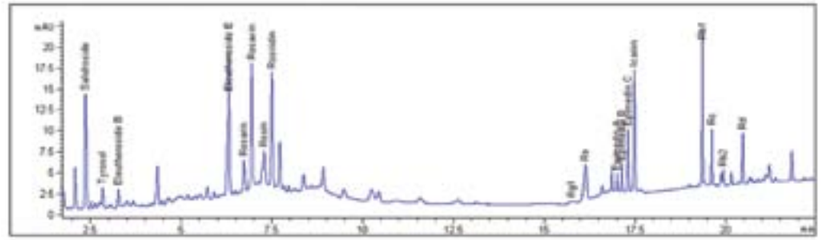


Figure 5. UHPLC profile for combination product of American ginseng roots, *Epimedium* leaves, eleuthero roots, and *Rhodiola rosea* roots.

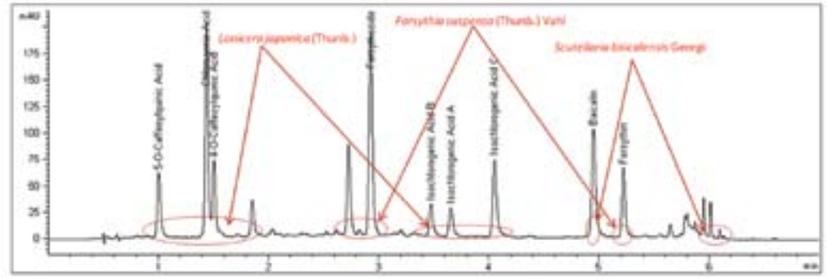


Figure 6. UHPLC profile for a *Shuang-Huang-Lian* multi-herbal preparation.


Rhodiola *Rhodiola rosea*. Photo ©2013 Steven Foster

extract to finished product — will assure the delivery of high-quality, safe, and efficacious products to market. Since DNA barcoding is not yet ready for widespread implementation, an interim solution would be for botanical product manufacturers to establish specifications that require testing and conformance of the raw herbal material or extract with a pharmacopoeial monograph. This includes organoleptic, microscopic, and chemical (TLC or HPLC) profiling. Furthermore, by better validating the quality of botanical ingredients used in products that may undergo robust pharmacological or clinical studies, there should be a higher level of confidence and scientific credibility in the clinical results. HG

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Chinese Skullcap *Scutellaria baicalensis*. Photo ©2013 Steven Foster

Update: FDA Approves Crofelemer as First Oral Botanical Drug

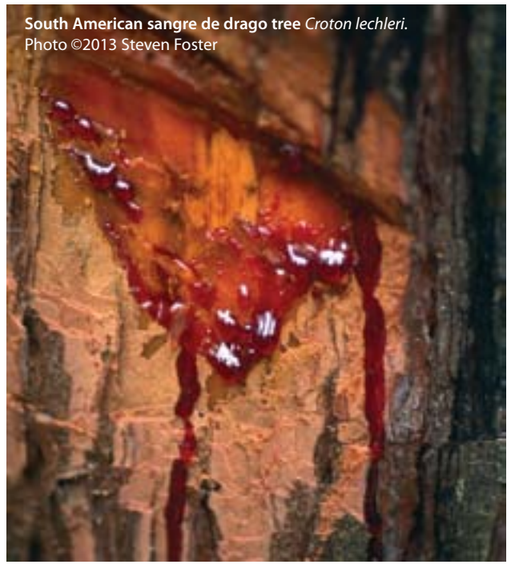
On New Year's Eve of 2012, the US Food and Drug Administration (FDA) announced its approval of crofelemer, marking the second time a botanical preparation — and the first time an orally administered botanical preparation — has received prescription drug approval from the Administration.[1] The first and only other drug in the United States approved under the FDA's botanical drug review process is a topical green tea extract, Veregen®, which was approved by FDA in 2006.[2] While several other botanical ingredients currently are approved as over-the-counter drugs, crofelemer and Veregen meet all US pharmaceutical requirements and can be dispensed only by prescription.

Crofelemer is derived from the latex of the South American sangre de drago tree (sometimes referred to as sangre de grado; *Croton lechleri,* Euphorbiaceae), which is used widely in the region's traditional medicine and known in English as dragon's blood.[2] A deep red latex leaks from the tree when its bark is cut, and it is this substance that contains the novel polymolecular structure crofelemer, originally discovered, isolated, and purified by Shaman Pharmaceuticals. Napo Pharmaceuticals of San Francisco now owns the intellectual property of crofelemer, and Salix Pharmaceuticals in Raleigh, North Carolina, is licensed to develop and market it in the United States under the brand name Fulyzaq™. (For an overview of the four companies involved in the drug's development, see Table I.) Crofelemer is the first US drug approved to treat HIV-associated diarrhea.

The Phase III Trial on which FDA based its crofelemer approval — called ADVENT and designed and initiated by Napo Pharmaceuticals — was a randomized, double-blind, multi-center study that featured a one-month placebo-controlled arm and a five-month placebo-free arm.[3] Patients had experienced diarrhea for one month or longer, and efficacy was analyzed based on "the proportion of patients experiencing less than or equal to two watery bowel movements per week, during at least two of the four weeks of the placebo-controlled phase of the study." The 125 mg delayed-release tablets, to be taken twice a day, are not intended to treat infectious diarrhea, and clinical trial evidence suggests that they do not interact with HIV medications.

According to FDA's press release announcing the approval, "The safety and efficacy of Fulyzaq were established in a clinical trial of 374 HIV-positive patients on stable antiretroviral therapy [ART] with a history of diarrhea lasting one month or longer….Results showed that 17.6 percent of patients taking Fulyzaq experienced clinical response compared with 8 percent taking placebo. In some patients, a persistent anti-diarrheal effect was seen for 20 weeks."[1]

FDA ushered the crofelemer decision out the door on the last day of 2012 — an action typical of efforts to complete pending drug reviews before the end of each calendar year.[4] Salix called the approval a "significant step forward in addressing the unmet medical need of people with HIV/AIDS on ART who experience non-infectious diarrhea."[3] The company expects Fulyzaq to be available to patients in early 2013. A Bloomberg analysis estimates the drug will bring Salix sales of $18 million in 2013 and $26 million in 2014,[5] and the market potential has been estimated at $300 million. A portion of any income will have to be paid to Napo as milestone payments and royalties. In the days following the announcement, Salix stock shares increased by about 5 percent, while Glenmark Pharmaceuticals, Ltd., the Indian manufacturer and supplier of crofelemer for 140 "emerging market" countries, experienced a 3.4% increase in market shares.[6]



South American sangre de drago tree *Croton lechleri.*
Photo ©2013 Steven Foster

Table I. Companies Involved in Crofelemer's Development

Shaman Pharmaceuticals: Originally isolated and purified crofelemer from the latex of the sangre de drago tree in the early 1990s using the company's ethnobotanical approach to drug discovery and development. Shaman owned all rights to crofelemer's intellectual property and development until filing for bankruptcy in 2001.

