HerbalGram 112 • Nov 2016–Jan 2017

Kratom: Medicine or Menace? • Passionflower Profile • Botanical Value Chains • Pomegranate Adulteration • Cranberry Clinical Efficacy • DNA Testing Update

www.herbalgram.org

Cranberry Clinical Efficacy • Passionflower Profile • Botanical Value Chains
Pomegranate Adulteration • DNA Testing Update

HERBALGRAM

The Journal of the American Botanical Council

Number 112 | Nov 2016 — Jan 2017

KRATOM

Medicine or Menace?

0 56698 81379 8 1 2>

US/CAN $6.95

greetings from josephine county, oregon

The forces that shaped the southern Oregon landscape endowed it with lofty mountains, sheltered valleys and crystal clear rivers. Blessed with early springs and long summers, a part of this unique region came to be known as Josephine County.

Herb Pharm planted its roots in this rich volcanic soil nearly four decades ago. We've been growing organic herbs and making effective liquid extracts with precision and environmental stewardship ever since. As one of the nation's first GMO-free counties, we are happy to make Josephine our home.

Certified organic *Echinacea purpurea* growing on the *Herb Pharm* farm.

HERB PHARM®

See how the natural therapeutic properties of plants can benefit you at www.herb-pharm.com.

THE WONDER OF
THE NATURAL WORLD.
THE POWER OF NATURAL PRODUCTS.
GO SEAMLESSLY.

NATURAL PRODUCTS

From biomarker and drug discovery to safety, quality control and manufacturing efficiency, Waters is equipped and committed to help labs navigate the wonderful complexity of natural products. Together as industry pioneers, let's embrace the challenges and pursue new possibilities that are waiting to be uncovered. To learn more about our application-specific, workflow-driven solutions and technologies, visit waters.com/naturalwonder

Waters
THE SCIENCE OF WHAT'S POSSIBLE.®

PHARMACEUTICAL ▪ HEALTH SCIENCES ▪ FOOD ▪ ENVIRONMENTAL ▪ CHEMICAL MATERIALS

dear *reader*

The latest herb profile in our series by ABC's Gayle Engels and Traditional Medicinals' Josef Brinckmann examines the beautiful passionflower. Passionflower's name can confuse consumers about its properties, but it is used in numerous herbal sedative formulations and does not actually arouse "passion." (In the 1980s, some male sexual-enhancement products were marketed with the misleading statement "Now with Passionflower!") The herb's name derives from its discovery in the New World by Spanish botanists who were reminded of the Passion of Christ by the striking anatomy of the flower.

Our main feature article covers the Southeast Asian herb kratom, which has become a *cause célèbre* after the US Drug Enforcement Administration (DEA) in August proposed placing two active compounds found in the herb in Schedule I of the Controlled Substances Act. (Schedule I is the most restrictive classification and is reserved for substances with no recognized medical value, such as heroin and LSD.) Kratom contains compounds that bind at opioid receptor sites, thereby producing not only analgesic effects but also the possibility of addiction and dependence, although some consumers use it to help ease opioid withdrawal symptoms. In a rare action, the DEA has responded to the public outcry and pressure from lawmakers, and rescinded its proposed scheduling of the kratom compounds, at least for now.

In his extensive article, *HerbalGram* Assistant Editor Connor Yearsley reviews the science and history of this controversial plant and includes testimonials from kratom users. Although we seldom cite testimonials in our publications, they serve, in this case, as examples of the attitudes and experiences held by a determined group of patients — the impact of which has helped result in the DEA's temporary acquiescence.

Our good friend Kerry Bone, an Australian herbalist, author, and researcher, has contributed an overview of recent clinical trials of various cranberry preparations for urinary tract health and other conditions. Cranberry products rank among the top-selling dietary supplements in US retail stores, based in part on consumer awareness of the growing body of evidence for cranberry's ability to prevent and, in some cases, successfully treat lower urinary tract infections.

Quality control is the theme of various articles in this issue. In our second feature article, our British colleagues Michael Heinrich and Tony Booker present a European perspective on the quality control of herbal medicinal products and discuss the concept of "value chains" for botanical ingredients. With so much interest in and concern about proper identity, contamination, and overall quality of botanical raw materials, the authors contend that vertically integrated value chains result in higher-quality finished products, in addition to many other benefits throughout the supply chain.

In our ongoing series of publications in the ABC-AHP-NCNPR Botanical Adulterants Program (BAP), John Cardellina and I have co-authored a report on the adulteration of pomegranate products, including juices sold as beverages and extracts sold as dietary supplements. Aside from the dilution of pomegranate juice with undisclosed amounts of lower-cost juices, pomegranate extracts claiming to contain high levels of ellagic acid (EA) have been found to contain externally sourced EA (either synthetic or from tree bark). EA is a naturally occurring antioxidant compound in many plants, and it occurs at a level of about 3% in pomegranate. Its presence in high amounts (40-70%!) may suggest that a product is a high-quality, highly concentrated pomegranate extract. However, these unusually high levels of EA are more likely the result of spiking with non-pomegranate-sourced EA. While there are no apparent health risks associated with this practice, we question the ethics of this form of economic adulteration.

Our Chief Science Officer Stefan Gafner has provided us with a summary of the paper he recently co-authored with medicinal plant experts at the respected National Center for Natural Products Research and the University of British Columbia on the strengths and limitations of DNA barcoding technology with respect to analyzing the identity of botanical materials (e.g., botanical extracts used in dietary supplements). As written in these pages previously, DNA barcoding is *not* reliable as a sole method of determining the identification of plant extracts, because DNA is often degraded and/or filtered out during the extraction process. This issue became front-page news last year when the New York attorney general (NY AG) misused DNA barcoding as the sole lab method to test finished herbal supplements in leading retail stores.

What's more, we include a short article about the NY AG's recent agreement with US supplement giant NBTY, which had produced some of the herbal supplements sold under the Walgreens and Walmart labels that were inappropriately tested by the NY AG and initially alleged as adulterated. The new agreement notes that the products in question *did* meet all federal requirements for identity and labeling, thereby again demonstrating the inadequacy of the NY AG's testing methods and overall investigation.

ABC Advisory Board

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

HERBALGRAM
The Journal of the American Botanical Council

Kratom *Mitragyna speciosa*.
Photo ©2016 ThorPorre

departments

On the Cover
Kratom *Mitragyna speciosa*
Photo ©2016 Prachaya Roekdeethaweesab

***HerbalGram*®** is printed on recycled paper at Craftsman Printers, Inc. Lubbock, Texas

Published by the American Botanical Council, P.O. Box 144345, Austin, TX 78714-4345.

Subscriptions to *HerbalGram* are a benefit of ABC membership at every level. One year memberships: Individual $50; Academic $100; Professional $150; Organization $250; Retailer $250; HerbClip Service $600; Small Business; Sponsor. Add $20 for memberships outside of the U.S. Student and Senior discounts are available. For information about Small Business or Sponsor Memberships, contact Denise Meikel at denise@herbalgram.org or 512-926-4900.

Passionflower

***Passiflora incarnata* L.**

Family: Passifloraceae

INTRODUCTION

Commonly known as passionflower, purple passion flower, or maypop, *Passiflora incarnata* is one of approximately 520 species in the family Passifloraceae. Species in this family are found primarily in Central and South America, and, less commonly, in North America, Australia, and Southeast Asia.[1] Growing up to 25 feet in length, passionflower is an herbaceous vine that climbs using axillary tendrils, and it spreads aggressively by root suckers. It has deciduous (or evergreen, depending on the climate), three-lobed, dark green leaves that are whitish on the underside. Conspicuous, largely lavender corona flowers with showy pistils and stamens appear in spring through fall and are followed by yellow edible fruit (berries).[2]

Passiflora incarnata is native to the southeastern United States[3] and is currently distributed from Florida west to Texas, north to southeastern Kansas, and east to Virginia,[4] where it is cultivated in gardens and found in disturbed sites, along fences, by roadsides, in thickets, and on waste grounds.[1] The northern limits of passionflower's current range are an extension of its original habitat due to increasing anthropogenic effects (i.e., the influence of human activities on nature). Archeological evidence indicates, for example, that *P. incarnata* did not occur in Arkansas or Kentucky prior to the 1550s.[4] In the 17th century, European colonizers brought *P. incarnata* to Europe, where it was introduced, domesticated, and is still cultivated today, particularly in Mediterranean France and Italy, where there are several certified organic farms growing passionflower for the herbal market.

While some of the material of commerce is obtained from cultivation in the United States and parts of southern Europe, much of the commercial supply of passionflower is still wild-collected in the southeastern United States. The entire vine, including stems, leaves, flowers, and fruits, is harvested by hand starting in the late spring (when it begins to flower) from disturbed areas, fields, and early successional habitats.[5*]

Passionflower *Passiflora incarnata*
Photo ©2016 Steven Foster

Although the second edition of the American Herbal Products Association's *Herbs of Commerce* also lists other passionflower species — namely, *P. caerulea* (blue passionflower), *P. coriacea* (bat-leaf passionflower), *P. edulis* (purple granadilla or purple passionflower), *P. foetida* (stinking passionflower), and *P. laurifolia* (yellow granadilla or bayleaf passionflower)[6] — this article focuses on *P. incarnata*.

HISTORY AND CULTURAL SIGNIFICANCE

Historically, various *P. incarnata* plant parts have been used as food or medicine by Native American tribes in the southeastern United States, including the Apalachee and Creek (both of Florida),[7] Cherokee (Georgia, North and South Carolina, Tennessee, Virginia), Houma (Louisiana),[8] and Powhatan (Virginia).[9] Seeds of *P. incarnata* are often found among archaeobotanical artifacts at excavation sites (e.g., at the Early Historic North American archaeological period [17th century] Creek town of Fusihatchee in Alabama, and at several Apalachee sites in North Florida).[7] According to archeological evidence, human use of *P. incarnata* began in the Late Archaic period (3,500-800 BCE) in North America. Seeds have been identified at Late Archaic period sites in Alabama and Tennessee; Early Woodland period (800 BCE-200 CE) sites in Georgia; Middle Woodland period (100 BCE-550 CE) sites in Alabama and Tennessee; Late Woodland period (550-1000 CE) sites in Alabama, Louisiana, and Tennessee; Mississippian/Protohistoric period (1000-1550 CE) sites in Alabama, Georgia, North and South Carolina, Tennessee, Mississippi, and Virginia; and Historic period (1550-1800 CE) sites in Georgia, North Carolina, and Tennessee.[4]

In his manuscript *The Historie of Travaile Into Virginia Britannia*, William Strachey, an English writer who served as the first Secretary of the Colony of Virginia in 1610, documented Algonkian food uses of wild passionflower fruits, which the indigenous referred to as "maracock," in coastal Virginia.[10] It has been suggested that the origin of one of passionflower's common names "maypop" is an alteration of "maycock," a name derived from the Powhatan (Virginia) name "mahcawq." But the name may also refer to the sound made when the buds begin popping in the month of May, or to the popping sound that is made when the fruits are crushed or stepped on.[7]

The genus name *Passiflora* and the corresponding vernacular name "passionflower" originate from the Italian *fiore della passione*, a name given to the flower in a context of Christian symbology (objects associated with the crucifixion of Christ).[4] This story can be traced back to 1605 CE at the start of the papacy of Pope Paul V (1552–1621), when a live *P. incarnata* plant was given to the pope and planted as a gift in his honor. First described in a treatise on New World flora written by the Italian Dominican monk Simone Parlasca and published in 1609,[11] as well as in a 1619 publication by Neapolitan Dominican monk and druggist Fra Donato d'Eremita,[12] the flower's corona was represented as resembling the crown of thorns, the three styles being the nails of the cross, the three-lobed leaves the spear, and the five anthers representing the marks of the five wounds, among other correlations.[13] Passionflower was first introduced into England in 1629 as a greenhouse plant later described in a folio (pamphlet) titled *Six Numbers of Coloured Figures of Passion Flowers* by Mary Lawrance.[14]

In 1838, W.B. Lindsay of Bayou Gros Tête, Louisiana, brought the clinical use of inspissated (thickened or congealed) passionflower juice to the attention of his friend David Lewis Phares of Newtonia, Mississippi, after having prescribed it for 30 years (since about 1808) with reportedly successful outcomes in cases of *tetanus neonatorum*.[†] In his early years of dispensing passionflower juice, Lindsay

* The National Resources Conservation Service (NRCS) defines early successional habitat as a "habitat with vigorously growing grasses, forbs, shrubs and trees which provide excellent food and cover for wildlife but need disturbance to be maintained."

