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Rose

The Timeless Beneficial Bloom

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Hawthorn

Crataegus monogyna, C. laevigata

Family: Rosaceae

INTRODUCTION

Hawthorn is a large shrub or small tree (15-30 feet on average) in the genus *Crataegus*, native to temperate North America, Europe, and East Asia.[1] The plants are indeterminately thorny, with variable shape, and have perfect, radially symmetrical, 5-petaled white to pink flowers (red in some cultivars) in corymbs (flat-topped clusters).[2,3] The red fruit are drupes (one-seeded and fleshy) but are commonly called berries in the trade. The genus *Crataegus* comprises approximately 250-280 species, the most commonly used in Western medicine being *C. laevigata* (syn. *C. oxyacantha*) and C. *monogyna*, both native to Europe; these 2 species are the subject of this article.[2] The *European Pharmacopoeia* accepts the interchangeable use of these 2 species or their hybrids, or other European *Crataegus* species such as *C. azarolus*, *C. nigra*, and *C. pentagyna*.[4] *Crataegus* species are highly variable, making species boundaries unclear.[2] Additionally, hybridization among hawthorn species is very common, suggesting that there are few pure populations.[2,3]

Traditionally, preparations of the fruit, such as syrups, were the most commonly used medicinal form, but preparations made from the flowers, leaves, and seeds also have been used in traditional European medicines and phytotherapy.[5-7] Plant material used in commercial products is primarily obtained from wild collection in Albania, Bosnia and Herzegovina, Bulgaria, Romania,[8] Hungary, Macedonia,[9] Poland,[10] and the United Kingdom.[12] Some of the commercial supply of *C. monogyna* is actually wild collected in non-native countries, namely in Chile, where it was introduced and has since escaped from cultivation.

HISTORY AND CULTURAL SIGNIFICANCE

The generic name, *Crataegus*, comes from the Greek *kratos*, meaning hard or strong, referring to the plant's wood.[13,14] The common name refers to the plant's thorns and fruit, known as haws, and may also refer to its use to form hedges, which were called haws in earlier times.[13] Other common names for *C. laevigata* include English hawthorn, white thorn, May tree (referring to when it blooms), and two-style hawthorn; and English hawthorn, one-seed hawthorn, and one-style hawthorn for *C. monogyna*.[3,12,15,16] General common names for the genus include haw, mayhaw, thornapple (not to be confused with *Datura stramonium* [Solanaceae], which is also called thornapple).

At least 1 hawthorn species that is not the focus of this article (*C. pinnatifida*) has been used in Chinese medicine dating back to 659 CE to treat arteriosclerosis, high blood pressure, and heart pain.[17] In current practice, the dried ripe fruit, either "stir-baked" (by placing the dried berries in a pot, stirring constantly over gentle heat until color darkens, removing and cooling) or "charred" (by stir-baking until the berries become burnt-brown externally and yellowish-brown internally), is indicated for treating stagnation of undigested meat with epigastric distension, diarrhea and abdominal pain, amenorrhea due to blood stasis (local stoppage or slowness of the blood flow or general sluggishness of blood circulation), epigastric pain (over the pit of the stomach), or abdominal colic after childbirth, hernial pain, and for hyperlipemia (aka hyperlipidemia; excessive quantity of fat in the blood).[18] Additionally, hawthorn fruit has been used in China for stomach complaints and for its vitamin C

Hawthorn *Crataegus laevigata*. Photo ©2012 Steven Foster

content to treat scurvy, as well as to make jam, sweet wine, and candied fruit slices.[17]

Infusions and decoctions of the bark, fruit, leaves, root and root bark, sap and sapwood, thorns, twigs, and young shoots of at least 11 species of *Crataegus* have been used by various North American tribes to treat conditions including back pain, bladder ailments, consumption (pulmonary tuberculosis), diarrhea, mouth sores, and stomach complaints, and also as a mild laxative, to promote appetite, to prevent spasms, to poultice swellings, and to stop menstrual flow.[19] Additional external and internal uses include treating "large stomachs," "female weakness," "general debility," and "to ward off tacklers." At least 1 tribe, the Cherokee, used an infusion of the bark of 1 species, *C. spathulata*, to promote circulation. Furthermore, the berries have been used as food, both fresh and dried, and were considered by the Thompson tribe as a good health food for general sickness. The inner bark was chewed as gum, and the thorns were used as fish hooks, awls, pins, and to probe boils and areas of arthritic pain.

The first mention of hawthorn's cordial actions on the heart may have been made by the Swiss physician Paracelsus (1493-1541).[12] The English physician Nicholas Culpeper (1616-1654) wrote that dried, powdered hawthorn berries added to wine would help with "stones" and dropsy (edema of lower extremities caused by congestive heart failure); an infusion of the flower would stop diarrhea or flux; and that the seed, bruised and boiled in wine, was "good for inward tormenting pains."[20] In her 1931 classic, *A Modern Herbal*, Maud Grieve attributes cardiac, diuretic, astringent, and tonic actions to *C. oxyacantha*.[13] While the plant mainly was used as a cardiac tonic, the flowers and berries also were used, due to their astringency, to treat sore throats.

The use of hawthorn for heart conditions had entered European clinical practice by the 17th century and became popular in the late 19th through early 20th centuries.[3] In North America, hawthorn was used for cardiac medicine by 1896. Today, hawthorn preparations are one of the best-selling botanical medicines in Germany.[16] Tea made from the leaf and flower are available loose and in teabags; dry and fluid extracts, tinctures, soft extracts, and injectable forms are also available. In France, hawthorn is used for anxiety and insomnia.[21] It also is utilized as a mild sedative, often in combination with lavender (*Lavandula* spp., Lamiaceae) or lemon balm (*Melissa officinalis,* Lamiaceae) in cases where mild heart disease is accompanied by nervousness.[14]

Hydroalcoholic extract of hawthorn leaf with flower (flowering twig tips of *C. monogyna*, *C. laevigata*, or other species of the genus *Crataegus* cited in a valid pharmacopeia and effective dosage preparations made from them) was approved by the German Commission E for decreasing cardiac output as described in functional Stage II (slight limitation of physical activity; comfortable at rest) of the New York Heart Association's 1994 *Revisions to Classification of Functional Capacity and Objective Assessment of Patients with Diseases of the Heart* (NYHA).[22] Hawthorn berry, flower, and leaf *as single components* received negative evaluations from the German Commission E in 1994 due to insufficient scientific evidence at that time supporting their use, although *combined* leaf with flower extracts were approved that year.[12] Other sources recommend it for Stage I of NYHA as well as cardiac degeneration that does not yet require digitalis, bradycardic arrhythmias, and a sensation of pressure in the chest. The European Scientific Cooperative on Phytotherapy (ESCOP) also recommended herbal tea and preparations other than a hydroalcoholic extract for support of cardiac and circulatory function in nervous heart complaints.[23]

CURRENT AUTHORIZED USES IN COSMETICS, FOODS, AND MEDICINES

In 2011, the European Medicines Agency (EMA) called for scientific data to be used by its Committee on Herbal Medicinal Products (HMPC) for assessment work toward the establishment of Community herbal monographs and/or Community list entries for both hawthorn and hawthorn leaf and flower preparations.[24,25] Once these monographs are established, they will have relevance for the registration of traditional herbal medicinal products and/or well-established use herbal medicinal products in the European Community. A prerequisite of product registration is that quality complies with the corresponding quality standards monographs of the *European Pharmacopoeia*, in which there are presently 4 hawthorn monographs (*i.e.*, Hawthorn Berries PhEur, Hawthorn Leaf and Flower PhEur, Hawthorn Leaf and Flower Dry Extract PhEur, and Quantified Hawthorn Leaf and Flower Liquid Extract PhEur).[26] Concerning use in cosmetic products, the European Commission Health and Consumers Directorate lists several hawthorn ingredients for skin-conditioning function, including Crataegus Monogyna Flower Extract, Crataegus Monogyna Flower Water (aqueous solution of the steam distillate), Crataegus Monogyna Fruit Extract, Crataegus Monogyna Leaf Extract, Crataegus Oxyacantha Extract (extract of the whole plant), Crataegus Oxyacantha Flower Extract, and Crataegus Oxyacantha Fruit Extract. However, Crataegus Oxyacantha Flower Water is listed for masking function while Crataegus Oxyacantha Stem Extract is listed for antimicrobial function.[27]

In the United States, hawthorn is regulated as a dietary supplement component requiring manufacturer notification to the US Food and Drug Administration within 30 days of marketing a product (if a "structure-function" claim is made), while in Canada hawthorn is regulated as an active ingredient of licensed natural health products (NHPs) requiring pre-marketing authorization from the Natural Health Products Directorate (NHPD). The authorized use for labeling of hawthorn berry NHPs (decoction or infusion, dried hydroalcoholic extract, fluidextract, or tincture) is "(Traditionally) used in Herbal Medicine to help maintain and/or support cardiovascular health in adults."[28] For labeling of hawthorn leaf and flower NHPs (infusion or decoction, or standardized hydroalcoholic extract), the authorized statement is the same as for the berries, except the qualifier "Traditionally" is removed because the claim statement in this case is based on clinical data rather than on traditional use evidence. The finished hawthorn NHP must comply with the minimum specifications outlined in the current NHPD Compendium of Monographs and the medicinal ingredient may comply with the specifications outlined in the aforementioned European pharmacopeial monographs or with those of the United States Pharmacopeia (USP).[28] For quality specifications of hawthorn dietary supplement components in the US and/or hawthorn NHP active ingredients in Canada, the USP has 2 monographs available, Hawthorn Leaf with Flower and Powdered Hawthorn Leaf with Flower.[29]

MODERN RESEARCH

Pharmacological studies suggest that the primary active components of hawthorn leaf and flower are the flavonoids and oligomeric procyanidins, specifically those with a lower degree of polymerization.[1] Hawthorn fruit consists mainly of oligomeric and polymeric procyanidins and relatively low levels of flavonoids.

In the 1990s, 13 clinical studies with 6,815 participants showed positive effects on cardiac insufficiency.[1] Most of these studies were conducted using a dry extract of hawthorn leaf and flower standardized to a dose of 9 mg or more per day of oligomeric proanthocyanidins (OPCs). Since the turn of this century, more than a dozen clinical trials have been conducted assessing the safety of hawthorn (occasionally in combination with other botanical components) and its cardiovascular benefits, especially cardiotonic activity.

Hawthorn's ability to lower blood pressure (BP) has been linked to nitric-oxide (NO)-mediated vasodilation, and brachial artery flow-mediated dilation (FMD) is an indirect measure of NO release. A 2012 randomized, placebo-controlled, double-blind, 4-period crossover study investigated the relationship between various dosages of hawthorn extract and FMD to determine a guide for dosing to help lower BP.[30] Randomly sequenced doses of hawthorn extract (1,000 mg, 1,500 mg, and 2,500 mg of Hawthorn Supreme Liquid Phyto-Caps [250 mg dried extract hawthorn leaf and flower standardized to 50 mg oligomeric procyanidins]; Gaia Herbs, Inc., Brevard, NC) were given to 21 prehypertensive or mildly hypertensive adults twice daily for 3.5 days followed by FMD measurement. There was no evidence of dose-response effect and the authors concluded that any BP-lowering effect hawthorn might have could be due to mechanisms other than NO. They noted that the subjects of the study may have had a more limited ability to produce NO as their average age was 51 and NO production declines after age 40. Additionally, the authors suggested that the preparation used in their study might not be representative of all hawthorn products.

A 2010 double-blind, placebo-controlled pilot study investigated the beneficial effects of *C. laevigata* on coronary heart disease (CHD) biomarkers.[31] For 6 months, 49 diabetics with CHD took a micronized leaf and flower preparation (400 mg standardized to 5% procyanidins and 2% flavonoids; Crataesor, Soria Natural SL, Spain) or placebo 3 times per day in addition to their existing conventional treatment. Participants in the hawthorn group showed decreased neutrophile elastase (NE) and a trend toward lowered low-density lipoprotein cholesterol compared to placebo. Since NE is elevated in patients with CHD and is correlated with the complexity and severity of blocked arteries (coronary stenosis), the inhibition of NE could provide a viable therapeutic option.

A randomized, double-blind, placebo-controlled trial published in 2009 sought to determine the usefulness of hawthorn in treating 120 ambulatory patients with NYHA class II-III chronic heart failure.[32] For 6 months, patients received, in addition to their conventional medicine, either 450 mg twice daily Crataegus Special Extract WS® 1442 (Crataegutt®, 80 mg hawthorn leaf with flower dry extract 5:1 [w/w], standardized to 18.75% OPCs; Dr. Willmar Schwabe GmbH, Karlsruhe, Germany) or placebo. Subjects took a 6-minute walking test prior to starting the study and at 3 and 6 months. There was no significant difference between the hawthorn and placebo groups in the 6-minute walking test at 6 months, nor in the secondary quality of life scores, heart failure symptom scores, functional capacity, risk or mortality, neurohormone profiles, or markers of inflammation and oxidative stress. As these results were not consistent with previous studies, the authors suggested various reasons why that might be, including the following: sample size, participants with milder NYHA scores, less rigorous tests, and/or wider variation in accepted medical treatments in earlier studies, or overlap of hawthorn mechanism of action with

Hawthorn *Crataegus monogyna*. Photo ©2012 Steven Foster

that of drugs being taken by participants in this study.

A 2008 study involving 2,681 participants investigated the efficacy and safety of hawthorn as an add-on treatment for patients with heart failure.[33] Participants in the hawthorn group received 900 mg daily Crataegus Special Extract WS 1442 for 24 months. While cardiac mortality reduction was insignificant, in a subgroup with left ventricular ejection fraction (LVEF), the hawthorn extract reduced sudden cardiac death by 39.7%.

In 2008, a meta-analysis addressed the benefits of hawthorn leaf and flower extract monopreparations as reported in 14 randomized, double-blind, placebo-controlled clinical trials.[34] A total of 1,100 participants took either 160-1800 mg/day of Crataegus Special Extract WS 1442 or Faros® LI 132 (100 mg hawthorn leaf with flower dry native extract 4–7:1 [w/w], standardized to 2.25% flavonoids; Lichtwer Pharma GmbH; Berlin, Germany). In a majority of the studies, hawthorn was used as an adjunct therapy to conventional treatment. Treatment with hawthorn extract increased maximum workload better than placebo; it significantly increased exercise tolerance; pressure-heart rate product (an index of cardiac oxygen consumption) decreased; and significant improvements in shortness of breath and fatigue occurred compared to placebo. The authors concluded that, while based on small numbers of studies and patients, hawthorn flower and leaf extract has significant effects as adjunct therapy for patients with chronic heart failure, but that further investigation was needed that reported clinical as well as physiological outcomes.

A 2006 study investigated the hypotensive effect of hawthorn.[35] For 16 weeks, 79 patients with type 2 diabetes were randomized to receive 1,200 mg hawthorn extract daily (Faros LI 132) or placebo. Data were collected at baseline, 8, and 16 weeks. There was no significant difference between groups regarding BP measurements or indices of glycemic control but there was a significant different in diastolic BP in the hawthorn group, indicating that hawthorn does have a hypotensive effect.

FUTURE OUTLOOK

In EU Member States as well as non-EU countries such as Switzerland, hawthorn dry extracts, fluidextracts, teas, and tinctures are labeled and marketed as non-prescription drug products available at pharmacies and drugstores.[36] There are about 4,000 native European plants with known pharmacological effects, of which about 500 are authorized for medicinal use. Of these, the top-10 best-selling medicinal plants account for one-third of the entire EU market. In recent years, hawthorn has ranked tenth in European herbal medicinal product sales.[36] In the US, hawthorn dietary supplement retail sales were ranked 24th, at $281,834, in the food, drug, and mass market channel in 2011, a slight increase over the previous year.[37]

Demand for hawthorn ingredients 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 hawthorn harvesting in a number of countries including Albania and Azerbaijan,[38] as well as Bosnia and Herzegovina, Poland,[39] and even Chile.[40] HG

—Gayle Engels and Josef Brinckmann

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dear *reader*

Rose Oil, Sports and Supplements, Large Echinacea Trial, and Bilberry Adulteration

When I was in Antalya, Turkey, in September 2011 for the annual scientific congress of the GA (the Society for Medicinal Plant and Natural Product Research), one of the exhibitors was Gülbirlik, the Turkish Rose Cooperative, a government-owned co-op of Turkish rose growers, distillers, and producers of roses, rose oil, rose water, and other products from this highly revered flower. For several years I have wanted to publish an article on rose, to include its rich history and varied ethnobotany, and I had been in communication with someone from a Bulgarian rose-producing group (Bulgaria lies just north of Turkey and both countries are known for the ultra-high quality of their rose oils). When I expressed my interest in such an article for these pages, our good friend, Hüsnü Can Başer, PhD, professor of pharmacognosy at Anadolu University in Turkey, and the principle host and organizer of the GA congress (and a recent addition to the ABC Advisory Board), volunteered to author it. Professor Başer, who recently co-edited a relatively massive book on essential oils, has written an extensive article documenting the high regard that roses and their products, particularly the rare and expensive rose oil, have had in Middle Eastern culture, and their history in Turkey and surrounding countries in particular. If only we could print *HerbalGram* in a scratch-and-sniff technique using real rose oil!

Moving on to other subjects, our associate editor and HerbalEGram managing editor Lindsay Stafford Mader was inspired this summer during the pre-Olympics media blitz to research the ways that athletes have used botanical preparations to help improve athletic performance. This research led to the highly controversial practice called "doping," and the complex situation of increasing frequency in which athletes blame dietary supplements for failed drug tests. Mader investigates the reality of these accusations and also provides details on potentially efficacious and legal botanicals for sports performance.

Some big news lies in our Research Review section: We present a summary of the recent clinical trial on the Swiss company Bioforce's echinacea extract (Echinaforce®), which showed safety and efficacy in preventing symptoms related to the common cold in the largest echinacea clinical trial ever published. This study initially enrolled 755 people, significantly more than the 399 subjects enrolled in what was previously the largest trial, which was published in the *New England Journal of Medicine* in 2005 and met with wide criticism (including our own) for using only about one-third of the generally recognized dose of echinacea extract.

And finally, as part of our ongoing series of articles focusing on the accidental and/or intentional adulteration of botanical raw materials, extracts, essential oils, etc., in global commerce, we include an article that author and esteemed botanical photographer Steven Foster and I have written on the intentional adulteration of bilberry extracts. This article is part of the ABC-AHP-NCNPR Botanical Adulterants Program that ABC is conducting with the American Herbal Pharmacopoeia and the National Center for Natural Products Research at the University of Mississippi, and which is now being underwritten, supported, and/or endorsed by over 85 industry companies, third-party analytical laboratories, universities and schools of natural medicine, trade and professional organizations, and others. Unfortunately, the bilberry issue is but one of numerous examples of economically motivated adulteration — an important subject that we intend to continue addressing in coming issues of *HerbalGram*.

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

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Nature's Defender

Tom Newmark Joins ABC's Board of Trustees

In October 2012, the American Botanical Council welcomed to its Board of Trustees Tom Newmark, a longtime, ardent environmentalist who is best known for his past role at the herbal supplements company New Chapter, Inc. Newmark was instrumental in helping New Chapter become the first dietary supplements company to have its entire line of vitamins certified as made with organic ingredients as well as verified by the Non-GMO Project, and he has remained a tireless activist for organic and non-GMO causes. He also is co-owner of Finca Luna Nueva, a biodynamic and organic herb farm in Costa Rica, and he co-founded Semillas Sagradas, a botanical sanctuary that preserves traditional and medicinal plants and the knowledge surrounding their important uses. Semillas Sagradas, which is on the Luna Nueva farm, was the first installment in what has grown into a worldwide network of approximately 16 similar projects under the nonprofit organization Sacred Seeds, of which Newmark is president and chair of the board.


Tom Newmark in India.

In addition to his new position on ABC's Board of Trustees, Newmark recently joined the natural products merchant banker 6Pacific as chairman, a role in which he will assist natural products companies in achieving greater commercial success. He also serves on the boards of Greenpeace, the Missouri Botanical Garden's William L. Brown Center, and Friends of the Children's Eternal Rainforest in Monteverde, Costa Rica.

"My dad is, by definition, a passionate man," said his daughter Sara Newmark, who is director of sustainability at New Chapter (oral communication, August 21, 2012). "No matter what he decides is his passion, you will not only hear about it, it will move you."

A self-described "recovering attorney," Newmark came to New Chapter in 1999 after serving as a legal consultant to his college friend and New Chapter co-founder Paul Schulick. Newmark started off at the company as president, and, over the next 13 years, held several titles including co-CEO, CEO, and chairman. Newmark describes Schulick as his "first and most important teacher with respect to herbal medicine." Together they co-authored *Beyond Aspirin* (Holm Press, 2000), *The Life Bridge* (Herbal Free Press, 2002), and created the current top-selling combination dietary supplement product in the United States, Zyflamend®, a multi-herbal extract formulation to promote healthy inflammation response that has been supported by laboratory studies and a Phase I clinical trial.

"Tommy was responsible for many, many roles," said Schulick (oral communication, August 28, 2012). "He is a visionary. He's able to look a little toward the future and see what trends might be most beneficial. And he also is very, very bright so he is able to wear many different hats at one time. He was able to communicate with scientists and regulators and staff in stores. He just has many skill sets."

During his time at New Chapter, Newmark had a profound impact on the company, particularly its success in becoming the first-ever dietary supplements company to have its entire line of vitamins certified as made with organic ingredients.

"He really championed the cause that our company was based on from the very start," said Schulick.

"He was the force behind going organic," said his daughter Sara. "He was the force behind making sure that we were certified by the Non-GMO Project. That legacy will live on as long as New Chapter does, and beyond as more companies are able to step into our footsteps and take advantage of those opportunities. His personal stamp is the heart of who I think New Chapter is and will always be."

Speaking to Newmark about organic foods and herbs, his passion for the cause is obvious. "I believe that organics are the only way to feed the planet," he said (oral communication, August 28, 2012). "They are the only way to, on a humane level, enable people to sustain themselves without the use of the toxic, obnoxious chemistries. Organic farming is an absolutely indispensable component to addressing and remediating carbon dioxide concentrations in the atmosphere. I think that any discussion on global climate change and resolutions that we must begin to implement must embrace organic farming and conversion of conventional [farming] acreage to organic acreage."

Shortly before retiring from New Chapter, Newmark and Sara spent weeks in India touring organic farms and the villages involved in farming the organic herbs used in some of New Chapter's products. Many of the organic and sustainability passions shared by the father and daughter were united and realized on this trip.

"It was an epiphany," said Newmark. "Seeing the villages that were dust in the wind and just down the road, organic communities that were not only producing brilliant and lively and healing botanicals for the Western world, but were also supporting the villages and supporting the people and reviving the ecosystems. Part of the responsibility of being a botanical company, being an herbal company, is knowing your farmers and knowing the supply chain and being confident that every step of your supply chain is in accordance with national law, with the needs of both humanity and the planet."

During Newmark's 13 years at New Chapter, he also made and maintained connections and financial arrangements between New Chapter and other members of the natural products industry. Newmark retired from the company after its purchase by Procter & Gamble in June of 2012 (though he is serving as a consultant during a short transition phase).

Now Newmark plans to spend half of his time in Costa Rica, working on Luna Nueva and Semillas Sagradas and expanding the network of Sacred Seeds sanctuaries around the world. Steven Farrell, who also co-founded Semillas Sagradas and is manager of Luna Nueva, said Newmark always has been the most enthusiastic supporter of these projects. From the beginning, Farrell said, "Tom was all over the idea. He was just, 'Yes! Do that!' His interest is always to stimulate us to improve and increase the plants. Tom's call was always, 'More, faster, quicker.' He's always been the best cheerleader and supporter of what we've been doing on the farm, including Semillas Sagradas. He stimulates others to do more, to learn more" (oral communication, September 7, 2012).


Tom Newmark in Costa Rican rainforest.

Semillas Sagradas started out with 68 plant species and has grown to feature about 300. Every day that Newmark is in Costa Rica, he strolls through the garden, which is only about 200 feet from his home. Sara describes Costa Rica as Newmark's "happy place."

"I have never seen him more at home and at peace than when he is walking through the rainforest of Costa Rica and dipping his head in the rivers of the jungle and hanging with the farmers and working on his important preservation work down there."

When discussing the tiny Central American country that he first visited about 15 years ago, Newmark's voice becomes giddy with excitement. "There is no place I've ever found on earth that is as beautiful in every direction, up and down, sideways, at once, with as much biodiversity as Costa Rica," he said. "It's a very lovely place and a place where I lose connection to a lot of the insanity of the world, and I gain connection to the things that are truly most precious. I'm thrilled that Costa Rica has welcomed these kind of starry-eyed gringos filled with dreams of green and peace."

Newmark describes his interest in plants as "something that was imminent," having been interested as a young boy inspired by his own father, whom he said was "an exquisite gardener who had an artistic and tender touch with respect to his gardens." The young Newmark, who often accompanied his father on weekend garden trips, described himself as a budding boy-scientist who delighted in telling adults that he wanted to be a microbiologist when he grew up just to see their reaction.

"I certainly had my trading card collection of baseball players," said Newmark. "But I also was collecting plants and doing taxonomies of plants."

After high school, Newmark graduated from Washington University in 1973 and went on to Yale for a graduate degree in political science. Not much more than one semester passed when he left to study Transcendental Medita-

tion and eventually became a teacher of meditation for several years. It was through meditation and his mentor Maharishi Mahesh Yogi, the well-known guru to The Beatles, that Newmark connected his own love of plants to their healing potential.

"Through his teachings," said Newmark, "I became more sensitized to the power of plants to heal and enlighten and it was through my studies of meditation that I first became aware of Ayurvedic medicine and the principles that had formed that exquisite, ancient, venerable healing system."

"He was the force behind going organic. He was the force behind making sure that we were certified by the Non-GMO Project. That legacy will live on as long as New Chapter does, and beyond as more companies are able to step into our footsteps and take advantage of those opportunities. His personal stamp is the heart of who I think New Chapter is and will always be."

Still, it was not at that point that Newmark began his official career with herbal medicine; instead he followed in his father and brother's footsteps by obtaining a law degree. "It felt like the logical thing for me to do," said Newmark. Though he carried on a family tradition, Newmark's trial law practice was unconventional and representative of his true spirit. Among other clients, he represented the Animal Legal Defense Fund pro bono, seeking to have underwater trapping of Missouri river otters banned "as an offensive and painful suffocation that was wrong." He also represented the Natural Law Party, which is based on the Maharishi's teachings, and Ross Perot's Reform Party, both of which sought to be included in the 1996 presidential debates, which Newmark described as an attempt "to break the stranglehold of the 2 dominating parties."

Newmark said he hopes always to use his law experience in ways that "are of benefit to the world," a goal he can strive toward through his nonprofit work. In addition to ABC and his roles on other boards, Newmark continues to champion the causes of organic farming and non-GMO foods and herbs — causes he describes as resonating "very deeply with my soul" — through public-speaking tours and editorial articles.

Newmark brings to the ABC Board of Trustees a deep devotion to environmentalism, conservation, and organic herb production, as well as a youthful energy and more than a decade of experience within the regulatory environments of the natural products industry.

"Tom Newmark is an extraordinarily talented individual," said New York Botanical Garden ethnobotanist and fellow ABC Board member Michael Balick, PhD (email, September 14, 2012). "In addition to his experience with supplements, particularly botanicals, he is an organic spice farmer, conservationist, and author, with an international perspective shaped by his devotion to protecting nature, public health, and the well-being of generations that someday will inhabit Planet Earth. It is also just plain fun to walk through a tropical forest with Tom and see his overwhelming excitement about the plants, animals, and even the less-obvious microbes that are to be found. I am thankful that Tom enthusiastically accepted this new assignment as a colleague on the ABC Board of Trustees, and know that in the years to come, he will contribute significantly to the Board's vital work in governing and expanding this important organization."

Photographer, author, and Chairman of the ABC Board of Trustees, Steven Foster, said, "The Board of Trustees of the American Botanical Council was deeply honored when Tom Newmark accepted our invitation to serve on our Board. Tom brings a combination of exceptional nonprofit and for-profit board experience to ABC along with a deep personal and professional understanding of the natural products industry and the herb consumer."

"The American Botanical Council," said Newmark, "is an extraordinary organization populated by some of the most wonderful scholars, ethnobotanists, scientists, thinkers. I am exceptionally proud to be on the Board. To me, it is a career achievement."

According to his daughter, Newmark also brings his intellect.

"He is a very smart guy," said Sara. "I've actually never met anybody as smart as him and I think I'm not saying that just as his daughter. He thinks things through and has a unique ability to understand situations and direct business and organizations. I think he's proven himself at that, and I think ABC will really benefit from it. I've never really seen him as excited and honored to be asked to serve in such a position." HG

—Lindsay Stafford Mader

American Botanical Council Unveils Digital Flip Version of *HerbalGram*

The American Botanical Council (ABC) is pleased to announce that members now have a new way to read and enjoy its peer-reviewed, quarterly journal *HerbalGram*. ABC has converted the latest issues of the highly respected magazine/journal into full-color, digital flip-page versions available to ABC members at the organization's website, www.herbalgram.org.

ABC will continue to publish its print editions of *HerbalGram*, as well as the text-based (HTML) online version with several articles in each edition freely available for non-members. The flip-page edition of the journal, designed for mobile phone and tablet users, is available via the *HerbalGram* link on ABC's website, once the member is logged in. A PDF edition, showing the complete view of a page layout, can be found on the same page (the PDF version does not have the page-flip option).

The flip-formatted *HerbalGram* creates a stunning visual display on numerous digital devices. Each issue contains dozens of full-color, high-quality photographs of botanicals that now can be appreciated on an even-greater scale. Recognizing the growing trend toward mobile readership across all segments of the publishing industry, ABC aims to continue to provide accurate, science-based and traditional information on herbal medicine in an easy-to-use format.

"All of us here at ABC are truly excited to make this new way of reading *HerbalGram* available to our thousands of members in many countries," said ABC Founder and Executive Director Mark Blumenthal. "I know that many ABC members, like those of us on the ABC staff, Board of Trustees, and Advisory Board, would like to be able to leaf through *HerbalGram* on our mobile devices. That time has now come."

"HerbalGram is best-known for its in-depth, referenced, peer-reviewed articles, as well as Steven Foster's beautiful photography," Blumenthal added. "Now, reading *HerbalGram* on a smart phone or tablet computer will allow ABC members to see his photos in ways they have not been able to previously."

HerbalGram Art Director Matt Magruder, who has been with ABC for nearly 6 years, said, "The magazine/publishing world is changing rapidly and this new e-Magazine implementation is a good way for *HerbalGram* to begin to adapt to the digital environment.

"It provides ABC members with a convenient way to enjoy *HerbalGram* on their computers, tablets, and smartphones in the same form that they have enjoyed the magazine in the past."