Napo Pharmaceuticals: Formed in 2001 by Shaman CEO Lisa Conte after Shaman's bankruptcy. Napo owns crofelemer's intellectual property and works in South America with local communities to sustainably harvest and replant sangre de drago trees. Napo has conducted clinical trials to assess crofelemer's safety and efficacy and designed and initiated the Phase III clinical trial called ADVENT.

Salix Pharmaceuticals: Licensed by Napo in 2008 to sell crofelemer in Western pharmaceutical markets and to complete the ADVENT trial. Upon the successful completion of the ADVENT trial, Salix filed the New Drug Application with FDA that resulted in the recent drug approval in December 2012. Salix will market the drug in the United States and other Western countries, and must pay Napo royalties.

Glenmark Pharmaceuticals: Licensed by Napo to manufacture and market crofelemer in 140 emerging markets, such as Africa and Latin America. Glenmark also must pay royalties to Napo.

Napo's Vice-President of Sustainable Supply and Ethnobotanical Research, Steven King, PhD, noted that the company has a commitment to share benefits with governments and indigenous South American communities that have been using sangre de drago for many years and working with Napo to sustainably harvest and replant trees. It will do this through its nonprofit Healing Forest Conservancy.

"This [agreement] was put in place during the Shaman work and adopted officially by Napo," said Dr. King (email, January 3, 2013). "The details will take a bit of time to unfold, and we of course have to receive royalties from our partners in order to begin this process."

The patent on crofelemer will expire in 2018, but Salix mentioned in its press release the potential for crofelemer to obtain patent term restoration,[3] which extends patent life by up to five years in order to "compensate patent holders for marketing time lost while developing the product and awaiting government approval."[7] Most US patents last for 20 years, but because a large portion of this time frequently passes while the drug is going through the long approval process, the US government wants to ensure that drug development and innovation will still be an attractive investment to patent holders, researchers, and pharmaceutical companies.

Following the breaking news of crofelemer's approval, some herbalists voiced concerns over how it might affect their ability to use sangre de drago — generally more common for herbalist practices in Latin America — as well as consumers' ability to access it as a dietary supplement. Because prescription crofelemer is an isolated and purified chemical from the tree's latex, its approval has no impact on the access of the tree's latex for use as a traditional medicine or dietary supplement; herbalists and consumers will continue to be able to access whole plant-based sangre de drago and any sangre de drago dietary supplements as long as these products do not make inappropriate health claims. FDA confirms this in its 2004 *Guidance for Industry on Botanical Drugs*, noting that as long as the dietary supplement has been on the market before the drug approval, it is not in jeopardy.[8]

"The latex is not crofelemer," said Dr. King. "It's nothing close to crofelemer. So the sale and use of latex anywhere in the world should be unaffected by the approval of this drug."

The drug's approval marks an important event in the decades-long history of crofelemer. The original Investigational New Drug application was submitted by Shaman in the early 1990s. In 2001, Shaman went bankrupt and later that year CEO Lisa Conte reorganized into Napo Pharmaceuticals, retaining Shaman's original intellectual property.[2] Napo continued to work toward crofelemer's NDA submission, conducting two Phase III trials. In 2008, Salix obtained a license from Napo in order to complete the ADVENT clinical trial started by Napo, and to complete crofelemer's development to treat HIV-associated diarrhea.

Salix filed the NDA for crofelemer in December 2011. Due to the serious nature of the medical condition crofelemer treats, FDA assigned the NDA "priority review" status, which indicates that the Administration would aim to approve or reject the application in approximately six months.[2] Although FDA accepted the NDA for filing in February 2012, it delayed its decision twice, including the most recent delay in September 2012, which added to Napo's concerns regarding the length of time it was taking Salix to move the product forward and adequately prepare for possible commercialization. In May 2011, Napo filed a legal complaint for breach of contract against Salix, claiming that Salix was "unnecessarily stalling the advancement of this compound." Salix has maintained that it proceeded with the NDA expeditiously. The lawsuit, currently before the New York Supreme Court, is still pending and a ruling is yet to be determined. HG

—Lindsay Stafford Mader

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BOOK REVIEWS

Available in the ABC Online Bookstore

Formulating, Packaging, and Marketing of Natural Cosmetic Products edited by Nava Dayan and Lambros Kromidas. Hoboken, NJ: Wiley; 2011. Hardcover; 444 pages. ISBN: 978-0-470-48408-1. $125.00

Since time immemorial, both men and women have used a wide array of products to enhance their physical appeal, improve skin texture, or favorably alter their appearance. In today's world, the use of cosmetics is especially popular for both sexes, and this desire to look and feel more attractive has spawned a multibillion-dollar global industry.

Plants and their byproducts have been a primary source of cosmetic ingredients since ancient times. Whether a fragrance, dye, coloring agent, skin emollient, or conditioner, herbal products continue to be of the utmost importance in cosmetology.

Unfortunately, some cosmetics contain synthetic compounds (*e.g.*, parabens, artificial colors, etc.) and even natural elements such as lead that have deleterious effects on health, yet they continue to be included in many formulations throughout the world. The last decade has witnessed important advancements in identifying new phytochemical compounds with potential cosmetic and health benefits, including phenolic compounds, lignans, alkaloids, and terpenes, among many others.

As markets for beautifying agents become increasingly competitive and consumers are more aware of the potential dangers of certain cosmetic ingredients, commercial, scientific, and educational companies continue their quest to find new, more effective, and safer ingredients.

So important have cosmetics become in our modern society that new words have been coined related to natural cosmetology. *Cosmeceutical*, for example, is a marketing term that combines "cosmetics" and "pharmaceuticals," suggesting an ability to ameliorate, treat, and perhaps prevent a number of skin conditions, disorders, and diseases. Related terms now commonly used in the cosmetic industry include *nutricosmetics* (implying that the natural product nurtures the skin), as well as *neoceuticals,* or newly discovered natural products that are used to treat hypersensitive skin conditions.

New and improved molecular techniques have focused on targets such as sirtuins (so-called "longevity proteins"); NFkB, a transcription factor that aids in various cellular processes; and PPARs (peroxisome proliferator-activated receptors), which play important roles in both human and animal aging.

Formulating, Packaging, and Marketing of Natural Cosmetic Products includes a wealth of information on various plants and their byproducts for beauty and healthy living applications. The approach used by the authors is scientific; the content discusses various regulatory approaches regarding botanically based cosmetics from around the world, as well as journal articles, clinical trials, and laboratory experiments on various natural products used as cosmetics.