[†] *Tetanus neonatorum*, a highly fatal disease, is a type of tetanus occurring in newborn infants, usually due to infection of the umbilical area with the bacterium *Clostridium tetani*.

had attributed observed differences in dosage strength and efficacy to an incorrect assumption that preparations were being made from different species of *Passiflora*. He was later convinced that the medicines had all been made from *P. incarnata* but that the differences were due to dissimilarities in season of gathering, mode of preparation, and locality of growth. (For example, Lindsay believed that passionflower wild-collected on uplands and in Bayou Gros Tête made the strongest medicine, while passionflower collected near dikes or levees around New Orleans was inferior.) Later, in their clinical practices, both Phares and his son, J.H. Phares, reported success using passionflower juice to treat *tetanus erectus* in horses.[14] D.L. Phares reportedly also carried out human trials, published in the *New Orleans Medical Journal*, using passionflower preparations made by Lindsay.

Passionflower *Passiflora incarnata*
Photo ©2016 Steven Foster

In the late 19th century, Isham Jabus Marshall Goss, MD (1819-1896), of Georgia introduced the use of passionflower into Eclectic medical practice. According to the 18th edition of *King's American Dispensatory* (3rd Revision), published in 1898, specific indications for use of passionflower liquid extracts in the Eclectic system of medicine included "irritation of brain and nervous system with atony; sleeplessness from overwork, worry, or from febrile excitement, and in the young and aged; neuralgic pains with debility; exhaustion from cerebral fullness or from excitement; convulsive movements; infantile nervous irritation; nervous headache; tetanus; hysteria; oppressed breathing; cardiac palpitation from excitement or shock."[15]

Traditional European uses of the plant include for anxiety, constipation, indigestion, insomnia, nervousness, and mild infections.[1] In Poland, it has been used for hysteria and neurasthenia, while, in Turkey, in addition to insomnia, it has been used for epilepsy, painful menstruation (dysmenorrhea), neuralgia, and neurosis.[1]

Defined as the dried herbage of "*Passiflora incarnata* Linné" collected after some of the berries have matured, "Passiflora" entered the fourth edition of the *National Formulary* (NF IV) in 1916[16] and remained officinal through the fifth edition (NF V) until 1936. A monograph for "Tinctura Passiflorae" was also included in the NF V.[17] The 20th edition of *The Dispensatory of the United States of America*, published in 1918, added monographs describing both "Passion Flower N.F." and "Tinctura Passiflorae N.F."[18]

In 1975, the US Food and Drug Administration (FDA) considered inclusion of "passion flower extract" as a sedative active ingredient in its proposal to establish a monograph for over-the-counter (OTC) nighttime sleep-aid and daytime sedative drug products. Although "passion flower extract" was a labeled active ingredient in marketed sedative drug products at that time, the FDA's Advisory Review Panel on OTC Sedative, Tranquilizer and Sleep-Aid Drug Products was unable to find sufficient evidence to demonstrate that it induced sedation. The panel initially classified the use of passion flower extract in nighttime sleep-aid products as "irrational."[19] In 1978, while still included in the ongoing review of nighttime sleep-aid active ingredients, the FDA issued a tentative final order placing passion flower extract into Category II, meaning "nonmonograph" or "Not Generally Recognized as Safe and Effective" (not GRASE).[20]

Another eleven years passed before the FDA would issue its final rule in 1989, which classified passion flower extract as nonmonograph. OTC nighttime sleep-aid drug products containing passion flower extract could no longer be marketed unless the product was the subject of an approved New Drug Application (NDA). Existing passionflower drug products were then required to be phased out of the market.[21] By the time the Dietary Supplement Health and Education Act (DSHEA) of 1994 was passed, passionflower-based products were transitioned from OTC drug to the newly established dietary supplement framework. In 2000, the FDA ruled that some

OTC drug monograph claims would be acceptable as structure-function claim statements, including claims listed in its nighttime sleep-aid monograph (in particular, "for the relief of occasional sleeplessness," because occasional sleeplessness is not a characteristic symptom of a disease).[22] In this case, it turned out that certain passionflower-based dietary supplements could now be marketed with the same claim statement as when previously labeled and marketed as OTC sleep-aid drug products, provided that the notifying company had compiled a substantiation file containing sufficient levels of evidence to support the claim for its specific product.

In 1985, the German Commission E approved the use of passionflower herb, prepared as an herbal tea infusion or equivalent galenical preparation, as a nonprescription medicine for treating nervous restlessness.[23] Since then, national labeling standards monographs of European Union (EU) member states, such as those of the German Commission E, have been superseded by monographs of the European Medicines Agency (EMA). In Germany, the aerial parts (herb) of *P. incarnata* remains classified as both medicine and food (depending on dose) and appears on List B in Germany's List of Substances, meaning that restricted use in foods is recommended because pharmacological effects occur above a certain dose.[24]

A quality standards monograph for "Passiflorae Herba" first entered the *European Pharmacopoeia* (PhEur) in the 2000 supplement to the 1997 third edition[25] and has remained official through the current ninth edition published in July 2016.[26] In 2007, a comprehensive monograph (quality and therapeutics) for "Herba Passiflorae" entered volume three of the *WHO Monographs on Selected Medicinal Plants*.[27] In the same year, the EMA published a labeling standards monograph (later superseded by a 2014 revised monograph),[28] and the following year, Health Canada published its labeling standards monograph.[29] Although a quality standards monograph for "Pasiflora, Parte Aérea" entered the *Mexican Pharmacopoeia* in 2013,[30] remarkably there is not yet an official quality standards monograph available in the *United States Pharmacopeia* (USP) for this widely used medicinal plant that is native to the United States.

Currently, herbalists employ *P. incarnata* for its analgesic, antispasmodic, hypnotic, nervine, and hypotensive effects. It has proven useful as a sedative for intractable insomnia, for relieving nerve pain, and for addressing seizures and asthma associated with spasms and tension.[31]

An online retrospective survey of the use of herbal anxiolytics by college students published in 2012 revealed that passionflower was the most commonly used herbal dietary supplement for reducing anxiety. Of 235 students who responded, 85 (36.2%) used passionflower in the previous 12 months (of those 85 students, 55 used it less than 10 times, 19 used it monthly, nine weekly, and two daily).[32] The most common reasons given for using an herbal dietary supplement were recommendation by friends or family (38%), ease of obtaining dietary supplement (36.3%), and lower cost compared to prescription drugs (23.1%).

Passionflower *Passiflora incarnata*
Photo ©2016 Steven Foster

CURRENT AUTHORIZED USES IN COSMETICS, FOODS, AND MEDICINES

In the United States, passionflower may be used as a natural flavoring substance, so long as the minimum quantity to produce the intended effect is used.[33] (The FDA regulation specifically lists "passion flower [*Passiflora incarnata* L.]," but it may be safe to assume that passionflower fruit and extracts thereof are included in the scope of the regulation.) Passionflower is also permitted as a component of dietary supplement products, requiring FDA notification within 30 days of marketing if a structure-function claim is made and product manufacturing according to dietary supplement current good manufacturing practices (cGMPs).[34]

In Canada, passionflower is regulated as an active ingredient of licensed natural health products (NHPs) requiring pre-marketing authorization from the Natural and Non-prescription Health Products Directorate (NNHPD). Labels of licensed NHPs prepared from British or European pharmacopeial-quality passionflower may carry the claim statement "Traditionally used in Herbal Medicine as a sleep aid (in cases of restlessness or insomnia due to mental stress)."[30] Additionally, passionflower is listed in the draft "Cognitive Function Products" monograph as a sedative active ingredient.[35] At the time of this writing (September 2016), 547 licensed NHPs list *P. incarnata* as an ingredient, of which 543 products list it as a medicinal ingredient, and four NHPs list it as a non-medicinal ingredient.[36]

For herbal medicinal product companies in the EU, or in non-EU countries where the PhEur is an official compendium (e.g., Australia and Canada), there are quality standards monographs established by the European Directorate for the Quality of Medicines (EDQM) for "Passion Flower Herb" containing a minimum of 1.5% flavonoids (expressed as vitexin), and "Passion Flower Dry Extract" containing a minimum of 2.0% flavonoids (expressed as vitexin), which can be used as the basis for active ingredient specifications.[29] Registered Traditional Herbal Medicinal Products (THMPs) composed of PhEur-quality passionflower and prepared as herbal teas, liquid extracts, or as solid dosage forms containing dry extract, may be labeled and marketed "for relief of mild symptoms of mental stress and to aid sleep."[28]

For use in cosmetic products, the European Commission Health and Consumers Directorate lists "Passiflora Incarnata Extract" (extract of whole plant) for astringent function. "Passiflora Incarnata Flower Extract" is listed for skin-conditioning and skin-protecting functions, and "Passiflora Incarnata Water" (aqueous solution of the steam distillates obtained from passionflower) is listed for masking and skin-conditioning functions.[37]

MODERN RESEARCH

Passiflora incarnata herb contains 1-2.5% flavonoids (pharmacopeial quality contains minimum 1.5% flavonoids, expressed as vitexin), consisting almost exclusively of C-glycosyl flavones. The proportion of each individual flavonoid is, however, highly variable. For example, isovitexin-2"-O-glucoside is present at 0.1 to 0.8%, isoshaftoside at 0.05 to 0.5%, shaftoside at 0.02 to 0.61%, and isoorientin-2"-O-glucoside at 0.1 to 0.46%, and in some types swertisin is present (at about 0.3%). There are only small amounts of vicenin-2 and lucenin-2, and very low levels of orientin and vitexin. Passionflower also contains polysaccharides (especially arabinoglucan), free amino acids including gamma-aminobutyric acid (GABA), and trace amounts of harmala alkaloids.[38] Wohlmuth et al. (2010) attribute the high variability of flavonoid levels in different samples to the existence of two distinct chemotypes. The type that contains swertisin is almost absent of shaftoside and isoshaftoside.[39]

In vivo and in vitro studies of *P. incarnata* show limited support of its anti-anxiety, antiasthmatic, anticonvulsant, antidiabetic, antiseizure, antitussive, and sedative properties.[1,40-44]

Passionflower is primarily used in combination with other herbs, and clinical evidence of its efficacy as a monopreparation is limited. There are, however, at least six clinical studies on *P. incarnata* alone for conditions including anxiety, sleep, and attention deficit hyperactivity disorder (ADHD).