Steven Foster, author, photographer, and chairman of ABC's Board of Trustees, said, "I love having *HerbalGram* 'in my pocket.' Like many individuals, increasingly I consume periodical content as PDFs or as electronic versions on my iPhone and/or iPad. The convenience and at-your-fingertips access actually mean that I spend more time reading, not less time, and in the process have more opportunity to really digest and refer to the information. I am delighted that *HerbalGram* is now available as electronic content to American Botanical Council members in addition to the print version. It's one more compelling reason to become a member of ABC."

To date, *HerbalGram* issues 93, 94, and 95 have been released in the flip-page format. ABC plans to make available all future issues of *HerbalGram* in this way, and with enough interest from members, ABC may start converting back issues to the new digital format. Text-based issues of the magazine — going back to 1990 — are archived and accessible at www.herbalgram.org.

HerbalGram was first published as a newsletter in 1983. Since that time, it has gained a reputation as an authoritative, reliable, peer-reviewed source of information on herb and medicinal plant research, regulatory and market issues, native medicinal and aromatic plant conservation, and other aspects of the expanding world of herbal medicine and phytotherapy.

"We hope that this type of mobile digital access to *HerbalGram* will bring a new community of readership and membership to ABC," said Blumenthal. "There is no other publication in the world like *HerbalGram*, and it is now even easier and more fun to read." HG

—Sara Ellis

IT Consultant Profile: **Eric "Rick" Valdez**

From installing the American Botanical Council's first file and e-mail servers to helping staff transition to newer hardware and software programs, Eric "Rick" Valdez has worked for the past 23 years to keep ABC up to speed with the rapid pace of technology. Although Valdez works off-site, his long-standing relationship with the organization, strong work ethic, and willingness to provide assistance at any hour of the day has more than qualified him as a valued ABC team member.

"Technically, I am an independent contractor, but because of the type of work I do along with my long-term association with ABC, they treat me as if I were a staff member," said Valdez.

Eric, a native Austinite, has spent most of his life in the city and currently calls southwest Austin home, where he lives with his wife of 32 years along with their son and daughter. "My grandmother's family has lived in South Austin since 'before Texas was a state,'" he said. "My mom and dad moved to San Antonio because my dad was in the military service. After high school, I moved back to Austin to attend the University of Texas and, like many others, I stayed here."

After attending the University of Texas, Eric finished his degree in accounting and minor in computer system administration at St. Edward's University, where his daughter is currently a student. His varied academic background is, in part, what makes Eric such a valuable team member.

"When you get an IT person, you're lucky to get someone who understands software and hardware, but you hardly ever get someone who understands the accounting side, which Eric does," said Cecelia Thompson, ABC's finance director. "He's so different from so many other IT people. He's grown through the years with all that knowledge and has just kept on going. That's why I call him Mighty Mouse — because he always saves the day."

Eric's relationship with ABC began in the late 1980s, when the organization was transitioning from one software package to another. "I started working with ABC in 1989. At the time, ABC used an accounting software package called CYMA, and Cecelia contacted the software company and asked for some assistance and they referred me to ABC," he said.

Before being hired officially, Eric offered his services pro bono to ABC, which at the time was still in its infancy. "Eric actually supported us in answering all of my questions for about 2 years before we ever went with him on something, and he did it for free," said Thompson. "When it was time to go from whatever platform we were on, I went with him because he had helped us all along. From then on, he was our supporter of almost everything we did."

"There's no way for us to express adequately how important Eric is to the success of ABC," said ABC's Founder and Executive Director Mark Blumenthal. "Eric has been with us since almost the beginning, for over 23 years. The incredible vault of institutional memory he holds is a key asset for ABC, as it would be for any nonprofit organization or even a for-profit company. And, what's more, he really, genuinely *cares* about ABC, its mission, and its people."

Before coming to ABC, Eric worked as an account manager for the City of Austin for almost 10 years, and then started his own consulting business. Currently, Eric acts as a consultant to ABC for virtually every aspect of the organization's technological framework.

"For ABC, my company, Corsair USA, basically functions as the Chief Technology Officer. I advise on the purchase of hardware and software, provide accounting software support, help desk support, [and] manage the computer network," he explained. "I also have a few behind-the-scenes staff that manage ABC's website infrastructure and the content management system of ABC's website."

In addition to the wide variety of technical assistance Eric provides, his availability and willingness to help sets him apart from other consultants. "He's fabulous. Most software companies, their support is Monday through Friday from 8 to 5 — he's 24/7. Mark calls him anytime he needs assistance, and so do many other ABC staff members. He's always available to answer your question," said Thompson.

Despite all he does for the organization, Eric works with other clients in addition to ABC. "Today, my clients are primarily healthcare providers and professional service companies. Besides ABC, I have several other nonprofit clients that rely on my firm to provide computer network security and support, accounting software support, and website development/support," he said. "I consider it a privilege to serve others and I have been very fortunate to have several clients that 'make a difference' in one way or another."

When not working, Eric enjoys spending time with his wife and children. "I spend most of my free time with my family and I occasionally enjoy a round of golf," he said.

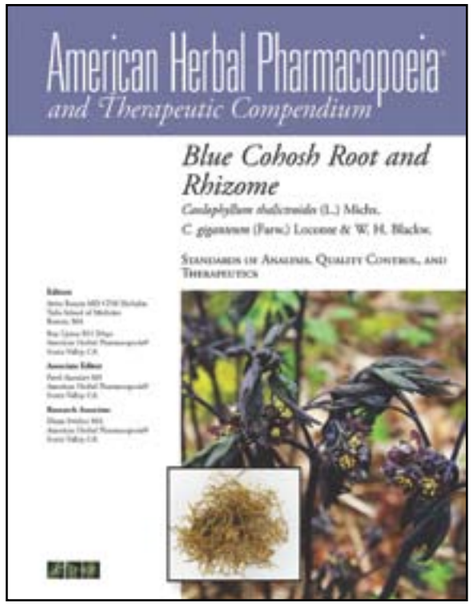
And, just as ABC benefitted from his services before he was officially hired, Eric still finds time to give back to the community. "He does a lot of donating of his time and energy," said Thompson. "He does that for some organizations and individuals who can't afford to pay for anything; he'll go over and fix their computer on his own time." HG

—Tyler Smith

American Herbal Pharmacopoeia Publishes Blue Cohosh Monograph

The American Herbal Pharmacopoeia (AHP) announced in June the publication of a new monograph and therapeutic compendium for blue cohosh (*Caulophyllum thalictroides*, Berberidaceae) root and rhizome.[1] AHP monographs provide standards for determining herb purity and authenticity, as well as information on quality control issues. The therapeutic compendium — which, depending on the herb in question, can be used by companies to help substantiate product safety claims — offers a comprehensive review of available pharmacological data on the plant and includes information on dosage, side effects, toxicology, and drug interactions, as well as guidance on the development of structure-function claims.

Reports of toxicity associated with blue cohosh, combined with its continued popularity as a natural birthing aid, prompted AHP to publish the monograph — its 33rd. "Blue cohosh has been implicated in a few cases of toxicity that include neonatal cardiac toxicity and maternal toxicity," said AHP Executive Director Roy Upton (email, July 18, 2012). "Because blue cohosh was the primary herb used in birthing practices of herbalists, integrated medical doctors, and midwives for more than 100 years, we felt it was important to address this concern."



Aviva Romm, MD, a co-author of AHP's latest monograph, began research on blue cohosh as a medical student at Yale. "I wanted … to explore whether in fact risk outweighed the benefits of use so that midwives could be appropriately informed, or whether a case for relative safety could be established so that those who chose to use it could do so in the most informed, evidence-based manner," she said (email, July 18, 2012).

Blue cohosh is unrelated to the similarly named black cohosh (*Actaea racemosa*, Ranunculaceae), for which an AHP monograph is also available. "However, these are taxonomically unrelated plants that are not typically confused," wrote Upton and Dr. Romm in the monograph.[1] "According to Lloyd and Lloyd (1931), 'cohosh' is an Algonquin word meaning 'it is rough' (with hairs) and was originally applied to the bristly fruit of *Ribes lacustre* [Grossulariaceae; also known as prickly black currant or bristly black gooseberry]," explained Upton.

Traditionally, blue cohosh has been used as a diaphoretic (sweat inducer), diuretic, expectorant, and for arthritis, but it is used most commonly in pregnancy and gynecology, most specifically as a way to avoid conventional methods of induction, which contribute to the high rate of premature births in the United States. According to Upton, "the safety of blue cohosh has to also be considered in this context." Case reports of adverse events in recent years, however, have called for an evaluation of the plant's pharmacological and safety data, which AHP believes it has provided.

A review of the data suggests that blue cohosh is indeed associated with certain adverse events reported, but confounding factors make it impossible to establish a causal relationship. "What I walked away with most from this monograph is the need to use the herb within the context of those most experienced with it and in the context of how it was most widely used traditionally, in combination with other botanicals," said Upton.

The monograph notes that Eclectic physicians in the latter part of the 19th and early part of the 20th centuries almost always used the herb in combination formulas, "which inherently limits the exposure to potentially toxic substances," Upton added. "It may still prove to be a safe and effective induction agent when used by highly trained and experienced birthing professionals, but concern regarding potential toxicity has limited its use in birthing."

The blue cohosh root and rhizome monograph is available through AHP's website, www.herbal-ahp.org. A PDF version of the publication is available for $35.95, and a hard copy can be purchased for $44.95. HG

—Tyler Smith

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American Academy of Neurology, American Headache Society Recommend Special Butterbur Root Extract for Migraine Prevention

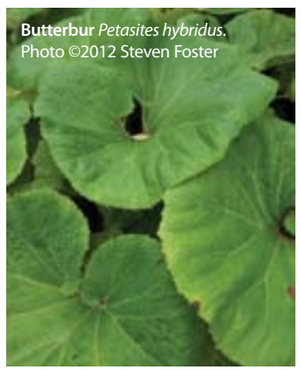
In a joint report published in April 2012 by the American Academy of Neurology (AAN) and the American Headache Society (AHS), researchers concluded that a proprietary extract of butterbur (*Petasites hybridis*, Asteraceae) root is effective in reducing the frequency of episodic migraines.[1] The finding, published in the journal *Neurology*, was part of the organizations' updated evidence-based treatment guidelines, which specifically examined the efficacy of what they term "complementary treatments" and non-steroidal anti-inflammatory drugs (NSAIDs), such as aspirin and ibuprofen.

"Non-prescriptive treatments are important for many patients," said Frederick Freitag, MD, a co-author of the new guidelines and medical director of The Headache Center of Baylor Health Care System in Dallas, Texas (email, July 25, 2012). "As with any treatment for migraine, appropriate discussion with the patient's clinician regarding choices and subsequent monitoring for safety and efficacy can be very beneficial."

To assess the effectiveness of non-prescription treatments, a panel of headache and methodology experts conducted a literature review of migraine prevention studies from June 1999 through May 2007. Treatments were considered to have established efficacy if two or more supporting Class 1 human clinical trials existed in the literature. According to its website, *Neurology* defines a Class 1 trial as a "randomized, controlled clinical trial of the intervention of interest with masked or objective outcome assessment, in a representative population."[2]

Only 2 studies of butterbur extracts for migraine prevention met the criteria for inclusion, each of which compared placebo treatment to various dosages of the butterbur root extract supplement Petadolex®(Linpharma Inc., Orlando, FL; manufactured in Germany by Weber & Weber), which has been commercially available in Europe for more than 25 years. It has been available in the United States as a dietary supplement since 1999 (V. Gallichio, email, August 14, 2012).

Both studies concluded that certain doses of Petadolex were significantly more effective than placebo. "Petadolex brand of butterbur root is a reasonable alternative to prescriptive medication and when properly prescribed and monitored can be a very effective and safe preventative treatment for migraine," said Dr. Freitag.


Butterbur *Petasites hybridus*.
Photo ©2012 Steven Foster

Although this is not the first case of an American medical organization recommending a specific herbal treatment option for an illness or disorder, it does not happen frequently due to the amount and type of research required for such recommendations. In its clinical practice guidelines, the American Urological Association notes positive outcomes of studies using saw palmetto (*Serenoa repens*, Arecaceae) berry extract and stinging nettle (*Urtica dioica*, Urticaceae) for the treatment of benign prostatic hyperplasia (BPH), but it does not offer an endorsement of these herbal options, describing the quality, size, and length of available studies as "suboptimal."[3] Saw palmetto, however, is described as a secondary recommended treatment ("Grade B") for patients with BPH by the American Association of Clinical Endocrinologists in their medical guidelines for the clinical use of dietary supplements and nutraceuticals.[4]

In its 2009 review of evidence-based clinical practice guidelines, the Society for Integrative Oncology explains why complementary therapies, including herbal medicine, are often not formally recommended by medical organizations, despite promising research. "A gap exists between the current level of scientific evidence and what we need to know to provide evidence-based advice, but rigorous scientific research is ongoing," the authors wrote in the report.[5] "A demonstrably favorable risk/benefit profile is essential for the use of complementary therapies, as it is for any form of medicine. The advantages of a rigid, evidence-based approach based on reductionism, however, do not translate easily into the holistic approach required for complex health issues."

The National Center for Complementary and Alternative Medicine (NCCAM) has compiled a list of clinical practice guidelines from a variety of medical organizations on its website, which includes botanicals with varying levels of supporting evidence. The list is available at http://nccam.nih.gov/health/providers/clinicalpractice.htm.

In their 2001 paper in *Alternative Medicine Review* — one of the studies included in the recent migraine prevention literature review — researchers Werner Grossman and Hanns Schmidramsl explained Petadolex's presumed mechanism of action.[6] "Petadolex is an extract of the rhizome from *Petasites hybridus*, and petasine and isopetasine are the main components," they wrote. "It has been shown that petasine and isopetasine are strong vasodilatory substances, whereby this effect on smooth muscle preparations *in vitro* is equivalent to papaverine." (Papaverine is a medication prescribed for migraines in adults and children, derived from the opium poppy [*Papaver somniferum,* Papaveraceae].)

The etiology of migraines, which are 3 times more common in women, is still contested. Once thought to be primarily related to cranial vasculature, new theories — including genetic predisposition, hyperexcitable neurons (particularly the trigeminal nerve), and inflammation — have emerged in recent years.[7]

In addition to its use for migraine prevention, butterbur root has been used traditionally for pain management, anxiety, fever, and gastrointestinal conditions. In its "Herbs at a Glance" factsheet published in March 2012, NCCAM noted the well-known fact that the butterbur plant contains chemicals known as pyrrolizidine alkaloids (PAs), which have been shown to cause liver damage.[8] NCCAM cautions consumers to use only butterbur products labeled as PA-free. European regulatory agencies allow butterbur root and aerial parts preparations to be marketed only if the daily dosages stay within a very low prescribed maximum level of PAs. For example, the German Commission E monograph (under the common name Petasites Root in the English translation) states that the daily dose of butterbur root preparations must not exceed 1 mcg of PAs.[9]

Accordingly, Petadolex supplements are processed in a manner that reduces PAs to undetectable levels. As stated on the company's website, "Petadolex is manufactured by a patented method for extracting the beneficial liquid of the butterbur plant without the PAs. This purification process guarantees that Petadolex is free of detectable PAs."[10]

In addition to butterbur root extracts, experts involved in the recent *Neurology* report reviewed studies on antihistamines, Co-Q10, estrogen, hyperbaric oxygen, magnesium, and MIG-99, a supercritical carbon dioxide-extract of the herb feverfew (*Tanacetum parthenium*, Asteraceae) that is no longer being manufactured (V. Gallichio, email, August 14, 2012).[1] A single Class 1 study and 2 Class 2 studies on MIG-99 and migraine prevention were available in the time period reviewed by the authors, which was enough evidence to label feverfew extract a "Level B" treatment (medications that are "probably effective").

While Petadolex has been shown to be effective in reducing episodic migraines, more research is needed on other formulations of butterbur, as well as other herbs that may offer relief to migraine sufferers. Revised guidelines for acute migraine treatment, separate from preventative treatment, are currently in development. HG

—Tyler Smith

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UK and Irish Governments' Echinacea Warning Criticized

On August 20, 2012, the United Kingdom's Medicines and Healthcare products Regulatory Agency (MHRA) advised parents not to use echinacea products in children under the age of 12 and also required manufacturers to re-label their echinacea products with the advisory warning.[1] The Irish Medicines Board (IMB) has issued the same warning.[2] The decision is being denounced by various herbal medicine groups and a major manufacturer of echinacea products, who say echinacea has been used safely in children for numerous years.[2,3]

MHRA is the UK Department of Health agency responsible for ensuring safety and efficacy of medicines and medical devices.[1] In a press release, MHRA stated that its advisory on echinacea (*Echinacea* spp., Asteraceae) was based on precautionary conclusions from the European Herbal Medicinal Products Committee (HMPC) as set out in its *Echinacea* species monographs and the UK Herbal Medicines Advisory Committee, both of which found that "the perceived benefits of the use of echinacea in children under 12 years are outweighed by the potential risks in this age group and there is a low risk of allergic reactions but these could be severe."[1] MHRA told the American Botanical Council that it also considered case details from the World Health Organization and the IMB (email, M. Niizeki, September 20, 2012). According to the MHRA press release, the documented adverse reactions — which authorized echinacea products in the United Kingdom already feature on their package information — include "rashes, hives, swelling including swelling of the skin due to fluid and swelling of the face, difficulty breathing, asthma and life threatening anaphylactic shock."

Richard Woodfield, MHRA's director of herbal policy, stressed in the press release that "this is not a serious issue," and that the risk faced by children under 12 is "low."[1] Even considering the precautionary nature of the advisory, that any warning was issued at all is proving incomprehensible for many involved parties.

Scientist Roland Schoop of A. Vogel Bioforce AG, which manufactures the popular Echinaforce® line of products, pointed out that the adverse events listed by MHRA are observed rarely and "should be considered in the light of the estimated number of courses of treatment, more than 10 million annually" (email, August 24, 2012). (A peer reviewer of this article noted that such evidence is impressive considering the *mandatory* adverse event reporting required of echinacea products registered as traditional medicinal products and those that are fully authorized as medicines.)

"If compared with the thousands of deaths attributed to over-the-counter anti-inflammatory drugs or decongestants," said Schoop, "the safety of Echinaforce appears very favourable."[4,5] Other review papers also have concluded that echinacea is essentially safe.[6,7]

A director of the European Herbal and Traditional Medicines Practitioners Association echoed Schoop's sentiments, telling the *Daily Mail* that "the new guidance was 'arbitrary' and not based on any new research."[3] The president of the Irish Association of Health Stores (IAHS) told *The Irish Times* that children have been safely using echinacea products in Ireland for about 20 years, that "there was 'no up-to-date evidence' to show the product was unsafe for use by" children under 12, and that "there might be more sense in banning the sale of peanuts."[2] Additional opponents of the ban have created an online petition calling on the UK and Irish health ministers to reverse their warning. As of press time, the petition had collected 4,247 of its 5,000-signature goal. (It is available at: www.avaaz.org/en/petition/Reverse_Decison_on_Banning_Echinacea_in_Children_by_the_MHRA_and_the_IMB/.) The MHRA, however, has said it "would not at this time consider revisiting the warning given out advising parents and carers to not use Echinacea in children under 12, but does consistently monitor new safety and clinical data for Echinacea" (email, M. Niizeki, September 20, 2012).

Echinacea *Echinacea purpurea*. Photo ©2012 Steven Foster

Schoop — whose 2006 echinacea meta-analysis was selected as one of the top 25 research papers by the US National Institutes of Health Office of Dietary Supplements[8] — said that MHRA based its decision on the 2008 HMPC monograph even though Section 4.4 of the monograph "explicitly states that 'specific risk in children over 1 year of age is not documented.'"[9]

"While the clinical evidence on echinacea in children might be sparse," said Schoop, "there exists a tremendous experience on the use of echinacea/Echinaforce in children [for] over 50 years."

Many European countries already recommend that echinacea products state the potential of allergic reactions in those who have known allergies to plants in the Asteraceae family (also known as Compositae, which includes the genus ragweed [*Ambrosia* spp.]) or who have genetic dispositions to develop allergic reactions.

"The MHRA recommendation substantially diverges from newer recommendations from the European Scientific Cooperative on Phytotherapy or by Health Canada," said Schoop. "Countries like Switzerland, Canada, Croatia, Australia, but also Germany and Austria today acknowledge the use of echinacea in children."

The moves on echinacea as an "herbal medicinal product" in Europe may be seen as part of a wider pressure on regulators across the world, including in the United States, to restrict the use of medicines in children under 12, in response to the paucity of clinical trial and safety data on conventional medicine dossiers.

The MHRA/IRB decision on echinacea warning applies primarily to over-the-counter echinacea medicines, which make up the vast majority of echinacea products sold to the public, said Simon Mills, herbal practitioner and Advisory Board member of the American Botanical Council. It may have less impact on trained herbalists, who can prescribe patients echinacea preparations after conducting personalized consultations including routine screenings for atopic sensitivities, allergies, and asthma, he added (email, September 4, 2012).

"It is only advice, not a legal instruction or ban," said Mills. "Herbalists can take a decision based on their experience and standards of practice, to take professional responsibility for their use of echinacea in children. I reckon most will choose to carry on as before."

American Botanical Council Founder and Executive Director Mark Blumenthal pointed out MHRA's failure to distinguish the important differences between echinacea products using the roots of the plant and those using the aerial (above-ground) parts.

"Any reactions that may be reported," said Blumenthal, "are most likely associated with echinacea preparations containing aerial parts of the plant (*e.g.*, dried leaves and/or flowers, or fresh-pressed juice), which may contain pollen, thereby possibly causing a reaction in a highly sensitized individual. Such reactions are probably very seldom, if ever, associated with alcoholic (ethanol) echinacea preparations made from echinacea roots only, as such preparations rarely, if ever, contain pollens. Further, its probable that the alcohol in extracts of either roots and/or aerial parts would most likely inactivate any pollens."

Manufacturers of echinacea products available on the UK market are currently in the process of labeling products with the new advisory and over-labeling products presently on the shelves. Donald Brown, ND, a natural products research consultant, told ABC that he does not foresee the US Food and Drug Administration issuing any warnings on echinacea products (oral communication, September 5, 2012). HG

—Lindsay Stafford Mader

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Federal Action against Medicinal Cannabis Businesses Continues

Just over one year ago, on October 7, 2011, 4 US attorneys in California held a news conference to warn medicinal cannabis dispensaries to shut down their operations or be served with criminal charges.[1] The months following this announcement have been characterized by medicinal cannabis advocates as an all-out assault of federal powers extending into California, Colorado, Washington, and other states where medicinal cannabis (*Cannabis* spp., Cannabaceae) has been legalized — shocking and angering many who interpreted a 2008 campaign statement by President Barack Obama as a promise that he would leave this industry alone.

Several states' US Attorneys, who are part of the Department of Justice (DOJ), have been taking action by sending letters to landlords who own property where dispensaries are located, warning of asset forfeiture proceedings if tenants are not evicted.[2] They are also posting forfeiture notices onsite at some businesses. The DOJ defines asset forfeiture as an "initiative that removes the tools of crime from criminal organizations, deprives wrongdoers of the proceeds of crimes, recovers property that may be used to compensate victims, and deters crime."[3] Forfeiture statutes enable the federal government to seize property if it can prove that the property was used for criminal purposes or is the result of criminal activities. Some businesses in Colorado, meanwhile, are being ordered to shut down based on Title 21, Section 860 of the Controlled Substances Act, which states that controlled substance manufacturers and distributors cannot be located within a 1,000 feet of a school or college.[4]

Materials used in a September 2012 protest in Oakland, CA, against the ongoing federal crackdown on state-based medicinal cannabis businesses. Photo ©2012 Americans for Safe Access

Many businesses that received warning letters during the last year, including dispensaries and medicinal cannabis cultivation operations, have shut down and more have closed voluntarily out of fear — to the tune of about 400 businesses in California, a reported 57 in Colorado,[4] and dozens more in other states with legalized medicinal cannabis.[2] In July of 2012, one of the country's largest and best known dispensaries — Harborside Health Clinic in Oakland and San Jose, California — received a forfeiture letter. It is currently appealing the order in federal court, though every similar appeal thus far has been rejected.[5] The City of Oakland also has filed a lawsuit against the federal government on Harborside's behalf.[6] As of press time, Harborside was still open but trying to fight eviction by its landlords, who want the business to leave the property, as well as claims from the Internal Revenue Service that it must stop deducting wages and other expenses from its income taxes according to section 280e of the federal tax code that "prohibits companies from deducting most expenses if they are 'trafficking in controlled substances.'"[7]

"State-based medical cannabis business[es] have been severely traumatized by the Obama Administration's actions," said Kris Hermes, media specialist of the nonprofit Americans for Safe Access. "Some have gone underground. Most won't conduct interviews or make public comments for fear of reprisal. Some are also now reluctant to register with city or state governments. Many dispensary operators who have been shut down as a result of federal threats have reopened as delivery services with no fixed address or easy way for the authorities to identify them" (email, August 27 and September 3, 2012).

One of the major impacts of this federal crackdown are the jobs lost as dispensaries close, said Amanda Reiman, PhD, California policy manager of the Drug Policy Alliance. "Berkeley Patients Group, one of the oldest and most respected facilities in [California] was forced to close in May and lay off over 60 people," said Dr. Reiman, "and if Harborside has to close, they will be laying off over 100 people" (email, September 19, 2012).

Are the federal government's actions legal? No, according to attorney Robert Corry of Denver-based Corry & Associates, which represents many medicinal cannabis businesses.

"The Federal Government's actions are unconstitutional under the US Constitution Commerce Clause and the Tenth Amendment, which provides for a limited federal government of limited powers, and provides that the People retain the power within the several states," said Corry (email, September 3, 2012).

Others say that the federal government *is* acting within the law. Richard Meyer, special agent and public information officer for the US Drug Enforcement Administration's (DEA) San Francisco office, said in 2004:

"According to the United States Constitution there is a supremacy clause, which says that in case of conflict, federal law precedes state law."[8]

And Seattle attorney Deborah Jacobs wrote in *Forbes* on September 12, 2012, "Marijuana is a controlled substance under the Federal Controlled Substances Act. Growing, distributing and possessing marijuana in any capacity, other than as part of a federally authorized research program, is a violation of federal law… All of the [state] legislation is preempted by federal legislation, making the activities a federal crime."[9]

The Obama Promise

The federal action has caused a mix of shock, disappointment, and feelings of betrayal toward the administration of President Obama, who famously said during his 2008 campaign about the state-based medicinal cannabis industry:

"What I'm not going to be doing is using Justice Department resources to try to circumvent state laws on this issue simply because I want folks to be investigating violent crimes and potential terrorism. We've got a lot of things for our law enforcement officers to deal with."[10]

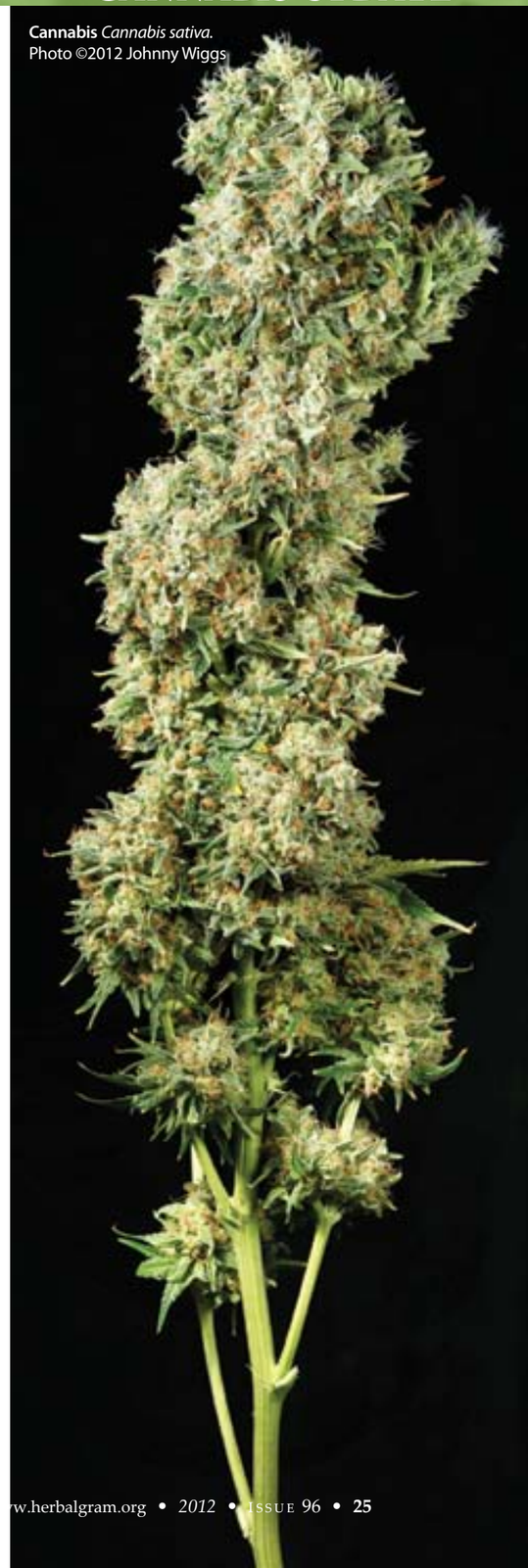
Obama also told the media that doctors and patients using medicinal cannabis would not be bothered because "there really is no difference between that and a doctor prescribing morphine or anything else."[10] When Obama was elected as the 44th President of the United States, his Attorney General Eric Holder followed suit and announced in 2009, "It will not be a priority to use federal resources to prosecute patients with serious illnesses or their caregivers who are complying with state laws on medical marijuana."[11]

Many people in states with legalized medicinal cannabis used these statements as a basis for growing their industry. But the Obama administration's policy always has been somewhat unclear. In fact, Obama said in the same interview quoted above that he had some concerns about medicinal cannabis businesses: "I think there are legitimate concerns in not wanting to allow people to grow their own or start setting up mom and pop shops because at that point it becomes fairly difficult to regulate."[10] And according to the *Washington Post*, Holder said "federal prosecutors should focus only on cases involving higher-level drug traffickers, money launderers, or people who use the state laws as a cover."[11]

In April 2012, well into the current federal crackdown, the president sought to explain his administration's actions in an interview with *Rolling Stone:*

> What I specifically said was that we were not going to prioritize prosecutions of persons who are using medical marijuana. I never made a commitment that somehow we were going to give carte blanche to large-scale producers and operators of marijuana — and the reason is because it's against federal law. I can't nullify congressional law. I can't ask the Justice Department to say, 'Ignore completely a federal law that's on the books.' What I can say is, 'Use your prosecutorial discretion and properly prioritize your resources to go after things that are really doing folks damage.
>
> The only tension that's come up — and this gets hyped up a lot — is a murky area where you have large-scale, commercial operations that may supply medical marijuana users, but in some cases may also be supplying recreational users. In that situation, we put the Justice Department in a very difficult place if we're telling them, 'This is supposed to be against the law, but we want you to turn the other way.' That's not something we're going to do.[12]

Based on these statements, it would appear that the federal government is taking action against dispensaries and businesses that are noncompliant with even state laws, *i.e.*, providing cannabis to non-medical users.[13] And authorities have claimed that they are focusing on cannabis businesses within 1,000 feet of a school or park frequented by children.[1]



Cannabis *Cannabis sativa.*
Photo ©2012 Johnny Wiggs

All sources interviewed for this story, however, unequivocally said that the shutdowns are random and are affecting honest and legitimate businesses. John Davis, chief executive of Northwest Patient Resource Center in Seattle, has been analyzing data on cannabis businesses in the Western district of Washington, including letters from federal authorities and locations of targeted and non-targeted businesses.