The applications of botanical cosmetic formulations mentioned in this book remind the reader of the fine line between cosmetic and therapeutic uses for botanical compounds. The authors also discuss skin penetration of various phytochemicals, vehicles, surfactants, thickening agents, penetration enhancers, and preservatives, as well as the potential adverse side effects of various topical formulations.

The book contains 21 chapters and is divided into six sections. Part 1 explores market trends for "natural" and "organic" products used by the cosmetic industry. This section mentions the origin of the natural products industry, as well as the history and development of regulatory agencies and statutes for the functional classification and labeling of diverse products derived mainly from plant sources.

Also, this section both concisely and conveniently expands on the development of non-governmental standards that establish credibility for natural products used as cosmetics. The chapters contained therein define and explain the theory of nonstate market-driven governance (NSMD) and its impact on the industry as well as the consumer. Furthermore, this section includes an overview of the existing standards of quality control for the personal care industry in the United States and Europe.

Part 2 includes an in-depth focus on the regulatory aspects of a wide array of natural cosmetic ingredients, including the classification of natural and organic claims for natural products. Various other regulatory schemes are mentioned for Canada and Europe.

Part 3 mentions the safety aspects of natural products of vegetable origin and, at length, discusses the uses and health-related aspects of natural preservatives as well as microbial contamination and other risks related to the processing and packaging of cosmeceuticals. For cosmetic products, the botanical evaluation includes the assessment of four important routes of application or exposure: systemic, ocular, dermal (topical), and inhalation — the latter being of utmost importance in assessing perfumes and essential oils. A chapter in this section is devoted to evaluating consumer safety of various botanical ingredients, with emphasis on type 1 allergic reactions, which occur in sensitized persons within minutes after contact.

Part 4 details the multiple uses of natural ingredients such as natural oils, fats, butters, and waxes, among others. Here, the physical properties and chemical structure of triglycerides are explained, as well as other important compounds such as carotenoids, vitamin E derivatives (tocopherols), and plant-derived sterols. Lipid peroxidation and its role in the rancidity and decomposition of certain oils is also elaborated upon here. According to the text, plant-derived antioxidants (also known as *phytoantioxidants*) are employed not only to prevent rancidity, but also because of their anti-inflammatory and anti-cancer properties. These natural compounds are not only contained in herbal cosmetics, but are also commonly found in foods and spices such as cucumbers (*Cucurbita* spp., Cucurbitaceae), onions (*Allium cepa,* Liliaceae), apples (*Malus* spp., Rosaceae), and turmeric (*Curcuma longa,* Zingiberaceae), just to name a few.

Section 4 includes two particularly interesting chapters: one about Ayurveda from India and the other on Traditional Chinese Medicine. Both chapters emphasize the importance of certain botanicals and their cosmetic use by two of the world's oldest systems of traditional medicine. The role of antioxidants in combating free radicals and oxidative stress is emphasized in this section, as well as the quantification of antioxidant capacity of various phytochemicals and the deleterious impact of reactive oxygen species on aging.

The correct appraisal of the botanical contents in cosmetics (and by extension, for all natural products) is of great importance in quality control, and Part 5 of this text includes two specific and comprehensive chapters on biochemical methods of analyzing natural compounds in cosmetics — high-performance liquid chromatography (HPLC), gas chromatography, and nuclear magnetic resonance (NMR) spectroscopy, among others — crucial in the detection and identification of various phytochemicals.

Finally, Part 6 includes two chapters that are devoted to the topic of biodegradation of cosmetic ingredients and its relationship to packaging methods. This section explains the process of biodegradability and also mentions examples of tests and predictive models employed to determine the biodegradability of various compounds.

The authors are researchers and consultants in natural products. Nava Dayan, PhD, is director of research and development at Lipo Chemicals, Inc., as well as an adjunct professor in the School of Pharmacy at Rutgers University. Lambros Kromidas, PhD, is a consultant and principal of OnPoint Scientific Solutions, LLC.

Formulating, Packaging, and Marketing of Natural Cosmetic Products eloquently fills a gap in the scientific literature regarding various plant and fungal products that may be useful not only as cosmetics for aesthetic purposes, but, perhaps more importantly, it brings to the reader's attention the diverse types of natural products that can have important benefits for general health as well.

I highly recommend this book for professionals interested in cosmetics as well as physicians, pharmacists, naturopathic doctors, and those interested in understanding the intricate world of production, regulation, packaging, benefits, and risks inherent in various natural products used as cosmetics.

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Available in the ABC Online Bookstore

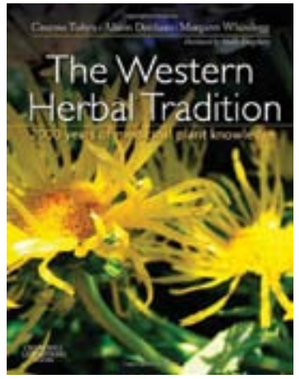
The Western Herbal Tradition: 2000 Years of Medicinal Plant Knowledge by Graeme Tobyn, Alison Denham, and Margaret Whitelegg. Edinburgh, UK: Churchill Livingstone; 2011. Hardcover; 392 pages. ISBN: 978-0-443-10344-5. $81.95.

This is a unique book covering an often-ignored topic. There is a rich diverse basis for modern Western herbalism whose roots can be traced back beyond the Greek physician Dioscorides (1st century CE). From botany to pharmacy, from theory to practice, there are clear precedents that, if ignored, undermine the modern contribution of herbal medicine to modern healthcare.

In recent discussions with the Canadian National Heath Products Directorate (NHPD), this reviewer was told that there is no Western herbal tradition. After a lifetime of involvement in an apparently non-existent tradition, I realized that they actually meant there was no book that spelled it out for them. Now there is.

In today's regulatory environment it has become too easy to ignore the rich theoretical basis of what the authors call "The Western Herbal Tradition." However, this is the first book for clinicians (as opposed to medical historians) I am aware of that gives the tradition the quality of attention it deserves. As well-respected practitioners of medical herbalism, the authors are uniquely qualified to explore this fascinating topic. Their historical overview of theory and concepts is made meaningful to the modern mind by being grounded solidly in the reality of clinical practice. Sheila Kingsbury, chair of botanical medicine at Bastyr University, provides an insightful foreword.