In a randomized, single-blind study from 2013, 63 patients needing periodontal treatment were randomly assigned into one of three groups of 21 to test the efficacy of passionflower in reducing dental anxiety. One group was given 20 drops of passionflower extract (Pasipay, 30% hydroalcoholic extract with total flavonoid content of 4% w/w, including vitexin and rutin; Iran Darouk Pharmaceutical Co.; Tehran, Iran) the night before treatment and 20 drops following treatment. In the placebo group, the placebo drops were administered in the same way. The third group received no intervention. Patients filled out the Corah's Dental Anxiety Scale, Revised (DAS-R) at the initial interview and following the intake of medication before periodontal treatment. The passionflower group experienced a significant reduction in anxiety following administration of the drops, from 12.09 ± 2.42 down to 8.47 ± 2.08 ($P < 0.0001$). There was no significant reduction in anxiety in the other two groups.[45]

A randomized, double-blind, placebo-controlled (RDBPC) prospective study published in 2011 investigated the effect of passionflower on preoperative anxiety. Forty-five minutes prior to receiving spinal anesthesia, 60 patients completed both parts of the State-Trait Anxiety Inventory (STAI) questionnaire to measure basic anxiety and induced anxiety. Sedation level and psychomotor function were also measured. Thirty minutes prior to receiving anesthesia, hemodynamics were measured via heart rate and systolic, diastolic, and mean arterial pressures, and the patients were randomly assigned to two groups. Patients received either passionflower syrup (700 mg/5 mL aqueous extract; Sandoz, Kocaeli, Turkey; no additional information provided) or placebo. All of the tests were performed again just prior to administration of anesthesia, and there was a statistically significant increase in STAI scores in the placebo group but no other statistically significant differences. The authors state that oral administration of *P. incarnata* suppresses the increase in anxiety before spinal anesthesia without affecting psychomotor function, sedation level, or hemodynamics.[46]

Another RDBPC study published in 2008 evaluated the efficacy of passionflower in reducing preoperative anxiety. Sixty patients scheduled for inguinal herniorrhaphy (surgical repair of a hernia in which a loop of the intestine has protruded through a weak area of the adominal wall) were randomly assigned into one of two groups. One group received 500 mg of Pasipay 90 minutes before surgery; the other received placebo. Each patient's anxiety and sedation were assessed using a numerical rating scale (NRS) before taking medication and at 10, 30, 60, and 90 minutes after. Psychomotor function also was assessed upon arrival in the operating room and 30 and 90 minutes after tracheal extubation. The Pasipay group experienced significantly lower mean NRS scores over time ($P < 0.001$) with no other significant differences between groups. This suggests that oral administration of passionflower prior to surgery can reduce anxiety without inducing sedation.[47]

In 2001, a randomized, double-blind, controlled study compared the efficacy of passionflower to the conventional pharmaceutical sedative drug oxazepam in treating generalized anxiety disorder (GAD). Outpatients diagnosed with GAD (N = 36) at least six months prior to the study were randomly assigned to receive either 45 drops/day of Pasipay plus a placebo tablet or 30 mg/day oxazepam plus placebo drops for four weeks. Both Pasipay and oxazepam were effective in treating GAD, and while there were no significant differences between the two groups regarding total side effects, patients on oxazepam experienced significantly more problems related to impairment of job performance.[48]

One double-blind, placebo-controlled, repeated-measures study published in 2011 investigated the effects of passionflower tea on sleep. Healthy volunteers (N = 41) were recruited and provided information regarding their health and sleeping patterns. All had mild sleep difficulties and were not taking any medications or remedies other than contraception. Passionflower tea bags (2 g of dried *P. incarnata* leaves, stems, seeds, and flowers; Hilde Hemmes' Herbal Supplies Pty. Ltd.; Ridgehaven, South Australia) or parsley tea bags (2 g of *Petroselinum crispum* [Apiaceae]; same producer) were provided with brewing instructions. Each participant drank one tea or the other each night for a week while keeping a sleep diary (which included a subjective report of their sleep, as well as the number and duration of naps, types and amounts of caffeine and alcohol consumption, and bedtime). Participants also completed the STAI questionnaire on the seventh morning. After a one-week washout period, participants switched to the other tea and repeated the process for

another week. Additionally, 10 volunteers participated in overnight polysomnography (PSG) on the last night of each treatment period, the results of which were used to validate sleep diaries. Of the PSG and subjective sleep parameters analyzed, subjective sleep quality alone was significantly better in the passionflower group than in the placebo group. The authors opined that the small sample size limited the power of the statistical analysis. Furthermore, they stated that the passionflower tea dose was three times less than the recommended dosage and questioned if tea might not be the most effective way of administering passionflower. They also suggested that using volunteers with mild sleep issues rather than clinically diagnosed insomnia left little room for improvement and that their study may have been too short to observe significant improvement.[49]

Based on the German Commission E's approval of passionflower for nervous restlessness and the *British Herbal Compendium*'s indication of passionflower for ADHD, researchers in 2003 conducted an eight-week, randomized, parallel group study on 34 children diagnosed with ADHD. One group was administered Pasipay (0.04 mg/kg/day, twice daily) and the other methylphenidate (1 mg/kg/day, twice daily). Patients were assessed by a child psychiatrist at baseline, 14, 28, 42, and 56 days. There were no significant differences between the two groups at baseline or during the course of the study, and both groups showed significant improvement over eight weeks of treatment. The methylphenidate group did experience more probable side effects than the Pasipay group, including decreased appetite (seven subjects vs. two subjects, respectively) and anxiety/nervousness (six subjects vs. no subjects, respectively). The authors suggest that passionflower may be an appropriate treatment for ADHD, especially in children who do not tolerate pharmaceutical stimulants, but that larger studies are needed to confirm their findings.[50]

One RDBPC study from 2001 investigated the efficacy of passionflower as an adjuvant to help with anxiety and insomnia during detoxification from opioids using clonidine. Male opioid addicts (N = 65) were randomly assigned to receive either 0.8 mg/day of clonidine plus 60 drops of "passiflora extract" (no further information provided) or 0.8 mg/day of clonidine plus 60 drops of placebo, three times per day in divided doses. Severity of opioid withdrawal syndrome was measured on days 0, 1, 2, 3, 4, 7, and 14 using the Short Opiate Withdrawal Scale (SOWS). Both groups experienced significant alleviation of physical withdrawal symptoms, but the passiflora-clonidine group experienced a significant reduction in mental symptoms starting on day 2, which was not the case in the clonidine-only group. The authors suggest that passiflora may indeed be an effective adjuvant in the management of opioid withdrawal but that further, larger studies are needed to confirm these results.[51]

As mentioned previously, passionflower is most often used in combination with other herbs, and there have been studies that have investigated the efficacy of these combinations. In a randomized, controlled trial published in 2013, NSF-3 (410 mg of polyherbal extract containing 80 mg of passionflower, 300 mg of valerian [*Valeriana officinalis*, Caprifoliaceae], and 30 mg of hops [*Humulus lupulus*, Cannabaceae]; M/s Tablets India; Chennai, India) performed as well as the conventional pharmaceutical sedative zolpidem in improving total sleep time, sleep latency, and insomnia index scores, and decreasing number of nightly awakenings.[52]

An Italian study published in 2011 showed that children taking 0.5 mL/kg body weight of Vagostabil Junior (containing California poppy [*Eschscholzia californica*, Papaveraceae] aerial parts dry extract titrated to 0.8% total alkaloids expressed as protopine, and passionflower aerial parts dry extract titrated at 4% minimum total flavonoids expressed as vitexin; Cristalfarma; Milan, Italy) had significantly improved sleep quality without adverse effects over the course of 14 days.[53]

FUTURE OUTLOOK

There are no known comprehensive reports available on the conservation status of wild *P. incarnata* in its native southeastern United States habitat. However, the passionflower vine thrives in human-disturbed areas, and its geographical distribution has expanded over time. In some places where it has been introduced outside of its native habitat, the species is considered invasive.[8] Even within its geographical origin, the vines spread from its natural areas along edges of forested areas into agricultural fields, pastures, and citrus groves.[5] According to Lockard and Swanson (1998), "Many farmers find this plant to be a nuisance and might very well accept your offers to harvest it."[54] For sustainable wild-collection, Lockard and Swanson recommend that harvesters should not disturb the roots, leave at least 10% of a passionflower vine patch unharvested in order to facilitate regeneration, and rotate patches rather than returning to the same patch year after year. Harvesting should be carried out "on sunny days, late in the morning after the dew has dried."[54]

In recent decades, some herbal product companies have switched from wild-collected passionflower herb to material produced under controlled cultivation. One reason for this switch is that passionflower vines are climbers that attach to, and get tangled up with, other plants, particularly with other climbing vines. This can make it difficult for harvesters to completely separate out passionflower aerial parts and avoid unintentional adulteration with plant parts of non-target species.[54] Furthermore, highly invasive Asian climbing vines, including kudzu (*Pueraria montana* var. *lobata*, Fabaceae) and precatory (*Abrus precatorius*, Fabaceae), now share habitat with *P. incarnata* vines in the southeastern US. Both kudzu and precatory are listed as noxious weeds in Category I of the Florida Exotic Pest Plant Council (FLEPPC) list of invasive plant species. Category I species are defined as "invasive exotics that are altering native plant communities by displacing native species, changing community structures or ecological functions, or hybridizing with natives."[55] Toxic precatory vine plant parts have been implicated in the past as potential adulterants to various wild-harvested materials.[56] And for passionflower cultivated outside its native habitat, potential contamination with pyrrolizidine alkaloid (PA)-containing weeds (particularly in Europe) was identified in a May 2016 public statement by the EMA. The EMA listed "Passiflorae herba" among the top 10 herbal ingredients most likely affected by PA contamination and therefore made recommendations for risk management and quality control, including that farms should implement "significantly enhanced" good agricultural and collection practices (GACPs) to mitigate the risk.[57]

Although in recent years there have been occasional market shortages of certified organic passionflower of pharmacopeial quality, there is evidence that passionflower production is occurring increasingly through sustainable agricultural practices, along with very recently enhanced GACPs to avoid contamination with non-target weed species. Presently, the main source countries for certified organic cultivated passionflower are France and Italy, but organic cultivation is also increasing in the United States, especially at farms in Kentucky, Missouri, North Carolina, and California. Given that *P. incarnata* is not an endangered or threatened species in its native habitat (although potentially competing with highly invasive climbing vines), and that controlled cultivation is also increasing, it appears that increased global demand can be satisfied through sustainable production methods.

The use of passionflower herb (or extracts thereof) as an active ingredient of traditional herbal medicines, modern phytomedicines, and herbal dietary supplements is likely to continue to increase globally, as are sustainable production systems, whether through controlled cultivation or wild-harvesting. Some experts, however, have cautioned that care must be taken by companies to identify and select specific chemotypes in order to ensure reproducible quality and efficacy.[39] HG