"In looking at [the data], there are many locations that did not receive letters that, in my opinion, had an inappropriate proximity to schools," said Davis. "Around half of those that received letters were businesses that I know and they were attempting to do things right. I believe the actions taken are intended to have a chilling effect on the industry, to cool the market and make it less inviting both to entrepreneurs and property owners" (oral communication, email, September 17, 2012).

Hermes of ASA also said that the federal government is targeting a variety of dispensaries with no clear method.

"There is no real pattern except to intimidate," said Hermes. "The federal government may make claims that certain facilities are making a profit, but no evidence of that has been supplied and many if not most of the locations are in full compliance with local and state laws. The feds may focus on areas with more dispensaries, but this is not always the case. For example, the feds have threatened and successfully shut down more than 200 dispensaries in San Diego, but for whatever reason they haven't focused as much attention on Los Angeles, which has far more facilities."

There has been some speculation in the industry that federal authorities are targeting states controlled by fewer regulations.[14] Many more raids and shutdowns have occurred in California versus Colorado, which requires dispensaries to be licensed and comply with all local zoning codes, and dispensary operators to oversee 70% of cultivation of the business's cannabis.[15] California has no such state regulations.

"Yes, most [shutdowns] are occurring in California but I think the only reason for this is the fact that California has the largest medical marijuana industry," said Aaron Smith, executive director of the National Cannabis Industry Association. "It seems that the federal government is prioritizing enforcement action against some of the most well-respected and well-regulated facilities in the industry" (email, August 31, 2012).

Hermes also disagreed with this theory.

"This interpretation of the federal government's tactics completely miss[es] the aim of the attacks. Colorado has not been immune from federal attacks. Montana and Washington tried to pass dispensary licensing laws, but legislators were threatened by US Attorneys for trying to implement such schemes, derailing those laws. There are more than 50 municipalities in California that have adopted dispensary ordinances, a far cry from an unlicensed environment."

And, apparently going against Obama's persistent vow to not target actual patients, Hermes stressed that the administration's action against dispensaries "has been devastating" to patients.

"The vast majority of the hundreds of thousands of patients across the country rely on centralized distribution to safely and legally obtain their medical cannabis," said Hermes. "Without such a supply, patients are being forced to either go without a medication that is legal under state law, or they now need to travel long distances to a still-operating facility, or they have to get it from the illicit market, thereby putting themselves in harm's way and complicating the job of law enforcement. This is especially relevant because the Obama Administration goes to great pains to underscore that it is not targeting sick patients. Unfortunately, it's sick patients who are most widely and adversely affected."

The Obama Administration goes to great pains to underscore that it is not targeting sick patients. Unfortunately, it's sick patients who are most widely and adversely affected.

Dr. Reiman of Drug Policy Alliance pointed out that the federal crackdown is driving businesses back underground, which she said, "Jeopardizes the safety and well-being of not only patients, but the community as a whole."

"I don't know how people expect patients to have safe access if businesses aren't able to run," said Davis of Seattle's Northwest Patient Resource Center. "The only way to get a legitimate source of medicine is through a business."

Medical Marijuana Business Daily, an online news site, has suggested that President Obama is allowing these actions to happen in order to avoid election-year "accusations that he allowed the medical marijuana industry to grow out of control under his watch."[15] Davis indicated that perhaps the Obama administration feels little connection or responsibility to the situation by basically claiming, "It's not us; it is the US Attorneys," who are brought in by presidents but answer to their own localities, and often have their own political futures in mind.

Legislation and Strategies for Industry

In April 2012, senators and representatives from California, Colorado, New Mexico, Maine, and Washington sent an open letter to the federal government, calling for an end to the interference and arguing that states are trying to help ill patients and are entitled to "depart from federal policy and chart their own course on the issue of medical marijuana" based upon the United States' "federalist system of government."[17]

Some federal lawmakers are taking it one step further, proposing national legislation in Congress that would address the current situation. In 2011, HR 2306 Ending Federal Marijuana Prohibition Act was introduced, followed by the Truth in Trials Act in July 2012, and later Representative Barbara Lee's (D-CA) introduction of HR 6335, the States' Medical Marijuana Property Rights Protection Act, on August 2, 2012.[2,18]

The 2012 presidential election season, however, made it unlikely that such controversial legislation received any attention. So what can state cannabis businesses do in the meantime? Though many cannabis businesses are shutting down their operations, Davis — one of the few business owners who speaks to the media — said his Northwest Patient Research Center will "keep doing what we're doing."

"Not only is it a business, but a great deal of my life is tied to it," he said. "I serve these people. There is a sense of responsibility that comes with it. I want people to know what's going on. I don't want it to be us hiding in the shadows. Can the DEA close me? Absolutely. Tomorrow if they like. Until then, I'm going to stay open."

"It's vital that operators in the industry maintain the highest of ethical standards and maintain best business practices in every area," said Smith of trade organization NCIA. "However, there will be no guarantee that they won't end up in the federal crosshairs since we're seeing some of the most well-run facilities being unfairly targeted. The most important thing these businesses can do is get involved with the fight to change draconian federal law."

Dr. Reiman said that cannabis reform organizations are going to propose to the federal authorities that they "freeze all actions against licensed medical cannabis businesses until an independent review can determine whether they are indeed in compliance with state law." Meanwhile, hundreds of medicinal cannabis patients, industry members, and supporters in several states are organizing large protests of the federal crackdown.

As for the presidential election this November, Colorado attorney Corry said he is "encouraging cannabis voters this fall to vote 'ABO,' Anybody But Obama." Davis disagrees with this strategy.

"Is Romney going to be better on it? Hell no," he said. "I believe [Obama will] be reelected and I hope that in a second term, he will have a little more political capital to do something about it. This industry will survive. It will move on. It fills a need within society." HG

—Lindsay Stafford Mader

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Swiss Echinacea Extract Shown Safe and Effective in Preventing Colds in Largest Echinacea Clinical Trial

Reviewed: Jawad M, Schoop R, Suter A, Klein P, Eccles R. Safety and efficacy profile of *Echinacea purpurea* to prevent common cold episodes: a randomized, double blind, placebo-controlled trial. *Evid Based Complement Alternat Med*. 2012:841315. Epub 2012 Sep 16.

Colds and flu, associated with a variety of viral infections, are characterized by symptoms such as sore throat, cough, and nose irritations, as well as systemic complaints such as headache, malaise, and fever. The common cold alone causes great discomfort and is a major reason for school and work absences, as well as physicians visits.[1] Preventative strategies have included antiviral agents or vaccines targeted towards infection prevention or inhibition of viral replication; however, common problems arise with adverse side effects (ASE) and/or the failure to protect certain populations.

Echinacea (*Echinacea purpurea*, Asteraceae) is used widely as an immune system modulator as well as in common cold prevention strategies.[2] Many clinical studies investigating the use of echinacea in cold prevention have shown conflicting results or have had too small a sample size to detect significant effects. However, significant preventive effects were observed when 3 trials on standardized echinacea extracts were combined in a meta-analysis.[3] (These studies were conducted by Bioforce AG in cooperation with Sebastian Johnston, MD, PhD, from the Imperial College in London.) Finally, tolerability and safety are critical considerations for therapies designed for long-term, preventive use. The most recent randomized, double-blind, placebo-controlled trial investigated the safety profile and efficacy of the long-term usage of a proprietary echinacea formulation for prevention of colds and flu.

Echinacea *Echinacea purpurea*. Photo ©2012 Steven Foster

This study took place at the Common Cold Center at Cardiff University in Cardiff, Wales. Healthy subjects were randomized to either echinacea or placebo for 4 months. At the initial clinical visit, subjects received study medication for 1 month in addition to a diary for documenting ASEs, incidences of colds and associated symptoms, and medication use other than given treatments. Subjects brought unused treatments and completed diaries to monthly clinical visits and also were given kits to take nasal swabs for viral identification.

An alcoholic extract of fresh echinacea extract was used in this trial (Echinaforce®, made from *E. purpurea*, 95% aerial parts and 5% roots, prepared by Bioforce AG; Roggwil, Switzerland). Material was standardized to 5 mg/100 g of dodecatetraenoic acid isobutylamide and tested negative for endotoxin. Placebo was comparable in appearance, smell, and taste, with the same percentage of alcohol and identical packaging. Total dosage was based on Bioforce AG's instructions and consisted of 0.9 ml of extract or placebo 3 times per day in water; this material was held in the mouth for 10 seconds (2,400 mg of extract daily) in order to achieve maximal local antiviral and anti-inflammatory effects at the pharynx. If subjects had a cold, they were asked to increase dosage to 0.9 ml 5 times per day (4,000 mg of extract). Leftover bottles were weighed for remnant of extract, and diaries were consulted to assess compliance.

Subjects were recruited on campus, at least 18 years old, and in good health with a recent history of 2 or more colds per year. Those pregnant, who had a chance of becoming pregnant, who were breastfeeding, who had a cold at the time of recruitment, who were on either antiviral or antibacterial medication, who abused drugs or alcohol, or who suffered from psychological diseases or epilepsy were excluded. Exclusion criteria also did not permit subjects with the following: a history of suicide attempts, upcoming surgery, chronic or autoimmune diseases, and asthma or allergies, particularly to members of the Asteraceae plant family. A preliminary study showed blinding to be efficient as approximately half the subjects in both the echinacea and placebo groups guessed that they had the echinacea treatment. Additionally, a power calculation based on a beneficial effect of 25% with the echinacea treatment and a protocol deviation and drop-out rate of 20% yielded an ideal sample size of 750 participants for the efficacy variable (number of days with colds).

Blood samples were taken from subjects for screening of blood cell counts and hematological and other measurements. Both subjects and physicians were asked to rate echinacea tolerability. Descriptions for ASEs as related to the treatments ranged from "not related" to "certain." Those ASEs that were "possibly" associated with treatment were considered adverse drug reactions (ADRs). Parameters for colds included the amount of colds, the total number of days with colds, and colds that required addition medication. Characterization of viral infections was also conducted.

Out of 755 subjects included and randomized, 82 subjects dropped out, leaving 673 who finished the study regularly. Reasons for subject dropout included loss of contact (there was no contact post randomization; n=38), withdrawal of consent (n=16), "technical reasons" (n=3), health or ASE problems (n=3), and unknown reasons (n=22). There were no baseline differences between groups with the exception of cold susceptibility; subjects randomized to the echinacea group were, by chance, significantly more susceptible to colds than those in the placebo group ($P<0.05$). This was expected to bias the efficacy results against the echinacea group.

ADRs were reported by 9.0% of the echinacea group and 10.0% of the placebo group; the echinacea treatment was identified to be non-inferior to placebo treatment in regard to the rate of occurrence, as even fewer ADRs were observed. In the echinacea group, 177 subjects documented 293 ASEs, and 172 subjects in the placebo group mentioned 306 ASEs. Also, in the echinacea group, 4 ASEs resulted in discontinuation of treatment, while 3 ASEs caused discontinuation in the placebo group. One severe ASE was reported in the placebo group while none were reported from the echinacea group. No significant differences were detected in the amount of ASEs between groups. Also, no significant differences were reported in the blood parameters either after echinacea treatment or between groups. Assessment of tolerability by subjects resulted in ratings of "good" or "very good" in 64% of the echinacea group and 71% of the placebo group.

Those in the echinacea group experienced 149 colds lasting a combined total of 672 days, while subjects in the placebo group reported 188 colds with a length of 850 days. The total number of days with colds was significantly fewer in the echinacea group than the placebo group ($P<0.05$, as measured in the intention-to-treat population). Those in the echinacea group also experienced fewer recurring colds than those in the placebo group (65 vs. 100, respectively; $P<0.05$). In addition, a greater number of subjects with colds in the placebo group used medication such as aspirin, paracetamol (acetaminophen), and ibuprofen as compared with those in the echinacea group (88 vs. 58, respectively; $P<0.05$).

Of the nasal swabs collected (n=201), viral infection was identified in 54 samples from the echinacea group and 74 in the placebo group. Significantly fewer samples from the echinacea group contained influenza, corona-, metapneumo-, respiratory syncytial-, and parainfluenza viruses as compared the placebo group (24 vs. 47, respectively; $P<0.05$). Additionally, in subjects with 100% protocol compliance, 36 colds with a combined total duration of 155 days were reported from the echinacea group (n=88) as compared with 58 colds in 268 days in the placebo group (n=99, $P<0.0001$).

In summary, preventive therapies for colds and flu should be both well tolerated and efficacious. The echinacea preparation used here exhibited a very "good" safety profile for long-term usage. This study reports that echinacea long-term prevention was associated with fewer cold episodes, fewer days with colds, and fewer colds that required additional medication, suggesting efficacy against infection. The study mentions that these data may have been confounded by the significant difference of cold susceptibly between groups and less use of pain-relieving pharmaceutical drugs in the echinacea group. If an adjustment for these co-variables had been conducted, an even more beneficial preventive effect for the echinacea formulation probably would have been shown.

This study also characterized viruses. Although the sample size was small, those in the echinacea group had significantly fewer viral infections than those in the placebo group. This may preliminarily indicate clinical antiviral activity as it agrees with the authors' *in vitro* results on the same proprietary extract (Echinaforce). In conclusion, this study claims to be not only the largest ever conducted on the clinical effects of echinacea, but the first to employ the detection of specific viruses in this manner. The conclusions from this well-powered, robust clinical trial contribute substantially to the case for the use of echinacea preparations, particularly this specific formulation, in common cold prevention. HG

—Amy C. Keller, PhD

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Systematic Review and Meta-Analysis of Cocoa and Chocolate on Important Cardiovascular Risk Factors Finds Multiple Benefits

Reviewed: Hooper L, Kay C, Abdelhamid A, *et al*. Effects of chocolate, cocoa, and flavan-3-ols on cardiovascular health: a systematic review and meta-analysis of randomized trials. *Am J Clin Nutr*. 2012 Mar;95(3):740-751.

Observational and prospective data (*i.e.*, information from long-term, non-controlled studies) have shown evidence that consumption of cocoa (*Theobroma cacao*, Sterculiaceae) and various types of chocolate preparations are associated with a decrease in cardiovascular disease (CVD) risk and mortality, as well as reduced blood pressure (BP) and cholesterol. Short-term, randomized, controlled trials (RCTs) have brought to light the mechanisms involved in producing these effects. Several systematic reviews and meta-analyses have been performed for different outcomes, but many did not remove lower quality studies or are now out of date. The authors — of the Norwich Medical School, University of East Anglia in Norwich, United Kingdom — have therefore endeavored to perform a systematic analysis of RCTs to assess the effects of cocoa, chocolate, or cocoa flavan-3-ols on classic cardiovascular biomarkers.

The biomarkers included were modifiable Framingham risk measures (as determined in the Framingham study, a large-scale epidemiological study of cardiovascular parameters that commenced in 1948), including systolic and diastolic BP and total, low-density lipoprotein (LDL), and high-density lipoprotein (HDL) cholesterol, as well as independent predictors of CVD risk such as fasting glucose, insulin, triglycerides, hemoglobin A1c (HbA1c), C-reactive protein (CRP), and flow-mediated dilation (FMD). Effects on body mass were also studied. The review was conducted in accordance with Cochrane methodology and presented in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Controlled parallel or crossover trials were retrieved from MEDLINE and EMBASE (both on Ovid, www.ovid.com), and the Cochrane Library (CENTRAL, www.thecochranelibrary.com), up to May 2011, using complex, structured searches. For each study found, the following data were gathered: quality characteristics, funding and blinding (to assess potential bias), and the similarity of fat intake between the treatment and control arms. Statistical analyses included the following: tests to assess the variability among studies, sensitivity analyses to assess the robustness of results, and funnel plots (statistical tools to determine if a large or small study comports with averages) to assess the evidence of small study or publication bias. For all outcomes for which there were more than 10 studies, assessments were done for effects of dose, study duration, sex, intervention type, and baseline CVD risk.

Of 1,637 potential studies initially identified, 42 trials (total n=1,297 subjects) examined cocoa, chocolate, or flavan-3-ols and had relevant outcomes. The studies variously included subjects who were healthy, overweight, hypertensive, hypercholesterolemic (high cholesterol levels), diabetic, and subjects who had elevated CVD risk, congestive heart failure, stable coronary artery disease, smoking-related endothelial (inner arterial tissue) dysfunction, chronic fatigue, or combined hypertension and impaired glucose tolerance. They consisted of 15 parallel-design and 26 crossover trials.

Interventions included cocoa drinks (21 trials), dark or milk chocolate (15 trials), cocoa supplements (3 trials), solid chocolate plus cocoa drinks (2 trials), and a whole diet (all foods provided) including cocoa powder and chocolate (1 trial). The controls were with low flavan-3-ol versions of the same foods, drinks, or supplements and were fairly well controlled in 23 studies. The placebos were unclear in 4 studies.

All studies were at medium-to-high risk of bias due to poor reporting of allocation concealment, blinding, dropouts, and use of commercial funding, according to the authors. Allocation concealment was adequate in 10 trials, inadequate in 1 trial, and unclear in 31 trials. Participant blinding was adequate in 24 trials, inadequate in 13 trials, and unclear in 5 trials. Provider/researcher blinding and outcome-assessor blinding were adequate in approximately 50% of the studies and were unclear in the rest. There was no reported funding from commercial companies in 8 studies and commercial funding reported in 28 studies, while 6 were unclear with regard to funding. The assessed percentage of energy from saturated fat in the intervention group was 2% or more of that in the control group in 8 studies, and 2% or more in 6 studies (suggesting significant dissimilarity of diet between intervention and control groups that may have impacted outcomes); the remainder of the studies did not report on fat intake.

The meta-analysis suggested improvement in FMD both acutely (2 hours after ingestion of chocolate/cocoa; 3.19%; 95% confidence interval [CI]: 2.04%, 4.33%; 11 studies, 373 participants, I^2=84%) and after chronic intake (1.34%; 95% CI: 1.00%, 1.68%; 11 studies, 382 participants, I^2=0%). There was also a significant reduction in fasting serum insulin concentrations (-2.65 µU/mL), serum insulin after glucose challenge (-17 µU/mL; 95% CI: -20.7, -13.4 µU/mL), and homeostasis model assessment-insulin resistance (HOMA-IR; -0.67; 2 trials, 70 participants, I^2=60%) after chocolate or cocoa interventions. The combined effect of reduced HOMA-IR with improved FMD could be substantial for reducing cardiovascular risk. There was no effect on fasting glucose, HbA1c, or triglycerides.

Significant reductions in diastolic BP (-1.60 mmHg; 95% CI: -2.77, -0.43 mmHg; 22 trials, 918 participants, I^2=52%) and mean arterial pressure (-1.64 mmHg; 95% CI: -3.27, -0.01; 4 trials, 163 participants, I^2=0%) after chronic intake were observed. Marginally significant effects on LDL (-0.07 mmol/L; 95% CI: -0.14, -0.00 mmol/L; 21 studies, 986 participants, I^2=58%) and HDL (0.03 mmol/L; 95% CI: 0.00, 0.06 mmol/L; 21 studies, 986 participants, I^2=67%) cholesterol were found. There were no significant effects on diastolic BP after acute intake, or on CRP, total cholesterol, or systolic BP after acute or chronic intake. Too few trials reported on body weight, body mass index (BMI), and waist circumference to do an analysis.

The effects of other factors, such as sex, dose, duration, etc., were examined where there were enough studies reporting on those outcomes. There were significant improvements in FMD for all doses of epicatechin (an antioxidant flavanol compound found in cocoa and chocolate ingredients), for either short or long durations, with greater improvements at higher doses. There were also improvements with epicatechin for systolic and diastolic BP at doses >50 mg/d, and in fasting glucose and triglycerides at doses of 50-100 mg/d. Only short-term studies (<3 weeks) reduced fasting glucose, LDL, and total cholesterol; and only long-term studies (>3-wks. duration) increased HDL cholesterol.

Removing studies funded by industry did not change the results for FMD or HOMA-IR, but the effects on BP and HDL and LDL cholesterol were no longer significant. Removing studies with unclear allocation concealment also did not change the results for FMD or HOMA-IR, but the short-term chronic effects on diastolic BP and the effects on systolic BP became statistically significant.

Funnel plots showed a minor trend towards bias for FMD, and no bias for systolic BP (though in the latter, the power was limited due to small study size).

According to the authors, this is the first systematic review and meta-analysis to assess the effects and validity of all RCTs on cocoa and chocolate with respect to many important CVD risk factors. It shows (for the first time) that cocoa and chocolate reduce insulin resistance as a result of reduced insulin secretion. It also shows a strong effect on FMD that is of real clinical significance. There was a moderately robust effect on diastolic BP, triglycerides, and mean arterial pressure, and marginally significant effects on LDL and HDL cholesterol. The authors also noted, "Our results support the reciprocal relation between insulin resistance and endothelial function . . . epicatechin dose may be a key contributor to the effects observed." HG

—Risa Schulman, PhD

Cocoa *Theobroma cacao*. Photo ©2012 Steven Foster

Meta-Analysis Shows Cranberry Juice May Be Effective for Treatment of Urinary Tract Infection in Certain Populations

Reviewed: Wang CH, Fang CC, Chen NC. Cranberry-containing products for prevention of urinary tract infections in susceptible populations: a systematic review and meta-analysis of randomized controlled trials. *Arch Intern Med*. 2012;172(13):988-996.

Urinary tract infections (UTIs) are the most common bacterial infections, causing approximately 7 million office visits to health professionals each year in the United States and approximately 100,000 hospitalizations. Clinical evidence shows that 20 to 30% of women who had a UTI will have a recurrence. Cranberry (*Vaccinium macrocarpon*, Ericaceae) has been a traditional remedy for UTIs for decades. Its mechanism of action originally was thought to be acidification of the urine, but later it was found that A-type proanthocyanidins in cranberry prevent the adhesion of the *E. coli* bacteria to the urinary epithelium, preventing infection. This paper is a review and meta-analysis of the factors influencing the effectiveness of cranberry for UTI. It goes beyond the 2008 Cochrane meta-analysis[1] by including some new studies and providing a more thorough analysis.

The meta-analysis was performed according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. Two authors independently searched MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials (CENTRAL) from inception to November 2011. Abstracts for conference proceedings and registered clinical trials (*i.e.*, not yet completed) were not searched. Studies were not excluded because of language, population, or year of publication. Inclusion criteria were as follows: (1) randomized controlled trials (RCTs); (2) comparison of cranberry-containing products vs. placebo or non-placebo control for prevention of UTI; and (3) outcomes reported as incidence of UTIs.

Information gathered from each suitable trial included the following: (1) type of study and study design; (2) characteristics of the study population; (3) types of intervention and controls; (4) definitions of UTI; (5) types of outcomes measured; and (6) number and reasons of participants lost to follow-up. The primary outcome was incidence of UTI.

Thirteen trials were included, consisting of 9 parallel and 4 crossover studies; none of the latter had washout periods. The total population was 1,616 subjects. Eight trials were conducted according to the intention-to-treat principle, and 5 trials used per-protocol analysis. All trials but one were conducted in the free-living community (*i.e.*, not part of a hospital or institutional setting). Each study population was sub-divided into the following categories: women with recurrent UTIs, elderly patients, patients with neuropathic bladder, pregnant women, and children.

The forms of cranberry used included cranberry juice (9 trials) or cranberry capsules/tablets (4 trials). Cranberry-containing products provided by the manufacturer Ocean Spray (Lakeville-Middleboro, MA) were used in 6 trials. The dose ranged from 0.4 g to 4 g/day cranberry contained in a capsule, and 64.8 to 194.4 g/day of cranberry contained in a juice and was administered for 6 months in most trials. A formulated placebo was employed in 10 trials; placebo was not used in 2 trials; and water was used as the placebo in 1 trial. Compliance was measured indirectly in most trials; methods included periodic interviews, self-reported questionnaires, and pill counting of remaining study medication.

The definition of UTI varied widely among the studies. In most trials (10), UTI was reported as a cumulative incidence rate. These trials were used in the quantitative data synthesis (n=1,494; 794 in the cranberry group and 700 in the control group). There was significant heterogeneity among included trials (relative risk [RR]: 0.68; 95% confidence interval [CI]: 0.47-1.00; I^2=59%). Several analyses showed that 1 trial was a source of heterogeneity with a large impact on the pooled summary estimate, and so it was excluded, which improved heterogeneity. Following this, cranberry was shown to be effective in preventing UTIs (RR: 0.62; 95% CI: 0.49-0.80; I^2=43%). It was also effective in women with recurrent UTIs (RR: 0.53; 95% CI: 0.33-0.83; I^2=0%), female populations (RR: 0.49; 95% CI: 0.34-0.73; I^2=34%), children (RR: 0.33; 95% CI: 0.16-0.69; I^2=0%), cranberry juice users (RR: 0.47; 95% CI: 0.30-0.72; I^2=2%), and people using cranberry-containing products more than twice daily (RR: 0.58; 95% CI: 0.40-0.84; I^2=18%), although the P values were not significant in meta-regression.

A funnel plot (a statistical tool) did not show evidence of publication bias.

Results of the effectiveness of cranberry for UTI were similar to those of the Cochrane review once the trial with heterogeneity was excluded (when included, the results were non-significant). The excluded study did not show effectiveness, but had the most stringent definition of UTI (the lowest bacterial threshold) and a placebo that included ascorbic acid, which is also known to counteract UTIs.

Sensitivity analysis showed that there was greater effectiveness in non-controlled trials, suggesting that an expectation of efficacy may have biased the results. Other analyses showed that sub-populations with certain characteristics were more likely to benefit, including those of younger age, female sex, and individuals with recurrent UTI history. 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 that may not be present in capsules or tablets. On the other hand, juice has the potential drawbacks that it is high in sugar and may cause gastrointestinal or other adverse side effects. A dosing frequency of twice a day was shown to have a better preventive effect.

Only 1 trial addressed dose response, and most trials did not explain their choice of dosage. There is an ongoing study currently examining this aspect. More recent trials (3 total) measured the concentration of the naturally occurring proanthocyanidins in the dose given, but it was not possible to determine an effective dose from these data. Further studies should include declaration of the concentration of proanthocyanidins so that their effect can be elucidated.

The authors conclude that while the results of the meta-analysis showed that cranberry is effective for UTIs, the results should be interpreted with great caution, because of study heterogeneity. Cranberry may be most beneficial in a twice-daily dose in the form of juice, specifically in women with recurrent UTIs, female populations generally, and in children. HG

—Risa Schulman, PhD

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Cranberry *Vaccinium macrocarpon* Photo ©2012 Steven Foster

Systematic Review Suggests Bacopa Extracts Improve Free Recall Memory

Reviewed: Pase MP, Kean J, Sarris J, Neale C, Scholey AB, Stough C. The cognitive-enhancing effects of *Bacopa monnieri*: a systematic review of randomized, controlled human clinical trials. *J Altern Complement Med*. 2012;18(7):647-652.

Bacopa (*Bacopa monnieri*, Scrophulariaceae) has been used in Ayurveda since the 6th century for treating various mental conditions and as a potent memory enhancer. Similarly, bacopa leaves and their extracts currently are used for cognitive enhancement. The authors of this study point to preclinical data suggesting that several activities may be involved with bacopa's mechanisms of action. They include antioxidant effects, scavenging of and protecting against the toxicity of beta-amyloid (an arterial plaque in brains of Alzheimer's patients), and modulation of acetylcholine (a neurotransmitter involved with memory) levels in the hippocampus. According to the authors, this is the first report to systematically review published clinical trials testing the cognitive-enhancing benefits of bacopa in humans.

The following databases were searched through April 2011: Scopus, PubMed, and the Cochrane Library. The following keywords and truncations were used: "cognit" or "memory" or "neuropsychology" or "neurocognit" or "executive function with bacopa" or "brahmi" or "baco-side" or "water hyssop" (one of the common names for bacopa). Studies included in the review had to meet the following criteria: (1) they were randomized, controlled trials conducted in adult humans with no significant cognitive impairment; (2) bacopa was a monotherapy — *i.e.* no other herbal substances were included; (3) methodologic quality was 5 or more on the modified Jadad scale; (4) efficacy was based on valid tests of cognitive outcomes; and (5) bacopa treatment lasted for 4 or more weeks. Studies in all languages were included.

Each trial was analyzed for methodologic quality using a purpose-designed modified Jadad scale. The original Jadad scale has a maximum score of 5 points. This modified version has a 10-point scale. For the modified score, 1 point was given when each of the following criteria was satisfied, with higher scores reflecting superior methodologic quality: (1) Was the study randomized?; (2) Was randomization detailed and appropriate?; (3) Was the study double-blind?; (4) Was the blinding detailed and appropriate?; (5) Was there a control group?; (6) Was the control described in detail and appropriate?; (7) Were the exclusion criteria adequate?; (8) Was the dosage administered at a therapeutic level?; (9) Were withdrawals and dropouts described?; and (10) Were the data reported clearly and adequately? The data gathered from each study included general study descriptives as well as all cognitive outcomes and their reported significance. Only results from the longest time points for each study were included. Cognitive outcomes from each study were grouped into "true" cognitive abilities by 2 neuroscientists.

A total of 64 studies were located; only 6 met all inclusion criteria. All of the studies were randomized, double-blind, placebo-controlled, parallel-group studies with a 12-week duration. Study populations were described as comparable in age range, and all subjects were healthy. One study recruited a sample with subjective memory complaints, but the patients did not have cognitive impairment. The average quality of trials was high, with a modified Jadad mean score of 8.5. Three studies evaluated KeenMind® (Flordis/SFI; Crows Nest, New South Wales, Australia), 2 trials evaluated BacoMind® (Natural Remedies Pvt. Ltd.; Bangalore, India), and 1 trial evaluated Mediherb® Bacopa (Mediherb; Warwick, Queensland, Australia). Dosages of these dry extracts (herb-to-extract ratio of 20:1, except Mediherb Bacopa, 50:1) ranged from 300 to 450 mg/day. All 3 products use different extraction solvents and methods, different plant parts, and different dosage equivalents to dried herbs.

None of the studies included cognitive tests for abilities in auditory perception or in producing and retrieving ideas, words, and figural creations.