The discussion of the Western tradition is informed by a scholarly presentation of material from original sources — many of which are inaccessible to the modern practitioner. The following list includes authors cited in the book, as many texts can be ascribed to each. Greco-Roman sources include Dioscorides, Pliny the Elder, Galen, and Pseudo-Apuleius. Arabic sources are referenced through Ibn Sina (Avicenna) and Serapio the Younger. Insights from Anglo-



Saxon and Late Middle Ages come from the Old English Herbarium, Macer, the Salernitan Herbal, Hildegard of Bingen, and the Welsh physicians of Myddfai. Renaissance and early modern texts include those by Fuchs, Mattioli, Turner, Dodoens, D'Alechamps, Bauhin, Gerard, Parkinson, and Culpeper. Eighteenth and 19th century American and British herbalists include Quincy, Miller, Hill, Cullen, Coffin, Fox, Cook, and Ellingwood. The 20th century is represented by Pelikan, Wren, Hool, Grieve, Weiss, Priest and Priest, and Bartram.

The core of the book's discussion is based on the 21st century texts written by modern clinicians of medical herbalism including Chevallier, Hoffmann, Menzies-Trull, Mills and Bone, Williamson, and Wood.

Thirty plants are placed in this historical, conceptual context, and discussed in 28 monographs. I find the selection rather limited, but I suppose there is only so much space for such. I would have appreciated it if the unique treatment the authors applied to their herbs was given to such essentials of modern herbal practice as, for example the following: skullcap (*Scutellaria lateriflora,* Lamiaceae), valerian (*Valeriana officinalis,* Caprifoliaceae), and nettles (*Urtica dioica,* Urticaceae).

The monographs cover the following herbs, listed in order of appearance in the text, many of which are not highly popular in the dietary supplement market in the United States: agrimony (*Agrimonia eupatoria,* Rosaceae); lady's mantle (*Alchemilla vulgaris,* Rosaceae); marshmallow (*Althaea officinalis*, Malvaceae); common mallow (*Malva sylvestris,* Malvaceae); hollyhock (*Alcea rosea*, Malvaceae); wild celery (*Apium graveolens,* Apiaceae); burdock (*Arctium lappa,* Asteraceae); wormwood (*Artemisia absinthium,* Asteraceae); mugwort (*Artemisia vulgaris,* Asteraceae); centaury (*Centaurium erythraea,* Gentianaceae); wild carrot (*Daucus carota,* Apiaceae); squill (*Drimia maritima.* Asparagaceae); fumitory (*Fumaria officinalis,* Papaveraceae); goosegrass (*Galium aparine,* Rubiaceae); ground ivy (*Glechoma hederacea,* Lamiaceae); hyssop (*Hyssopus officinalis,* Lamiaceae); elecampane (*Inula helenium* (Asteraceae); white deadnettle (*Lamium album,* Lamiaceae); basil (*Ocimum basilicum*, Lamiaceae); peony (*Paeonia officinalis,* Paeoniaceae); tormentil (*Potentilla erecta,* Rosaceae); damask rose (*Rosa damascena,* Rosaceae); raspberry (*Rubus idaeus,* Rosaceae); rue (*Ruta graveolens,* Rutaceae); figwort (*Scrophularia nodosa,* Scrophulariaceae); wood betony (*Stachys officinalis,* Lamiaceae); coltsfoot (*Tussilago farfara,* Asteraceae); vervain (*Verbena officinalis,* Verbenaceae); sweet violet (*Viola odorata,* Violaceae); and heart's-ease (*Viola tricolor,* Violaceae).

[*Editor's note: The common names listed above were taken from the reviewed text and may vary slightly from the standardized common names found in* Herbs of Commerce*, 2nd edition (American Herbal Products Association, 2000).*]

The monographs discuss modern usage followed by an in-depth look at the developing thoughts about the herb through the written history of the Western *materia medica*. The modern indications benefit greatly from the insights and experiences of the authors as authoritative clinicians. The indications are not simply those given in modern pharmacopeias, but rather a wonderfully complex therapeutic palette when seen in the context of traditional herbal polypharmacy. The erudite review of historic precedents for the herb leads to useful recommendations for the herb's use and insights about safety.

Where important theoretical considerations arise, they are explored in a refreshing degree of depth. For example, the discussion of the "alterative" action is, in my humble opinion, the most comprehensive yet written. This discussion alone justifies the reading of this book by all clinicians and students of Western herbal medicine. Similar depth is applied to the theoretical foundations for the clinical concepts of astringency, bitterness, and *partus preparator* (a term that describes herbs used in preparation for childbirth).

The focus is clearly on the modern form of medical herbalism that uses the insights of the Physiomedicalists and Eclectics, as opposed to the much newer phytotherapy which can be said to use medicinal plants within the modern paradigm. The profound impact of the principles and practice of physiomedicalism on the development of modern herbalism in the United Kingdom is clearly shown. This is reflected in the herbs used and the approach to protocol development. The social upheaval of 19th century Britain (the Chartist movement, etc.) is appropriately presented as the context for the welcoming of Physiomedicalism to UK herbalism.

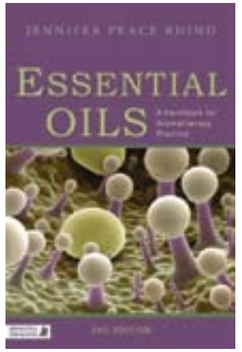
It is especially refreshing to see the continuity of focus on the quality of wild medicinal plants from Dioscorides through the International Standards for Sustainable Wild Collection of Medicinal and Aromatic Plants and the Medicinal Plant Specialist Group.

The Western Herbal Tradition is an important contribution to the rational and informed use of medicinal plants in modern health care.

—David Hoffmann, BSc, FNIMH
Medical Herbalist
Traditional Medicinals
Sebastopol, CA

Essential Oils: A Handbook for Aromatherapy Practice, 2nd edition, by Jennifer Peace Rhind. London, England: Singing Dragon; 2012. Softcover; 318 pages. ISBN: 978-1-84819-090-0. $35.00.

The author's PhD in mycotoxicology is evident in the clinical leanings of this publication, which will be especially valuable for the professional aromatherapist or other botanical practioner. Her UK roots and involvement in integrative care are apparent in her access to clinical applications of essential oils, which is quite rare in America. She distinguishes this book from previous advanced aromatherapy writings by taking a more therapeutic approach focused on aromatic chemistry of essential oils, which she refers to as the "molecular approach," a topic frequently addressed in foreign languages such as French, German, or Italian. The front cover depicting clary sage's (*Salvia sclarea*, Lamiaceae) secretory cells is indicative of the level of technical expertise within the book.



Expanding on the field of aromatherapy, this book focuses on the uses of essential oils from a research perspective of pharmacologic activity of their chemical components. The author introduces the subject with an overview of the origins of aromatic medicines from Greek, Chinese, and Ayurvedic perspectives and provides detailed information on the processes by which aromatic extracts are produced.