–Gayle Engels and Josef Brinckmann

Passionflower *Passiflora incarnata*
Photo ©2016 Steven Foster

REFERENCES

1. Miroddi M, Calapai G. Navarra M, Minciullo PL, Gangemi S. *Passiflora incarnata* L.: Ethnopharmacology, clinical application, safety and evaluation of clinical trials. *J Ethnopharmacol.* 2013;150:791-804.
2. Passiflora incarnata. NPIN Native Plant Database. Lady Bird Johnson Wildflower Center website. Available at: www.wildflower.org/plants/result.php?id_plant=PAIN6. Accessed September 9, 2016.
3. Allen GM, Bond MD, Main MB. 50 Common Native Plants Important In Florida's Ethnobotanical History. Gainesville, FL: Wildlife Ecology and Conservation Department, Institute of Food and Agricultural Sciences, University of Florida; 2002.
4. Gremillion KJ. The development of a mutualistic relationship between humans and maypops (*Passiflora incarnata* L.) in the southeastern United States. *Journal of Ethnobiology*. 1989;9(2):135-155.
5. Arbogast RT, Kendra PE, Mankin RW, McDonald RC. Insect infestation of a botanicals warehouse in north-central Florida. *Journal of Stored Products Research*. 2002;38(4):349–363.
6. McGuffin J, Kartesz JT, Leung AY, Tucker AO. *American Herbal Products Association's Herbs of Commerce*, 2nd Edition. Silver Spring, MD: American Herbal Products Association; 2000.
7. Stickler JC. Plant Utilization at Fort Mitchell (1RU102), 1813-1840: An Archaeobotanical Analysis. Tallahassee, FL: The Florida State University College of Arts and Sciences; 2004.
8. Immel DL. Plant Guide: Purple Passionflower *Passiflora incarnata* L. Washington, DC: US Department of Agriculture; 2003.
9. Weaver RE. Botany Section. *TRI-OLOGY*. 2004;43(2):1-14.
10. Major RH, ed. *The Historie of Travaile into Virginia Britannia; expressing the cosmographie and comodities of the country, together with the manners and customes of the people*, by William Strachey. London: Printed for the Hakluyt Society; 1849.
11. Parlasca S. Il Fiore della Granadiglia, overo della Passione di nostro Signore Giesù Christo. Bologna, Italy: Bartolomeo Cocchi; 1609.
12. d'Eremita D. Vera effigie della granadiglia detta fiore della passione. Napoli, Italy; 1619.
13. Marzell H. *Wörterbuch der deutschen Pflanzennamen.* 3. Band. Stuttgart/Wiesbaden, Germany: S. Hirzel Verlag/Franz Steiner Verlag; 1977.
14. Phares DL. *Passiflora Incarnata*, a remedy for tetanus. *The Richmond Medical Journal*. 1867;IV:10-14.
15. Felter WH, Lloyd JU. *King's American Dispensatory*. 18th ed.,Third revision, In Two Volumes. Portland, OR: Eclectic Medical Publications (Reprinted 1985); 1898.
16. Committee on National Formulary of the American Pharmaceutical Association. *The National Formulary.* 4th ed. Philadelphia, PA: American Pharmaceutical Association; 1916.
17. Committee on National Formulary of the American Pharmaceutical Association. *The National Formulary.* 5th ed. Philadelphia, PA: American Pharmaceutical Association; 1926.
18. Remington JP, Wood HC. *The Dispensatory of the United States of America,* 20th ed. Philadelphia, PA and London, UK: J.P. Lippincott Company; 1918.
19. Food and Drug Administration (FDA). Proposal to Establish Monographs for OTC Nighttime Sleep-Aid, Daytime Sedative, and Stimulant Products. *Federal Register* 1975;40(236):57292-329.
20. Food and Drug Administration (FDA). Over-the-counter nighttime sleep-aid and stimulant products: Tenative final orders. *Federal Register*. 1978;43(114):25544-602.

21. Food and Drug Administration (FDA). Nighttime Sleep-Aid Drug Products for Over-the-Counter Human Use; Final Monograph. *Federal Register.* 1989;54(29):6814-27.
22. Food and Drug Administration (FDA). Regulations on Statements Made for Dietary Supplements Concerning the Effect of the Product on the Structure or Function of the Body; Final Rule. *Federal Register*. 2000;65(5):1000-1050.
23. Blumenthal M, Busse WR, Goldberg A et al, eds. Klein S, Rister RS, trans. *The Complete German Commission E Monographs: Therapeutic Guide to Herbal Medicines*. Austin, TX: American Botanical Council; Boston, MA: Integrative Medicine Communication; 1998.
24. Bundesamt für Verbraucherschutz und Lebensmittelsicherheit (BVL). *List of Substances of the Competent Federal Government and Federal State Authorities: Category "Plants and plant parts."* Cham Heidelberg New York Dordrecht London: Bundesamt für Verbraucherschutz und Lebensmittelsicherheit (BVL); 2014:112.
25. European Pharmacopoeia Commission. *Europäisches Arzneibuch Nachtrag 2000*. Stuttgart/Eschborn: Deutscher Apotheker Verlag/ Govi-Verlag — Pharmazeutischer Verlag GmbH; 2000.
26. European Pharmacopoeia Commission. *European Pharmacopoeia Ninth Edition* (PhEur 9.0). Strasbourg, France: European Directorate for the Quality of Medicines; 2016.
27. World Health Organization. *WHO Monographs on Selected Medicinal Plants Volume 3*. Geneva, Switzerland: World Health Organization; 2007.
28. Committee on Herbal Medicinal Products. Community herbal monograph on *Passiflora incarnata* L., herba. London, UK: European Medicines Agency; 2014.
29. Natural and Non-prescription Health Products Directorate. Passionflower. Ottawa, ON: Health Canada; 2008.
30. Comisión Permanente de la Farmacopea de los Estados Unidos Mexicanos. *Farmacopea Herbolaria de los Estados Unidos Mexicanos (FHEUM), Segundo edición*. México: Secretaría de Salud; 2013.
31. Hoffmann D. *Medical Herbalism: The Science and Practice of Herbal Medicine*. Rochester, VT: Healing Arts Press; 2003.
32. Birkett M. Use of anxiolytic natural products by college students. *J Altern Complement Med.* 2012;18(6):527-528.
33. US Food and Drug Administration (FDA). § 172.510 Natural flavoring substances and natural substances used in conjunction with flavors. *Code of Federal Regulations,* Title 21. Washington, DC: US Government Printing Office; 2016:57-60.
34. US Food and Drug Administration. 21 CFR Part 111 Current Good Manufacturing Practice in Manufacturing, Packaging, Labeling, or Holding Operations for Dietary Supplements; Final Rule. *Federal Register*. 2007;72(121):34752-34958.
35. Natural and Non-prescription Health Products Directorate. Cognitive Function Products. Ottawa, ON: Health Canada; 2014.
36. Natural and Non-prescription Health Products Directorate. Licensed Natural Health Products Databases. Ottawa, ON: Health Canada; 2016.
37. European Commission Health & Consumers Directorate. Cosmetic Ingredients and Substances (CosIng) Database. Brussels, Belgium: European Commission; 2016.
38. Blaschek W (ed.). *Wichtl — Teedrogen und Phytopharmaka — Ein Handbuch für die Praxis*. 6. Auflage. Stuttgart, Germany: Wissenschaftliche Verlagsgesellschaft. 2016;472-475.
39. Wohlmuth H, Penman KG, Pearson T, Lehmann RP. Pharmacognosy and chemotypes of passionflower (*Passiflora incarnata* L.). *Biological and Pharmaceutical Bulletin* 2010;33(6):1015-1018.
40. Elsas S-M, Rossi DJ, Raber J, et al. *Passiflora incarnata* L. (passionflower) extracts elicit GABA currents in hippocampal neuron in vitro, and show anxiogenic and anticonvulsant effect in vivo, varying with extraction method. *Phytomedicine.* 2010;17:940-949.
41. Appel K, Rose T, Fiebich B, Kammler T, Hoffmann C, Weiss G. Modulation of the γ-aminobutyric acid (GABA) system by *Passiflora incarnata* L. *Phyto Res.* June 2011;25(6):838-843. doi: 10.1002/ptr.3352.
42. Traub M. Passionflower (*Passiflora*): An Overview of the Research and Clinical Indications. Brevard, NC: Gaia Herbs; 2012.
43. Nassiri-Asl M, Shariati-Rad S, Zamansoltani F. Anticonvulsant effects of aerial parts of *Passiflora incarnata* extract in mice: involvement of benzodiazepine and opioid receptors. *BMC Complementary and Alternative Medicine*. 2007;7:26.
44. Schulz H, Jobert M, Hübner WD. The quantitative EEG as a screening instrument to identify sedative effects of single doses of plant extracts in comparison with diazepam. *Phytomedicine.* December 1998;5(6):449.458.
45. Kaviani N, Tavakoli M, Tabanmehr MR, Havaei RA. The efficacy of *Passiflora incarnata* Linnaeus in reducing dental anxiety in patients undergoing periodontal treatment. *J Dent Shiraz Univ Med Scien.* 2013;14(2):68-72.
46. Aslanargun P, Cuvas O, Dikmen B, Aslan E, Yuksel MU. *Passiflora incarnata* Linneaus as an anxiolytic before spinal anesthesia. *J Anesth.* 2012;26:39-44.
47. Movafegh A, Alizadeh R, Hajimohamadi F, Esfehani F, Nejatfar M. Preoperative oral *Passiflora incarnata* reduces anxiety in ambulatory surgery patients: a double-blind, placebo-controlled study. *International Anesthesia Research Society.* June 2008;106(6):1728-1732.
48. Akhondzadeh S, Naghavi HR, Vazirian M. Shayeganpout A, Rashidi H, Khan M. Passionflower in the treatment of generalized anxiety: a pilot double-blind randomized controlled trial with oxazepam. *Journal of Clinical Pharmacy and Therapeutics.* 2011;26:363-367.
49. Ngan A, Conduit R. A double-blind, placebo-controlled investigation of the effects of *Passiflora incarnata* (passionflower) herbal tea on subjective sleep quality. *Phytother Res.* August 2011;25(8):1153-1159.
50. Akhondzadeh S, Mohammadi MR, Momeni F. *Passiflora incarnata* in the treatment of attention-deficit hyperactivity disorder in children and adolescents. *Therapy.* 2005;2(4):609-614.
51. Akhondzadeh S, Kashain L, Mobaseri M, Hosseini SH, Nikzad S, Khani M. Passionflower in the treatment of opiates withdrawal: a double-blind randomized controlled trial. *J Clin Pharm Ther.* 2001;26:369-373.
52. Maroo N, Hazra A, Das T. Efficacy and safety of a polyherbal sedative-hypnotic formulation NSF-3 in primary insomnia in comparison to zolpidem: a randomized controlled trial. *Indian J Pharmacol.* January-February 2013;45(1):34-39.
53. Sannia A, Forti S, Cesarani A. Efficacy of complex herbal compound of *Eschscholtzia californica* and *Passiflora incarnata* (Vagostabil® Junior) on sleep disturbances during pediatric age [in Italian]. *Minerva Pediatrica.* December 2011;63(Suppl. 1, N. 6):1-6.
54. Lockard A, Swanson AQ. *A Digger's Guide to Medicinal Plants*. Eolia, MO: American Botanicals; 1998.
55. FLEPPC. List of Invasive Plant Species. Florida Exotic Pest Plant Council; 2015.
56. Flaster T, Lassiter J. Quality control in herbal preparations: using botanical reference standards for proper identification. *HerbalGram*. 2004;63:35-37.
57. Committee on Herbal Medicinal Products. Public statement on contamination of herbal medicinal products/traditional herbal medicinal products with pyrrolizidine alkaloids: Transitional recommendations for risk management and quality control. London, UK: European Medicines Agency; 2016.

New Employee Profile: Anna Moreno

In November 2015, Anna Moreno joined the staff at the American Botanical Council (ABC) as the executive assistant to ABC Founder and Executive Director Mark Blumenthal. In this multifaceted position, Moreno handles correspondence for Blumenthal, assists with projects for the development department, and arranges travel, meetings, and conference appearances for Blumenthal and other ABC staff members. Though Moreno began at ABC as a temporary hire, she became part of the permanent staff in March 2016.

"The most challenging part is keeping track of everything that Mark, ABC, and the rest of the staff have going on," Moreno explained. "Since I handle multiple projects at once, organization and planning are the key to making sure everything is running as smoothly as possible with the least amount of hiccups."

"Working with Anna is a true pleasure," said Blumenthal. "She has a tremendously positive attitude, is eager to get things done quickly and accurately, and is always open to learning new skills and working on new projects. She's a true asset to the entire organization."

Born and raised in Austin, Texas, Moreno attended the University of the Incarnate Word and San Antonio College in San Antonio, with three years as a nursing major, before moving back to Austin in 2012. Before coming to ABC, she worked for several years as the executive assistant for a real estate broker and as a recruiter for a call center. Outside of ABC, she works for a marketing promoter and as a bartender around the city. With a diverse working background, adjusting to the demands of her position at ABC proved to be well within her ability, and Moreno also appreciates the intangible benefits of working at a close-knit nonprofit organization.

"I like working for ABC so much," said Moreno. "I enjoy that my job duties change a lot and encompass a wide variety of skills. I also really enjoy the family work environment ABC has, as it makes me feel like everyone here is part of my extended family."