Two studies evaluated reasoning abilities, and bacopa was not effective in this domain. One study evaluated language behavior and number facility, and bacopa also was ineffective. Five studies used 9 cognitive tests of visual perceptual abilities, and in 1 study bacopa was effective for reduced reaction time, while in 1 other study bacopa was effective for rapid visual information processing tasks. Three studies evaluated mental speed, and bacopa was effective for only inspection time. All of the studies evaluated memory; the majority of tests were in the domain of free recall memory (auditory verbal learning test was used most frequently). Across all of the studies, bacopa improved free recall memory in 9 of 17 tests in this domain.

The authors conclude that some of the clinical evidence suggests that bacopa extract is efficacious in improving free recall of information in subjects without significant memory impairment. The authors believe that bacopa could potentially be prescribed as a memory enhancer. However, longer-term studies are needed with manipulation of dosage sizes, as well as studies that evaluate reasoning, mental speed, idea production, language behavior, and number facility.

It is particularly impressive that the included studies had such a high modified Jadad score. It would be of value to see how the studies would score using the regular Jadad score, which is used more frequently in systematic reviews. It is interesting that the commercial bacopa products tested were relatively different, and yet they still benefited the same clinical domain. HG

—Heather S. Oliff, PhD

Bacopa *Bacopa monnieri*. Photo ©2012 Steven Foster

Aromatherapy Effective Treatment for Postoperative Nausea

Reviewed: Hunt R, Dienemann J, Norton HJ, *et al*. Aromatherapy as treatment for postoperative nausea: a randomized trial. *Anesth Analg*. March 5, 2012; [epub ahead of print]. doi:10.1213/ANE.0b013e31824a0b1c.

Patients undergoing surgery with general anesthesia often have the adverse side effect of postoperative nausea. The authors hypothesize that aromatherapy may reduce postoperative nausea. Aromatherapy is appealing because it is (1) noninvasive; (2) any medical staff or patient can use it; and (3) it costs less than antiemetic medication (*i.e.*, medicines that treat nausea and vomiting). However, it is unknown which aromas or combinations of aromas are effective in reducing postoperative nausea. The purpose of this prospective, 4-arm, placebo-controlled clinical trial was to examine the reduction in severity of post-surgery nausea using several essential oils compared with placebo.

Patients (n = 1,151) 18 years of age or older were recruited from 1 ambulatory surgical site in Charlotte, North Carolina. Included patients were not receiving warfarin (Coumadin®), heparin, 325 mg aspirin, or clopidogrel (Plavix®), and did not have a history or diagnosis of bleeding diatheses (a genetic susceptibility to bleeding), or any known allergies to ginger (*Zingiber officinale*, Zingiberaceae), spearmint (*Mentha spicata*, Lamiaceae), peppermint (*Mentha* x *piperita*), or cardamom (*Elettaria cardamomum* var. *cardamomum*, Zingiberaceae). Patients with clotting disorders were excluded.

Patients rated their level of nausea from 0 to 3, with 3 being severe. Those who reported zero or no nausea were not assigned to a treatment group. The control group of this 4-arm clinical study was treated with saline, while the other 3 groups were administered essential oil of ginger; a blend of the essential oils of ginger, spearmint, peppermint, and cardamom (the exact blend was not described); or 70% isopropyl alcohol (which is not normally considered a component of aromatherapy).

One cubic centimeter of the randomly selected aromatherapy was placed on a 2-inch by 2-inch gauze pad. The study could not be blinded because of the specificity of odors. Each patient was instructed to inhale the scent through the nose and exhale through the mouth 3 times. After 5 minutes, each subject was asked to rate the level of nausea again, then the aromatherapy was discontinued. If nausea was rated 1 to 3 at the end of 5 minutes, participants were offered conventional antiemetic medications. The primary endpoint was the change in the postoperative nausea score 5 minutes after aromatherapy administration.

A total of 301 patients reported postoperative nausea and received aromatherapy; 73 patients received normal saline, 78 received 70% isopropyl alcohol, 76 received essential oil of ginger, and 74 received the blend of essential oils of ginger, spearmint, peppermint, and cardamom. There were no significant demographic differences among the groups. Although all 4 groups had shifts toward reduced nausea, ginger alone and the blend produced statistically significant reductions in nausea compared with saline ($P = 0.002$ and $P < 0.001$, respectively) and compared with alcohol ($P = 0.017$ and $P < 0.001$, respectively). Although nausea was slightly reduced after alcohol aromatherapy, the reduction was not significantly different from saline. There was a trend toward statistical significance indicating that the blend was more effective than ginger alone ($P = 0.07$). Ginger and the blend also reduced the number of requests for antiemetic medication compared with saline ($P = 0.0002$ and $P \leq 0.001$, respectively).

The authors conclude that aromatherapy with the essential oil of ginger or a blend of the essential oils of ginger, spearmint, peppermint, and cardamom was effective in reducing nausea severity and the need for antiemetic medication after surgery in an acute-care setting. Future research should examine (1) aromatherapy and vomiting prevention, (2) a longer duration of aromatherapy, (3) comparison of these aromatherapeutic agents with additional aromatherapies, (4) a larger study with standardized antiemetic medication treatment before and after surgery with stratified risk factor groups, and (5) efficacy of prophylactic aromatherapy.

One of the problems that occurred during this study was that the oils underwent oxidation, evaporation, and layering (so they were not mixed properly). Accordingly, patients complained that the aromatherapy was not pleasant. The study had to be halted, and the problem remedied. The oil degradation and improper mixing may be a problem in a real-life setting that is not controlled as well as a clinical trial. This may limit the effective use of aromatherapy in a natural postoperative setting. Essential oils are volatile, and proper storage is important. Also, the quality of the essential oil can be a significant factor in efficacy. HG

—Heather S. Oliff, PhD

Turkey Tail Mushroom Mycelium Is Safe and May Enhance Immune Response in Women with Breast Cancer in Phase I Trial

Reviewed: Torkelson CJ, Sweet E, Martzen MR, *et al*. Phase I clinical trial of *Trametes versicolor* in women with breast cancer. *Oncology*. May 30, 2012; [epub ahead of print]. doi:10.5402/2012/251632.

The mushroom known as turkey tail (*Trametes versicolor*, Polyporaceae; referred to as *Tv* below) is prevalent in traditional Asian medicine. Hot-water extracts of turkey tail fruitbody containing various polysaccharides have been shown to be active against a number of cancers and are commonly used by cancer patients in Japan. Also, *Tv* mycelium-based products are sometimes prescribed to breast cancer patients in the United States by physicians trained in botanical medicine. Previous studies have suggested that the immunomodulatory mechanisms of action of *Tv* include Toll-like receptor agonist activity, the alleviation of immune-system dampening as a result of cancer treatment, immune system amplification, and defeating tumor tolerance of antigens.

Recent studies have suggested that breast cancer patients undergoing chemotherapy, surgery, and radiation treatment (RT) also suffer from a compromised immune system; thus, the investigation of treatment effects on the immune system may lead to the discovery of adjuvant agents that enhance the immune response to cancer. This dose-escalation study in breast cancer patients — who had completed surgery and chemotherapy and were about to begin radiation treatment — addressed the safety and tolerability of *Tv* use.

This study was conducted at the Cancer Center at the University of Minnesota in Minneapolis, MN, and Bastyr University in Kenmore, WA. Enrolled patients were women between 21 and 75 years old, diagnosed with stages I-III breast cancer, who had completed surgery and chemotherapy and were about to begin RT. Participants had normal laboratory values at baseline and agreed to avoid taking mushrooms and immunomodulatory herbs during the study. In total, 11 women were enrolled in the study; 2 women dropped out due to transportation problems, leaving 9 women who completed the study. The patients were between 38 and 68 years of age with both estrogen receptor (ER) negative and ER positive stage I-III breast cancer, and one patient did not have chemotherapy treatment before radiation.

In this study, the primary outcomes were the safety and tolerability of *Tv* use for breast cancer patients after RT. Adverse side effects were reported each week by patients during clinical visits or by telephone. Secondary outcomes were the comparison of pre- and post-radiation concentrations of immune system markers including complete blood count, natural killer (NK) cell activity, T/B/NK cell subset assay, phagocytic index, and cytokine concentrations. Where possible, the authors combined the data from this *Tv* study with data from a separate observational study (n=14) to increase sample size to n=23.[1] The paper notes that the inclusion criteria for the 2 studies are identical.


Turkey Tail *Trametes versicolor* Photo ©2012 Magnus Manske

The freeze-dried, powdered turkey tail mycelium was produced by Fungi Perfecti, Inc. in Olympia, WA, a leading producer of fungal extracts and preparations. The *Tv* capsules (500 mg) were processed by Beehive Botanicals; Hayward, WI. Patients took 3 g, 6 g, or 9 g per day in 2 daily doses with a total of n=3 in each dosage group. After finishing radiation treatment, patients began the 9-week study consisting of 6 weeks of treatment and 3 weeks of wash-out. Patients were asked to attend 6 clinical visits; the first visit served as a baseline and occurred before radiation treatment. The second visit was after the RT was completed, and the remaining visits were 2 weeks apart with the final visit occurring at the end of the wash-out period.

In total, 7 mild, 1 moderate, and 1 severe (anxiety attack) adverse side effects were reported. These included heartburn, chest pain, and cold and flu symptoms. Notably, no nausea was observed despite being reported previously from fruitbody-based extracts. Red blood cell, hemoglobin, hemocrit, white blood cell, and neutrophil counts were at normal concentrations both before and after RT; however, NK activity decreased significantly after RT (19.941 ± 18.959 lytic units [LU] vs. 9.872 ± 13.454 LU, P=0.043). The lymphocyte count also decreased in all patients (n=23) after RT (1.027 ± 0.298 cells vs. 0.681 ± 0.254 cells, P<0.001). After 2 weeks of *Tv* treatment, the 9 g dosage group had significantly more lymphocytes than the observational group (P<0.042).

Only the immunological markers of the dose-responsive patients were assessed (n=9). The CD8+ cytotoxic T cells (lymphocytes) were significantly greater in the 9 g dosage group as compared with the 3 g and 6 g groups (P=0.0003). In addition, CD19+ B cells (lymphocytes) were significantly greater in the 6 g group as compared to the 3 g group (P=0.0334). The actual cell count of CD16+56+NK cells did not significantly change in response to either RT or *Tv* supplementation, despite the decrease of NK cell activity after RT.

This study shows that *Tv* dosages of 3 g, 6 g, and 9 g daily are generally safe and tolerable in breast cancer patients with few moderate or severe adverse side effects. In addition, this study reports a decrease in immune system markers (lymphocyte counts and NK cell activity) after RT, suggesting a dampening effect of this treatment. Patients taking 9 g of *Tv* showed a significant increase in lymphocyte numbers, and those taking 6 g trended towards an increase. These findings suggest that a daily *Tv* dosage of 6 g and 9 g may be worthy of further investigation for immune support in breast cancer patients.

There are a few methodological problems with this study. Primarily, the statistics used to analyze the immune markers are not well described, and there are no figure legends to clarify specifics of the data presented. Also, a one-way analysis of variance (ANOVA) was used to analyze the different dosages at various time points; a 2-way ANOVA would have been more appropriate, as there is no mention that the duration of treatment was taken into account in the analysis. A second criticism is the inclusion of historic controls. The 14 subjects in the observational study were not recruited or analyzed as an arm of the present dose-response study, making the combination and comparison of these data questionable. Also, adverse side effects will need to be assessed with a larger sample size. Despite these problems, this study suggests a rationale for the relative safety of *Tv* as a potential adjuvant for breast cancer treatment that should be studied in more rigorous, randomized, placebo-controlled trials designed to assess the efficacy of *Tv* in supporting immune system function in breast cancer patients. HG

—Amy C. Keller, PhD

Reference

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Rose (*Rosa damascena)* spread out prior to distillation. Photo ©2012 Gülbirlik Cooperative

TURKISH ROSE

A Review of the History, Ethnobotany, and Modern Uses of Rose Petals, Rose Oil, Rose Water, and Other Rose Products

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Introduction and History

Rose is a common name given to the thorny shrubs and climbing vines of the genus *Rosa* in the Rosaceae family. More than 100 *Rosa* species have been recorded throughout the world. Because rose is a popular garden plant, it is virtually impossible to determine the number of currently existing cultivars. The *Flora of Turkey and the East Aegean Islands* identifies 24 *Rosa* species growing in this region of the world.[1]

Fossil records indicate that *Rosa* species have existed on the planet for at least 40 million years.[2] The earliest historical records on Mesopotamian cuneiform tablets indicate that rose became known to humans about 5,000 years ago. A clay tablet about Sargon I, King of Akkadia (2684-2630 BCE), records that the king brought rose saplings during his military campaign to the countries across the Tigris River. Because he formerly lived in the ancient city of Ur near Babylon, his trip was most probably to Southeastern Anatolia (present-day Turkey).[3]

Assyrian tablets tell of rose and rose water. Of course, it is not possible to identify the rose species discussed in these ancient texts, but its scent is praised, suggesting fragrant rose species such as *R. gallica, R. centifolia, R. moschata,* or *R. damascena* of Anatolia. Cuneiform texts also indicate that the roses were not directly distilled but boiled with water to produce fragrant water. The very small quantities prescribed — as little as one carat (3 grains) [0.2 g] — illustrate how precious it was.[4]

Roman naturalist Pliny the Elder (23-79 CE) described rose as astringent, and wrote that the petals, flowers, and heads were useful in medicine; health conditions for which rose was prescribed represented many parts of the body, including the head, ears, mouth, gums, tonsils, stomach, rectum, and uterus.[5] The flowers taken in oxycrate (a mixture of water and vinegar) were said to arrest fluxes in females and blood-spitting. The seed was used as a liniment for toothache and as a diuretic, and its fragrance could be inhaled to clear the brain.

Dioscorides (40-90 CE) wrote of rose's cooling and astringent qualities, and that the liquor of roses cooked in wine was useful for treating headaches and ailments of the eyes, ears, gums, anus, and womb. Powdered, dried rose flowers were sprinkled on food for pain of the gums.[6]

According to an anonymous Syriac medical treatise of the 4th century CE, roses were used externally for eyes, mouth, foul breath, liver (as plaster), sores, and internally to treat the chest and stomach.[7]

In traditional Ayurvedic medicine in India, rosebuds are regarded as astringent and as having cardiac and cephalic tonic properties. The petals are used to relieve uterine hemorrhage and are applied locally for oral ulcers.[8] The oil or attar is used to disguise the unpleasant odor of certain ointments.[9] This, in general, correlates with the cuneiform medical texts. It appears from cuneiform tablets that Assyrian doctors were precise in their use of rose water. *Penny Cyclopaedia* (ca. 1839)[10] includes details for various medicinal uses of rose, such as the petals of *R. gallica* and *R. damascena*. The buds were to be collected before they expanded. The calyx and lower parts of the petals were dried, with about 2,000 flowers yielding 10 pounds of dry petals. The chief employment of the conserve of *R. gallica* was as a vehicle for other medicines. For the preparation of rose water, *R. centifolia* petals were plucked from fully grown flowers and then dried in the open air rather than in an oven (desiccation impairs the fragrance of *R. centifolia* while heightening that of *R. gallica*). A syrup could be made from the rose petals, but their chief use was distillation. One hundred pounds of rose flowers yielded less than 3 drachs of rose oil. According to Flückiger and Hanbury,[11] the ancients did not know how to distill rose oil; the rose oil of the Greek physician Dioscorides was a fatty oil in which roses had been steeped.

A confection of roses was made from fresh red rose petals, which were beaten and combined with refined sugar and then rubbed together (as a vehicle in the preparation of pills). The Hittites of Anatolia (1750-1180 BCE) knew rose as *pillu* and prepared medicines with it. However, it is not clear which species of rose they used.[12]

A picture of a rose discovered in a fresco in the Knossos Palace of Crete dating back to 1600 BCE is evidence of the use of rose by the Minoan civilization.[13]A hieroglyph depicting a rose was found in the tomb of the Egyptian Pharaoh Thutmose IV (1600 BCE), and is the earliest record of the

Rose *Rosa damascena*. Photo ©2012 Gülbirlik Cooperative

rose in ancient Egyptian civilization. Egyptian queen Cleopatra (69-30 CE) was said to lay rose petals on Marcus Antonius's path to impress him. A wreath of roses was discovered later in an Egyptian burial chamber dating back to 400-200 CE.[11]

The Chinese philosopher Confucius (551-479 BCE) wrote about the rose and its significance within the Chinese Empire. According to Confucius, roses were highly esteemed by the Emperor during the Zhou dynasty. They were said to be planted in the Royal Gardens in China, and the Royal Library is supposed to have contained over 600 books on rose and rose cultivation.[13]

The Significance of Rose in Religious, Spiritual, and Cultural Traditions

In Greek mythology, rose is the flower of the goddesses. Cloris, the goddess of flowers, wore a crown of roses. Rose was the symbol of Aphrodite, the goddess of love and beauty. When Aphrodite presented a rose to Eros, the god of love, rose became the symbol of love and desire. It is also the symbol of silence and secrecy, as Eros gave a rose to Harpocrates, the god of silence. In today's parlance, *sub rosa* ("under the rose") refers to something confidential, and is derived from medieval diplomatic meetings where a rose was hung as a sign of secrecy and confidentiality.[14] In Homer's *The Iliad* (ca 900 BCE), Achilles' shield was decorated with roses and Aphrodite anointed Hector's dead body with rose oil.[13] The Greek poet Sappho (600 BCE) was the first to call rose "the Queen of Flowers" in her verses.[13]

According to Greek historian Herodotus (490-420 BCE), the Phrygian king Midas, who reigned in Central Anatolia near Eskisehir in 700 BCE, grew fragrant roses in his gardens. After his defeat by the Persian army, he brought his roses to Macedonia. Those roses were believed to be *R. damascena* var. *semperflorens* (ever-flowering damask rose), which is still grown in some parts of Anatolia and referred to as "King's rose."[13] Theophrastus (300 BCE), the Greek naturalist, wrote the botanical description of varieties of roses containing anywhere from 5 petals to 100 petals.[13]

Romans appreciated the rose and used it in their meetings, feasts, and parties because of its exquisite fragrance. Rose cultivation was initiated in Italy for local consumption and export. Early Christians repudiated rose as a pagan symbol; however, rose later became a symbol of Jesus as well as other martyrs who died under torture. The Virgin Mary was dubbed "the thornless rose," and, to some extent, pagan legends about Aphrodite began to be attributed to Mary.[3]

Rose appears in the ancient Zoroastrian religious book *Avesta* (written in Iran during the 9th century CE) as one of the symbols of immortal angels. Its religious significance expanded into countries where Zoroastrian culture spread, such as India, Syria, and Egypt. It was believed that the beautiful fragrance extracted from the flowers had mystical powers and played an important role in the worship of the god of light, Ahura Mazda.[13]

Rose is one of the most important symbols used by Oriental-Muslim poets, as well as within the mystical Muslim tradition known as Sufism. The exquisite beauty and purity of rose flowers placed on a thorny branch rooted in the earth symbolizes the mystic path to Allah. Rose is also a symbol of the prophet Muhammad, whose perspiration purportedly smelled of rose, and rose oil and rose water are highly respected and often used in religious ceremonies and rituals throughout Turkey and the Middle East. Each year during the Muslim pilgrimage to Mecca known as Hajj, the black cloth of the Ka'ba's (the holiest shrine in Islam, located at the mosque in Mecca) is sprinkled with rose water from Iran or Turkey, and rose oil is burnt in Ka'ba's oil lamps.

Furthermore, rose is considered the flower of heaven in this tradition. When Abraham was thrown into the fire by the King Nimrod in Urfa (old Edessa) in Eastern Turkey, the fire is said to have turned into a pond surrounded by roses. Saint Ali, Muhammad's son-in-law, requested a bouquet of roses from Selman-i Farisi and died only after smelling the fragrant roses. Therefore, the rose is also a significant symbol of the Bektashi order of Sufism. Rose is a recurring motif in Rumi's (Mewlana) *Masnawi*: "Rose is sent to earth by the gardeners of paradise for empowering the mind and the eye of the spirit."[13]

Sultan Mehmet II, the conqueror of Istanbul in 1453, once depicted in miniature smelling roses, is said to have converted the Aya Sophia (Saint Sophia) church in Istanbul into a mosque after thoroughly washing it with rose water.[13]

History of Rose Oil and Water

Rose oil and rose water are obtained by hydro-distillation of fresh rose material. According to literature records, distillation is a recent invention. Most attribute it to Arabs' Alembic (9th century CE) and some attribute it to the alchemists of Alexandria (from 50 BCE onwards). According to one record, however, distillation by earthenware ceramic pots was first employed by the Indus Valley civilization (5000 BCE). The remnants of a distillation pot were excavated in Harappa.[15] These ancient distillation assemblies resemble the attar production stills used to this day in Kannauj, India, which distill fragrant materials in water and then trap the distillate in sandalwood (*Santalum album*, Santalaceae) oil. If rose flowers are used in distillation, the product is called "rose attar" or "rose otto."

According to Mesopotamian clay tablets and unearthed extraction jugs dating back to 3500 BCE, Sumerians and Assyrians (1200 BCE) mastered the art of extracting fragrances. Fragrant materials were submerged in boiling water for a day and then drained. After adding oil, the mixture was slowly heated. The perfumes prepared with this method by the Assyrians were renowned.[13] As rose also was cultivated in the Hanging Gardens of Babel, according to Herodotus, one can assume that rose oil also was also produced this same way.

In India, rose oil was once named *Itr-i Cihangiri* (Jahangir's fragrance) after the Mogul Emperor Jahangir who ruled from 1605 to 1627. According to the legend, when his wife Nurjahan was bathing in a warm water pond filled with roses, she discovered highly fragrant oil droplets on the surface of water. This legend appears in nearly all texts

Rose *Rosa gallica*
Photo ©2012 Steven Foster

related to rose oil. A competing version claims that ponds of the Shalimar Gardens in Lahore, Pakistan, were filled with roses during wedding feasts. On hot summer days, oil droplets would cover the water's surface, emitting rose fragrance into the air.[13]

Rose in Islamic Medical Texts

The 3 rose-derived drug products most predominantly discussed in ancient Islamic medical texts are rose water (distilled water of roses), rose confection or rose paste (a thick jam produced by blending roses with sugar or honey), and rose oil (made by steeping roses in sesame seed oil or olive oil left under the sun).[13]

Arab physician Al-Kindi (9th century CE) prescribed rose products for stomach pain, ulcers, liver and mouth diseases, and sore throat. He used rose oil for burns, ulcerated wounds, and as an ingredient of hemorrhoid salves.[16] Al-Dinawari's (9th century CE) texts noted the refreshing effects of rose water and recommended it for fever. He also recommended the application of rose oil to the head for alleviating fever and due to its calming effect.[13] Abu Bakr Mohammad ibn Zakariya Al-Razi (Rhazes), the 9th century (CE) Arab physician, called attention to the therapeutic value of rose and stated that "the rose diminishes drunkenness."[13]

The great physician Ibn-i Sina (Avicenna, 11th century CE) was the first scientist to emphasize rose fragrance's beneficial effects on the heart and the brain. "Because of its exquisite fragrance, the rose addresses the soul," he wrote. "It has a calming effect and is highly beneficial for fainting and for rapid heart beats." He praised rose water's effects on mind and spirit, and its beneficial effects on brain function and cognitive power — "It enhances comprehension and strengthens memory."[17] Like Ibn-i Sina, Ibn-Al-Baitar also noted rose water's beneficial effects on the brain: "Rose water strengthens the mind and the brain, sharpens the senses, increases the life force; It is beneficial for rapid heart beats due to anxiety; because of its beneficial fragrance it empowers the body."[18] Ibn-Al-Baitar also stated that boiling rose water and exposing the head to its steam had healing effects and that it was especially beneficial for eye diseases. Additionally, he recommended inhalation of the steam to alleviate drunkenness and headaches.

In his famous medical book *Kemaliye*, Mahmud of Shirvan (15th century CE) described a powder prepared by crushing dried rose petals in a mortar for application to the neck, breast, and armpits after bathing — while the skin is still moist — to impart a favorable smell to the body and to "treat the spirit." He claimed that this scent empowered spirituality and purified the heart. He wrote that "the fragrance of rose is the fragrance angels like."[19] The same powder also is mentioned in the *Ediye-i Müfrede* (*Simple Drugs*) of Ishak bin Murat (14th century CE) for use in Turkish baths (*hamams*). It was said to be beneficial for those suffering from scabies. If rubbed on pimples, it reportedly cleared them.[20] Salih bin Nasrullah (17th century CE) said of rose water in his book *Gayetül Beyan* (*Human Health and Sanitation Techniques*) that when rubbed on the body, it gives a pleasant smell, and when rubbed on the head, it alleviates headache. He wrote that ground, dried rose can be rubbed on mouth ulcers to alleviate pain. It is reportedly also beneficial for smallpox or measles lesions if sprinkled on the skin.[21] *Marifetname* (*Talent Book*) of Ibrahim Hakki of Erzurum (18th century) recommended rose water for headaches due to fever and as a treatment for fainting.[22]

Eşref bin Muhammed (15th century CE), in his book *Haza'inü's-Saa'dat* (*Treasures of Happinesses*), recommended food prepared with rose water as the most appropriate food for babies. He wrote, "…white honey is boiled with rose water until it has the desired consistency, its froth is skimmed, and delicately baked bread's crumb is put in that water and blended to make a sherbet, and it is fed to the baby at the next feeding…"[23]

Importance of Rose Water in the Turkic Cultures

In the early history of Central Asian Turks, sacrificial horses and other sacrificial animals were washed with fragrant waters. It is highly probable that rose was one of the flowers used in the making of those fragrant waters, as it is said to be of Central Asian origin. In attempting to trace the steps of the Turks in their use of rose water, the available written sources reach back only as far as the 11th century.[13]

Two lengthy works written in the 11th century mention the use of rose in the Turkic societies: *Kitab-u Divan-i Lugat-it Turk* (*The Dictionary of Turkic Words*) by Mahmud Kashgari — a dictionary recognized as an important source for information on Turkic culture in its entirety, including its history, ethnology, geography, mythology, and folk literature — and *Kutadgu Bilig* (*Wisdom of Royal Glory*) by Yusuf Has Hajib, composed of recommendations for attaining happiness in the 2 worlds. In the latter monumental work, when Ugdulmish, the vizier's son, is advising Odgurmish, the ascetic, on "the rules of conduct at a banquet," he suggests that Odgurmish offer *culab* and *culengebin* syrups prepared with rose water. Ugdulmish says, "If drinks are not served with the meal, then that meal is spoiled for the diners. Serve *fuka* [slightly fermented millet drink], or *mizab* [a beverage that can induce drunkenness], or the syrups *culengebin* or *culab*. Do not ask me what else you can offer, ask others." *Culab* and *culengebin* are said to be beneficial for the stomach, and they have been included in medical manuscripts since the 9th century CE. The aforementioned text confirms that the Turks were preparing syrups using rose water.[24]

In *The Dictionary of Turkic Words*, Mahmud Kashgari refers to a copper rose-water vessel as *kumgan*, supporting the fact that Turks were making rose water and thus had a word for it in their language. Further investigation of the word *kumgan* uncovers interesting historical information. Cosmographer and geographer Al-Dimashqi (1256-1327), a prominent scholar of the 13th century Muslim world, notes the important centers of rose-water production in the Middle East in his book *Nuhbetu'd-Dehr fî Acaibi'l-Berr ve'l-Bahr* (*Important Interesting Creatures of the World's Lands and Seas*). He particularly emphasizes an outstanding center in Syria, called Mezzeh. He describes the art of making rose water practiced in Mezzeh as follows: "The storage vessels were filled with roses or other flowers, then the alembics were put in their places. When each alembic was filled with rose water, the rose water was poured into huge glass jugs, or into copper vessels with two handles, called *kumkum*."[25] The term used by rose water manufacturers in Mezzeh sounds much like *kumgan*.

In Isparta, the modern-day center of rose cultivation in Turkey, the special vessel with a narrow mouth in which distilled rose oil is stored is still called *kumkuma*. The word also is commonly used by the people in the saying "gossip kumkuma," which alludes to gossiping women. That the word for the copper ewer holding rose water, *kumgan*, was in use for 900 years illustrates the expansive time period of the tradition of rose water.

Ottoman physicians favored the psychologically beneficial effects of smelling roses. *Young girl smelling a rose. Image courtesy Mr. Metin And Osmanlı Tasvir Sanatları: 1 Minyatür. İstanbul: Türkiye İş Bankası Kültür Yayınları.*

Anatolian Seljuki Turks used motifs of rose, rose water, and rose oil in their literary works. One of the careers of the Seljuk period was *gulab-ger,* meaning rose water manufacturer: "The one practicing that profession, would make rose water, bottle it, and sell it in his shop."[26] The 13th century Persian poet and mystic Rumi also mentions *gulab-ger* in his *Divan-i Kebir*: "Wake up, find a way to move out of that cup, from that bottle of 'the artisan making rose water,' like sweat oozing out, and be free."[27]

The famous traveler Ibn Battuta (1340-1369) provided one of the earliest sources of information on rose-water production in Anatolia. In his travelogue, he wrote about the rose water produced in Nusaybin, near Mardin, and in its vicinity in 1330: "The rose water produced in this region is unique in its fragrance and its taste." He also describes the tradition of using rose water after bathing in the *hamam* in Ladik.[18]

A study on an Ilhanate city (part of the Mongol empire in the area of ancient Persia) cites sources that discuss a "rose house" (*gülâb-hane*) beside the hospital. In the city, newly discovered in 1309, the rose-water manufacturing shop was one of the standing buildings.[28] The same was observed in the Ottoman city of Edirne, where the Edirne Darussifası (hospital), founded in 1488, also had a *gülâb-hane*, or *gulhane*. The official documents dating from 1489 note, "There are three lead furnaces for making rose water."[29] Since rose water was used abundantly in the hospital in those days, the expenses of making rose water in the *furun-i gul* (rose furnace) were recorded.

Rose Production, Trade, and Cultivation During the Ottoman Period

In Edirne, rose water was manufactured in the Royal Palace. Roses were cultivated in the *gulhane* where rose water was also produced.

In addition, there was a *gulhane* in the Topkapi Palace in Istanbul. Ottoman sultans resided in the Topkapi Palace for more than 350 years. There were huge gardens situated south of the palace near the shore of the Marmara Sea, and a large tract of those gardens — the Gulhane Gardens — was dedicated to roses. However, the palace's rose-water consumption was far greater than it could sustain, and the rose water demand of *Dersaadet* ("door of happiness" — one of the old names of Istanbul) was supplied from Edirne. According to a sultan's edict (*ferman*) dating from 1587, roses were brought from Edirne for cultivation in the Old Palace Gardens where the sultan resided before moving to Topkapi Palace. The Old Palace was also in Istanbul, located at Beyazıt, in the area where the Rectorate of Istanbul University now stands. Roses were cultivated in its gardens as well.