In Part I, the author deliberates over the philosophy and theory of essential oil uses from an historic perspective and reviews the pioneers of this discipline from ancient figures to early 20th century and modern-day practitioners. Her overview of contemporary practices encompasses theoretical perspectives, the uses of essential oils from the beauty profession, to applications in psychology and clinical use. The author provides an extensive chart on the biological properties of essential oils with sections pertaining to their action, therapeutic potential, and personal comments. Her description of olfaction lays the groundwork for the pertinence of the sense of smell in healing and stress reduction, and her experience as a massage therapist is palpable in the segment detailing the application of this modality.

Part II addresses essential oil synergies and the influence of functional groups of aromatic chemistry in a molecular approach to efficiency blending, introduced by the French medical model. Another approach goes beyond symptomology, addressing the psychosensory effects of essential oil blending, which move beyond the realm of the physical and tap into intuitive insights based on the work of French practitioner Phillippe Mailhebiau. Perceptions and applications of the Chinese Five-Element theory are discussed, as is an Ayurvedic approach to blending.

Part III contains four chapters, beginning with "Botanical Principles in Aromatherapy." The *materia medica* segment is categorized into two sections — essential oils from the Angiospermae and the Gymnospermae — and assumes the reader's knowledge of botanical classification. More than 100 essential oils, absolutes, and resinoids are covered. Rarely are the therapeutic activities of these last two extractions used for aromatherapy practice, so it is interesting to see them addressed here.

The less-advanced student will appreciate the six-page technical glossary of scientific and medical terms used throughout the publication. Charts of significant chemical constituents in essential oils help to clarify the extensive body of knowledge surrounding functional groups of aromatic compounds in essential oils. Examples of essential oils and their corresponding isolated constituents are listed for 16 categories encompassing nine pages. An appendix provides odor description and therapeutic potential for 15 of the groups. The pharmacokinetics are explained in a question-and-answer format, and lists of essential oils are categorized by their active components and functional uses. (*e.g.*, antibacterial, antifungal, antiviral, etc). Additionally, there are three pages listing the characteristics and properties of carrier oils for the dilution of essential oils, including what one must assume are herbal-infused oils such as gotu kola (*Centella asiatica*, Apiaceae), comfrey (*Symphytum officinale*, Boraginaceae), and marigold (*Calendula officinalis*, Asteraceae). Latin name use is inconsistent and, with the exception of the *materia medica*, most references are to their common names only. Common names also are used in the last appendix for indications and actions for absolutes and resinoids in aromatherapy, wherein the author discusses the pros and cons of solvent extraction. This category of extracts, as noted above, is rarely discussed in other publications that focus on the therapeutic uses of essential oils; these are usually the domain of books specific to the perfume industry.

There is a hefty list of references to original citations, lending an air of authority to a subject with less acknowledged research than other botanical therapies. Overall, this book is a welcome addition to the English-speaking world of published work on the therapeutic value of essential oils and other aromatic extracts. It expounds on the diversity of this growing modality of professional aromatherapy with a broad and scientific approach to the properties and potentials of essential oils by connecting biological properties, scientific research, and clinical applications of this particular form of botanical therapy. The professional aromatherapist, educator, herbalist, student, and complementary care practitioner will find it most useful. The author succeeds in weaving scientific research and clinical rationale with holistic principles of healing in a practical text suitable for more in-depth training courses in botanical therapies.

—Mindy Green, MS, RA, RH (AHG)
Blaine, MN
www.greenscentsations.com

Available in the ABC Online Bookstore

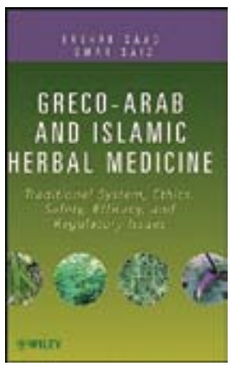
Greco-Arab and Islamic Herbal Medicine: Traditional Systems, Ethics, Safety, Efficacy, and Regulatory Issues by Bashar Saad and Omar Said. Hoboken, NJ: Wiley; 2011. Hardcover; 533 pages. ISBN: 978-0-470-47421-1. $142.00.

As its title suggests, *Greco-Arab and Islamic Herbal Medicine* intends to provide a comprehensive account of a school of traditional medicine that deserves its fair share of attention and understanding. To achieve this goal, the book includes 19 chapters followed

by a short appendix that explains the origins and relevance of Latin binomial nomenclature of plants. Many monochrome figures, illustrations, portraits, and pictures are featured as well. Of these, the plant pictures are presented in two identical sets, with color images placed in the middle section and the same pictures, in black and white, distributed alongside their respective topics in the text. The sources of these pictures are not disclosed.

The first five chapters complement one another in outlining the origins and history of Arab-Islamic medicine and its interaction with its Greek counterpart, which resulted in the concept of Greco-Arab medicine. In these chapters, general definitions and historical timelines are introduced together with the contributions of such notable scholars as Abulcasis, al-Biruni, and Rhazes to various areas of medical and biological sciences. Later chapters of this section also highlight the translation efforts of Arabian scholars and the contributions of Arab-Islamic medicine, from the Dark Ages to modern medical practices.

Beyond the historical section, the book starts to wander among different topics, old and new, general and specific. For example, while chapters 6 and 8 focus on general natural products and specific medicinal plants/animal products of Arabia and the Mediterranean region (more than 30 are mentioned), Chapter 7 reverts to common modern and historical practices of Islamic medicine. Chapters 9 and 10 further describe other plants of the Mediterranean region and beyond (Turkey, India, Pakistan, China, and northwestern Africa), as well as other established schools of traditional medicine such as Ayurveda, Unani, and traditional Chinese medicine. Chapters 11 to 14 discuss the concepts of biosafety and toxicology, including earlier practices of Arabian scholars, in addition to preclinical and clinical evaluation of herbal drugs, encompassing selected examples from the authors' own research. Again, this sequence is disrupted with Chapter 15, which describes the ethics of Arabian medicine before the discussion of such general topics as extraction, isolation, and herbal drug development is resumed in chapters 16 and 18. Chapter 17, which should have been placed to follow Chapter 8 or 10, examines common edible crops and natural products used as therapeutic agents, *e.g.*, honey, dates (*Phoenix dactylifera*, Arecaceae), olive oil (derived from *Olea europaea*, Oleaceae), figs (*Ficus carica*, Moraceae), and others. The main body of the book concludes with Chapter 19, which provides a summary of the global use, demographics, and regulatory issues of herbal medicines in the Arab/Islamic world, the United States, Europe, and the remainder of the globe. Each chapter includes a list of references (ranging from 12 to 116, and averaging 32 references per chapter) to support its content.