ABC Development Director Denise Meikel added: "Anna is wonderfully unflappable. She approaches each new task calmly and with confidence, and she's fun to be around. We're thrilled she agreed to join the ABC team."

Moreno currently lives with her fiancé and their six-year-old boxer, Sienna. In addition, her family still lives in the Austin area, including her older brother and sister. "It makes me the baby of the family," she said.

She travels as frequently as she can, with a goal of making two international trips every year. Recently, she completed a six-week backpacking trip through Colombia and explored the rich street food culture of Mexico City. For her next adventure, she looks forward to seeing the European continent for the first time, and visiting Paris and Amsterdam — well on her way toward her dream of traveling "all around the world." When she's not getting her passport stamped, Moreno enjoys outdoor activities, such as hiking, camping, swimming, and snorkeling. She is an open-water-certified diver, and dreams of shark cage diving.

"I am looking forward to my future at ABC, as every day is something new to learn here, not only with the organization, but with herbs and plants," said Moreno. "My knowledge of herbs, tinctures, and home remedies has increased so much already, and this is only the beginning. I have recently started my own herb garden with plants from ABC."

—Hannah Bauman

ADOPT-AN-HERB

HerbMedPro™ PROGRAM

The American Botanical Council's Adopt-an-Herb Program provides a mutually beneficial opportunity to support ABC's nonprofit educational efforts and promote a company's most important herbs.

One of the benefits of supporting the Adopt-an-Herb Program is that it ensures that the most current information on the adopted herb is available through ABC's powerful HerbMedPro™ database.

HerbMedPro provides online access to abstracts of scientific and clinical publications on more than 250 commonly used medicinal herbs. A free version, HerbMed®, is available to the general public. HerbMed features 20 to 30 herbs from HerbMedPro that are rotated on a regular basis with an emphasis on adopted herbs. HerbMedPro is available as a member benefit to all ABC members at the Academic Membership level and up.

In addition to ensuring that recently published information on an adopted herb is up to date on HerbMedPro, another benefit adopters enjoy is being included among their peers in each issue of ABC's acclaimed quarterly, peer-reviewed scientific journal, *HerbalGram*, on the ABC website, and at scientific, medical, and other educational conferences. Press releases also are issued on new adoptions, bringing attention to the program, the adopted herb, and the adopting company. Each adopted herb is featured on its own page on the ABC website.

Parties interested in taking part in the Adopt-an-Herb Program are invited to contact ABC Development Director Denise Meikel at 512-926-4900, extension 120, or by email at denise@herbalgram.org.

AMERICAN BOTANICAL COUNCIL
SINCE 1988

Herbal Adopters

- DMH ingredients
- Baobab — *Adansonia digitata*
- Rooibos — *Aspalathus linearis*
- afrigetics BOTANICALS
- Bulbine — *Bulbine natalensis*
- Broccoli — *Brassica oleracea* Broccoli Group
- indena®
- Indian Frankincense — *Boswellia serrata*
- DownUnder enterprises
- Tea Tree — *Melaleuca alternifolia*
- Aromatics INCORPORATED
- Peppermint — *Mentha x piperita*
- HERBALIFE
- Aloe vera — *Aloe vera*
- lavn USA
- Monk Fruit — *Siraitia grosvenorii*
- travel medic travelmedic.com
- Kratom — *Mitragyna speciosa*
- utzy naturals
- Black Chokeberry — *Aronia melanocarpa*
- Elderberry — *Sambucus nigra*
- Stinging Nettle — *Urtica dioica*
- AFS APPLIED FOOD SCIENCES, INC.
- Kava — *Piper methysticum*
- AMAZING HERBS
- Black Cumin — *Nigella sativa*
- FOUR ELEMENTS
- Lemon Balm — *Melissa officinalis*
- Teawolf Natural Extract Solutions
- Guayusa — *Ilex guayusa*
- biotropics MALAYSIA
- Tongkat Ali — *Eurycoma longifolia*
- Gaia Trading Company, Inc.
- Hops — *Humulus lupulus*
- THE ACTIVES FACTORY
- Birch — *Betula* spp.

Herbal Adopters

- NATUROPATHICA HOLISTIC HEALTH
- Arnica — *Arnica montana*
- FUTURE CEUTICALS
- CoffeeBerry® — *Coffea* spp.
- KSM-66®
- Ashwagandha — *Withania somnifera*
- INDFRAG®
- Garcinia — *Garcinia cambogia*
- DIANA Performance from nature FOOD
- Acerola — *Malpighia* spp.
- SCHWABE NORTH AMERICA™
- Nature's Way®
- Enzymatic Therapy®
- INTEGRATIVE THERAPEUTICS™
- Black Cohosh — *Actaea racemosa*
- Ginkgo — *Ginkgo biloba*
- Hawthorn — *Crataegus* spp.
- Umckaloabo — *Pelargonium sidoides*
- Lavender — *Lavandula angustifolia*
- Natac
- Olive — *Olea europaea*
- Natac
- Grape — *Vitis vinifera*
- PHARMATOKA
- Cranberry — *Vaccinium macrocarpon*
- ECOSO DYNAMICS
- Devil's Claw — *Harpagophytum* spp.
- EuroPharma
- Turmeric — *Curcuma longa*
- CONTAINS Zembrin
- Sceletium — *Sceletium tortuosum*
- MARS symbioscience
- Cocoa Flavanols — *Theobroma cacao*
- RFI
- Hibiscus — *Hibiscus sabdariffa*
- SFI
- Bacopa — *Bacopa monnieri*
- Vit-Best Nutrition
- Cinnamon — *Cinnamomum verum*

ABC Recognizes New Herb Adoptions by Applied Food Sciences and EcoSo Dynamics

The American Botanical Council (ABC) is pleased to announce the adoptions of kava (*Piper methysticum*, Piperaceae) by Applied Food Sciences, Inc. (AFS), and devil's claw (*Harpagophytum procumbens* and *H. zeyheri*, Pedaliaceae) by EcoSo Dynamics.

The Adopt-an-Herb Program supports ABC's robust HerbMedPro database, an invaluable resource for consumers, students, and all members of the herb and dietary supplement community. The generosity of AFS and EcoSo Dynamics in adopting their respective herbs allows this vital resource to remain up to date with the latest research and pharmacological information.

HerbMedPro is a comprehensive, interactive online database that provides access to important scientific and clinical research data on the uses and health effects of more than 250 herbs.

Applied Food Sciences Adopts Kava

"Kava is an herb with a long ethnobotanical history in Polynesia, and it produces clinically documented anti-anxiety benefits," said Mark Blumenthal, ABC's founder and executive director. "ABC is deeply grateful to Applied Food Sciences for its adoption of kava on the HerbMedPro database, which will allow ABC to stay current with emerging research on kava's benefits and new information that helps to clarify prior concerns about its relative safety."

Chris Fields, vice president of scientific affairs at AFS, noted that "Kava's long history of use in the South Pacific islands demonstrates that it is a safe, effective, and useful tool with many important health benefits when used in the right form and when the correctly identified cultivars are used.

"Applied Food Sciences is fully invested in working together with farmers, agronomists, and the research community to provide the entire supply chain with the appropriate tools to bring sustainable, safe, and high-quality kava ingredients to the market," Fields continued. "We are doing this by leading collaborative changes in implementing the six-point plan that has been defined by the kava industry working groups, developing and executing effective growing and harvesting practices, acquiring and improving methods for cultivar identification and kavalactone content, and investigating and educating on optimum standards and best practices in the industry. Awareness of these efforts is essential. Therefore, it is so important for us to partner with ABC to help our industry make educated, responsible choices about sourcing kava."

About Kava

Kava, also known as kava kava, is both the common name for *Piper methysticum* and the name of a ceremonial beverage made from the root of the plant, which is a member of the pepper family. It is native to Southeast Asia and the islands of the South Pacific, where the drink, made from the ground root macerated in water, has been consumed as part of rituals for hundreds of years. Currently, kava is being investigated by researchers for its anxiolytic, sedative, anticonvulsive, and antispasmodic properties for conditions including anxiety, insomnia, and related stress and nervous disorders.

The formerly official *German Commission E Monographs* approved kava for use in conditions of nervous anxiety, stress, and restlessness. Another monograph compiled by the European Scientific Cooperative on Phytotherapy (ESCOP), a group of medicinal plant research experts in Europe, noted the use of kava preparations for anxiety, tension, and restlessness arising from various causes of non-psychotic origin.

About Applied Food Sciences, Inc.

AFS specializes in the research and development of functional botanical ingredients for use in foods, beverages, and nutritional supplements. The six-point plan the company has helped implement involves educating people at the farm level to cultivate only Noble Kava cultivars and about best practices for harvesting and processing them. The plan outlines the importance of standardizing the concentrations of specific kavalactones to achieve optimum safety and efficacy at the recommended intake. Finally, AFS stresses the importance of developing a validated laboratory method for the accurate quantification of kavalactones (i.e., a class of lactone compounds found in kava) in extracts, root powder, and finished product formulations.

The company's recent kava white paper is available on its website at www.appliedfoods.com.

Kava *Piper methysticum*
Photo ©2016 Steven Foster

Devil's Claw *Harpagophytum procumbens*
Photo ©2016 Steven Foster

EcoSo Dynamics Adopts Devil's Claw

"ABC is deeply grateful to EcoSo Dynamics for adopting devil's claw on ABC's robust HerbMedPro database," said Blumenthal. "ABC also appreciates EcoSo Dynamics' strong commitment to environmentally sustainable and culturally supportive harvesting of devil's claw roots. Devil's claw is a traditionally used herbal remedy with a growing body of scientific and clinical research that supports its safe and effective use to reduce lower back pain and benefit other conditions," he added.

About Devil's Claw

Devil's claw is a perennial herb that grows horizontally and can reach up to one meter (3.3 feet) in length. It produces several prostrate annual stems from a succulent taproot, with additional tubers on lateral roots. Other common names for devil's claw are grapple plant and wood spider, referring to the fearsome-looking, hook-like fruits of the plant, which can cripple large animals.

The plant's anti-inflammatory benefits are derived mostly from its secondary root tubers, which are cut and dried and contain iridoid glycosides (primarily harpagoside), among other constituents.

Clinical studies have demonstrated that preparations of the secondary tubers can reduce pain sensation and improve mobility in humans. In addition, they appear to be safe and effective when used for conditions such as degenerative painful rheumatism, osteoarthritis, tendonitis, headaches, allergies, and more. Traditionally, they have also been used to address digestive ailments.

Devil's claw is native to Kalahari savannas in Namibia and parts of South Africa, Botswana, Angola, and Zimbabwe. The tubers are obtained by sustainable wild-collection and also, on a small scale, by harvesting cultivated plant material on farms. On average, between 400 and 450 tons of dried devil's claw is exported annually from Namibia.

About EcoSo Dynamics

Namibia-based EcoSo Dynamics, established in 2004, emphasizes ecological and social sustainability in its sourcing and processing of devil's claw, and has an annual turnover of about 250 metric tons of devil's claw. "EcoSo's mission is to establish a sustainable supply chain for devil's claw that takes into consideration the ecology, economy, and social needs of thousands of [impoverished] villagers throughout southern Africa," said Gero Diekmann, managing director and owner of EcoSo Dynamics. "EcoSo is the frontrunner in establishing contracts with harvester groups to support sustainable harvesting and processing in order to achieve either organic certification and/or processing according to good agricultural and [collection] practices (GACP). At our facility we maintain good manufacturing practice (GMP) certification. Through this, EcoSo has full traceability in place and can 100% assure its clients of the purity of the material, be it *H. procumbens* or *H. zeyheri*. We see ourselves as leaders in the industry [and our] adoption of devil's claw shows our commitment to our values, and to make these known in the US."