Rose water and rose products, such as rose confection and syrups, were used abundantly in the Ottoman Empire. In his travelogue, the Ottoman traveler Evliya Chelebi (1611-1682) mentioned the tradesmen of Istanbul in the 1640s, as well as *esnaf-i gulabciyan* (rose-water manufacturers). He wrote of 14 rose-water shops in the Old Bazaar, which employed a total of 70 people. Women from Edirne sold rose water in huge copper cauldrons in front of the Bazaar, and others in the shops sold fragrant waters, distilled water, and rose water. Although Chelebi is known for his exaggerations, records from 1642 indicate that 2,000 kilograms of rose water were bought for the Palace.[30]

Rose water was offered during the banquets and meetings at the palaces of sultans, viziers, and high-ranking administrative officers. It was an ingredient of the famous fragrant soaps (*miski*) prepared in the *Helvahane* (halva kitchen) of the Topkapi Palace, as well as in other substances cooked there. The *Helvahane Book*, a register of the goods and substances bought for and prepared in the Helvahane, reports that fresh roses, rose water, and rose sherbets were purchased from Edirne. During the 15th, 16th, and 17th centuries, rose sherbet, rose confection (*gul-i mukerrer*), and other rose products occupied an important place among the comestibles bought for the Palace. Usually those rose products were purchased from Edirne.

Chelebi detailed the beauty of the flowers and the roses of Edirne in his travelogue. He praised the rose water produced there, writing, "and its rose water is unique among the lands of the world. And its roses and rose gardens adorn the world."[12]

In the Ottoman tradition, "offering rose water" was a precious treat; the custom was practiced not only in the palaces, but in the most modest houses as well. To better grasp the importance of rose water, it is sufficient to

consider the lists of gifts presented to the sultans, the most outstanding of which were cited as high-quality rose water and exclusively created rose-water bottles.

Rose water use was abundant during all periods of the Ottoman history. However, there are limited sources that explain where rose water was produced or where and how the fragrant roses were cultivated. Historians presume that the tradition of rose water production in the Middle East continued during the Ottoman reign after the empire reached its farthest borders. Ample evidence suggests that rose water was produced in the Anatolian lands in the past, as in the example of Nusaybin, which is cited as an important center for fragrances, particularly high-quality rose water. In the 13th century, Ibn al-Baitar wrote "the roses with the sharpest fragrances are found in Nisibis [Nusaybin], and they produce rose water here."[18] Again in the 13th century, al-Dimashqi, the prominent cosmographer and geographer of the Muslim world, mentions the important centers of rose-water production in the Middle East in his book *Nühbetü'd-Dehr fî Acâibi'l-Berr ve'l-Bahr* (*Important Interesting Creatures of the World's Lands and Seas*).

> Firuzâbad, and Quwar and the al-Jazeera regions in Iran, and the city of Nusaybin, were famous in producing rose water. Rose water of those regions was world renown. Rose water was bottled and sent from those lands, via marine route, to Khuzestan [a province in southwestern Persia], Khorasan [a former province of northeastern Persia, southwestern Afghanistan, and southern parts of Tajikistan, Turkmenistan, and Uzbekistan], India, China, Anatolia [Turkey], Hijaz [western Saudi Arabia on the Red Sea, the location of the Islamic holy cities of Mecca and Medina], Yemen, Syria, Egypt, Maghreb [Northwestern Africa, west of Egypt], Andalusia [Spain], and to various European countries.[25]

Information about rose cultivation in Anatolia is found in the travelogue of Ibn Battuta (1304-1369), who wrote that rose water produced in Mardin, at Nusaybin and in its vicinity in 1330, had a "unique fragrance and a unique taste."[31] According to the aforementioned sources, in the 13th and the 14th centuries, exquisitely fragrant roses were cultivated in Nusaybin, and the rose water of Nusaybin was world-famous. Did the rose water tradition of Nusaybin persist in the same region during the Ottoman reign? There are no documents citing Nusaybin as a center of rose cultivation at this time, nor any suggesting that rose water was sent to the Ottoman palaces from that region. Historical sources convey that Edirne was the site for rose-water production that sated the huge demands of the Ottomans.

Kâtip Chelebi, in enumerating the significant products of Edirne, wrote about the rose gardens of the city and about rose water prepared in those gardens: "…Edirne has 450 gardens lying on the riverbanks of its three rivers. The rivers flow pleasantly under the shades of the high trees of the gardens, yet the gardens cannot get even a sip of the rivers' waters, but survive on the tear drops (rains) of their own land. At the end of the winter, the rivers overflow and flood the neighboring settlements."

Evliya Chelebi also praised Edirne's gardens. Chelebi left Istanbul in 1639, and after travelling for more than 30 years, settled in Egypt in 1670. During his travels, he recorded his observations in great detail. He allocated more than 20 pages in his book for Edirne.[30] "The great city of Edirne is covered all over with rose and hyacinth [*Hyacinthus orientalis*, Asparagaceae] and sweet basil [*Ocimum basilicum*, Lamiaceae] gardens, heavenly gardens resembling the gardens of Eden, and is covered with orchards forming a network, lying afar off with no limits or borders, the measure of which only God the Almighty knows," he wrote. "There is no country in all the lands of Anatolia with such fertile soil, extending to all corners, and with such an abundance of grains." In another page, he added to his praises of the city: "In those special gardens … the varieties of flowers ornamenting this city of Edirne are roses and hyacinths and Anatolian musk and tulips [*Tulipa* spp., Liliaceae] and violets [*Viola* spp., Violaceae] and hyacinths and sweet basils and jasmines [*Jasminum* spp., Oleaceae] and Judas trees [*Cercis siliquastrum*, Fabaceae] and daffodils [*Narcissus* spp., Amaryllidaceae] and irises [*Iris* spp., Iridaceae] and gillyflowers [*Matthiola incana*, Brassicaceae] and peonies [*Paeonia* spp., Paeoniaceae] and carnations [*Dianthus* spp., Caryophyllaceae] and other thousand colored, fragrant, and decorative plants."

Historical records document the cultivation of roses in Edirne, and that the rose saplings needed for Palace Gardens in Istanbul were delivered from Edirne. In 1587, Sultan Murad III issued a *ferman* (edict) "on the transfer of roses required for the Imperial Gardens, from Edirne,"[32] confirming that roses for the Imperial Gardens were in fact transferred from Edirne. There is additional evidence that

Fatih the Conqueror had opened the Istanbul mosque Hagia Sophia to prayer services only after it was washed with rose water, and ordered incenses and balms to be burnt inside for the temple to smell beautifully. *The miniature of Fatih the Conqueror, smelling a rose. Image courtesy Nurhan Atasoy. Hasbahçe.*

fragrant roses were cultivated in the Imperial Gardens, and, during spring, palace attendants picked the roses to prepare rose confections.[33] An Ottoman agriculturist of the 19th century, Agop Zakarian, cited Edirne among the cities that produced "rose oil and rose water" in his book *Roses and Rose Products*, written in 1895.[34]

The Rose Water Center of the Ottomans: Kazanlik

Post-18th century information on rose water and rose oil is more abundant. Sources note that rose cultivation was much advanced in Kazanlik and Zagra, the towns of the Chermen Province (Sanjak) of the Ottomans, and that rose water and rose oil were produced in both towns (which are located in modern-day Bulgaria).

Kazanlik developed into a significant rose-oil and rose-water center in the 18th century. Dervish Mehmed, the chief of the Imperial Food Store in the Topkapı Palace, recommended that the rose oil in one of his drug prescriptions was to be brought from Kazanlik. In his article on "oil preparations" he wrote: "In the past, the best rose oils used to come from the lands of India, then someone was able to produce this blessed oil in a place called Kazanlik, in Rumeli, and from then onwards that blessed oil began to come to Asitane [Istanbul] from Kazanlik, and began to be distributed to other countries from here. Every year a thousand miskals [1 miskal = 4.25 grams] rose oil is sent from Kazanlik to our much honored sultan's palace. And sometimes a hundred, two hundreds, five hundreds are brought."[35]

The Rose, Its History (1906), written by Bulgarian P.I. Orozoff, confirms the above information. Orozoff founded the famous Bulgarian rose-oil manufacturing facilities, and he wrote that rose cultivation and the method of rose-oil production was "brought to Bulgaria by a Turkish tradesman at the end of the 17th century."[12] By 1750, Bulgaria had become the principle source of rose oil. At that time, rose oil was produced by water-distillation of fresh roses, and cohobation of the distillates in open-fire copper stills. The oils collected by merchants were exported from the ports of Gallipoli, Istanbul, and Izmir. Records show the annual production of rose oil in the region during the 1850s was 1,500 to 1,800 kg.[36]

At one time, various rose species were used for the production of rose oil. Later, *R. damascena* (known by common names such as Damask rose, Isparta rose, and Oil rose) was established as the only source. *Rosa damascena* is believed to be a hybrid of the *R. gallica* and the *R. phoenicia* species, created in years long past. Both parents are native rose species growing among the 25 species of *Rosa* recorded in the *Flora of Turkey*.[1] *Rosa damascena* var. *trigintipetala* (30-petalled rose) is widely cultivated in Turkey and Bulgaria.

In his book *Old Garden Roses in Turkey* (1994), Turhan Baytop wrote, "One of the most important evidences that the rose oil industry of Bulgaria was originally built by the Turks, is that the rose oil factories in Bulgaria are still using Turkish words like 'baş, ayak, *sherbet,* çorba*, aşılama',* even today." Baytop pointed out that the rose gardens and rose distilleries in Bulgaria were not only founded by the Turks, but also were owned by them for a long time (approximately 200 years), and that the Bulgarians took them over after the owners left the country during the Russo-Turkish War from 1877 to 1878.[31]

The rose garden was an indispensible pleasure for the Ottomans. Image from *A Prince and a Princess in the Rose Garden. P Dergisi Bahçe ve Sanat Bahar. 2004.*

An old record tells of rose-oil production in Edirne by an elderly woman, Mrs. Hadji Fatma:

> The oil roses bloom in May, and the oil cauldrons are set on May 6th, the day of Hidrellez; they keep boiling continuously for about 25-26 days, til the end of May. There are two kinds of oil roses, light red roses and white roses. The white roses are not fragrant, and they stand among the red roses; they carry only a scant amount of oil; they are placed among the red roses because they freeze rapidly. The purest rose oil is the one that freezes rapidly. The lowly tradesmen add geranium to rose oil…
>
> The time when the roses are in full bloom is called *doruk* [peak time]. During *doruk*, sometimes the rose

During the rose season, the sick are carried to the wells, and are immersed in the pulp residue.

Village-type rose oil distillation facility in Turkey.
Photos ©2012 Gülbirlik Cooperative

cauldrons boil nonstop for four days and four nights. Then, the workers sleep in shifts. When the roses are boiling, the nights are festive. Players come from the town. They are fed by the landlord, drinks are offered, and the players play their violins, clarinets, drums, tambourines, and zurnas, and sing till sunset. Every day, when ten cauldrons are set up for rose water, two are set up for rose oil. The most beautiful folk songs of Rumeli were created when the roses were boiling. 'Only if I could see my love at dawn…'[37]

The Second Period of Rose Cultivation in the Ottoman Empire

In 1908, several years after the Russo-Turkish War of 1877 to 1878, Bulgaria separated from the ottoman Empire and became an independent state. Turkish immigrants who left their homes in today's Bulgaria and migrated to Anatolia cultivated oil roses that they had brought along with them, initially in Bursa (a city in northwestern Turkey) and Istanbul. The second period of rose cultivation and rose distillation began in 1880; rose water and rose oil were first commercially produced in those regions in 1885.

Sultan Abdulhamit encouraged rose cultivation in Ottoman lands by providing rose saplings and stills to farmers in Istanbul and numerous other areas of Turkey and Syria. Eventually, Isparta and Burdur provinces proved to be the most suitable for rose cultivation and oil production. In the early 1900s, Ismail Efendi started planting roses and distilling rose oil independently from the state and firmly established rose cultivation in Isparta. Rose cultivation in all of the other provinces ceased since the Isparta rose yielded 1 kg of rose oil from 4 tons of roses, while in other provinces as much as 6 to 12 tons of roses were needed to produce 1 kg of rose oil, making the oil non-profitable. (The Anadolu University research team of this article's primary author was able to acquire an old sample of rose oil produced in Bursa province and found it to have a pleasant fragrance despite being stored non-refrigerated for more than 60 years.)

Woman picking roses in a garden in Turkey.
Photo ©2012 Gülbirlik Cooperative

The Modern Rose Industry in Turkey

Method of Production

Rose oil is produced by water distillation of fresh *R. damascena* flowers. Commercial oil-bearing rose is an entirely cultivated plant. After planting the rose twigs in a rose field, it takes at least 3 years for a rose plant to attain maturity. A mature rose field normally yields 5 tons of fresh roses per hectare. However, in a carefully nurtured field, the yield may increase to 7-to-8 tons per hectare. It is normal for a field to be productive for as long as 20 to 30 years. Rose harvest lasts for approximately one month between mid-May and mid-June. Roses are handpicked in the early hours of the day and transported either to factories or to the collection sites of various firms. A skilled worker can pick about 40 kg of roses in 8 hours. Factories remain open 24 hours a day — broken into 3 shifts — for one month. When the season is over, the factories are cleaned and closed down until the next season.

In village-type distillation, freshly picked flowers are loaded into 150- to 1,000-liter copper or galvanized steel open fire stills; most stills have a 300-liter capacity and consist of a retort and a head. The removable spherical head is connected to a pipe which leads through a pool filled with lukewarm water to cool the condensate. At the outlet, there is a 9-liter glass collecting flask. Typically, 10 kg of flowers and 60 liters of water are loaded into 300-liter stills and are distilled for 1 to 2 hours in order to collect 2 flasks full of the distillate (18 liters). The oil does not separate due to the low concentration of oil in the distillate. Therefore, about 60 liters of the distillate are redistilled, yielding another 18 liters of distillate from which the oil that floats to the top is decanted. The aqueous phase is diluted with distilled water and marketed as rose water.

Generally, industrial production employs larger 3,000-liter copper or stainless-steel stills. Each still has a charge size of 400 to 500 kg flowers and can hold 1,500 to 2,000 liters of warm water. The stills are steam-jacketed, *i.e.*, they contain an inner double-wall inside of which steam is circulated. There may also be provision for the injection of live steam into the still to speed up distillation. The distillation process takes 1.5 hours. The condenser temperature is kept at 95°F (35°C) to avoid the solidification of waxes.

The distillate is collected in 200-liter stainless-steel Florentine flasks. The oil that separates out is called crude oil, first oil, or direct oil. Distillation is terminated when the distillate no longer has a bitter taste. The overflow of the Florentine flasks is collected in 500-liter tanks. These "bottom waters" or "first waters" are then pumped into 5,000-liter stainless-steel still tanks. These are cohobated in 3,000-liter stills for 1 to 1.5 hours to obtain what is called the second oil, cooked oil, or indirect oil. The distillate that remains after oil removal is sold as rose water. The first and second oils are filtered and kept in glass flasks in the dark. When production season is over, the first and second oils are mixed to yield Turkish rose oil and packed in special 2- to 5-liter tinned-steel containers called *kumkuma*. Generally 3.5 to 4 tons of flowers yield 1 kg rose oil — about 0.02% oil.

Rose concrete is obtained by extracting fresh roses with n-hexane and then removing the hexane, which leaves behind a highly fragrant solid extract that resembles shoe-polish wax. When rose concrete is extracted with ethanol and cold-filtered upon evaporation of ethanol under vacuum, the dark liquid obtained is known as rose absolute. Annually, about 7,000 tons of roses are processed to produce about 1,600 kg of rose oil and 2,400 kg of rose concrete. Four hundred kg of roses are required to produce 1 kg of rose concrete. The primary constituent of rose concrete is 2-phenylethyl alcohol, which also is the main constituent of the headspace odor of roses and rose water.[36,38] One company in Turkey produces concentrated rose water without redistilling the waters of the first distillation.

The global rose-oil market is estimated to be about 3 tons annually. The world's annual demand for [rose concrete] is reportedly 9 tons.[39] Turkey presently supplies 50 percent of the demand for rose oil.

There are 15 rose-oil factories in Isparta, Turkey, some owned by the state-controlled Gülbirlik Cooperative and others by private companies; five of them are relatively large complexes. Isparta ranks at the top in terms of the total amount of rose oil produced and the rate of rose oil and rose concrete produced per unit of rose flowers. In Turkey, 80 percent of the oil-bearing roses are cultivated in Isparta, and the remaining 20 percent are cultivated in Burdur, Afyon, and Denizli. According to 1998 statistics, 8,200 farmers were growing roses on about 1,772 hectares (1 hectare is roughly 2.5 acres) *in toto*. The total amount of rose flowers harvested was 6.034 tons, 2.901 tons of which came from Gülbirlik, and the remaining 3.133 tons from private enterprises. The amount of rose oil distilled from those flowers was 1.562 kg altogether; Gülbirlik distilled 751 kg, and private enterprises distilled 811 kg. The total funds paid to the farmers was 850 billion TL (Turkish lira; approximately $469,000 USD). Exports amounted to $2.5 million USD, with Gülbirlik accounting for $1.5 million, and private enterprises accounting for $1 million. Certified organic cultivation of rose also is carried out in Isparta. Two companies export about 30 kg of organic rose oil and about 4 tons of organic rose water. One of them also exports 1,250 kg of rose concrete and 750 kg of organic rose absolute.

More recently, in the Province of Isparta, approximately 8.5 tons of rose flowers, nearly 1.5 tons of rose oil, more than 8 tons of rose concrete and rose absolute, and 259 tons of rose water were produced in 2009; almost $19 million of such rose products were exported. In 2008, the sale price of rose oil was $6,384 per kilogram, and $3 per kilogram for rose water, $525 per kilogram for rose concrete, and $1,300 per kilogram for rose absolute. In 2009, Turkey exported 1.2 tons of rose oil for a return of $11.7 million, and in 2010, $10.5 million in revenue was obtained from the export of 1 ton of rose oil. Nearly 90% of Turkish rose oil is exported to France, Switzerland, and the United States. Rose concrete is exported primarily to France, and Germany is the foremost importer of Turkish rose absolute.[13,39] Table 1 shows 2011 and 2012 figures.[39]

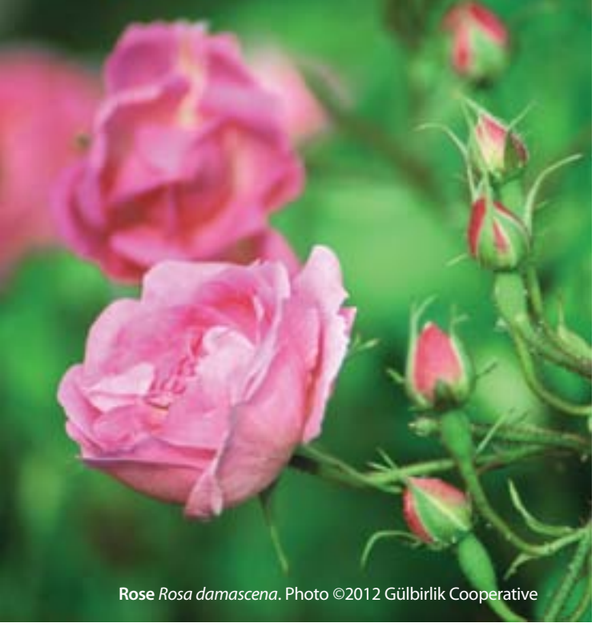
Chemical and Olfactive Features of Rose Oil

Citronellol is the main component of factory-produced Turkish rose oil (31 to 44%). It determines the basic rosaceous character of rose oil. Higher citronellol contents lead to increased sweetness which, when compared with near-equivalent quantities of geraniol (9 to 24%), contributes to strength and fortification of the body note. Conversely, when geraniol content of rose oil is comparatively low, the sweetness of the body note is maintained while strength diminishes. In some village oils, the geraniol content was observed to be higher than the citronellol content. In

Table 1. Turkish Rose Material Exports

Year	Rose Flower (Ton; TL/kg)	Rose Oil (kg; Euro/kg)	Rose Concrete (kg; Euro/kg)	Rose Water (kg; TL/kg)
2011	6000; 2.25	800-1000; 6250	6000; 700	60.000; 7
2012*	6500; n/a	1000-1100; n/a	6500; n/a	60.000; n/a

n/a = not available
*The 2012 figures indicate only the amounts of rose and rose materials produced but not the prices, as rose oil production ended in early July 2012, at which time this article was being completed. The data were obtained by the principal author, from Gülbirlik (A. Doğaner, oral communication, July 2012).



Rose *Rosa damascena*. Photo ©2012 Gülbirlik Cooperative

such cases, while the rosaceous character is maintained, it acquires an undesirable green, grassy quality.

In order to simplify the comparison of gas chromatographic results, citronellol/geraniol ratios of each of the oils are taken. Village oils give a ratio of 0.83 to 1.92%, while in factory oils the ratio is 2.30 to 4.84%. In Bulgarian rose oil the citronellol/geraniol ratio is around 1%.

The basic character of rose oil, mostly dependent upon citronellol and geraniol, is further modified by nerol (5 to 11 %) and farnesol (0.2 to 1.4 %). Their contents are slightly higher in village oils. Higher farnesol content leads to the establishment of strong floral character and an overall improvement of body-note volume. Nerol not only adds to the rosaceous character but also to its freshness.In those cases where the geraniol content is low, however, the freshness of nerol manifests itself as slightly citrusy. When geraniol content is high, the combination of citronellol, geraniol, farnesol, and nerol results in a strong, sweet, floral, fresh rosaceous character. Other typical constituents of rose oil are geranyl acetate, nonanal, citronellyl formate, citronellyl acetate, eugenol, methyl eugenol, cis-rose oxide, alpha-terpineol, phenylethyl alcohol, and linalool. Damascenones and some sulfur compounds are among the minor components. Stearoptenes (paraffins) are natural constituents of rose oil (the major one being nonadecane) and due to their presence, rose oil solidifies at room temperature and when refrigerated. Stearoptene content in village oils is lower.[35,36]

Table 2. Twenty-One Years of Turkish Gülbirlik Rose Oil (1986-2002 and 2008-2011)

Compound	Main components (%)	
	Min.	Max.
Citronellol	30.9	43.9
Geraniol	9.3	14.4
Nonadecane	8.2	14.7
Nerol	5.2	10.7
1-nonadecene	2.0	4.9
methyl eugenol	2.1	4.0
Heneicosane	2.5	4.2
geranyl acetate	1.0	2.3
phenylethyl alcohol	1.2	2.0
β-caryophyllene	0.7	1.6
citronellyl acetate	0.7	1.4
germacrene D	0.7	1.4
Linalool	0.6	2.1
(2E, 6E)-farnesol	0.6	1.4

Gülbirlik is the largest rose-oil manufacturer in Turkey. The Pharmacognosy Department at the Faculty of Pharmacy at Anadolu University in Turkey has been analyzing the company's oils each year for the past 21 years. Table 2 summarizes the levels of major components found in rose oil during this 21-year period.

Production of Rose Oil Outside Turkey and Bulgaria

Bulgaria and Turkey are the main sources of rose oil to international markets, and these oils are generally preferred by perfumers. *Rosa damascena* is grown and rose oil is produced in Russia, Iran, Saudi Arabia, India, and China. Iran produces much of its rose water in Kashan (in north-central Iran). In Saudi Arabia, rose oil is produced in Taif, near Mecca. *Rosa centifolia* commonly is grown in Morocco, Uzbekistan, France, and Egypt, and is particularly desirable for the production of rose water. In China, rose oil is also produced from *R. rugosa*.

Rose Pharmacology

Several pharmacological studies have been performed with rose extracts and oil. Most studies have been conducted on products from *R. damascena*, while a few examined *R. centifolia*. The studies' results are summarized in Table 3. There is also a recent review paper available on the pharmacological effects of *R. damascena*.[40]

Ancient texts mention that rose is good for disorders of the brain and the heart. (See "Rose in Islamic Medical Texts.") Several recent studies have provided scientific evidence for this information. The hydroalcoholic extract of *R. damascena* flowers has been shown to potentially increase heart rate and contractility in isolated guinea pig heart, possibly via a stimulatory effect on β-adrenergic receptors.[48] Furthermore, cyanidin-3-O-β-glucoside from rosebuds significantly suppressed angiotensin-I-converting enzyme (ACE) activity, suggesting a possible role in improving cardiovascular function since ACE is a key enzyme in the production of angiotensin II, a potent vasoconstrictor.[73]

In a double-blind study on 16 patients (age 3 to 13 years; 9 girls and 7 boys), children with refractory epilepsy were administered 5 mg per kg of 10% of rose oil in vegetable oil or placebo 3 times per day. All had been under treatment for 3 to 6 weeks (baseline phase). They received either the essential oil or placebo for a period of 4 weeks and in between these periods, they took only their pre-existing antiepileptic drugs for 2 weeks (washout phase). The mean frequency of seizures in those using essential oil was significantly lower compared to those using placebos (p=0.00). The results showed that rose oil had an anticonvulsant effect and could reduce frequency of seizures in children who were resistant to anti-epileptic drugs (AEDs).[70]

Rosa damascena has beneficial effects on brain function and has potential applications for the treatment of dementia. A chloroformic extract of the *R. damascena* significantly induced neurite outgrowth activity and inhibited amyloid β (Aβ).[68] Aβ is thought to be a major pathological cause of Alzheimer's disease. Aβ(25-35), the major fragment of the full peptide Aβ found in the

Table 3. Pharmacological Activities of Rose Materials

Type of Extract/Essential Oil	Activity Shown	Technique	Reference
Aqueous and/or ethanolic extract	Hypnotic	Pentobarbital-induced sleep time	41, 42
Aqueous and/or ethanolic extract	Analgesic	Hot plate, tail flick, acetic acid, and formalin tests	43, 44
Aqueous and/or ethanolic extract	Antitussive	Citric acid method	45
Aqueous and/or ethanolic extract	Bronchodilatory	Inhibition of calcium channels of guinea pig tracheal chain	46, 47
Aqueous and/or ethanolic extract	Potentiation of heart rate and contractility	Isolated guinea pig heart	48
Aqueous and/or ethanolic extract	Anti-inflammatory	Carrageenan-induced rat-paw edema	45, 49
Aqueous and/or ethanolic extract	Laxative Constipation	Rats by gavage and intraperitoneal injection	50
Aqueous and/or ethanolic extract	Anti-solar	Sun Protection Factor (SPF) determination	51
Aqueous and/or ethanolic extract	Antiaging	Mortality rate in adult Drosophila flies	52
Ethanolic extract (*R. centifolia)*	Antitussive	Mouse model induced by sulphur dioxide gas	53
Hydroalcoholic, ethanolic extracts, and essential oil	Antioxidant	Measurement of free radical scavenging activity	54-56
Methanolic extract	Antidiabetic	Measurement of α-glucosidase activity	57, 58
Methanolic extract	Anti-lipase	Reduction in turbidity of a triolein emulsion by porcine pancreatic lipase	59
Flavonoid compounds isolated from methanolic extract	Anti-HIV	Effects on C8166 human T lymphoblastoid cells infected with HIV-1MN and H9 human T-cell lymphoma cells chronically infected with HIV-1IIIB	60
Essential oil and absolute	Antimicrobial	Disk, well-diffusion, microdilution methods	55, 61-67
Essential oil	Anticonvulsant	PTZ (Pentylenetetrazol)-induced seizures in Wistar rats The amygdala electrical kindling seizures in rat	68-70
Essential oil and phenylethyl alcohol	Neuroprotective, memory enhancing	Inhibition against acetylcholine esterase (AChE)	71
Chloroform extract	Neuroprotective, treatment of dementia	Neurite outgrowth activity testing	72
Cyanidin-3-O-β-glucoside from rose buds	Cardiovascular function	ACE (Angiotensin-I-converting enzyme) inhibition	73
Fresh flower juice	Hepatoprotective	Antioxidant activity tests	74
Herbal eye drop containing *R. damascena* extract	Ophthalmic disorders	Clinical tests	75

brains of Alzheimer patients, causes neural cell death, neuritic atrophy, synaptic loss, and memory impairment. The primary active ingredient in the chloroformic rose extract was found to be a very long, polyunsaturated fatty acid known as VLFA, which has a chemical formula of $C_{37}H_{64}O_2$. It protected atrophy induced by Aβ(25-35) and displayed strong neurite outgrowth activity.[72]

An additional recent study suggested that rose oil and a main component of the rose fragrance, phenylethyl alcohol, significantly inhibits acetylcholine esterase (AChE) and butyrylcholine esterase (BChE).[71]

Lastly, dried rose flower buds are used in herbal teas; rose jam and syrups are prepared from fresh rose flowers; rose water is often sprinkled on participants of religious ceremonies and is added to traditional Turkish deserts such as *güllach* and *su muhallebisi* (a thick rice-flour pudding) for flavoring. *Gülbeşeker* is a rose-flavored confectionary which was particularly popular during the Ottoman period.