Considering its size and format, the book succeeds in drawing attention to its topic but it may leave the reader with a feeling of incomplete satisfaction, depending on how the included material is approached. In their efforts to maximize coverage and benefit, the authors reviewed a plethora of topics that span history, geography, modern practice, global regulation, fundamental concepts of pharmacology/toxicology, natural product isolation/identification, and drug discovery under one cover. This is the book's strength *and* weakness as it attempts to be as comprehensive as possible, but fails to provide enough depth on certain topics — such as methods of natural product isolation and testing in drug discovery — whose inclusion was not essential considering that superior coverage exists elsewhere.

Thus, the most successful sections of the book are those that are most relevant to its main title (chapters 1 through 9, and 15), and where the authors' knowledge truly shines. These chapters are highly recommended for priority reading. For those interested in specific medicinal herbs of the region, Chapter 8 contains the most comprehensive coverage and the most references (116 total) and illustrations (26 total) of all the book's chapters.

Aside from its inconsistent pacing and organization, the book also suffers from frequent spelling and style errors that may be distracting at times. However, the authors are to be complimented for their comprehensive review of the literature and for the inclusion of a considerable number of references to provide the reader with resources for further investigation of the various topics presented. The formula adopted in *Greco-Arab and Islamic Herbal Medicine* makes it appealing to a broad spectrum of readers on both regional and global levels. Better organization and focus of its content may further enhance the appeal and value of future editions.

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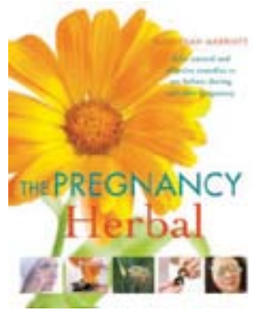
Chicago, IL

The Pregnancy Herbal: Safe, Natural and Effective Remedies to Use Before, During and After Pregnancy by Susannah Marriott. London: Carroll & Brown Limited; 2012. Softcover; 128 pages. ISBN: 9781907952081. £14.99. [approx. $24.00 USD]

The Pregnancy Herbal by Susannah Marriott is a delightful, user-friendly book. As a midwife and naturopathic physician, I am pleased to have such a well-done resource for women, moms, and health practitioners alike. The author has done an excellent job of incorporating a wealth of safe, useful herbal information and recipes for use before and during pregnancy, as well as in the postpartum period.

The book begins with a section on basic herbal terms, preparations, and useful equipment to have on hand for creating herbal preparations. Marriott includes many instructive photos to illustrate the making of preparations and recipes. She masterfully provides valuable pregnancy information without overwhelming the reader with superfluous details or facts.



In the following section, Marriott addresses specific herbs and their corresponding use during various times of pregnancy, starting with a useful section on pre-pregnancy health for those women who want to incorporate some simple wellness practices to encourage fertility including foods, herbal baths, and teas.

The next three sections cover the trimesters of pregnancy and include several herbs and foods that are recommended specifically in each trimester, depending on the types of health challenges that may occur. The first trimester includes herbs such as ginger (*Zingiber officinale*, Zingiberaceae), dandelion (*Taraxacum officinale*, Asteraceae), and garlic (*Allium sativum*, Alliaceae). Second trimester herbs include chamomile (*Matricaria recutita*, Asteraceae), blueberries (*Vaccinium angustifolium*, Ericaceae), and lemon (*Citrus* x *limon*, Rutaceae). The third trimester subsection covers red raspberry leaf (*Rubus idaeus*, Rosaceae), lavender (*Lavandula angustifolia*, Lamiaceae), and alfalfa (*Medicago sativa*, Fabaceae).

Each herb entry has a brief description of the herb's history and usage and a recipe or two on how it may be used in pregnancy. Marriott has included pictures of the plants and many of the recipes as finished products or in the process of being made, and easy-to-follow directions. She has given reasonable consideration to which herbs are included in which trimester, offering pregnancy-friendly information while keeping in mind the special needs of pregnant women and their connection with the herbs. The recipes range from herbal soaps, baths, body products, teas, desserts, scents, and garlands of citrus and cinnamon (*Cinnamomum verum*, Lauraceae). For example, the book presents a simple recipe for garlic cough syrup made from three common kitchen ingredients: garlic, honey, and water. This recipe can be made easily on the stove top in about an hour and will store for up to six months. It makes for a great, safe cough syrup to soothe and break up mucus during pregnancy.

The same format is used in the sixth chapter of the book, the postpartum period, which includes herbs such as arnica (*Arnica montana*, Asteraceae), fennel (*Foeniculum vulgare*, Apiaceae), and jasmine (*Jasminum officinale*, Oleaceae) to address healing after delivery, breast-feeding support, and wellness support for emotional challenges that may crop up during this time. I particularly like the rose (*Rosa* spp., Rosaceae) recipe Marriott has included for use as a mister for the baby's room.

The last chapter focuses on several herbs that can be used in baby care, giving mom several helpful recipes and safe uses of these common herbs for baby. This section comprises a number of lovely photos of moms and their babies, making it very attractive and visually encouraging mothers to use these plants and preparations.

I highly recommend this book as a reliable guide to safe and useful herbal information for the pregnant woman and postpartum mom, and I encourage them to incorporate these simple, healthy wellness ideas into their pregnancy selfcare. Additionally, I encourage other healthcare providers to pregnant women to read and share this book, as well as to students, herbalists, and naturopathic physicians.

—Mary Bove, ND
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Brattleboro, VT

Medicinal Herbs: A Beginner's Guide by Rosemary Gladstar. North Adams, MA: Storey Publishing; 2012. Softcover; 224 pages. ISBN: 978-1-61212-005-9. $14.95.

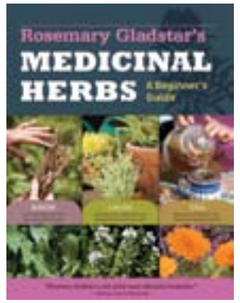
At first glance, this *Beginner's Guide* seems to be just that: a comprehensive resource to introduce the public to medicinal herbs. It is only when you read further into each of the aptly named sections that you realize this is more a compilation of the insights and wisdom gained from a lifetime of practice using medicinal herbs, rather than just another treatise on the most basic information.

This book is comprised of four sections meant to take the beginner from basic theory to medicine-making to a concise *materia medica*. Complemented by enticing photos of mason jars filled with flowers and captivating images of the plants themselves, *Medicinal Herbs* is a convincing companion for anyone inclined to get outside and find (and hopefully correctly identify!) something green to put into a teapot.

An herbalist from a young age, Rosemary Gladstar has become an iconic figure in the herbal medicine community, celebrated for her practical and applied system of herbal medicine, which focuses on the wisdom of the generations and of the plants themselves. It is Gladstar's natural approach to her work and her style of folk herbalism that makes this text a breath of fresh air. With *Medicinal Herbs,* Gladstar does not try to create a clinical guide, or an evidence-based resource, or the latest trend in herbal health. Rather, the book emphasizes the system of herbalism, which is intended to be practiced in people's daily lives among friends and family (and has been practiced in this way for centuries).