Diekmann also said he hopes the adoption helps assure stakeholders in the United States of the purity and quality of the raw material, and that it helps establish direct trade links between Namibia and the United States. "Unfortunately, we assume that 90% of devil's claw used in the US comes to the US via Europe," Diekmann said.

ABC's Adopt-an-Herb Program & HerbMedPro

Applied Food Sciences and EcoSo Dynamics are two of the 40 companies that have supported ABC's educational efforts to collect, organize, and disseminate reliable, traditional, and science-based information, including clinical studies, on herbs, medicinal plants, and other botanical- and fungal-based ingredients through the Adopt-an-Herb program. This program encourages companies, organizations, and individuals to "adopt" one or more specific herbs for inclusion and ongoing maintenance in the HerbMedPro database. To date, 45 herbs have been adopted.

Each adopted herb is continuously researched for new scientific articles and pharmacological, toxicological, and clinical studies, ensuring that the HerbMedPro record stays current and relevant. The result is an unparalleled resource not only for researchers, health professionals, industry, and consumers, but for all members of the herbal and dietary supplements community.

This database is available to ABC members at the Academic level and higher. Its "sister" site, HerbMed, is available to the general public at no cost. In keeping with ABC's position as an independent research and education organization, herb adopters do not influence the scientific information that is compiled for their respective adopted herbs. HG

New Botanical Adulterants Bulletin Focuses on Arnica Adulteration

In August, the ABC-AHP-NCNPR Botanical Adulterants Program published its sixth Botanical Adulterants Bulletin on arnica (*Arnica montana,* Asteraceae).

Arnica extract is a popular ingredient in topical gels and ointments for the relief of bruises, sprains, and localized muscular pain, and is also widely used in cosmetic preparations. According to data from the market research firm SPINS, sales in all channels (excluding sales from Walmart, Whole Foods, club stores, and dollar stores) of topical arnica products, sold predominantly as homeopathic remedies, exceeded $20 million in 2015.

Research has shown that some raw botanical materials labeled as "*Arnica montana*" contain so-called false arnica (*Heterotheca inuloides*, Asteraceae), also known as Mexican arnica, or other yellow-flowering species from the family Asteraceae. The new Bulletin was co-authored by Wendy Applequist, PhD, associate curator at the William L. Brown Center at the Missouri Botanical Garden, and Stefan Gafner, PhD, chief science officer of the American Botanical Council (ABC) and technical director of the Botanical Adulterants Program. The Bulletin provides information on the cultivation, harvest, and market status of arnica, and lists the known adulterants, potential therapeutic and/or safety issues with the adulterating species, and analytical approaches to detect adulterants. Thirteen expert peer reviewers provided input on the arnica Bulletin.

The goal of the Bulletins is to provide accounts of ongoing issues related to botanical identity and adulteration, thus allowing quality control personnel and lab technicians in the herbal medicine, botanical ingredient, dietary supplement, cosmetic, conventional food, and other industries in which botanical ingredients are used to be informed about relevant adulteration concerns. As with all publications of the Program, the Bulletins are freely accessible to ABC members and registered users on the Program's website.

"Arnica is a widely used ingredient in topical products in the United States and internationally, including in the homeopathic medicine industry," said Mark Blumenthal, founder and executive director of ABC and director of the Botanical Adulterants Program. "Our research suggests that it is possible that a considerable amount of the 'arnica' being used in some of these products may be adulterated with a totally different species. We hope that industry members will heed this Bulletin and double- and triple-check their incoming arnica raw materials to ensure that they are purchasing the authentic arnica plant."

Gafner added: "The occurrence of arnica adulteration with *Heterotheca inuloides* has been known for over half a century, and is readily detected by macroscopic, microscopic, chemical, and/or DNA analyses. Nevertheless, reports as recent as 2012 show that arnica adulteration is still quite common in the marketplace. Some of this may be due to the use of the common name 'arnica' for a number of different plant species, particularly in Spanish-speaking communities. However, the comparatively high price for the authentic arnica raw material has also provided an incentive for economically motivated adulteration."

Two Bulletins on goldenseal (*Hydrastis canadensis*, Ranunculaceae) root and rhizome and black cohosh (*Actaea racemosa*, Ranunculaceae) root and rhizome were published in June 2016, preceded in April by the first three Bulletins on bilberry (*Vaccinium myrtillus*, Ericaceae) fruit extract, grape (*Vitis vinifera*, Vitaceae) seed extract, and skullcap (*Scutellaria lateriflora*, Lamiaceae) herb. Additional Bulletins are scheduled for release in the coming months, including one examining St. John's wort (*Hypericum perforatum*, Hypericaceae) herb.

The ABC-American Herbal Pharmacopoeia (AHP)-National Center for Natural Products Research (NCNPR) Botanical Adulterants Program is an international consortium of nonprofit professional organizations, analytical laboratories, industry trade associations, industry members, and other parties. The Program advises industry, researchers, health professionals, government agencies, the media, and the public about the various challenges related to adulterated botanical ingredients sold in commerce. To date, more than 175 US and international parties have financially supported or otherwise endorsed the Program. HG

Ole Miss and Waters Corp. Establish Cutting-Edge Natural Products Training Center

On April 13, 2016, the west wing of the Thad Cochran Research Center (TCRC) was dedicated at the University of Mississippi (UM/Ole Miss) in Oxford, Mississippi. About 3,000 square feet of the new wing will be used for the activities of the new Natural Products Training Center (NPTC) program. This program falls within the operations of the National Center for Natural Products Research (NCNPR), which is housed within the TCRC.[1]

The new NPTC program is a collaboration between the NCNPR and Waters Corporation, a company established in 1958 that offers a range of chemical analysis system solutions, software, and services for scientists.[2]

The NCNPR is "a university-based academic research unit devoted to the discovery and development of new pharmaceutical and agrichemical technologies based on the amazing chemical diversity of living organisms — plants, animals, and microbes," according to its website.[3] The NCNPR is also a primary partner with the American Botanical Council (ABC) and the American Herbal Pharmacopoeia (AHP) in the ABC-AHP-NCNPR Botanical Adulterants Program.

The west wing of the TCRC is still under construction, and it is estimated that the total cost of the expansion will be $40 million when it is completed in 2017. The space allocated for the NPTC program includes a botanical methodology laboratory, a microscopy laboratory, an analytical laboratory, and an informatics laboratory, as well as botanical exhibits.

The state-of-the-art research space "will provide hands-on training in plant taxonomy, laboratory analytical techniques, and quality standards for botanical-based products," said Don Stanford, assistant director of the university's Research Institute of Pharmaceutical Sciences (which includes the NCNPR), in an article released by the university.[1] "In addition, the NPTC will expand the capabilities of the School of Pharmacy to discover new drugs, and to expand the scientific knowledge base of medicinal plants and other natural products."

The NPTC space will be used to educate government officials, academic and industry professionals, scientists, and others about good manufacturing practices (GMPs) for natural products and botanical dietary supplements.[1] According to Ikhlas Khan, PhD, associate director of the NCNPR and member of ABC's advisory board, the space is intended for any interested parties, including Ole Miss pharmacy students (email, April 25, 2016).

"This training lab was created while keeping the future of the dietary supplement industry in mind," Khan is quoted as saying in the news article.[1]

Waters contributed software and several cutting-edge analytical systems for the new space, including three high-performance liquid chromatography-mass spectrometry (HPLC-MS) systems, which allow for the separation, detection, and potential identification of chemicals that are contained in complex mixtures, based on their specific molecular weights and fragmentation pattern. Waters also contributed an accelerated supercritical fluid extraction system, which allows for the extraction of compounds without using an organic solvent (e.g., ethanol or acetone).

"The ACQUITY UPLC/TQ-S [ultra-performance liquid chromatography tandem quadrupole mass spectrometer]

West wing of the Thad Cochran Research Center at the University of Mississippi. Photo ©2016 University of Mississippi.

provides ultimate sensitivity to identify and quantitate trace-level constituents of natural products," Stanford is quoted as saying about one of the analytical tools provided by Waters.

"Two other [HPLC] and [UPLC systems], coupled to mass spectrometers, photodiode array and evaporative light-scattering detectors, will offer training experience in a multitude of applications. The Waters Empower enterprise network system will allow multiple users in the NPTC informatics training lab to control the instruments remotely," Stanford said.

According to Kelly Johnson, the senior manager of worldwide strategic relations at Waters, the partnership between Waters and Ole Miss focuses on their mutual interests in improving the scientific knowledge base in the areas of natural products and botanical dietary supplements (email, April 27, 2016).

"Through expert-driven curricula and best practices that extend far beyond the laboratory, both institutions hold a sincere belief that this shared initiative will achieve beneficial results to raise the analytical bar on a global scale," Johnson wrote. "Waters is proud to be at the forefront of innovation and collaboration with our UM colleagues, aligning our customers' needs with the [NCNPR] mission to substantially progress research and training."

The NCNPR was established in 1995, and it has had a partnership with the US Food and Drug Administration (FDA) since 2000.[1] The TCRC opened in 1995 and has housed a number of programs and departments of the Ole Miss School of Pharmacy. HG

—Connor Yearsley

References

1. Smith E. UM Dedicates Natural Products Training Center. Ole Miss website. Available at: http://news.olemiss.edu/um-dedicates-natural-products-training-center/. Accessed April 26, 2016.
2. About Waters Corporation. Waters website. Available at: www.waters.com/waters/en_US/About-Waters-Corporation-/nav.htm?locale=en_US&cid=134614448. Accessed April 27, 2016.
3. Welcome. NCNPR website. Available at: http://pharmacy.olemiss.edu/ncnpr/about-ncnpr/welcome/. Accessed April 27, 2016.

Traditional Medicinals Foundation's Social Initiatives Empower Botanical Farmers

When Drake Sadler co-founded Traditional Medicinals with Rosemary Gladstar in 1974, Gladstar was eager to educate the public on the benefits of herbal medicine, and Sadler was interested in applying the Buddhist precept of Right Livelihood to re-invent the business of plant-based medicine. Decades later, Traditional Medicinals is a leading seller of wellness teas in the United States, and Sadler, having stepped down as CEO of Traditional Medicinals in 2007, is focused on the Traditional Medicinals Foundation (TMF) he co-founded with his wife Nioma.

Guided by the Sadlers's vision, the Foundation is unique in that it works in partnership with Traditional Medicinals to advocate for social sustainability in herb-sourcing communities. Using a portion of the company's profits and resources, TMF goes to the sources of the company's raw materials, many of which are remote and indigenous communities that rely on income from collecting or cultivating botanicals. Using a disciplined community-engagement strategy, TMF focuses on building schools, training village health workers, improving water and food security, providing women with opportunities for empowerment, and preserving culture and ancestral herbal knowledge.

"The Traditional Medicinals Foundation is the product of the Sadlers's shared vision and a profoundly strong commitment to empowering people at the very beginning of the value networks producing high-quality botanical ingredients," said Mark Blumenthal, founder and executive director of the American Botanical Council (ABC). "The Foundation is an integral part of Traditional Medicinals's mission, as well as a meaningful, evolutionary step in the company's purposeful history. Serving as a social business model, it is destined to become a highly positive and constructive force in the global herbal community."

One example of this model is The Revive! Project, which seeks to reduce

Girls ride bikes to school in Revive Project villages. Photo ©2016 Traditional Medicinals Foundation

poverty among senna (*Senna alexandrina*, Fabaceae) farmers in the northwestern Indian state of Rajasthan. Senna is a popular ingredient because of the laxative properties of its leaves and fruits. In keeping with its sustainability commitments, Traditional Medicinals introduced the first organic senna farming practices in Rajasthan. Since 2009, the Foundation has sought ways to improve the quality of life for these smallholding farmers by focusing on the greatest threats to their well-being and security: food and water scarcity and lack of educational opportunities. To date, Traditional Medicinals has invested more than $1 million in The Revive! Project, impacting more than 12,000 people in six villages in Rajasthan.