Conclusion

Rosa damascena and other fragrant rose species have been esteemed for centuries by almost every culture that has had access to their wonderful aromas. Rose has inspired artists to create masterpieces and kings and sultans to establish gardens for their beauty and fragrance. Rose has inspired legends, and humans throughout recorded history, and only recently, modern technology and chemical analyses have opened up new possibilities for this much-praised botanical. HG

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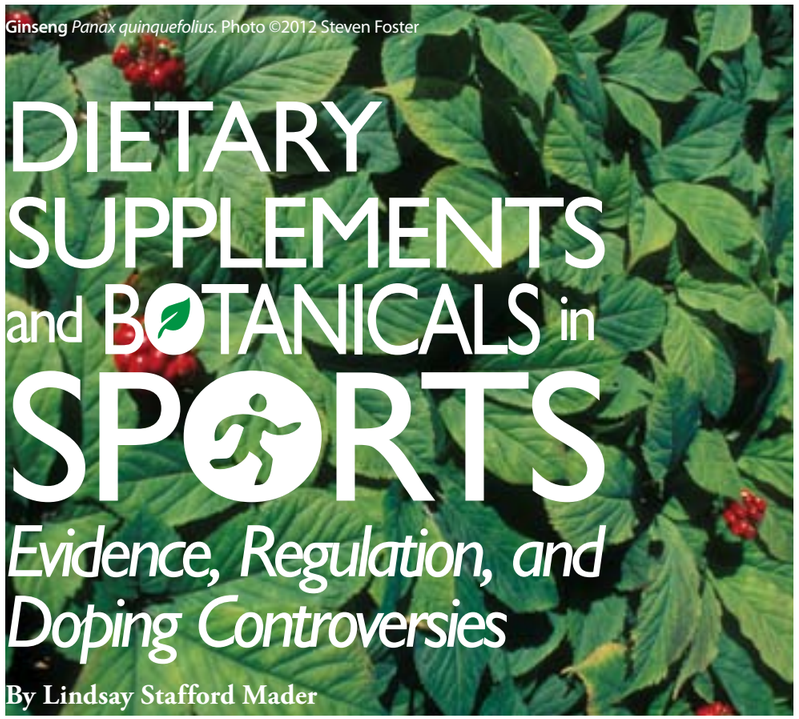

Ginseng *Panax quinquefolius*. Photo ©2012 Steven Foster

DIETARY SUPPLEMENTS and BOTANICALS in SPORTS

Evidence, Regulation, and Doping Controversies

By Lindsay Stafford Mader

Introduction

As US swimmer Michael Phelps fiercely splashed his way to a record 19 Olympic medals at the London Games last summer,[1] most spectators sat on their couches and watched in awe at his near-superhuman abilities. Few people doubt the physical differences among athletes and non-athletes. While many people struggle to run a mile in 10 minutes, world record-holder Hicham El Guerrouj of Morocco ran the fastest mile in 3 minutes and 43 seconds;[2] most sports viewers would jump ship at the mere thought of doing a cartwheel, while US Olympic gold medalist Gabrielle Douglas spun, leaped, and kicked her way to becoming a modern legend known as the "Flying Squirrel."[3]

One experience that *does* unite most modern humans is the desire to be a better version of oneself. Athletes yearn to run faster, jump higher, train longer. Non-athletes long to be thinner, healthier, or more energized. Millions of Americans turn to herbal and dietary supplements with these objectives every year,[4] and that athletes also consider these products as a natural way to improve their wellbeing and performance should be easily understood. As sports nutrition consultant Susan Kundrat, RD, wrote for the Gatorade Sports Science Institute, "Athletes, coaches, and health professionals who work closely with athletes are consistently looking for sound, effective ways to enhance health and performance with foods, fluids, and dietary supplements."[5]

Still, dietary and herbal supplements almost always have a negative reputation when discussed in the context of sports. During the recent 2012 Summer Olympic Games, mainstream media outlets and several sporting and anti-doping organizations vilified supplements, calling them ineffective and risky, and warned athletes to steer clear.[6] These reporters and officials make both the problem and solution seem clear and simple: supplements are unequivocally ineffective and dangerous, and athletes should stop taking them. Upon closer inspection, however, the facts reveal a different story.

The Blame Game: Illegal, Misbranded Products Posing as Dietary Supplements

From a Czech kayaker and Welsh boxer to an American NASCAR driver and a Greek high-jumper, many athletes who test positive for banned substances attribute it to a dietary supplement. In one of the best-known cases, a Jamaican-born sprinter for Great Britain named Linford Christie tested positive for ephedrine at the 1988 Seoul Olympics.[7] He blamed the outcome of the test on his consumption of a ginseng (*Panax* spp., Araliaceae) tea that allegedly contained undisclosed, prohibited ingredients. Christie was let off the hook and took home a silver medal.

Steven Dentali, PhD, chief science officer of the American Herbal Products Association (AHPA), expressed doubts over Christie's excuse. "Was the tea ever identified or just claimed to be the source?" asked Dr. Dentali. "Attributions of herbal effects, good or bad, must begin with proper determination of what was actually ingested. With the available evidence, the Christie case does not rise to the level of a banned substance found in an herbal product" (oral communication, July 26, 2012). (About 10 years later, Christie tested positive for 100 times the limit of a prohibited anabolic steroid and was banned from the Olympics for 2 years. Many sources report that he spuriously attributed this to eating avocados.)

The Christie situation embodies the most complex — and likely the most significant — issue of the supplements-doping controversy: Are the supplements blamed for failed drug tests really at fault or are these athletes bluffing in order to maintain a false innocence? In other words, who is telling the truth? In most cases, unfortunately, the answer is unclear.

"Misbranded supplements and athletes blaming supplements is an issue that cuts both ways," said Edward Wyszumiala, head of the dietary supplements, functional foods, and athletic banned substances programs at NSF International, a nonprofit organization that monitors and sets standards for consumer goods. "For example, we've seen cases recently where a NASCAR driver was blaming his positive doping test on a dietary supplement, but when the story was investigated further, it was proven he was actually not taking a contaminated supplement, but actually a pharmaceutical product. On the other side, there have been cases that have been traced back directly to a contaminated supplement" (email, July 20 and August 23, 2012).

The World Anti-Doping Agency (WADA) is an independent organization responsible for sports-related anti-doping activities like standards-setting and drug testing.[8] It works with governments of numerous countries, sporting organizations, and analytical laboratories to address doping in sports. When an athlete fails a doping test, WADA's World Anti-Doping Code states that a tribunal of officials will consider the athlete's arguments if he or she wishes to appeal.[9] This tribunal can be one of a variety of sports arbitration boards, such as the American Arbitration Association (AAA), the Court of Arbitration for Sport, or other international bodies.

According to Gabriel Dollé, director of the Medical and Anti-Doping Department of the International Association of Athletics Federations (IAAF) — the world-governing body of international athletics — the burden of proving a supplement was at fault falls on the athlete. The arbitration boards, he said, do not test supplements, although the IAAF can order a counter-analysis if it has doubts over the test or submitted evidence.

"The IAAF orders very rarely counter-analysis of supplements," said Dr. Dollé (email, September 11, 2012).

Sometimes, the US Anti-Doping Agency (USADA) — an independent Olympics-related anti-doping organization — will take part in the testing of supplements on behalf of American athletes, said Amy Eichner, PhD, USADA's special advisor on drugs and supplements. "If the results indicate that a prohibited substance plausibly could have come from a supplement, it is up to the arbitration panel of independent judges to determine whether the evidence bears this out. The arbitration panel makes that decision," she said. If testing results do not indicate a supplement, any potential appeal will likely be dropped and the initial penalties enforced (e-mail, July 25 and September 11, 2012).

Reduced penalties are possible if the athlete "can establish to the satisfaction of the tribunal how the substance entered his or her system, demonstrate that he or she was not at fault or significant fault, or in certain circumstances did not intend to enhance his or her sport performance."[10] Most importantly, said Dr. Dollé, the athlete must show that he or she took steps to ensure the supplements taken did not contain prohibited ingredients. Ignorance about what is present in a dietary supplement, or any other nutritional product chosen by an athlete, is considered an unacceptable defense.

If the athlete can convince the panel that a supplement was at fault, the panel may decrease the athlete's penalty, as was the case with US swimmer Jessica Hardy. At the 2008 US Olympic trials in Omaha, Nebraska, Hardy qualified for several Beijing Olympics swimming events. She also tested positive for the banned substance clenbuterol and was no longer eligible to compete in Beijing.[11] Hardy took the case before AAA, which found that she satisfactorily demonstrated that the AdvoCare® Arginine Extreme dietary supplements she was taking contained clenbuterol based on analysis done by the "father of drug testing in sports," Don Catlin, MD, of Anti-Doping Research Inc., in Los Angeles.[13] AAA ruled that she had taken various measures in an attempt to ensure that her supplement was safe, including the following: she had a promotional endorsement contract with the Plano, Texas-based AdvoCare; she spoke with AdvoCare representatives about the supplements' purity prior to taking them; the

company's website stated that its products were "formulated with quality ingredients" and were considered "natural bodybuilding;" she obtained the supplements directly from AdvoCare; and several additional examples. Hardy's penalty was decreased from a 2-year ban to a 1-year ban — the maximum possible reduction — and she was permitted to compete in the 2012 Olympic Games in London, where she won a gold and a bronze medal.[12]

Dr. Dollé noted, however, that a very small percentage of investigations conclusively find that a sports supplement was contaminated.

"Most of the time," said Dr. Dollé, "athletes do not even attempt to test the supplement. Cases of spiked supplements are difficult to investigate because the content changes from one batch to another and that the athlete, most of the time, no longer has the batch he used at the time of the doping control."

Even when an arbitration panel agrees with athlete-produced evidence, supplement companies often contest the lab findings and an absolutely conclusive answer remains somewhat at large.[14] Regarding the AdvoCare and Hardy case, the company argued that it specifically tested the lots of products provided to the swimmer, as well as every lot of every ingredient (M. Miller, email, October 2, 2012). It appears that the analysis groups employed by the company, NSF International and Informed-Choice, did not find clenbuterol while Anti-Doping Research, which Hardy hired to test the products, did find it. This might be explained by various analysis/certification companies' usage of different testing and validation processes. AdvoCare also asserted that it was absent from some of the meetings and thus unable to present its findings to the officiating organizations. Ultimately, the ruling favored Hardy.[13]

Anthony L. Almada — a co-investigator on a number of university-based clinical trials on sports nutrition products and CEO of the sports nutrition brand GENr8 — voiced concern for the difficulty in establishing an appropriate threshold of detection for substances in varying dosage frequencies and sizes.

"Testing for banned substances is a step forward, but the sensitivity of the testing methods, the testing 'limbo' of how low can a lab's analytical methods go in detecting a banned substance, is rarely if ever considered by a dietary supplement manufacturer," said Almada (email, September 20, 2012).

Government and Industry Response

The dietary supplements industry often stresses the fact that if a product labeled as a dietary supplement does contain prohibited or designer pharmaceutical ingredients, it is no longer a dietary supplement and is instead a drug being sold illegally as a supplement. It also often claims that companies participating in such activities, referred to as economically motivated adulteration, represent a small, rogue portion of the industry and that most manufacturers and retailers are reputable businesses.

"I think that's a bit of miscalculation on the industry's behalf," said Daniel Fabricant, PhD, director of the US Food and Drug Administration's (FDA) Division of Dietary Supplement Programs. "It is their reputation, after all. It's really incumbent on the industry to remain vigilant. The problem isn't going to auto-correct. Saying it's not your problem doesn't make it go away" (oral communication, September 6, 2012).

According to Dr. Fabricant, FDA has no official data on the number of companies marketing tainted products as sports supplements. He did note, however, that sports supplements represent one of the top 3 areas of concern for FDA, along with supplements marketed for weight loss and sexual enhancement.

"If there's a drug in a supplement, generally it's not there by accident," he said. "And [drug substances are] not at levels that would indicate a cross-contamination problem. They're at large levels intended to have a profound biological effect. I don't think there's one archetype that participates in these activities. We've seen tainted products in a variety of different environments of distribution. You know, retail, internet. You name it, we've seen it — a variety of large and small. There's not one type, per say, that fits the bill."

Sometimes dietary supplement trade publications reinforce the image of an industry whose problems have been unfairly exaggerated. NutraIngredients USA, for example, reported after the London Olympics that the synthetic substance DMAA — a banned stimulant also called methylhexaneamine, or MHA — was implicated in only one Olympics doping ban.[16] (Some companies say DMAA can be found in extremely small quantities in the oil of the geranium plant [*Pelargonium graveolens*, Geraniaceae], and therefore, according to the companies, is actually a natural product, although at least 3 peer-reviewed analytical studies have determined that it is synthetic.*[15] This lone DMAA doping case represented 12.5% of the 8 total 2012 Summer Olympics doping cases. According to the Anti-Doping Database, 172 professional athletes have tested positive for DMAA since 2009[17] — a number that includes failed drug tests in all sports, not just the 2012 Olympics, and thus provides a more comprehensive assessment. (The most suspensions occurred in 2011 when 95 athletes tested positive for DMAA.)

Although many mainstream media stories (and some sports governing bodies) claim that dietary supplements are not regulated and thus athletes have no protection against adulterated sports supplements, in fact, FDA can provide some degree of enforcement through market surveillance, inspections of facilities' Good Manufacturing Practices (GMPs), and more.

"We're really looking to use whatever tools we have at our disposal to take action on manufacturers who are really marketing drugs as dietary supplements," said Dr. Fabricant.

In August of 2012, for example, the largest online retailer of bodybuilding supplements — Bodybuilding.com — was ordered to pay $8.1 million for selling steroid products labeled as dietary supplements, which FDA uncovered at a GMP inspection in 2008.[18]

"The inspections revealed some of the challenges the firm had, let's just say," said Dr. Fabricant. "We get a lot of information on just visiting a firm. It's part of our authority, you know, getting eyes into the firm and seeing what's going on."

Still, FDA has experienced a high rate of non-compliance with GMP inspections, according to Dr. Fabricant. Furthermore, inspections do not prevent tainted products from entering the marketplace, nor do they offer total protection against the few banned substances that are legal for normal consumers not involved in professional sports.

"It seems the FDA has greatly increased the number of GMP inspections," said USADA's Dr. Eichner, "which is great, but the fact that so many companies — roughly half* — have failed such inspections speaks to poor quality-control across the industry. Hopefully improved compliance with GMP regulations will help, but GMP regulations don't require companies to test for contamination by substances prohibited in sport, and companies could be compliant with GMP but still produce a supplement that contains a prohibited substance (such as [the hormone] DHEA)." (**Editor's Note: FDA spokesperson Sebastian Cianci confirmed this figure, noting that* more than half *of the firms inspected by FDA for GMPs thus far during 2012 had problems needing correction [email, September 21, 2012]. GMP non-compliance can be due to a variety of reasons and is not necessarily indicative of manufacturers spiking supplements with banned substances or illegal drugs.*)

> "Most of the time athletes do not even attempt to test the supplement. Cases of spiked supplements are difficult to investigate because the content changes from one batch to another and that the athlete, most of the time, no longer has the batch he used at the time of the doping control."

"If someone has spec sheets around that indicate that something that shouldn't be there was added to the product, of course that would obviously get uncovered in an inspection," said Dr. Fabricant. "If it's something that is completely criminal and has been hidden all the way, then that's a different scenario. I think the issues are, 'Does the FDA regulate dietary supplements?' Yes. We have different tools to do that with. But the bottom line is that manufacturers and distributors are ultimately responsible for insuring their products are safe and in compliance with all applicable laws and regulations."

Most anti-doping and sports organizations' solution is to strongly caution athletes against using all dietary supplements. It seems entirely unavoidable, however, that all athletes will abstain. Some researchers have estimated that anywhere from 65 to 99% of elite athletes use dietary supplements,[19] a figure likely impacted by the intense pressure they experience to maintain certain body weights and extreme physical abilities. If an athlete chooses to take a dietary supplement or an herbal product, various measures and certification programs can enable him or her to be more confident that it does not contain a prohibited substance.

"We encourage [athletes] to be fully informed and educated about the risks, and to weigh the risks and the benefits carefully as they make their own decision," said Dr. Eichner. "While there may be high-quality herbal products on the market, to an athlete it is difficult to distinguish between legitimate herbal products and those that are adulterated or spiked with prohibited substances."

USADA advises athletes to choose single-ingredient or few-ingredient herbal and dietary supplement products. "Dietary supplements that contain fewer ingredients require fewer manufacturing steps (on average) than products containing dozens (or many dozens) of ingredients," said Dr. Eichner. "The more ingredients there are, the more opportunities for error in manufacturing and identification, and the greater chance for ingredient interactions with other supplements or drugs.

"They should also do enough of their own research on the company that they feel comfortable in using their products," she continued. "This research would include visiting Supplement411.org, the FDA website, the [Federal Trade Commission] website, the Better Business Bureau, and also the companies' own websites. Athletes who want health benefits from a particular plant should generally be aware of adulteration issues globally and query herbal companies about how they avoid purchasing adulterated raw materials."

While certified laboratories and anti-doping organizations test athletes' urine and blood samples for prohibited substances, neither WADA nor anti-doping agencies test dietary supplements for ingredient purity or approve labs to conduct such testing. A few independent companies and organizations do provide these services. The Banned Substances Control Group's BSCG Certified Drug Free™ program certifies that products contain no banned substances.[20] BSCG — run by Dr. Catlin as chief science officer and his son Oliver Catlin as president — was one of the first to start certifying dietary supplements, almost 8 years ago, and currently certifies products for more than 30 dietary supplement manufacturers. Dr. Catlin also serves as CEO of the nonprofit Anti-Doping Research.

"At the beginning, we stated we could test for all the substances on the WADA list as we could in urine," said Oliver Catlin (email, September 26, 2012). "As we gained more experience, we realized the difficulty that dietary supplements present through their variability, making testing them particularly demanding. While urine samples present a fairly standard matrix and are relatively easy to analyze, dietary supplement matrices can present much greater challenges. To ensure that we can detect everything in our menu in every product, we conduct a unique step called product validation. During validation we actually spike all the compounds we test for into a representative sample of a product and run it through our tests to demonstrate that we can

*See feature article "New Research Supports Synthetic Origin of DMAA in Supplements" in *HerbalGram* 95 for more details on this topic.

detect the substances if they were to be present and to establish the detection levels for that unique matrix."

"The process begins with initial ingredient review [of the product's stated ingredients] to ensure that nothing listed is banned or could lead to a positive drug test if used as directed. Once accepted to the program," continued Catlin, "BSCG tests all finished batches of a product in order for a product to be certified. In so doing, we are auditing not only the raw materials that went into the product but also the manufacturing process, the 2 areas where accidental or purposeful contamination can be introduced."

> Athletes who want health benefits from a particular plant should generally be aware of adulteration issues globally and query herbal companies about how they avoid purchasing adulterated raw materials.

SPORT SAFE Testing Service provides testing and education for student athletes.[21] NSF also has a sports supplements testing program, which is currently supported by several professional US sports organizations, including Major League Baseball, the National Football League, the Professional Golfers' Association, the Ladies Professional Golf Association, and the National Hockey League.[22]

"Each supplement we test, we screen for over 170 of the listed WADA-banned substances," said Wyszumiala. "For companies looking to certify selective batches, the costs can be a few thousand dollars a year if their manufacturer is already GMP-certified by NSF. For larger programs that certify all lots of their products, the costs can go into the tens of thousands of dollars for a product line."

Currently, NSF's Certified for Sport® program has certified products from about 44 manufacturers.[23] In order to have products certified, manufacturers must submit their products to a strict testing and review process, which includes analysis of the product's formulation, labeling, ingredient suppliers, and toxicology, as well as inspections of the manufacturing facilities to ensure that "that no banned substances are stored or manufactured at the facility."[22] Inspectors also conduct a variety of tests and analyses each year to assess the product for any heavy metals, pesticides/herbicides, disintegration, or banned substances, and to ensure that the label accurately lists what the product contains. If a manufacturer's product satisfies all components of the process, it can feature the NSF label and be listed on NSF's website as a Certified for Sport company. In addition, Wyszumiala suggests that companies conduct tests on random batches and/or raw ingredients.

Dr. Dentali, of the trade group AHPA, noted the website KeepSupplementsClean.org,[24] a resource AHPA created in order to help educate industry and consumers on supplement issues, including international enforcement efforts.

In addition to efforts from within the industry, US legislators are seeking to eradicate products containing banned substances that pose as dietary supplements. On July 25, 2012, US Senators Orrin Hatch (R-Utah) and Sheldon Whitehouse (D-RI) proposed the Designer Anabolic Steroid Control Act of 2012.[25] If passed through Congress and signed by the President, this bill — which does not apply to botanicals or their derivatives — would amend the Controlled Substances Act so that the Drug Enforcement Administration has more authority to regulate anabolic steroids and products containing these substances that are illegally being marketed and misbranded as dietary supplements.

"The bill corrects the terrible design and drafting of previous anti-steroid legislation from 1990 and 2004," said Rick Collins, a New York lawyer whose firm represents numerous sports nutrition and dietary supplement companies (email, September 22, 2012).

But Collins noted that the designer-steroids problem is partly attributable to the original law itself, which he said enumerates only specific steroid compounds and thus inadvertently fostered creative efforts to bypass the Controlled Substances Act through marketing a plethora of unlisted, synthetically designed steroids.

"The new bill, if passed, is structured to accomplish what Congress likely intended in its prior botched efforts: to criminalize a long list of specific compounds as well as unlisted steroidal substances that are *similar* to them," said Collins.

The Illegal and Legal Uses of Botanicals in Sports

Although the term *doping* carries a negative connotation, it does not always indicate that a substance is harmful. According to WADA, which publishes an annual document listing the substances banned in sports competitions worldwide, a substance will be prohibited if it meets at least 2 of the following criteria: "1) It has the potential to enhance or enhances sport performance, 2) It represents an actual or potential health risk to the athlete, or 3) It violates the spirit of sport."[26]

Of the approximately 200 substances and methods on WADA's 2012 Prohibited List, only one whole botanical is prohibited: cannabis (*Cannabis* spp., Cannabaceae). WADA additionally prohibits the use of several botanical derivatives and their synthetic counterparts, including the stimulants ephedrine, methylephedrine, and pseudoephedrine, all of which come from ephedra (*Ephedra* spp., Ephedraceae); the stimulant cocaine, which comes from coca (*Erythroxylum coca*, Erythroxylaceae); the stimulant cathine, which comes from the African medicinal plant khat (*Catha edulis*, Celastraceae); and morphine and diamorphine (heroin), which are derived from the opium poppy (*Papaver somniferum*, Papaveraceae) and considered by WADA to be narcotics. (All of the above are illegal in dietary supplements in the United States).

Instances in which botanicals are implicated in doping sometimes make headlines. Most recently, on August 6, 2012, an American judo fighter was sent home from the 2012 London Olympics after testing positive for cannabis,

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HISTORY OF HERBS IN SPORTS

Public disapproval of doping increases with each news report of an athlete's failed drug test. The stance of official organizations reflects this, as WADA vowed to collect 5,000 samples in order to make the London Games the most tested and allegedly "cleanest" Olympics ever.[1] Still, doping scandals continue and some might find themselves reminiscing about a time when all athletes performed their sports wholesomely and without any outside aid.

What many spectators do not realize, however, is that the practice of ingesting substances — often botanicals — with the hopes of enhancing sports performance has existed to some extent for thousands of years.[2] In fact, athletes were never tested for performance-enhancing substances and illegal drugs until the 1960s, when the death of a Danish cyclist, who passed out while riding and had a severe crash, was attributed to an amphetamine overdose.[2,3]

The Ancient Greeks are reported to have ingested herbs and fungi for performance enhancement, as well as to have used honey to boost energy and carbohydrate levels.[2] Physicians gave Olympic athletes bread prepared with spices and juices extracted from the poppy, and Roman gladiators allegedly ingested caffeine and the bitter alkaloid strychnine from the nux-vomica tree (*Strychnos nux-vomica*, Loganiaceae). The Roman naturalist Pliny the Younger (61 – 12 CE) recorded that runners would attempt to increase their muscle mass and strength by consuming a plant called mare's tail (*Hippuris vulgaris*, Hippuridaceae).

According to John Riddle, PhD, a history and botany professor at North Carolina State University and an expert on the use of botanicals during ancient times through Classical Antiquity, the 1st century Greek physician Galen, who attended to Roman emperor Marcus Aurelius, got his start as a doctor for gladiators (email, July 18, 2012). Dr. Riddle's 1997 book, *Eve's Herbs: A History of Contraception and Abortion in the West*, reports that Galen wrote of "an athletic trainer [who] required his men to sleep on a botanical bed of chaste tree [*Vitex agnus-castus*, Lamiaceae],"[4] which was a reputed male contraceptive and erectile function preventative, in order to preserve their energy.*

Centuries later, in the late 1800s, an American long-distance walking athlete reportedly chewed coca leaves during a trek of approximately 110 miles completed within 24 hours.[5] Additional performance-enhancing substances during this period typically consisted of "sugar cubes dipped in ether, mixtures of brandy and cocaine, caffeine, cordials containing alcohol, and even nitroglycerine and strychnine."[6]

During the 1950s, the Union of Soviet Socialist Republics (USSR) began to study adaptogenic substances, including many herbs, with the goal of enhancing performance and work output of athletes, soldiers, and government workers.[7] According to the book *Adaptogens: Herbs for Strength, Stamina, and Stress Relief* (Healing Arts Press, 2007) by David Winston and Steven Maimes, "The Soviets' pursuit of superior military strength, performance in the Olympic Games, political power, and the excellence of the well known Bolshoi Ballet mattered so much to them that whatever they could do to accomplish the goal of dominance was pursued." Of the approximately 4,000 plants investigated, 12 herbs were considered adaptogens, including Siberian ginseng (now sold in the United States as "eleuthero"; *Eleutherococcus senticosus*, Araliaceae), rhodiola, and schisandra (*Schisandra* spp., Schisandraceae). Government scientists studied these herbs in Olympic athletes, miners, truck drivers, factory workers, and more, with results indicating improved physical performance and lower rates of sickness and fatigue, although the results published in Russian-language journals are difficult to access. One of the lead researchers of the Soviet adaptogens project, Israel I. Brekhman, created a multi-herb adaptogen product (sometimes marketed in the United States as "Prime One®"), which was reportedly used by more than 100 American athletes at the 1996 Atlanta Olympic Games.

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*The more commonly known and clinically documented use for chaste tree fruit preparations is for treating or preventing symptoms of pre-menstrual syndrome and difficult menstruation.

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which he claimed was due to eating a cannabis brownie.[27] Although it seems rather surprising that an athlete would consume the widely illegal substance, the Anti-Doping Database reveals that cannabis has been implicated in about 38 failed doping tests since 1997,[28] likely due to its recreational popularity. Several cases document South American soccer players testing positive for cocaine and morphine and attributing it to drinking traditional Bolivian coca leaf tea and eating poppy seed bread, respectively.[29] Again in 2011 — even after poppy seeds' effects were made famous by an episode of the television comedy *Seinfeld* in which the sitcom's character Elaine fails a drug test after eating poppy seed muffins — a New Zealand triathlete tested positive for morphine and argued that he had consumed poppy seed bread.[30] Studies have confirmed that consuming the parent plant or parts of the parent plant can yield traces of these isolated substances, and sometimes officials sympathize with the athletes' claims by reducing penalties or completely exonerating them.[29,30] Still, these cases are seldom.

"Adequate information does not exist to support the view that sports doping with botanical materials is an issue," said AHPA's Dr. Dentali. "Ephedrine-containing products are not allowed in foods, including dietary supplements in the United States. Most everyone is aware that poppy seeds may trigger a positive drug test, and generally speaking athletes are smart enough to know that drinking coca leaf tea might produce the same result" (e-mail, July 30, 2012). (A peer reviewer of this article noted that in Canada, low-dose ephedrine hydrochloride [8 mg] as well as the herb ephedra are widely available for purchase as licensed natural health products [NHPs]. NHPs, which include vitamins, minerals, herbs, homeopathic preparations, and more, are regulated as a special class of drugs in Canada, not as the United States regulates dietary supplements, which are considered foods.)

Coca, ephedra, and khat are the only traditionally used herbs whose derivatives are explicitly prohibited in sports, and the testing of additional herbs or other medicinally active plants for performance-enhancing properties is not common nor easy due to their complex chemistry and pharmacology.[31] Because different countries have a more accurate and detailed knowledge of culturally used herbs and substances, each can issue warnings for any botanical products suspected of affecting doping test results.

"There are many specialized, local botanical products used traditionally around the world, and monitoring them and their use is something left up to the local regulatory body," said NSF's Wyszumiala (email, July 20, 2012).

During the 2008 Beijing Olympics, for example, the Chinese Olympic Committee decided to forgo the use of traditional Chinese medicine (TCM) to treat athletes in order to avoid potential doping problems, and also banned products containing the herb Chinese angelica, or *dong quai* (*Angelica sinensis*, Apiaceae) for the same reasons.[31]

WADA previously prohibited the botanical stimulant caffeine,[32] which is found in many common food plants including coffee (*Coffea arabica*, Rubiaceae), chocolate (*Theobroma cacao*, Sterculiaceae), and tea (*Camellia sinensis*, Theaceae), as well as the popular Argentinian herbal beverage yerba maté (*Ilex paraguariensis*, Aquifoliaceae), among others. During this ban, athletes could not have 12 mg or more of caffeine per liter of urine. This would be caused by drinking at least 5 cups of coffee, at least 6 cups of tea, or eating 2-3 chocolate bars shortly preceding the collection of urine samples.[29] In 2004, WADA lifted its ban on caffeine, stating that it is "ubiquitous in beverages and food" and "metabolized at very different rates in individuals."[32] Caffeine remains on the organization's monitoring list, and some WADA officials continue to express concerns for the stimulant, especially when formulated in high-dosage pills.[33]

"Herbal or plant-derived stimulants can be a very interesting dilemma," said Oliver Catlin. "Some things like ephedrine are clearly banned, while other plant-derived stimulants like theobromine, which is in chocolate, are not considered banned. For an athlete, the pathway of determining what is or is not legal is challenging especially when the language in the stimulant section of the WADA Prohibited List includes, 'and other substances with a similar chemical structure or similar biological effect(s).' Determining what does or doesn't qualify under this clause can be a difficult job, and a moving target."

Even in regards to dietary and herbal supplements that are legal for use in sports, such as caffeine, many critics claim that athletes can receive all their nutritional and performance needs from diet and that there is no evidence these products actually work. In September 2012, for example, the Chief Medical Officer of Fédération Internationale de Football Association (FIFA) told the media that soccer players' widespread usage of dietary supplements was "alarming" because it is "definitely not based upon the scientific evidence or literature."[34] He continued, "Scientists and nutritional specialists agree that a well-balanced diet will supply the body with the appropriate amount of nutrients it needs for top performance."

WADA and IAAF take similar positions.

"Athletes do not necessarily need supplements," said Dr. Dollé of IAAF . "As a question of principle, we never engaged in recommending or advising supplements. Firstly, because it would not be consistent with our consensus statement, secondly, because we do not have the resources to test the supplements."

Some criticize anti-doping organizations for their one-way, hard-line stance against supplements.

"That mentality is certainly understandable as they don't want athletes to get caught up with inadvertent positive tests," said Catlin, "but is not in line with the reality that we face today, namely that athletes do take and will continue to take dietary supplements. The reality is that many supplements are indeed fine to take, while others can lead to positive drug tests and health complications. I really do appreciate [anti-doping organizations'] position and of course worked with them myself for many years. I just wish they could take a broader look at the supplement issue and accept the realities that athletes use them. I believe that if they did accept supplements and could help athletes find natural and safe alternatives to drugs that it would create trust and could help the anti-doping cause."

It is also important to assess the accuracy of anti-doping groups' claims of supplement inefficacy. A review of the evidence suggests some botanical supplements *can* produce performance-enhancing effects. According to a 2012 article, "Herbs in Exercise and Sports," published in the *Journal of Physiological Anthropology*, caffeine is documented as improving athletic performance in swimmers, endurance runners, and cyclists, as well as improving mental alertness.[35] The International Society of Sports Nutrition's (ISSN) 2010 recommendations for athletic supplements list caffeine as being "apparently effective," which the authors define as, "supplements that help people meet general caloric needs and/or the majority of research studies in relevant populations show is effective and safe."[36] The authors continued, "Suggestions that there is no ergogenic value to caffeine supplementation [are] not supported by the preponderance of available scientific studies."