That is not to say that this book would not be useful for a practitioner or advanced student of herbalism. The information in *Medicinal Herbs* makes it highly useful for anyone who wishes to bring herbs into their life (or their patients' lives) in a number of fun and practical ways and to play a greater role in their own healthcare. While

much of what is written on herbal medicine seeks to present a treatment alternative, *Medicinal Herbs* seeks to help readers include whole plants (or plant parts) as part of an array of wellness practices.



The opening section of *Medicinal Herbs* highlights what Gladstar does best in her teachings: It inspires the reader to incorporate medicinal herbs into their daily health practices. Each herb mentioned in the two sections, which elaborate upon specific medicines, is accompanied by one or more recipes as well as the beautiful images typical of Gladstar's earlier books with Storey Publishing. The recipes are reminiscent of those one might find, barely legible, on a tattered recipe card in an elder herbalist's kitchen from a lifetime of use — recipes conceived, crafted, and remade countless times.

The basics of safety and the routine disclaimers also are present and clear, although appropriately simple for an herbal text of this nature. And while there are recipes for common home remedies, such as for headaches and stress, housed within the sections on individual herbs, this text doesn't delve into the more complex issues or concerns of disease or treatment, thereby allowing it to retain its true purpose to support wellness and daily practices. A similar approach is apparent in the explanation of using the "simpler" method for medicine making. By not including medicinal dosing and compounding language, Gladstar allows the individual to feel comfortable attempting a new recipe without the intimidation factor of figuring out milliliters or grams.

It is difficult to find complaint with a book so comfortable in its own skin, so to speak. However, if you own the *Family Herbal* or any number of Gladstar's other texts, you will undoubtedly notice some overlap in the recipes. Also, the nod to some of the key constituents of the plants highlighted in *Medicinal Herbs* can seem a bit technical in comparison to the focus on sensory information, but it encourages the reader to begin to understand plant commonalities and characteristics.

There is not a lot of free space on my bookshelves nowadays, but I will make some room for *Medicinal Herbs* if only to remind me of the beauty of kitchen herbalism and the lineage of recipes and ideas as developed, refined, and applied over a lifetime.

—Bevin Clare, MS, RH, CNS
Associate Professor
Tai Sophia Institute
Laurel, MD

New Book Profiles

Advances in Botanical Research: Recent Trends in Medicinal Plants Research, Volume 62, by Lie-Fen Shyur and Allan S.Y. Lau (eds.). London, England: Academic Press; 2012. Hardcover; 468 pages. ISBN: 978-0-12-394591-4. $193.00.

Recent Trends in Medicinal Plants Research is the 62nd volume of the "Advances in Botanical Research" series published by Academic Press. The series is dedicated to exploring all aspects of medicinal plant research and covers topics such as ecology, biochemistry, plant genetics, physiology, and cell biology, among others. This volume is comprised of 11 chapters in the form of detailed research reviews written by researchers in a variety of scientific fields. The editors describe the book as a "major volume of reviews on the current research of elucidating bioefficacy and deciphering the mechanisms of action and molecular targets of specific bioactive phytocompounds or traditional herbal medicines for cancers, rheumatoid arthritis, cerebrovascular, stroke, and other inflammation-mediated chronic diseases, which are the main concerns of human heath." Other volumes in the series include *Plant Virus Vector Interactions* (Vol. 36), *Plant Innate Immunity* (Vol. 51), and *Plant Responses to Drought and Salinity Stress* (Vol. 57).

Healing Elements: Efficacy and the Social Ecologies of Tibetan Medicine by Sienna R. Craig. Berkeley, CA: University of California Press; 2012. Softcover; 344 pages. ISBN: 978-0-520-27324-5. $34.95.

Sienna R. Craig, an assistant professor of anthropology at Dartmouth College, explores the practice of Tibetan medicine in areas of China, Nepal, and the Tibet Autonomous Region in her latest book, *Healing Elements*. She begins by asking a simple question — "Does it work?" — for which, it turns out, there is no simple answer. Craig takes into consideration the varying definitions of efficacy as well as the politics involved in this much-disputed region of the world. As she explains in the book's introduction, "social ecological approaches demand we think holistically about how and why people fall sick, seek care, take medicines, experience the outcomes of these actions, and make sense of such events." The book is divided into seven chapters and includes an overview of Tibetan medical practices and practitioners (known as *amchi* in Tibetan), the global potential for Tibetan medicines, current manufacturing practices, and details about botanicals used in Tibetan medical practices. The last chapter focuses on the history and efficacy of an 11-ingredient Tibetan herbal formula known as *zhijé* II, which is commonly used in childbirth.

Narendra Singh
1935–2012

Narendra Singh, MD, was a man of numerous accomplishments who spent his lifetime dedicated to the study of Ayurveda and medicinal herbs in the context of his dual expertise in pharmacology and conventional medicine. He served as referee for numerous national and international journals, in addition to being on the editorial board of the *Journal of Medicinal and Aromatic Plant Sciences* and serving as editor of the *Journal of Biological and Chemical Research*, the *Journal of Biotechnology in Medicinal Plant Research*, and the book *Clinical Studies on Kamala (Jaundice) and Yakrit Rogas (Liver Disorders) with Ayurvedic Drugs* (1988). Dr. Singh was well-regarded professionally and held several honorary fellowships from a variety of organizations in science, nutrition, longevity research, herbal medicine, and brain research. He passed away on July 31, 2012.

Dr. Singh was born in the village of Kamhenpur in Uttar Pradesh, India, where he was introduced at a young age to Sanskrit and the Vedic tenets of Hinduism. This influence was pivotal to the evolution of his holistic approach to medicine. Following his training as a physician and surgeon (MBBS**,** Bachelor of Medicine and Bachelor of Surgery) at the Sarojini Naidu Medical College in Agra, and service in the Indian Army, he returned to academia. In 1967, Dr. Singh received his MD in Medicine and Pharmacology from King George's Medical College, Lucknow. He eventually was appointed as the college's Head of Ayurvedic Research in the Department of Pharmacology and Therapeutics, as well as Head of the Regional Ayurvedic Research Institute of the Indian government's Department of Health; he retained these titles until 1995. In 1999, Dr. Singh received a Doctorate in Alternative Medicine from the Indian Board of Alternative Medicine, Calcutta.

His most recent titles include Director of the International Institute of Herbal Medicine & Clinic (Lucknow**),** as well as President of the International Society for Herbal Medicine. In 1997, he was appointed Scientific Director of research and development at Organic India Pvt. Ltd, Lucknow.