Senna farming in Rajasthan.
Photo ©2016 Traditional Medicinals Foundation

In partnership with Traditional Medicinals, as well as global botanical supplier Martin Bauer Group, Indian herb extract manufacturer Umalaxmi, and California-based non-governmental organization WomenServe, TMF has built rainwater catchments for household, agricultural, and livestock use in Rajasthan. This allows the villagers to make better use of what little rain falls in this hot, desert climate, and reduces the labor needed to fetch water. Collecting water sometimes requires a 10-mile journey in extreme temperatures, and is a chore that usually falls to women and girls in the community. In addition, the Foundation has assisted in the construction of family gardens and communal grazing areas to help ease the burden of food scarcity for both the people and their livestock.

To help cultivate a sustainable future, community self-help and decision-making groups have been organized in Rajasthan, giving the villagers — including women of all ages and castes — the tools, education, voice, and confidence to foster permanent change in their communities. Martin Bauer Group has also constructed community resource centers in the villages, which serve as meeting places, schools, medical clinics, and training facilities, as well as clean, dry storage sites for the senna during harvest periods. As a result of this investment in the people, The Revive! Project villages now produce annually several thousand tons of very high-quality organic senna with high sennoside contents, demonstrating the long-term value of these community, social investments.

The Foundation will continue to expand its outreach, and incorporate the traditional knowledge of the company's supply communities with progressive social programs to reduce poverty and improve the quality of life of the people at the very beginning of the botanical supply chain. HG

—Hannah Bauman

Further Evidence for the Clinical Efficacy of Cranberry

A Brief Review of Recent Clinical Trials

By Kerry Bone

Recent clinical trials* provide further evidence for the role of cranberry (*Vaccinium macrocarpon*, Ericaceae) preparations in preventing urinary tract symptoms in a variety of circumstances, including radiation-induced cystitis, lower urinary tract infections (UTIs), infections after ureteral catheter placement, UTIs after gynecological surgery, and lower urinary tract symptoms (LUTS) in men. A growing body of scientific work supports the simple strategy of using appropriately manufactured cranberry preparations for lower urinary tract health.

Acute radiation cystitis (i.e., inflammation of the bladder caused by radiation therapy) is a common complication in men receiving external beam radiation for prostate cancer. Although several treatments provide symptomatic relief, there is no consensus treatment or standard prevention measure for radiation cystitis.

A New Zealand study aimed to determine the effect of a standardized cranberry extract encased in coated capsules (Naturo Pharm Ltd.; Rotorua, New Zealand; each capsule containing 72 mg proanthocyanidins [PACs]) on the incidence and severity of radiation cystitis.[1] Forty-one men with prostate cancer participated in this randomized, double-blinded, placebo-controlled (RDBPC) clinical trial. Participants took one capsule per day at breakfast during radiation treatment and for two weeks after treatment completion. They also were asked to follow a hydration regimen (8 cups [1.9 L] of water per day), but a low-hydration regimen (4-6 cups [0.9-1.4 L] of water per day) was added during the course of the trial since some patients, older men in particular, experienced discomfort with the recommended hydration protocol. Severity of urinary symptoms was measured using a modified version of the Expanded Prostate Cancer Index Composite (EPIC). At the end of the study, men in the cranberry group had lower incidences of cystitis and severe cystitis (65% and 30%, respectively) compared with those in the placebo group (90% and 45%, respectively), although these differences were not statistically significant ($P = 0.058$ and $P = 0.30$, respectively). Overall, the incidence of pain/burning was significantly lower in the cranberry group ($P = 0.045$) compared with the placebo group. Men on the low-hydration regimen in the cranberry group had less pain/burning ($P = 0.038$), stronger urine stream ($P = 0.030$), and used significantly fewer pads/liners ($P = 0.042$) compared to the placebo group. The authors concluded that men receiving radiation therapy for prostate cancer may benefit from using cranberry supplements, particularly those on low-hydration regimens or with baseline urinary symptoms.

In two recent clinical studies it was also found that cranberry may be able to effectively prevent recurrent lower UTIs. The first study was a small Italian study in which 22 people were offered a standardized cranberry extract (Anthocran; Indena SpA; Milan, Italy) with lifestyle advice, and 22 people were offered lifestyle advice without the cranberry extract (the control group).[2] The cranberry group experienced a 73.3% reduction ($P < 0.05$) in the frequency of UTI episodes during the study period compared with the two months before the trial, and the control group had a 15.4% reduction in frequency compared with the same period, a significant difference between groups ($P = 0.012$). Seven (31.8%) people in the cranberry group were symptom-free at the end of the study, but no patients in the control group were symptom-free, a significant between-group difference ($P < 0.05$). During the study period, the mean duration of UTI episodes was 2.5 ± 1.3 days in the cranberry group, compared with 3.6

Cranberry, *Vaccinium macrocarpon*
Photo ©2016 Steven Foster

* While this review comprehensively covers most of the clinical trials on cranberry preparations from 2010 to early 2016, this article is not meant to be exhaustive; accordingly, some studies have not been included.

± 1.7 days in the control group, a significant difference ($P < 0.05$). Urine evaluation for blood or bacteria was completely negative in 90.9% of those in the cranberry group and in 50% of those in the control group ($P < 0.005$). No adverse events were observed. The authors asserted that these preliminary results, which were obtained in a field-practice setting, indicate that a standardized cranberry extract can be effective and safe in the prevention of recurrent UTIs.

In the second, and much larger, study, 928 older adults (median age of 84; 703 women) living in nursing home facilities in the Netherlands took 500-mg cranberry capsules (containing 9 mg of PACs) or placebo capsules (both supplied by Springfield Nutraceuticals; Oud-Beijerland, Netherlands) twice daily for 12 months.[3] Participants were stratified according to UTI risk (risk factors included long-term catheterization, diabetes mellitus, and one or more UTIs in the preceding year). In participants with a high UTI risk at baseline (n = 516), the incidence of clinically defined UTIs was significantly lower with cranberry capsules than with placebo ($P = 0.04$). The treatment effect was 0.74 (95% confidence interval [CI] = 0.57-0.97), meaning the treatment reduced the risk of a clinically defined infection by 26%.

UTIs are among the most frequent complications after urinary tract surgical procedures, mainly when catheter placement is necessary. Although the use of cranberry has been linked to a reduced risk of UTIs, there has been no published study, until recently, reporting the value of its preventive effect against catheter-associated UTIs. A prospective trial of patients with double J catheters compared the UTI rate (confirmed by positive urine culture) of patients taking a cranberry extract (Urosens; Laboratorios Salvat; Barcelona, Spain) (120 mg per day) in addition to their routine prophylactic therapy (n = 31) to the rate of those receiving only routine prophylactic therapy (n = 31).[4] When the catheters were removed approximately 30 days after the start of the study, the UTI incidence was found to be significantly lower ($P = 0.04$) in the cranberry group (12.9%) compared to the placebo group (38.7%).

UTIs are a common hospital-acquired infection, and the risk is high after gynecological surgery during which a catheter is placed. Women (N = 160) undergoing such elective surgery were randomly assigned to take either TheraCran cranberry capsules (provided by Theralogix, LLC; Rockville, Maryland; equivalent to 480 mL per day of cranberry juice) or a matched placebo for six weeks after surgery.[5] The occurrence of UTIs during the study period was significantly lower ($P = 0.008$) in the cranberry group (19%) compared with the placebo group (38%) (odds ratio, 0.38; 95% CI = 0.19-0.79). After adjustment for known confounders, including the frequency of intermittent self-catheterization in the postoperative period, the protective effect of cranberry remained (odds ratio, 0.42). There were no significant differences between groups in terms of adverse events, such as gastrointestinal upset (56% in the cranberry group and 61% in the placebo group).

Finally, a cranberry powder (Flowens; supplied by Naturex-DBS LLC; Sagamore, Massachusetts) produced a clinically relevant, dose-dependent reduction in LUTS in men over 45.[6] This six-month, RDBPC study aimed to evaluate the effect of 250 mg or 500 mg cranberry powder on LUTS and urinary flow. A total of 124 volunteers with prostate-specific antigen (PSA) levels less than 2.5 ng/mL of blood and International Prostate Symptom Scores (IPSSs) of 8 or higher were recruited for the study. The primary outcome measure was the IPSS, evaluated at three and six months. Secondary outcome measures included quality of life, bladder volume (Vol), maximum urinary flow rate (Q max), average urinary flow rate (Q ave), ultrasound-estimated post-void residual urine volume (PVR), and levels of serum PSA, selenium, interleukin 6, and C-reactive protein, at six months. At the end of the study, volunteers in both cranberry groups had significantly lower IPSSs (-3.1 in the 250 mg group [$P = 0.05$] and -4.1 in the 500 mg group [$P < 0.001$]) compared to the placebo group, and a dose-response effect was observed. There were significant, favorable differences in Q max, Q ave, PVR, and Vol in the 500 mg cranberry group versus baseline ($P < 0.05$). A dose-dependent effect on Vol was observed, as well as on PVR for participants with a non-zero PVR. There was no effect on clinical chemistry or hematology markers.

Complex Mechanisms of Action

One of cranberry's most-studied mechanisms of action for preventing UTIs involves increasing the capacity of urine to prevent certain uropathogenic bacteria from adhering to epithelial cell receptors in the urinary tract. Many pathogenic bacteria contain fimbriae (thread-like appendages) that allow them to attach to epithelial cells. For example, the strains of *Escherichia coli* that cause UTIs can attach to uroepithelial cells. Cranberry's ability to prevent the P-fimbriated *E. coli* bacterium from adhering to these cells has been attributed to its content of A-type proanthocyanidins (A-PACs). PACs typically consist of molecules of catechin and epicatechin joined by carbon-carbon or carbon-oxygen bonds. Hence, catechin and epicatechin are referred to as monomers, and those polyphenols containing two to four of these monomers are referred to as oligomeric (meaning "a few") proanthocyanidins. In cranberry, they are also called procyanidins because they release colored cyanidin upon boiling with acid, hence the prefix "pro" (meaning "forming"). The linkage between the monomers in PACs can be either through one (B-type) or two covalent bonds (A-type). B-type PACs occur in grape (*Vitis vinifera*, Vitaceae) seed and pine (*Pinus* spp., Pinaceae) bark, whereas A-type PACs are found in cranberries.

Only the A-type PACs have demonstrated anti-adherence activity (larger PACs do not get absorbed in the bloodstream and are excreted in the urine due to their size), and urinary anti-adherence activity is correlated with a dose-dependent increase in PACs in cranberry products.[7] Preliminary studies suggest that larger PACs act in the gut to prevent *E. coli* invasion, thereby reducing the resident population capable of causing future UTIs, and may induce the indirect excretion of anti-adherence molecules into the urine. Further, the larger A-type PACs may bind to uropathogenic rectal isolates in the colon, rendering them unable to adhere in the urinary tract if they were to enter.[8]

A human study published in 2012 found procyanidin A2 (a dimer [i.e., a molecule composed of two identical or structurally similar, bonded monomers]) at 24 ng/mg creatinine in urine 11 hours after ingestion of cranberry.[9] (Concentrations of urinary metabolites are typically expressed per mg of creatinine due to the variability of a person's water intake, and hence excretion.) This was shared in a conference report, and the same group finally published more details of their findings in 2015, which indicate that other cranberry phytochemicals, or their metabolites, generally occur at much higher levels than procyanidin A2 (e.g., protocatechuic acid [a phenolic acid] at 21.1 mcg/mg creatinine is almost 1,000 times greater). However, these metabolites were not individually tested for anti-adherence activity.[10]

As studies continue to elucidate the details concerning the mechanisms of action, the anti-adherence activity of urine after cranberry consumption is now well-supported by clinical evidence. For example, two recent clinical studies from the same research group demonstrated a substantial rise in bacterial anti-adherence activity that peaked around three hours after cranberry beverage or extract consumption.[11,12]

Cysticlean (Vita Green Europa; Barcelona, Spain), at a dosage of 118 mg PACs per day, was found to reduce recurrent UTIs by 93% in a six-month, observational prospective study in 20 women.[13] And yet, 500 mg per day of cranberry fruit powder supplied by Naturex-DBS LLC, reported to contain only 2.8 mg A-type PACs per dose, also reduced UTIs in a trial involving 182 women with two or more UTI episodes in the past year.[14] Participants were randomly assigned to the cranberry (n = 89) or placebo group (n = 93) and received treatment for six months. Intention-to-treat analysis showed that in the cranberry group UTIs were significantly fewer than in the placebo group (10.8% vs. 25.8%, $P = 0.04$) over the course of the study. The cranberry group also experienced a longer time-to-first-UTI than the placebo group ($P = 0.04$).