ISSN recommended green tea extract as "possibly effective" (defined as "supplements with initial studies supporting the theoretical rationale but requiring more research to determine how the supplement may affect training and/or performance") for its ability to increase energy expenditure in humans and possible use for weight loss.[36]

Ginseng, one of the most commonly marketed herbs for athletes, also has been referred to as the most studied herb for performance enhancement. Research has shown various species of ginseng, particularly Asian ginseng (*P. ginseng*), to increase exercise endurance, lower blood pressure, support oxygen consumption, abbreviate post-exercise recovery, enhance chest and leg strength, and reduce stress responses through its adaptogenic properties.[35,37] Other studies, however, have found no significant effects on physical performance.[38] (One review article suggested that many of the ginseng trials used a relatively low dosage level, *i.e.*, usually those equivalent to about 8 mg total ginsenosides per day, compared to higher dosage levels used in traditional Chinese medicine.[39])

The Australian Institute of Sport (AIS) lists beet (*Beta vulgaris*, Chenopodiaceae) root juice as a Class B supplement ("Considered for provision to AIS athletes under a research proto-

Papaver somniferum Photo ©2012 Steven Foster

A cup of coca tea (*Erythroxy coca)* served in Villazón, Bo Photo ©2012 Ste

It is also important to assess the accuracy of anti-doping groups' claims of supplement inefficacy. A review of the evidence suggests some botanical supplements *can* produce performance-enhancing effects.

col") presumably due to its nitrate contents and several studies showing that consuming beetroot juice prior to exercise can enhance performance.[40] Furthermore, a 2010 double-blind, controlled clinical trial, published in the *Journal of the International Society of Sports Nutrition*, found that male weightlifters taking a fenugreek extract (*Trigonella foenum-graecum*, Fabaceae; Torabolic™, Indus Biotech) experienced significantly increased "upper- and lower-body strength and body composition in comparison to placebo" and had no side effects.[41] Another study on TestoSurge®, a fenugreek extract, found that it increased testosterone levels and the bioavailability of testosterone when compared to placebo.[42]

According to 2 studies, ginger (*Zingiber officinale*, Zingiberaceae) root extract has been shown to improve pain and joint stiffness in osteoarthritic individuals after standing and walking.[5] A study on rhodioloa (*Rhodiola rosea*, Crassulaceae) root extract, which is marketed for athletic-enhancing functions in the United States, reported that an acute dosage (200 mg) significantly increased endurance and somewhat increased oxygen intake in participants completing 17 minutes of cycling,[5] although this effect was no different than placebo after 4 weeks of taking the supplement.[43] A small study examining the use of an extract made from the traditional Chinese herb astragalus (*Astragalus membranaceu*s, Fabaceae) determined that it improved athletic endurance, though the study was criticized for its lack of standardization.[5] A 1997 study on cayenne pepper (*Capsicum* spp., Solanaceae) taken by male long-distance runners found it increased "respiratory exchange ratio and blood lactate concentration both at rest and during exercise," but that it had "no effect on oxygen consumption or energy expenditure."[38]

Several additional herbs exhibit the ability to decrease pain, inflammation, and other conditions that can negatively affect athletic performance, but have not been studied specifically in athletic situations.[5] Additional research has found no effect in athletic performance for some herbs, including cordyceps (*Cordyceps sinensis* and *C.* spp., Clavicipitaceae), yohimbe (*Pausinystalia johimbe*, Rubiaceae), puncture vine (*Tribulus* spp., Zygophyllaceae), and *Eurycoma longifolia* (Simaroubaceae) root, possibly due to short supplementation period and/or low concentration of *E. longifolia*.[5,35,37] More studies are warranted to support the initial investigations into botanicals' effects on sports and athletic performance.

According to Almada, most clinical trials performed on botanicals and other dietary supplements for sports performance "lack a key investigative, due diligence step" — testing the study's products for banned substances.

"Is it not sufficiently inspiring to the crafty, unscrupulous marketer to have a 'special batch' made just for a study, adulterated with a 'special ingredient' since the university research lab invariably does not have the capability, nor intent, to analyze what is being studied for banned substances? Testing study products for banned substances, by an expert independent lab, should be standard protocol before undertaking the study."

Conclusion

The relationship between professional athletes and dietary and herbal supplements is nothing less than complex. Despite the oft-negative representation and reputation of dietary supplements in and among mainstream media outlets as well as major sporting and anti-doping organizations, little hard evidence proves that herbal dietary supplements pose a risk in this context. Some evidence even suggests that various botanicals can have safe, beneficial effects on athletic performance. Still, evidence fails to exonerate all cases of potentially intentional adulteration by dietary supplement manufacturers. In order to progress toward resolving these issues, responsible parts of the dietary supplements industry, analysis labs, sports and anti-doping organizations, and the media must collaborate to support athletes through education, vigilance, and open-mindedness toward the reality of the situation. HG

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Bilberry *Vaccinium myrtillus*. Photo ©2012 Steven Foster

The Adulteration of Commercial Bilberry Extracts

By Steven Foster and Mark Blumenthal

Editor's note: *This paper is part of the series being published under the aegis of the ABC-AHP-NCNPR Botanical Adulterants Program, an educational program led by the American Botanical Council, the American Herbal Pharmacopoeia, and the National Center for Natural Products Research at the University of Mississippi. The Program is financially supported and/or endorsed by a coalition of herb and dietary supplement industry members, third-party analytical laboratories, professional and trade associations, nonprofit educational groups including accredited schools of natural medicine, and others.*

Background

Bilberry fruit (*Vaccinium myrtillus*, Ericaceae; heath family) is a common ingredient in food, health products, and cosmetics. In European countries the berries are sold fresh, frozen, in jams and preserves, and as a juice ingredient. Finished products made with bilberry (dried fruit, dried powdered fruit, and powdered extracts) are sold in the form of dietary supplements in the United States and as phytomedicines in the European Union (EU) and elsewhere.

Bilberry *Vaccinium myrtillus*. Photo ©2012 Steven Foster

The genus *Vaccinium* includes more than 140 mostly circumpolar species, with the highest concentration of representatives in North America.[1] Bilberry is an erect-to-freely-branching shrub, from 15-25 cm (up to 60 cm) in height, spreading from a creeping rhizome. Flowers are in axillary racemes with 1-2 flowers per group. The bluish-black fruit (including skin and flesh throughout) are globose and 6-10 mm in diameter. Bilberry is found throughout most of Europe, particularly in heaths, moors, and woods in northern Europe, and largely restricted to mountainous areas in southern Europe.[2] It is so common in much of Europe that in some areas it represents as much as 25 percent of the vegetation in forest understory. Based on the available evidence, there is no commercial cultivation of bilberry; the world's entire commercial supply is wildcrafted, mainly in Scandinavia and Eastern European countries.

Bilberry is a popular dietary supplement in the United States, where it ranked 15th best-selling in the mainstream market (*i.e.*, grocery stores, drug stores, mass-market retail stores — referred to as the FDM channel), although its sales in this channel have dropped by about 10 percent per year in the past 2 years for reasons that are not clear (Table 1). It is possible that the increased price of raw material, due to the relatively poor harvest in the past 2 years, might be responsible for finished-product price increases. That, in turn, may have had a negative effect on sales. However, contrary to the sliding sales seen in the mainstream market, 2011 sales for bilberry dietary supplements in the natural foods channel increased slightly (1.5%; $17,632) compared to 2010, to a total of $1,196,845 (sales in Whole Foods Markets are not included), according to market-tracking statistics from SPINS, a Schaumburg, Illinois-based market-research firm. In the natural food store channel, bilberry is ranked 53rd in sales, significantly lower than its rank in the FDM channel.[3]

Table 1. Bilberry Product Sales Ranking, Sales Estimates, and Percent of Change over Previous Years in Food, Drug, and Mass Market (FDM) Channel in US 2007-2011*

Year	Sales Rank	Retail Sales	% ± Over Previous Year
2011	15	$1,582,448	-11.24%
2010	15	$1,784,932	-9.95%
2009	15	$1,983,723	+7.41%
2008	17	$1,841,200	+1.92%
2007	15	$1,814,102	-9.48%

* Data do not include sales in Walmart stores. Information supplied for Food, Drug, and Mass Market retail stores, as compiled by Symphony IRI and published in ABC's annual Herb Market Report in *HerbalGram*.[6-10]

In the United States, only *V. myrtillus* is allowed to be sold as "bilberry," according to *The American Herbal Products Association's Herbs of Commerce,* 2nd ed., a book that enumerates the accepted common names of approximately 1,650 herbs and medicinal plants and their corresponding Latin binomials (scientific names).[4] This book, which also lists European blueberry, huckleberry, and whortleberry as other acceptable common names for bilberry, has been accepted by the US Food and Drug Administration (FDA) as a guide to botanical nomenclature for herbal products sold in commerce in the United States.[5] No other plant or plant material is acceptable for the commercial designation "bilberry" in the United States.

Health Benefits of Bilberry

Bilberry fruit extracts are among the best-selling herbal dietary supplement products in the US market, with benefits in the management of retinopathy and vascular conditions including venous insufficiency and capillary fragility.[5] Since the 1960s, numerous pharmacological and clinical studies have suggested bilberry's benefits for both vascular health and vision problems; however, many of the studies suffered from poor design, small population samples, lack of placebo controls, and other methodological deficiencies. Many early clinical reports or observational studies lacked the scientific rigor necessary for reproducibility.

More recent trials suggest that bilberry fruit extract can decrease vascular permeability and increase capillary resistance.[11] Bilberry extracts often are used to treat vascular insufficiency and associated symptoms such as edema, varicosities, paraesthesias (tingling or numb sensation in extremities), and cramping. By decreasing capillary fragility, an associated tendency toward bruising may be reduced. Pharmacological evidence shows that bilberry extract decreases vascular permeability, inhibits elastase and collagenase production and platelet aggregation, and is vasorelaxant and antioxidant.[5,12,13]

The vast majority of scientific and clinical studies have been conducted with the bilberry fruit extracts Myrtocyan® or Tegens®, both of which contain 36% anthocyanins* (equivalent to 25% by weight expressed as anthocyanadins). Myrtocyan is manufactured by Indena SpA, Milan, Italy. Tegens® is a proprietary formula from Indena's affiliated company, Inverni della Beffa, in partnership with Sanofi-Synthelabo,[12] and is the same extract as Myrtocyan. The extract is now marketed by Indena as Mirtoselect®.

Brinckmann (2011) emphasizes that reproducible results for safety and efficacy are intrinsically linked to consistent and reproducible quality. In world markets, botanicals are available in a wide range of grades and qualities from inexpensive grades of inferior quality to the highest quality grade; therefore, higher-priced ingredients tend to demonstrate reproducible efficacy and safety for a specified health benefit.[14] The health benefits expected from a bilberry extract were demonstrated in various clinical studies using a bilberry preparation with a quality marker based on standardization to anthocyanin content, which is believed to be the primary contributing constituent to therapeutic activity.[15]

For bilberry, reproducible benefits are relative to the extract equivalence used in the majority of clinical trials involving a standardized bilberry extract containing 36% anthocyanins at a dosage of 320-480 mg/day, corresponding to 100-200 mg/day anthocyanins.[16] Cassinese *et al.* (2007) analyzed 40 typical bilberry preparations from 24 different brands found in the American, European, and Japanese marketplaces and found that only 15 percent of the products provide the dosage of anthocyanins shown to be effective in clinical trials.[17]

Bilberry Supply Sources and Market Dynamics

Bilberry's broad distribution throughout much of northern Europe and mountainous areas of southern Europe, coupled with its widespread use and market acceptance has made it one of the most successful wild-harvested, nontimber forest ingredients of the region. Nordic countries, including Norway, Sweden, Finland, and Iceland have cooperated in detailed research on market needs, quality issues, plant biology, biodiversity, production, and utilization for global markets.[18,19]

The cooperation of governments and private-sector companies has given Nordic countries a distinct advantage in global markets in the supply of bilberry as a raw material. A survey of companies involved in the wild-berry industry in Nordic countries resulted in the creation of a database of 1,300 Nordic companies dealing with wild berries, including approximately 750 Swedish, 350 Norwegian, and 200 Finnish companies, both small- and large-scale. The focus of research is to develop uniform wild-berry quality within Nordic countries, a uniform traceability system, and the Nordic wild-berry brand as a guarantee of quality. As much as half of the Nordic bilberry product is exported to China and Japan. To help ensure authenticity of identity, DNA testing methods have been developed to assure that bilberry exports are not contaminated with other wild berries.[18,19]

Estimates of potential bilberry harvests have been calculated in yield variation studies for various Scandinavian countries. For example, in Finland, inventory yield data on wild berries was collected by the Finnish Forest Research Institute from 1997 to 2008. During that time period, annual bilberry potential yields in Finland varied from 92 to 312 million kg. Of the total yield estimate, 5 to 10 percent of berries are collected every year. Picking of wild berries, as well as mushrooms, has social and cultural significance in Finland. It is viewed as a traditional household and recreational activity, with approximately 60 percent of the population participating in wild-berry picking today, compared with 69 percent in 1981, indicating that its popularity as a recreational activity has remained relatively stable. In Nordic countries, the traditional social concept of "everyman's right" allows for open access to both private and public lands and the right to pick wild berries and mushrooms on them. The harvest also extends to commercial pickers, though commonly permission is obtained from the landowner or berry associations that negotiate exclusive rights for harvest on private lands. In Finland, where most people enjoy a high standard of living, berry picking is viewed as a leisure activity, providing healthy exercise and the opportunity to enjoy nature.[20]

Wild-berry picking in other Scandinavian countries is trending downward. A study conducted in the late 1970s estimated that Swedes collected 7 percent of available wild-berry volume for home consumption; 20 years later, participation in berry collection and volume of berries picked declined dramatically. In Russia, it is estimated that between 10-15 percent of available wild-berry volume is collected.[20]

In Russia, Balkan countries, and elsewhere in Eastern Europe, wild-berry picking provides an important additional income source in populations with high unemployment in rural areas. For example, one 12-year-old girl interviewed in August of 2011, in the Prokletije Mountains bordering the north of Montenegro and Albania, said that she expected to collect over 200 kg of bilberries in 2011. She sold fresh bilberries at a roadside stand for 3 €/kg. (It takes approximately 10-12 kg of fresh berries to produce 1 kg of dried fruit.)[19]

* Definition of anthocyanin, anthocyanidin, and anthocyanoside: (From Greek *anthos* [flower] and *kyanos* [dark blue]). Chemically, anthocyanins are phenolic compounds of flavonoid structure and an attached glucose (sugar) moiety, and anthocyanidins are anthocyanin counterparts without an attached glucoside group. These plant colorants are responsible for the red, purple, and blue hues in many fruits, vegetables, cereal grains, and flowers and have been counted as having up to 600-plus molecular structures.[34] Some sources claim there are over 1,000 such structures. Anthocyanoside is a synonym of anthocyanin.

The quantity of bilberries picked during the past year has averaged 35 million kg compared to 2005, when nearly 55 million were harvested, primarily in Scandinavia and the Ukraine. In terms of anthocyanin assay content of the berries, the highest level observed was 0.37% in 2009, with the average over recent years being 0.35% (Ris G., email to M. Blumenthal, October 2, 2012).

Timing of harvest is an important factor in quality. When bilberry buyers purchase the fruit from collectors, berry ripeness is determined with a handheld analog or digital refractometer. Values of less than 12 to 14 percent extractable solids are generally considered indicative of unripe berries. Ripeness is an important factor in the quality of bilberries. As fruit ripens, concentrations of flavonols and procyanidins decrease, while concentrations of the anthocyanins increase. Studies also suggest that bilberries must be handled with care, as damage of the skin or flesh can result in oxidization of the antioxidant anthocyanins. Bilberry is harvested traditionally by hand-picking. However, there is increased reliance on the use of berry rakes, which agronomists say damages the bushes and reduces flower buds, hence lowering berry production for the following year. Berry rakes also collect extraneous leaf and bud material which must be cleaned from the berries and capture both green and ripe berries at the same time. Depending upon the location in Europe, harvest of bilberry occurs between mid-July and the end of September, with about a 2-week harvest season of berry ripeness.[19]

The economics of obtaining raw materials suggest that there is adulteration in the marketplace. While pricing for labor in Asia and other parts of the world is generally lower than the cost in Europe, the relatively small region of growth for bilberries suggests that there is not much elasticity in the price of raw material. The range of pricing for the Indena bilberry standardized extract per kg is around "the high six hundreds [US dollars] in previous years up to the high eight hundreds this year" due to a poor crop last year, according to Greg Ris, vice-president of sales for Indena USA in Seattle, WA (personal communication to M. Blumenthal, October 1, 2012). His parent company is Indena SpA in Milan, Italy, universally acknowledged as the world's leading producer of bilberry

Bilberry *Vaccinium myrtillus.* Photo ©2012 Steven Foster

extract and pharmacological and clinical research on such extract.

Ris emphasized that it takes 100 kg of hand-picked bilberry fruit to make 1 kg of the 100:1 Indena bilberry extract, at an average range of 2.5 euros ($3.25 USD) to a "near record high" of 4.6 euros ($6.00 per kilo) in 2011. This variability is primarily due to weather conditions (either too damp to too dry). At such prices, a 100:1 extract would cost from $325 to $600 USD per kg of extract just for the raw material (Ris G., email to M. Blumenthal, October 2, 2012), plus the cost of refrigeration and/or frozen storage and transportation to keep the material fresh, as well as extraction costs and other overhead, plus profit. Therefore, says Ris, some of the bilberry extract currently being offered on the global market for as low as $200 per kg, and up to $400 per kg, is presumably or definitely adulterated. "You just can't make an extract that meets Indena's specifications for such a low price," he said (Ris G., personal communication to M. Blumenthal, October 1, 2012).

This pricing information is corroborated by Don Stanek, director of sales for Linnea, a European supplier of botanical extracts with US offices in Easton, PA. According to Stanek, bilberry fruit raw material costs range from $4-7 per kg; his company, a joint venture between Germany's W. Schwabe Pharmaceuticals and Ipsen-Beaufour in France, produces — like Indena — a bilberry extract at a 100:1 ratio of raw material to finished extract. Therefore, the cost of the bilberry fruit raw material in the Linnea extract would cost $400-700 USD per kg before shipping, storage, and extraction costs, plus a modest profit. He acknowledges that his company sells its bilberry extract for as low as $650 per kg and up, depending upon raw material costs and quantities purchased by customer, among other factors.

"With so much high cost of raw materials and such compression of profitability due to the market being virtually flooded with cheap, adulterated 'bilberry extract,' this item is not one of our most profitable extracts," said Indena's Ris, lamenting the downward pricing pressure that fraudulent extracts have had in the market.

The Confusing Morass of Adulterants

Given global demand for this relatively high-cost, wild-harvested berry, bilberry supplies are reportedly rife with economic adulteration.

Presumably, most of this adulteration is intentional, and not an accident based on poor or inadequate use of quality control techniques. In addition, anthocyanosides from unrelated plants, such as elderberry (*Sambucus nigra*, Caprifoliaceae), also have been identified as potential adulterants in bilberry extracts.[21] A leading independent analytical laboratory in the United States, Chromadex, Inc., has reported testing samples of "bilberry extract" determined to be adulterated with extract of Chinese mulberry (*Morus australis* and *M.* spp., Moraceae) (Jaksch F., email, September 10, 2012).

Research by Indena and others affirms that the anthocyanosides are the major active ingredients in bilberry, and that the mixture of delphinidin, cyanidin, malvidin, peonidin, and petunidin in bilberry produces a unique pattern set that distinguishes bilberry from all other anthocyanoside sources of both dietary and non-dietary origin,[21] although *V. corybosum* (North American blueberry) contains the same anthocyanins in significantly lower weight percentages; blueberry also contains significant amounts of proanthocyanins, which are almost entirely absent in bilberry extracts (Tempesta M., email, September 11, 2012). And yet, the relatively high price of authentic bilberry extract has made it a target for sophisticated adulteration.

In addition, extracts of 2 circumboreal species, *V. uliginosum* and *V. vitis-idaea*, which grow in northern areas of Europe, North America, and Asia, are being wild-harvested in China and offered to world markets as "homemade Chinese bilberry" and "Chinese domestic bilberry" extracts at prices as low as $10 per kg. According to a "Research Report of Chinese Blueberry Extract Market, 2009-2010," the Chinese market is divided into "European bilberry extract" and "Chinese bilberry extract," "standardized from 10%, 15%, 25%, to up to 40% anthocyanidins." "Homemade raw materials" (*V. uliginosum* and *V. vitis-idaea*) are wild-harvested in Northeast China and the Shaanxi Province. According to the report, in 2008, Chinese bilberry extract (excluding "European bilberry," *V. myrtillus*) production was approximately 60 tons, 95 percent of which was exported, mostly to the United States.[22]

Another recently documented adulterant is amaranth dye (also known as azo dye or Red Dye No. 2).[15,21,23] The HPTLC (high-performance thin-layer chromatography) analytical method for determining azo dye adulteration has been developed by CAMAG, a manufacturer of scientific laboratory instruments and methods of analysis in Muttenz, Switzerland. (*Editor's note: Amaranth dye has no relation to amaranth* [Amaranthus *spp., Amaranthaceae*], *a traditional plant food of the Aztecs in what is present-day Mexico*.)

Table 2. Known Adulterants of Bilberry Extract

Adulterant	Source/Reference
Red Dye No. 2 (Azo dye)	21, 23
Charcoal	21
Vaccinium species	
V. uliginosum	22
V. vitis-idaea	22
Anthocyanosides from unrelated plants:	
Sambucus nigra (elderberry)	21
Morus australis, M. spp. (Chinese mulberry)	3rd party lab data
Glycine max (Chinese black soybean hull)	21, 3rd party lab data
Oryza sativa (Black rice hull)	3rd party lab data

Amaranth dye also has been found as an adulterant in bilberry extract due to its color being similar to the color of bilberry extract, according to information from Indena,[21] and its presence as an adulterant in bilberry extracts is documented sufficiently enough to merit its appearance as the only bilberry adulterant mentioned by AHPA in its list of "Known Adulterants."[23]

The detection of amaranth dye and/or charcoal in commercial bilberry extracts is clearly the result of intentional adulteration.[21]

Further, confidential reports from third-party laboratories indicate determination of profiles consistent with black soybean hull in some commercial "bilberry" samples. Soybean hull (*Glycine max*, Fabaceae) extracts, at 35 percent and 50 percent anthocyanidins, contain mainly cyanidin 3-O-glucoside and delphinidin-and petunidin-3-O-glucoside.

In addition, some laboratories have uncovered the adulteration of bilberry fruit extract with extract of black rice (*Oryza sativa*, Graminae), which is known to contain anthocyanins that can trick a total anthocyanin content by UV-detection assay.

Language issues may contribute to the adulteration problem, because various *Vaccinium* species are translated from one language to another as "blueberry," "bilberry," or variations on the theme, depending on the language into which they are translated. Most refer to various species of *Vaccinium* cultivated or wild-harvested in Europe, North America, South America, and temperate regions of Asia.

In a recent study, for example, an Andean *Vaccinium* species called "Colombian wild bilberry" or "Colombian bilberry" (*V. meridionale*), was shown to have high antioxidant activity and a unique anthocyanin pattern with high proportions of both delphinidin and cyanidin, which can be used to authenticate and identify this species compared with other *Vaccinium* species.[24]

This is a good example of the application of a variation on the common English name "bilberry" in order to analyze, assess, and introduce a less well-known *Vaccinium* species to possible commercial potential among national or international markets. Called *agraz* in Colombia, *V. meridionale* is wild-harvested and available in local markets. The size, color, morphology, and tart fruit flavor give it a superficial food experience much more akin to cranberry than to bilberry. A simple Google search for "*Vaccinium meridionale*" also leads to websites that refer to it as "Jamaican bilberry." The adulteration of language usage in popular and scientific literature, and in particular on the Internet, contributes to consumer confusion and also may contribute materially to the intentional or unintentional adulteration of consumer products.

"In fact," said Frank Jaksch, founder and CEO of ChromaDex, Inc., a leading analytical laboratory, "virtually *any* anthocyanin-rich fruit can be a *potential* source of an adulterant to bilberry extract, or, in some cases, a lower-cost *substitute* for it, if, obviously, the fruit raw material is significantly lower in price than fresh bilberries. This would allow for the incentive for economic adulteration, that is, assuming that the adulteration with such fruits is not accidental" (personal communication to M. Blumenthal, October 8, 2012). Jaksch notes another important point about the growing list of anthocyanin-containing fruit extracts — such as acai berry (*Euterpe oleracea*, Arecaceae), cranberry (*Vaccinium macrocarpon*, Ericaceae), maqui berry (*Aristotelia chilensis,* Elaeocarpaceae), etc. — is that there usually will be another anthocyanin "super fruit" popping up on the market. "It is very important to understand the different anthocyanin profiles of these different fruits as the anthocyanin profiles of adulterated bilberry extracts will inevitably vary from one fruit source to the next," he said.

According to Roberto Pace, PhD, corporate quality control manager at Indena, the anthocyanoside profiles of other species of *Vaccinium* are well established by reliable analytical methods (*e.g.*, HPLC) and can be "unequivocally" determined via appropriate analytical testing (personal communication to M. Blumenthal, October 9, 2012). Such plants could include *V. angustifolium* (low-bush blueberry), *V. corymbosum* (high-bush blueberry), and their hybrids and cultivars, as well as *V. oxycoccos* (European cranberry) and *V.*

Bilberry *Vaccinium myrtillus.* Photo ©2012 Steven Foster

macrocarpon (cranberry), plus non-*Vaccinium* anthocyanin-rich fruits, *e.g*, black currant (*Ribes nigrum*, Grossulariaceae), raspberry (*Rubus idaeus*, Rosaceae), and wild cherry (*Prunus avium*, Rosaceae).

Michael Tempesta, PhD — managing partner of Phenolics LLC in Omaha, NE, and an expert in phenolic chemistry — noted that adulteration of bilberry extract with anthocyanosides from these plants, or preparations made from them (*e.g.*, juice concentrates), would not be economically competitive, as the price of raw materials of these plants and/or their concentrations are too high to warrant their use as economic adulterants (personal communication to M. Blumenthal, October 9, 2012).

Industry-Inspired Analytical Identification and Problem-Solving

Following passage of the Dietary Supplement Health and Education Act (DSHEA) of 1994, herb product sales experienced a meteoric increase in the late 1990s and early 2000s, resulting in many new companies entering the herb market supply chain at both the wholesale and retail levels. Prior to the market boom, many standardized herb extracts available in the market were produced by well-established European firms that were not only major suppliers to world markets, but also had significant scientific expertise with the ingredient. Such is the case with the Myrtocyan product sold by Indena SpA, which essentially established the market for bilberry extract and the pharmacological and clinical research to support the chemically defined ingredient.

As international markets increased for bilberry, many new extract suppliers raced to gain market share and a highly competitive industry rapidly evolved, especially for dramatically lower-priced extracts from Asian countries, particularly China. Adulteration of bilberry supplies and extract was relatively limited prior to the market boom. The 2001 *American Herbal Pharmacopeia* (AHP) monograph on bilberry fruit noted that historically, bog bilberry (*V. uliginosum*) and lingonberry (*V. vitis-idaea*) appeared as adulterants, but that was considered to be rare. Microscopic and macroscopic differentiation of these species from bilberry are included in this 2001 AHP monograph. Microscopic identification of *V. myrtillus* is also included in an extensive microscopy text by Upton *et al.* (2001), but without details on microscopic identification of purported adulterants.[12]

(*Editor's note: A number of methods for detecting bilberry adulteration have been published and some will be discussed here in general and in more detail in a forthcoming "Laboratory Guidance Paper on Bilberry Extract Adulteration."*)

Anthocyanins are ubiquitous compounds in fruits, flowers, and vegetables, often responsible for bright colorations such as reds, blues, and violets. In the 1990s, technical interest in natural colorants grew in response to consumer demand for natural products in general. In the mid-to-late 1990s and early 2000s, a growing body of scientific evidence and subsequent reports in the popular press began to draw more attention to anthocyanins for their potential health benefits as anti-inflammatory agents and antioxidants. Various common foods and beverages — including juices, wines, grapes, berries and vegetables — morphed into functional food products or dietary supplements. Analytical papers were published on the analysis of anthocyanins in various common food and beverage items, but according to Zhang *et al*. (2004),[25] few papers dealt with analysis of anthocyanins in botanical extracts used in the dietary supplement industry. More important, of the growing number of known anthocyanins, now estimated at more than 1,000, fewer than 100 anthocyanin reference compounds — necessary for the accurate chemical analysis in a laboratory — are commercially available.[26] Zhang *et al.* developed an acid hydrolysis-HPLC (high-performance liquid chromatography) method for quantifying the 6 major individual anthocyanidins in bilberry extracts, including pelargonidin, cyanidin, peonidin, delphinidin, petunidin, and malvidin.[25] A direct HPLC method was deemed useful for verification of raw material origin and standardization, and Zhang's approach completely separated 5 anthocyanidin aglycones (core compounds without a sugar residue attached), with the exception of petunidin (no reference compound was then available).

Concurrent with the continued commercial and consumer interest in anthocyanin-containing products and their potential health benefits, more refined and perhaps less expensive laboratory analytical refinements are frequently published.

Recently, a Turkish research group published an analytical method for the rapid determination of the 6 most abundant free anthocyanins in foodstuffs using HPLC-DAD (HPLC with diode-array detection).[27] The 3-glucoside forms of pelargonidin, cyanidin, peonidin, delphinidin, petunidin, and malvidin, using the aglycone cyanidin as an internal standard, could be separated using HPLC-DAD within 18 minutes. The innovation includes a fast-sample preparation method allowing for the direct injection of samples into the analytical equipment (the HPLC column), eliminating the step for chemical extraction. The concentration range of 80-420 ng/mL was demonstrated in 28 different vegetable, fruit, and commercial product samples. The accuracy of the method was stated to be 99.2 ± 0.2% with an average precision of 0.8%. The authors suggest that the method is a robust, lower-cost alternative to previous analytical methods relying on multi-step protocols of sample treatment. Developing technical innovations should help laboratories continue to make refinements in accuracy of methods and lowering costs, both of which will contribute to helping to solve adulteration problems.