Over the years, Dr. Singh's research focused on evaluating Himalayan community pharmacopeias and the medicinal herbs mentioned in ancient Ayurvedic texts. Throughout the course of his clinical career, he applied this knowledge to the formulation of Ayurvedic herbal remedies, sometimes combining them with Western medicine to elicit optimal clinical outcomes. His book *Herbal Medicine — Science Embraces Tradition* (2010), co-written with the clinical biochemist Marilena Gilca, MD, reflects his confidence in the integrative approach and in how holistic treatments can be developed with an appreciation of the limitations of each medical system.

Ever mindful of the need to develop natural herbal remedies in a safe and sustainable manner, Dr. Singh recently applied his expertise to create numerous herbal formulations under the auspices of Organic India, a private company that grows, manufactures, and markets certified-organic Ayurvedic herbs and teas through direct partnership with village agricultural communities. He is best known for his research on the adaptogenic and anti-stress properties of classic medicinal and Ayurvedic herbs. For example, his 2002 book, *Tulsi: The Mother Medicine of Nature*, written with Yamuna Hoette and Ralph Miller, elaborates upon the value of tulsi (*Ocimum tenuiflorum*, Lamiaceae) for a variety of medicinal uses associated with its adoptogenic and healing properties. Revered in India, tulsi (also known as holy basil) is described in terms of its traditional religious value and as an Ayurvedic remedy to heal mind, body, and spirit. Information regarding a wide range of current experimental and clinical research affirming the rationale behind its potential medicinal worth also is included.

Considered both a scholar and gentleman, Dr. Singh was well-respected by all who knew him. His winning smile, humble demeanor, and genuine congeniality will be missed by all of us who called him a friend and colleague. Most importantly, his lifetime of work toward providing a better understanding of the value of Ayurveda in the context of modern medicine is not only a well-deserved legacy, but also serves as an important example to those who continue to explore the value of traditional medicinal systems in a scientific context. For those wishing to review Dr. Singh's extensive contributions to science and medicine, his curriculum vitae is available at www.organicindia.com/doctor-narendra-singh.

Dr. Singh is survived by his wife Savitri, daughter Anita, and his three grandchildren Vaubhav, Abhisarika, and Parul. HG

—Memory Elvin-Lewis, PhD, DSc
Professor of Biomedicine in Microbiology and Ethnobotany
Adjunct Professor of Biology
Washington University, St. Louis, MO

Jacques Dikansky
1960–2012

Jacques Dikansky, founder and chairman of botanical ingredients manufacturer Naturex, died September 30, 2012, at the age of 52.[1] Dikansky had resigned from his daily activities at the company in April 2012 due to his declining health. He died in Avignon, France, surrounded by his children and other family members.

In 1992, Dikansky founded Naturex as a producer of plant extracts to supply the food industry. With just two factories initially — one in Avignon and another in Kenitra, Morocco — Dikansky guided the company to its present standing as a global botanical supplier that employs about 1,300 people and operates 15 production units, including six in Europe, two in the United States, and others in Brazil, Australia, and India.[2] The multimillion dollar company manufactures several hundred botanical products in varying stages of development, from raw materials to final ingredients, that are used by numerous businesses within the food, beverage, flavoring, dietary supplement, nutraceutical, pharmaceutical, and cosmetics industries.

"Jacques was an inspiring entrepreneur, intensely dedicated to developing a global company with an outstanding reputation," said Antoine Dauby, group marketing director of Naturex (email, November 28, 2012). "He envisioned a world in which natural ingredients would someday be in high demand. By anticipating market trends and through sizable investments in research and development, Naturex became a pioneer in the use of natural specialty ingredients. Jacques was a genuine leader and an excellent manager, who had the respect of everyone within the company."

After obtaining a chemistry degree from the University of Rennes in France, Dikansky soon took direction of his father's apple concentrate and beetroot alcohol distillery in the Brittany region of northwestern France, when he was 20 years old. Because the business was experiencing decreasing profits, Dauby explained, Dikansky knew he needed to diversify production and consulted with a professor at the French National Institute for Agriculture Research, who suggested he produce onion essential oils and concentrates for flavoring purposes.

"He followed the advice successfully," Dauby continued. "In light of this achievement, he predicted that industrial users and end consumers would be increasingly calling for natural ingredients."

Eventually, in 1982, Dikansky created a fruit and vegetable concentrate and powder business named Arômes de Bretagne (now known as Diana Naturals), which he sold in 1988 to found food flavor and extract company Saveur (now known as Savena). Then, in 1992, he founded Naturex. During his distinguished career, Dikansky won several awards, including the 2003 French Entrepreneurship Award given by the French President Jacques Chirac, Ernst & Young's 2006 Entrepreneur of The Year, and the 2007 French Ambition Award given by the French Minister for Trade Renaud Dutreil.

"When I met Jacques Dikansky in 2005, I realized quickly that he was a most unusual man," said Chris Kilham, an author, medicinal plant researcher, and Naturex's "Explorer in Residence" (email, December 6, 2012). "Jacques was driven to succeed in a way that few people are. He devoured opportunity, as though there was no limit to his insatiable capacity. A highly keen observer, he had the ability to assess situations quickly and most often with great accuracy, and to make decisions that typically produced very good results. He preferred to burn the candle for long hours, starting early, finishing late, moving from one continent to the next with tremendous rapidity, all the while checking no less than 300 emails per day, taking multiple dozens of calls, lining up deals, and making strategic acquisitions. For Jacques, the constant work seemed like nourishment."

Though he was very proud of his company, Kilham noted that Dikansky "cared not at all for the spotlight." And Dikansky was not only a businessman of great success and ambition, but also a person who had a concern for others, including his family, his employees, and the international communities from which Naturex sourced many of its ingredients. According to Kilham, Dikansky went out of his way to meet every new hire at Naturex; he also funded many years of Kilham's field research and was highly supportive of his investigations in foreign countries. Dauby noted that Dikansky's family, particularly his four children, was very important to him.

"Despite the pressures and commitment needed to run a successful global business, Jacques always found time for his children," he said.

In 2008, Dikansky created the Naturex Foundation as an outlet to give back to rural farmers around the world. Following Dikansky's death, the Naturex Foundation was renamed Naturex Foundation-Jacques Dikansky in his memory.

"Jacques was not interested in personal fame," said Dauby, "and he wanted to recognize the significance of these associations by being actively involved in supporting the welfare and growth of farmers. He decided to launch our Foundation with the aim to improve the living conditions of the communities where we source our raw materials. Our Foundation, in conjunction with local non-profit organizations, is able to make a difference to the education, medicine, and basic necessities of local people in the [more] deprived areas of the world, where we source our raw materials." HG

—Lindsay Stafford Mader

References

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