Despite the advances in accurate identification and quantification of bilberry anthocyanins, by the mid-2000s, Australian researchers published a paper revealing that the method based on the single-wavelength (528 nm) spectrophotometric assay, calculating anthocyanin content based on cyanidin-3-glucoside chloride specific absorbance values as published in the 2004 *British Pharmacopoeia* — then in common use to determine percentage of anthocyanins in bilberry fruit extracts — yielded false-positive results in the presence of intentional adulteration.[15] Therefore, the simple detection method published in the *British Pharmacopoeia* was not adequate to detect deliberate or accidental adulteration. The AHP monograph[12] on bilberry fruit warned that the same spectrophotometric assay, calculating total anthocyanin content as cyanidin-3-glucoside, was useful only if appropriate methods had assured authenticity and purity of the source material prior to chemical analysis. The AHP monograph further notes the inability of the method to detect intentional adulteration with added colorants including FD&C Red, cochineal (a natural red coloring derived from a small insect residing on species of prickly pear cacti, *Opuntia* spp., Cactaceae), or powdered beet (*Beta vulgaris*, Chenopodiaceae). The herb and natural products industry had been alerted.†‡

The study by Penman *et al*. (2006) also revealed that one extract obtained from China through an Australian distributor, which claimed to be a bilberry standardized dry extract powder with 25% anthocyanins, had a total measured anthocyanin content of 24% when analyzed using the simple spectrophotometric method from the 2004 *British Pharmacopoeia*.[15] When the same extract was analyzed with a more sophisticated HPLC method, only 9% anthocyanins were found. Further testing by HPLC, mass spectroscopy (MS), and nuclear magnetic resonance (NMR) confirmed that the "bilberry powdered extract" from China was adulterated with the napththylazo sulfonic acid dye known as amaranth dye (as noted above, not to be confused with plant members of the genus *Amaranthus*). Amaranth dye, [3-hydroxy-4-[(4-sulfo-1-naphthalenyl)azo-]2,7-naphthalenedisulfonic acid trisodium salt], also known as the coloring agent FD&C Red No. 2, or, more commonly, as Red Dye No. 2, was banned by FDA in 1976 due to its suspected carcinogenicity.[15] (The paper by Penman *et al*. was reported in the natural products industry trade literature in the United States.[28]

In 2007, scientists at Indena SpA developed and validated a new liquid chromatography method for measuring anthocyanins and anthocyanidins in dried, powdered extract of fresh bilberry fruit and in 40 commercial bilberry extract products representing 24 different brands.[21] This method, which measures free anthocyanins that are often associated with poor product quality, was modified in a relatively minor fashion (*e.g.,* removing the molecular weight correction for the content calculation, use of primary or secondary references), and has been adopted as the official analytical method for bilberry by the *European Pharmacopoeia* (EP).[29]

The EP started working on a bilberry fruit dry extract in 2005 with a proposal in *Pharmeuropa*, which became official in 2008 and was published in 2010. The monograph describes an authentication method by thin-layer chromatography (TLC) and an identification test by HPLC based on EP reference standards.[29]

USP 35/National Formulary 30 (2012) authentication method for bilberry powdered extract is a TLC identification test, based on USP Reference Standards.[30]

Bilberry *Vaccinium myrtillus.* Photo ©2012 Steven Foster

In the United States, the herb industry has formally recognized the adulteration of commercial bilberry extracts. AHPA provides guidance to its member companies on the proper identification and authentication of bilberry.[31] In 2007, AHPA published a press release and update to its members regarding the adulteration of bilberry extract with Red Dye No. 2 (azo dye).[32] According to the AHPA release, 2 methods of analysis were being posted to the AHPA website for members' access and utilization: "One method is a fairly simple procedure of raising the pH of dilute bilberry extract; the resulting color change from red to blue indicates the presence of anthocyanins. The other method utilizes high-performance thin-layer chromatography (HPTLC) to provide a visual image that separates anthocyanins from amaranth dye that has been discovered as an adulterant in some powdered material labeled as bilberry extract."[33]

Conclusions

The AHP monograph on bilberry fruit, although somewhat dated, contains nearly all of the information necessary for scientific validation of authentic bilberry supply sources.[12] In addition, the analytical methods cited in this

† Anthocyanidins are present in low quantities in fresh bilberry fruits and in Indena's Mirtoselect (at levels less than 1%); they "are anthocyanins without the sugar moiety and should be considered anthocyanin degradation products occurring when there has been incorrect extract production and/or storage. Anthocyanidins are rare in nature and the metabolism of the anthocyanins produces only trace amounts of bioavailable anthocyanidins."[34]

‡ It is worth clarifying the limits noted for all UV methods. A standard HPTLC and HPLC analysis also can be fooled if an analyst does not know what to look for in terms of ratios of the detected compounds. It is important to note that the inclusion of a pharmacopeial method in a quality control monograph means that all the identity and quantitative tests on the investigated botanical material must conform with the monograph. Thus, the bilberries would first have to have been properly identified by one of the identity tests given in the monograph. UV methods are not listed in any pharmacopeia to confirm identity. The application of a particular method (UV versus HPLC) is dependent on the analytical endpoint.

paper — including Cassinese *et al*., 2007;[17] Pace *et al*., 2010 (Indena, SpA);[21] Zhang *et al*., 2004 (Nature's Sunshine Products);[25] and Penman *et al*., 2006 (MediHerb)[15] — were all created by industry analytical labs in association with academic colleagues in an effort to solve the problem of bilberry adulteration, discovered through routine vetting of raw material suppliers. The problem could be solved with relative ease if companies offering retail consumer products comply with appropriate current Good Manufacturing Practices as required by law in the United States and many other countries.

The intentional, illegal adulteration of bilberry (*V. myrtillus*) extracts with synthetic, potentially dangerous, and banned dye materials, as well as ubiquitous fraudulent ingredients such as charcoal and other lower-cost anthocyanin-containing fruits creates problems for the natural products industry worldwide, in addition to eroding consumer confidence in bilberry itself and the herb and dietary supplement industry in general. The intermingling of species of *Vaccinium* as a "type" of bilberry because of linguistic confusion or purposeful language adulteration to enhance sales further complicates the matter. Various producers of authentic bilberry raw material and products, AHPA, non-governmental bodies producing authentication methods and monographs, and the academic community have taken the lead in helping to solve the problem of economic adulteration of bilberry.

***Editor's note*:** An expert reviewer of this article noted that it may be inappropriate to compare the values of any compound via UV and HPLC and suggest that one is more "accurate" than the other. As stated in the endnote on the previous page, it depends on the analytical endpoint. If the goal is to calculate total anthocyanidins, which is the case in the analysis of bilberry extract, and those include all known and possibly unknown similarly related compounds for which analytical reference compounds are unavailable, then UV is a better method. If the goal is quantitation of a few specific anthocyanidins for which analytical reference markers are available, and the analyst wants only to quantify those particular (not total) anthocyanidins, then HPLC is more accurate. The quantitation of bilberry anthocyanidins initially began with UV calculation of the compounds. Commercial interest moved the analysis to HPLC to detect adulteration, per the focus of this article. That does not make the use of a UV method inappropriate. The analytical goal has to match the nature of the method being used. The reason UV may be a superior method for quantitation in many cases is that not all compounds associated with activity in plant-based medicinal preparations are known, so general methods like UV can capture a range of compounds. UV is also a faster and less expensive method than HPLC, which can capture the presence of all compounds but takes more time, and it is much more expensive to utilize all the reference compounds. Most companies promoting the use of HPLC do it as a marketing tool because of the more distinct and accurate detection; one will rarely obtain an HPLC value to match a UV-determined value of 25% anthocyanins (the original standard applied to bilberry worldwide and what most clinical studies were based on). There is almost always a huge disparity because HPLC is calculating only a few analytes (according to the reviewer) and UV captures a broader range of compounds.

UV can be useful and applicable for these analyses if all other compendial standards are met, especially if the analytical standards for identity of the raw material are properly employed. However, in this context, the situation may be described as an effort to defeat UV analysis by adulteration with added anthocyanins/anthocyanidins from other, less-expensive sources. Differentiation of UV and HPLC is important because reliance on UV alone exposes a manufacturer (or consumer) to a greater risk of adulteration. It is possible that a less-than-scrupulous manufacturer can purchase bilberry (in this case) raw material that is authentic, then dilute it, and add anthocyanins from other, lower-cost sources. If this were done, the compendial (*e.g.*, pharmacopeial) standards for identity of the material can be met, as well as the UV standards, but the resulting (adulterated) extract is not a true, legitimate bilberry extract.

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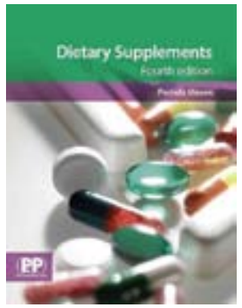
BOOK REVIEWS

Available in the ABC Online Bookstore

Dietary Supplements, 4th edition, by Pamela Mason. London: Pharmaceutical Press; 2012. Hardcover, 548 pages. ISBN: 978-0-85369-883-8. $85.00.

When I was asked to review the latest edition of *Dietary Supplements* by Pamela Mason, PhD, I was a bit conflicted. I had recently edited 2 similar books — *Prescriptions for Nutritional Healing* (Avery Publishing, 2010) and *Prescriptions for Herbal Healing* (Avery Publishing, 2012). Thus, I secretly hoped this book didn't measure up to mine. I was wrong.



Dr. Mason, who has a doctorate in nutrition, has written a reference book using an encyclopedic format in which key dietary supplements (herbs, vitamins, *et al.*) are evaluated. It is written for those pharmacists, nurses, physicians, and dietitians who have less knowledge of dietary supplements than some of their patients. The book is presented in such a fashion that a busy clinician can easily find a specific dietary supplement and see if it is appropriate for his or her patient. One of the book's most useful features is the summary table at the end of each section, which draws pithy and sensible conclusions about using the supplement for a particular clinical condition. I think that Dr. Mason must have erred on the side of caution, however, because when one reads these summaries, one would think that nothing worked. That can't be true given the robust sales of dietary supplements and the reported benefits to many people.

No book can claim to be all-inclusive, but Dr. Mason's book hits the highlights of the most commonly used supplements, except for maybe St. John's wort (*Hypericum perforatum*, Hypericaceae) and saw palmetto (*Serenoa repens*, Arecaceae). The book has a well-written style and uses a linear format that is the same for each entry. The literature reviews are extensive, with most of the key references included. The author correctly (and graciously) summarized the snafu regarding policosanols and the Cuban data, the extensive sports studies on quercetin, and also included interesting probiotics like *Lactobacillus plantarum* (Lactobacillaceae) and *Saccharomyces boulardii* (Saccharomycetaceae) for antibiotic-associated diarrhea. However, lacking was mention of probiotic strains for vaginosis (*L. rhamnosus* and *L. reuteri*), each with multiple supportive studies. Some other omissions include newer forms of folic acid (L-methylfolate) for women with defective genes for folic acid metabolism; the study that showed increased mortality from multivitamin use (but this may not have been published before the book went to print); and in the vitamin E discussion, there was no consideration that the null results (or even harmful results) were related to the use of alpha-tocopherol, rather than mixed tocopherols. But these are minor omissions, and the majority of the important clinical studies are present.

As I did my doctoral work on omega-3 fatty acids, I read with interest Dr. Mason's thoughtful assessment of how they are involved with heart disease. This should be required reading for anyone treating patients using fish oil. Omega-3s, as Dr. Mason pointed out, do not work by lowering total and LDL-cholesterol, but rather work by other mechanisms (which is well supported by the literature). It is an excellent section, but I wished that there was more discussion of algae-based DHA (an omega-3 fatty acid) science; products containing this supplement are quite popular in the US.

I particularly like the tables of the nutrient contents of substances such as chlorella, royal jelly, and spirulina. Most people have no idea what is in these things. In addition, the author lists tables of food sources where one can get the same nutrient being discussed. Such information is included for fish oils, folic acid, calcium, and magnesium. Some foods listed are available mostly in the UK, but there are enough food sources listed for Americans to understand sources of the supplement being discussed. This is an excellent way for a healthcare provider to offer patients the best of both worlds — supplements and foods.

Importantly, the book is very UK-focused in its spelling (*e.g., diarrhoea, fibre, oestrogen*) and emphasis on British nutrient needs and surveys, as well as European regulations. The US dietary nutrient guidelines are included (Estimated Average Requirements [EAR], Recommended Dietary Allowances [RAD], and Tolerable Upper Intake Levels [UL]), but it would have been more useful if the Percent Daily Value (%DV) also was included, as this is the reference value on dietary supplement labels. There was no mention of the new Good Manufacturing Practices for Dietary Supplements in the United States or that the US Federal Trade Commission has a key role in dietary supplement regulation. Finally, the US Food and Drug Administration's health claim on phytosterols was omitted. So, this isn't a book one can buy to learn about US dietary needs or regulation. Rather, this is a somewhat thorough review of the published human science on selected dietary supplements. To that end, the studies reviewed by Dr. Mason are relevant for both sides of the Atlantic.

At the end of the book, I wasn't sure why the section "Additional Resources" was included. The list was short and the items didn't seem that relevant to healthcare professionals. Also, there was no index, which is fine as the book is alphabetized by supplement. However, if a patient wants advice on which supplements to take for a specific condition, there is no way a healthcare provider can find that information readily.

In terms of writing an encyclopedic reference book on dietary supplements, Dr. Mason achieved her goal. Despite a few minor limitations, I would strongly recommend this book to any healthcare provider who sees patients who regularly use dietary supplements. I am happy to have a copy and will certainly be using it often.

—Stacey Bell, DSc, RD
Nutritional Consultant
Boston, MA

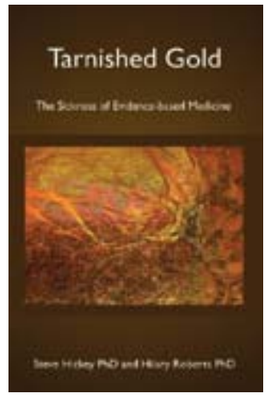
Tarnished Gold: The Sickness of Evidence-Based Medicine by Steve Hickey and Hilary Roberts. Create Space; 2011. Paperback, 342 pages. ISBN: 978-1466397293. $39.95.

This is a remarkable book that, in the tradition of Thomas Kuhn's groundbreaking *Structure of Scientific Revolutions* (1962), provides important tools to help one understand how *data* become useful *information* (or not) in improving our understanding of nature and human biology and in guiding medical practice.

Originally conceived as a post-WWII cost-saving strategy for the UK National Health Service, by the 1990s, evidence-based medicine (EBM) was becoming the latest fashion in medical science. The authors make a convincing argument that it has become, in fact, a cloak for establishing credibility and "scientific high ground" by statisticians who lack a working understanding of what my faculty advisor, Nobel Laureate Baruch Blumberg, liked to call "biological plausibility," and, in turn, by physicians intimidated by elaborate uses of statistics. Further, the authors argue that EBM has become a superficial marketing slogan for respectability of costly big pharma and "big science" projects, which increasingly crowd out other valid kinds of experimentation, observation, and research. This problem will be painfully familiar to anyone working in the fields of natural medicine, nutritional medicine, complementary or alternative medicine, integrative medicine, etc. The human biological paradigm, model, or theory underlying any scientific approach and medical practice may differ, but it is important to have one in order to develop any sense of the plausibility for assigning a statistical association to having an actual role in the causation of health or disease.

The authors expose the fascinating and troubling tale about the politicization and massive government intervention into the scientific process for "proving" that smoking is *the* cause of lung cancer. They argue that this unprecedented government intervention set a different, more legalistic standard for how scientific *data* are translated into *information* about human biology to help guide public health and medical practices. Despite the body of evidence linking heavy smoking to lung cancer, this process leaves behind a lot of valid information about genetic and other risk factors and the fact that many non-smokers still get lung cancer. The smoking and lung cancer precedent also helped create a role for government and industry bureaucrats in using statistics to force social agendas onto public health and medical practices. They argue that the diversity among patients and circumstances (a critical component of holistic, complementary or alternative, and integrative medical practices) is lost and replaced by arbitrary and illusory standards that in fact represent nothing.

Additionally, the authors show that the modern preoccupation with statistical manipulations forcing every observation into an arbitrary placebo-controlled clinical trial — and now "evidence-based" medicine — has left physicians and scientists in the dark and half-blind to critical observations from the daily realities of clinical practice, as well as understanding basic biological sciences and how nature operates in the universe. Therefore, calling such approaches a "gold standard" in medical research is limiting and counter-productive and undermines true scientific innovation. Thus, the title of the book: *Tarnished Gold*.



The book is full of colorful and illuminating quotations from notable characters in science. One of the shortest and my personal favorites is by Nobel Laureate Ernest Rutherford: "If you need a statistician, then you should design a better experiment." The authors present several issues that are critical to understanding the limitations of the information gained from EBM, including the following:

- The information that is lost about individual patients in conducting statistical studies;
- The huge bias in what research gets funded and the kinds of questions asked (and not asked);
- The reductionist, hierarchical approach to what constitutes evidence;
- Withholding results due to corporate ownership of data;
- Publication bias where only certain kinds of data get published due to decisions by researchers, authors, editors, and reviewers;
- Medicalization of human biology whereby new diseases are continually being discovered; and
- Disreputable statistical analyses, including deliberate cheating, fraud, and misrepresentation in *up to half* of the scientific literature due to academic careerist and funding pressures (according to *The New York Times*, April 2012).

The authors conclude that EBM is "junk science" and there is little, if any, prospect for a rational defense of its methods. They argue that EBM harms patients and suppresses true medical innovation and progress. They also argue for patient-based rather than evidence-based medicine. This should be particularly evident to those familiar with natural medicine where the theories, methods, funding, and authority are all stacked against it. Fortunately, the average patient and physician may not be concerned with all these considerations but only with what works, that is, "good medicine." To which it might be added, as taught by my then-medical school professor and eventual US Surgeon General, C. Everett Koop, "The least medicine that works is the best medicine." And, per Lord Rutherford, the fewer statistics needed to reach a conclusion, the better.

—Marc S. Micozzi, MD, PhD
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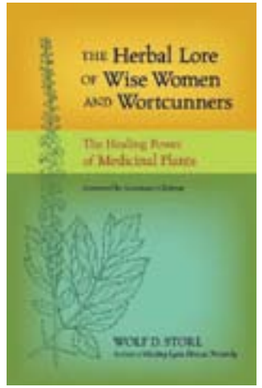
The Herbal Lore of Wise Women and Wortcunners: The Healing Power of Medicinal Plants by Wolf D. Storl. Berkeley, CA: North Atlantic Books; 2012. Softcover, 392 pages. ISBN: 978-1-58394-358-8. $27.95.

The ambitious purpose of anthropologist Wolf D. Storl's book is to illuminate differences among Western traditions of herbal medicine (which originated

in ancient Egypt, Greece, and Rome) through the rise of Europe and the New World, and to contrast them with traditional Chinese models, Ayurveda, and other systems of healing. In particular, the author seeks to explain the differences between traditional Western herbalists and scientists immersed in only the biomedical model. In this regard, this book may be most successful with a readership comfortable in both science and myth. The title tells the story: Language such as "wortcunners" speaks of old wisdom.



In 15 chapters, Storl spans the underpinnings of Western herbal medicine, explaining astrology without apology, and provides enough detail to empower the novice while surprising the old hand. The first 3 chapters have a leisurely pace, yet they pack in a wealth of historical context enlivened with colorful detail. Herb lore, medical models, and philosophy are made understandable especially when explained in terms of language and cultural movements. Further chapters are devoted to plant qualities; becoming an herbalist; basic descriptions of phytochemicals; how to choose foods; making culinary, medicinal, and external preparations; growing herbs; harvesting in the right mindset; and women's use of wisdom, magic, and consciousness-changing herbs. The section on growing will appeal to any beginning gardener, self-sufficient homesteader, or urban herbalist with limited space and time. While the discussion of herbal preparations covers familiar methods, the chapter provides enough detail for competent self-care. Storl also includes easily understood directions for dosing herbs with enough of a safety margin to reassure professionals (or even natural products lawyers).

Avoiding the cookbook style of "this herb for that condition," the lessons on how to understand spinach, for instance, encourage the reader to integrate common knowledge with new facts so that he or she can approach a variety of conditions with different doses, combinations, or cautions. Further, the author provides an abundance of useful examples so that abstract philosophical or astrological ideas become more comprehensible. Storl's 38 illustrations help make complex concepts easy to grasp visually as well. In the chapters on foods, Storl begins with staples and ends with poisons and includes a concise lexicon of active ingredients. Describing vegetables as medicine reiterates the concept that herbalists treat an individual's way of life — including diet and mind-body modalities — as part of the prescription.

Because plants remain central to this wide-ranging exploration of healing traditions, the final chapter examines 6 botanical families in detail. These botanical "Family Portraits" provide technical, medical, and relational information that transmits to the reader a sense of the unique characteristics differentiating poppies from peas, and similar-acting herbs from each other. These 6 families include: Euphorbiaceae (spurges), Papaveraceae (poppies), Papilionaceae (aka Fabaceae; peas), Urticaceae (nettles), Rubiaceae (madders), and Ranunculaceae (buttercups).

The dense nature of each chapter may reflect the fact that the manuscript began as class lecture notes for Mr. Storl. Because of his interest in cultural ecology, Storl includes information about relationships among plants, people, culture, and physical matter from the soil to planets. Lest the reader doubt why a man is writing about women's wisdom, Storl handles this material with the same great respect he affords what he terms "peasant shamanism." German by birth, he created research opportunities for himself with healers from Switzerland to Benares, India, and Wyoming. When Storl explains the difference between treating herbs as commercial replacements for drugs or healing via relationships with plants, he speaks for holistic clinicians, biodynamic gardeners, and herbal educators who decry the emphasis on chemistry to the exclusion of energetics, or indeed, the attitude of the harvester, songs of the herbalist, and transcendent versus academic reality.

It is in the 5 chapters devoted to arcana, soul, consciousness, and plant drugs that Storl most directly challenges the evidence-based, reductionist model of phytotherapy. Few general herbals today include fly agaric (*Amanita muscaria*, Amanitaceae) mushroom or talking to plants in such a matter-of-fact manner. Select illustrations seem hand-drawn to express ideas not often found in other herb literature, and the appendix and endnotes make good reading as well. A bibliography includes authors familiar to *HerbalGram* readers as well as less commonly cited published literature.

I approached the task of reviewing this book with some reserve, never having heard of Wolf D. Storl, which may reflect poorly on my breadth of herbal education. But also I had legitimate concern regarding a title about wise women authored by someone who is not a wise woman. My reserve is dissolved. This is a book I wish I had written. However, I could not have done so, not having had the same earthy experience with plants and plant healers around the world that Storl communicates so generously. I recommend this book to any practicing herbalist and serious researcher who seeks a source of literature previously lacking in our discipline.

— Amanda McQuade Crawford
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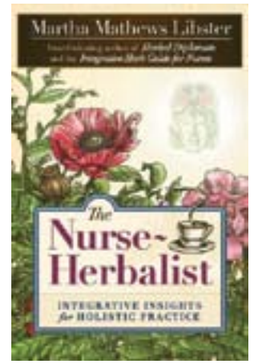
The Nurse-Herbalist: Integrative Insights for Holistic Practice by Martha M. Libster. University Park, IL: Golden Apple Publications; 2012. Softcover, 450 pages. ISBN: 978-0-97550-184-9. $39.95.

Martha Libster, PhD, a registered nurse who specializes in complementary healing traditions and herbal therapies, has a new book titled *The Nurse-Herbalist: Integrative Insights for Holistic Practice*. This book follows her other titles *Herbal Diplomats* (Golden Apple Publications, 2004) and *Delmar's Integrative Herb Guide for Nurses* (Cengage Learning Publications, 2001). In her latest book, Dr. Libster describes a legacy of herbal practice and presents a model for a nurse-herbalist practice. She lays a foundation that links the use of medicinal plants with the essential elements of holistic nursing care. Additionally, the author situates the integrative use of herbs both historically and theoretically in the health and healing domains of nursing. She unites her knowledge of cross-cultural herbal practices, her scientific knowledge of botany, and what she describes as "integrative insight" for a synergistic understanding of nature and the plant world.

Dr. Libster presents 3 practice models — consumer, herbalist, and integrative — to organize the various approaches to a nurse-herbalist practice. The consumer model focuses on educational resources and information. This is the most common model for nurses who are new to herbal therapies, as it generally involves using single herbs and is similar to using medications for specific conditions. The herbalist model focuses on the arts and experiences with herbs, and builds on traditional approaches to herbs found in traditional Chinese medicine, Ayurveda, and Western herbal medicine that link herbs to nature and an understanding of the larger natural order. She describes several exercises to heighten the herbalist's perception in the use of herbs and relates this to the nursing process.



The integrative model includes 3 views or paradigms of health and healing: biomedical, traditional, and holistic healing. She connects the integrative model to nursing and midwifery with their historic use of herbal treatments and promoting the health of the patient. The integrative model combines the biomedical and traditional models. She outlines the importance of the biomedical model and the scientific study of herbs, but cautions against the limitations of relying only on that model.

New Book Profiles

Let Thy Food Be Thy Medicine: Plants and Modern Medicine by Kathleen Hefferon. New York, NY: Oxford University Press; 2012. Hardcover, 240 pages. ISBN: 978-0-19-987397-5. $55.00.

In her latest book, scientist and author Kathleen Hefferon, PhD, presents an overview of the process of identifying plants with healing properties and turning them into useful and accessible medicines for a rapidly increasing global population. The book begins with a brief discussion of the history of medicinal plant use and continues with an explanation of the process of locating potential medicinal plants — often with the help of ethnobotanical research — through modern chemical analyses of phytochemicals and the development of plant-based drugs. The author discusses the often-neglected issue of intellectual property rights of indigenous people who have used such herbal medicines for generations, as well as techniques for improving agricultural practices in a sustainable and responsible manner. Finally, Hefferon looks at the future of the food industry and the challenges facing the development of new medicines.

Dreaming the Future: Reimagining Civilization in the Age of Nature by Kenny Ausubel. White River Junction, VT: Chelsea Green Publishing; 2012. Softcover, 240 pages. ISBN: 978-1-60358-459-3. $17.95.

According to Kenny Ausubel, co-founder of Bioneers — a nonprofit organization that uses nature-based ideas and solutions to tackle social and environmental challenges — the world is on the cusp of great change. In *Dreaming the Future*, Ausubel outlines the state of the earth's abused ecosystems and suggests that solutions to some of humanity's most pressing issues already exist and can be found in nature. As he writes in the book's introduction, "At the same time the world faces escalating climate change and extreme environmental and social disruption, we're also witnessing a profound transformation taking hold around the globe. It signals the dawn of a human civilization that honors and emulates the wisdom of nature's design sophistication.…It's a revolution from the heart of nature and the human heart." The book is divided into 3 sections: Part 1, "It's All Alive . . .," which expands on the idea of the earth as an interconnected, living organism; Part 2, "Hungry Ghost Stories," which looks at how corporations have affected our current global state; and Part 3, "Value Change for Survival," which looks at current innovations and ideas at a time when "the shift is about to hit the fan."

Cereals and Pulses: Nutraceutical Properties and Health Benefits by Liangli Yu, Rong Tsao, and Fereidoon Shahidi (eds.). Hoboken, NJ: Wiley-Blackwell; 2012. Hardcover, 328 pages. ISBN: 978-0-8138-1839-9. $199.95.

Cereals and pulses — a term that encompasses legumes such as beans, peas, and lentils — are crops grown around the world that have the potential to provide important nutrients to millions of people. This reference guide examines each of the major cereal and pulse crops in detail and explores their phytochemical properties. According to the book's summary, "Chapters for each crop discuss methods to improve crop utilization, nutraceutical components and properties, bioactive compositions, antioxidant properties, beneficial health effects, disease prevention activities, and areas for future research." The book is divided into 19 chapters, each written by experts in their respective fields. Examples of chapters include Chapter 2, "Effects of Barley Consumption on Cardiovascular and Diabetic Risk;" Chapter 9, "Antioxidant and Health Promoting Properties of Wheat (*Triticum* spp.);" and Chapter 16, "Soy Isoflavones and Bone Health."

The second paradigm, the traditional and herbal perspective, includes stories of herbal remedies from various times and cultures and extends the concept to remedies that go beyond treatment of a disorder. She describes the healer's engagement with the plants, which provides a very different perspective and changes the focus to the use and understanding of the person and the plants as opposed to the biomedical perspective of standardization and mechanisms to treat a disease or disorder. These 2 paradigms may often clash; however, the integrative paradigm is a holistic blend of the biomedical and the traditional perspectives. This paradigm is founded on discernment, pattern recognition, and self-care. Dr. Libster links this approach with some of the holistic nursing theorists and frames an integrative insight as a partnership with plants. She views plant remedies as affecting body, mind, emotion, and spirit.

Dr. Libster devotes over half of the book to describing personal insights and reflections that underlie her nurse-herbalist practice. She describes some of the historic studies and uses of plants by being observant of the presence and patterns of plants, including how and where they grow, as well as the patterns, colors, and shapes of the plants. She uses the 5 elements in nature — earth, air, water, fire, and ether — as a structure for nurses who are developing an herbal healing practice. She argues that the exercises that focus on these elements are consistent with the nursing process in developing a practice plan. The first step is labeled "Entering the Earth Element," which relates to the physical self, and she invites the nurse to focus on the physical connection to the environment and healing plants. "Awakening to the Air Element" deals with engaging one's intuition and mind in assessing and diagnosing health patterns, while integrating biomedical, nursing, and herbal perspectives. In "Welcoming the Water Element," Dr. Libster links the importance of water to health, along with the flow and understanding of emotions. This is a step in recognizing the importance of relationships in patient care. "Fanning the Fire Elements" is associated with the spiritual self as well as the transformation of healing. The final chapter, "Effecting the Ether Element," refers to the higher self and extends the practice to the ethics of peace and planet healing.

This book is aimed at a nursing audience with the intention of integrating herbs into the well-known nursing process. Holistic nurses, in particular, should find this book useful and engaging. The addition of the many examples of experiences with herbs and vivid descriptions of the human relationship with plants make for both educational and entertaining reading. Holistic nurses will likely find this book enjoyable as well as informative. This book may have appeal beyond a nursing readership, particularly for those who are interested in herbs and the history and practice of herbal healing. It also provides a perspective of nurses and nursing of which many may not be aware.

—Joan Engebretson, DrPH, AHN-BC, RN
Judy Fred Professor in Nursing
University of Texas Health Science Center
Houston, Texas

Classifieds

Publications

American Herb Association Quarterly Newsletter: $20/yr. AHA, P.O. Box 1673, Nevada City, CA 96969.

Australian Journal of Medical Herbalism: Quarterly publication of the National Herbalists Association of Australia (founded in 1920). Deals with all aspects of Medical Herbalism, including latest medicinal plant research findings. Regular features include Australian medicinal plants, conferences, conference reports, book reviews, rare books, case studies, and medicinal plant reviews. AUD/$96 plus AUD/$15 if required by airmail. National Herbalists Association of Australia, 33 Reserve Street, Annandale, NSW 2038, Australia.

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

Other

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Moringa oleifera (Moringaceae)

Commonly known as the horseradish tree or the Moringa tree, *M. oleifera* is native to tropical Africa and Asia and has many medicinal and food uses. Its seeds contain oil that is used as a salad dressing as well as in cosmetics, and the seeds also have been shown to remove 90% of germs from drinking water. Its root, which can be used as a horseradish substitute, has been shown to yield anti-bacterial properties *in vitro*. Functional foods and food supplements are prepared from the leaves. All parts of the tree are used to make many traditional medicine remedies, such as drops made from root juice to treat ear infections.

Adapted from *Medicinal and Aromatic Plants of Indian Ocean Islands* by Ameenah Gurib-Fakim and Thomas Brendler (MedPharm, 2004). Photo ©2012 Ameenah Gurib-Fakim.

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[1] *Journal of AOAC International*. Vol. 90, No. 4, 2007: 911-919.