Future Research Directions

The clinical trials summarized above add to the evidence that cranberry is a viable option for the prevention of UTIs in at-risk populations, or in those suffering from recurrent infections. The potential of cranberry for LUTS in older men is worthy of clinical consideration, and has been demonstrated in previous research.[15]

Vaccinium macrocarpon illustration from *Flora Batava of Afbeelding en Beschrijving van Nederlandsche Gewassen* (1872)
Image courtesy of Wikicommons.

There is controversy about label claims for, and measurement of, A-type PACs found in cranberry. This may explain some of the discrepancies in the clinical findings, meaning that the PAC contents of tested products may have been rather different than what was claimed in the studies, depending on the analytical method(s) used. Evidence of these complexities is provided in a study in which four products on the Swiss market with labeled PAC levels were tested by two different analytical techniques.[16] Results were provided by a photometric DMAC method (which uses 4-(dimethylamino)cinnamaldehyde [DMAC] as the color reagent) and an ultra high-performance liquid chromatography-tandem mass spectrometry (UHPLC-MS^2) assay. Per the DMAC method, PACs ranged from 16-61% of the label claim. The UHPLC-MS^2 assay yielded an even more stunning deviation, with PAC levels found to be 1.4-7.2% of what was declared on the labels. The discrepancies between the two methods may be explained in part by the fact that the UHPLC-MS^2 method quantified only catechin/epicatechin dimers and trimers, while the DMAC method included PACs

of higher polymerization degrees as well. However, all results, regardless of the method used, were still short of the label claims. The DMAC method is appropriate for measuring total PACs in soluble cranberry products, but results depend on the type of standard used.[17] Standardization of methods used to quantify A-type PACs in cranberry products of different tissue types (juice or pomace) and accurate labeling of products by type are essential to reduce consumer confusion and increase accuracy in reporting A-type PAC contents in clinical trials.

Many questions remain to be answered before the true mechanisms of action of cranberry in preventing UTIs are properly understood and corresponding quality/activity markers can be agreed upon with appropriate methods of analysis. Anti-adherence activity of urine is likely part, or perhaps even all, of the story, but the specific metabolites that deliver this activity remain to be unequivocally established. HG

Kerry Bone *is the co-founder of and innovation driver at MediHerb, where he serves as director of research and development. In 2016, MediHerb was awarded the American Botanical Council's (ABC's) Varro E. Tyler Award for Excellence in Phytomedicinal Research. As part of his educational role, Bone is principal of the Australian College of Phytotherapy and also adjunct professor at New York Chiropractic College, providing input into their postgraduate applied nutrition program. Bone has co-authored more than 30 scientific papers on herbal research, including original research and systematic reviews. He has also written or co-written six popular textbooks on herbal medicine, including his latest with Simon Mills, the long-awaited second edition of* Principles and Practice of Phytotherapy, *which was awarded ABC's 2013 James A. Duke Excellence in Botanical Literature Award.*

References

1. Hamilton K, Bennett NC, Purdie G, Herst PM. Standardized cranberry capsules for radiation cystitis in prostate cancer patients in New Zealand: a randomized double blinded, placebo controlled pilot study. *Support Care Cancer*. 2015;23(1):95-102. Available at: https://ourarchive.otago.ac.nz/bitstream/handle/10523/4839/hamiltonkatelin-2014brthons.pdf?sequence=3. Accessed September 20, 2016.
2. Ledda A, Bottari A, Luzzi R, et al. Cranberry supplementation in the prevention of non-severe lower urinary tract infections: a pilot study. *Eur Rev Med Pharmacol Sci*. 2015;19(1):77-80. Available at: www.europeanreview.org/wp/wp-content/uploads/77-80.pdf. Accessed September 20, 2016.
3. Caljouw MA, van den Hout WB, Putter H, Achterberg WP, Cools HJM, Gussekloo J. Effectiveness of cranberry capsules to prevent urinary tract infections in vulnerable older persons: a double-blind randomized placebo-controlled trial in long-term care facilities. *J Am Geriatr Soc*. 2014;62(1):103-110. Available at: www.ncbi.nlm.nih.gov/pmc/articles/PMC4233974/pdf/jgs0062-0103.pdf. Accessed September 20, 2016.
4. Barnoiu OS, Sequeira-García Del Moral J, Sanchez-Martínez N, Díaz-Molina P, Flores-Sirvent L, Baena-González V. American cranberry (proanthocyanidin 120 mg): its value for the prevention of urinary tracts infections after ureteral catheter placement. *Actas Urol Esp*. 2015;39(2):112-117.
5. Foxman B, Cronenwett AE, Spino C, Berger MB, Morgan DM. Cranberry juice capsules and urinary tract infection after surgery: results of a randomized trial. *Am J Obstet Gynecol*. 2015;213(2):194.e1-8. Available at: www.ncbi.nlm.nih.gov/pmc/articles/PMC4519382/pdf/nihms680709.pdf. Accessed September 20, 2016.
6. Vidlar A, Student V Jr, Vostalova J, et al. Cranberry fruit powder (Flowens™) improves lower urinary tract symptoms in men: a double-blind, randomized, placebo-controlled study. *World J Urol*. 2016;34(3):419-424.
7. Howell AB, Botto H, Combescure C, et al. Dosage effect on uropathogenic *Escherichia coli* anti-adhesion activity in urine following consumption of cranberry powder standardized for proanthocyanidin content: a multicentric randomized double blind study. *BMC Infections Diseases*. 2010;10(94):1-11.
8. Feliciano RP, Meudt JJ, Shanmuganayagam D, Krueger CG, Ree JD. Ratio of "A-type" to "B-type" proanthocyanidin interflavan bonds affects extra-intestinal pathogenic *Escherichia coli* invasion of gut epithelial cell. *J Agric Food Chem*. 2014;62(18):3919-3925.
9. Zampariello CA, McKay DL, Dolnikowski G, Blumberg J, Chen CYO. Determination of cranberry proanthocyanidin A2 in human plasma and urine using LC-MS/MS. *FASEBJ*. 2012;26:124.8.
10. McKay DL, Chen CY, Zampariello CA, Blumberg JB. Flavonoids and phenolic acids from cranberry juice are bioavailable and bioactive in healthy older adults. *Food Chem*. 2015;168:233-240.
11. Kaspar KL, Howell AB, Khoo C. A randomized, double-blind, placebo-controlled trial to assess the bacterial anti-adhesion effects of cranberry extract beverages. *Food Funct*. 2015;6(4):1212-1217.
12. Mathison BD, Kimble LL, Kaspar KL, Khoo C, Chew BP. Consumption of cranberry beverage improved endogenous antioxidant status and protected against bacteria adhesion in healthy humans: a randomized controlled trial. *Nutr Res*. 2014;34(5):420-427.
13. Sánchez Ballester F, Ruiz Vidal V, López Alcina L, et al. Cysticlean® a highly PAC standardized content in the prevention of recurrent urinary tract infections: an observational, prospective cohort study. *BMC Urol*. 2013;13:28.
14. Vostalova J, Vidlar A, Simanek V, et al. Are high proanthocyanidins key to cranberry efficacy in the prevention of recurrent urinary tract infection? *Phytother Res*. 2015;29(10):1559-1567.
15. Vidlar A, Vostalova J, Ulrichova J, et al. The effectiveness of dried cranberries (*Vaccinium macrocarpon*) in men with lower urinary tract symptoms. *Br J Nutr*. 2010;104(8):1181-1189.
16. Chrubasik-Hausmann S, Vlachojannis C, Zimmermann BF. Proanthocyanin content in cranberry CE medicinal products. *Phytother Res*. 2014;28(11):1612-1614.
17. Krueger CG, Chesmore N, Chen X, et al. Critical reevaluation of the 4-(dimethylamino)cinnamaldehyde assay: Cranberry proanthocyanidin standard is superior to procyanidin A2 dimer for accurate quantification of proanthocyanidins in cranberry products. *J Funct Foods*. 2016;22:13-19.

Cranberry *Vaccinium macrocarpon*
Photo ©2016 Steven Foster

Oral Lavender Oil Reduces Anxiety and Depression in Patients with Mixed Anxiety and Depressive Disorder

Reviewed: Kasper S, Volz H-P, Dienel A, Schläfke S. Efficacy of Silexan in mixed anxiety-depression — A randomized, placebo-controlled trial. *Eur Neuropsychopharmacol*. February 2016;26(2):331-340.

Editor's note: *The manufacturer of Silexan, Dr. Willmar Schwabe Pharmaceuticals, provided funding for this study. Two of the authors (Dienel and Schläfke) are employed by Schwabe, and the other two authors (Kasper and Volz) have served as consultants, on advisory boards, and/or on speakers' bureaus for the company.*

In some cases, patients present to their physicians with both anxiety and depression, and neither condition is dominant. These cases, which cannot be classified solely as generalized anxiety disorder (GAD) or as major depression, fall under the diagnosis of mixed anxiety and depressive disorder (MADD), per the World Health Organization's *International Statistical Classification of Diseases and Related Health Problems*, 10th Revision (ICD-10).

Silexan, the patented active substance in Lasea (both produced by Dr. Willmar Schwabe Pharmaceuticals; Karlsruhe, Germany), contains 80 mg of lavender (*Lavandula angustifolia*, Lamiaceae) flower oil in each capsule. Randomized, double-blind, placebo-controlled trials have shown that Silexan is an effective anxiolytic in patients with GAD or subsyndromal anxiety disorder. Secondary outcome measures used in these trials suggest that Silexan may also have an antidepressant effect.

Lavender *Lavandula angustifolia*
Photo ©2016 Steven Foster

The purpose of this randomized, double-blind, placebo-controlled study was to evaluate the efficacy and safety of Silexan in patients with MADD.

Outpatients (N = 318; aged 18-65 years) diagnosed with MADD according to the ICD-10 participated in this study that was conducted at 35 psychiatric practices in Germany between November 2012 and February 2014. Patients had scores of 18 points or greater on the Hamilton Anxiety Rating Scale (HAMA), with at least two points (indicating moderate symptom intensity) for HAMA items of "anxious mood" and "depressed mood," at inclusion and baseline. Patients were excluded if they had any previous suicide attempts or clear auto-aggressive behavior, scored two or more points on the "suicidal thoughts" item on the Montgomery-Åsberg Depression Rating Scale (MADRS), had other clinically relevant psychiatric or neurological diagnoses within the six months preceding randomization, abused substances, or used psychotropic drugs within the 30 days preceding randomization. Concomitant psychotherapy and psychotropic co-medication were not permitted during the study.

Patients received either 80 mg per day of Silexan or placebo for 70 days. Silexan complies with the lavender oil monograph of the *European Pharmacopoeia*, and the dosage was established in accordance with the German marketing authorization for the product. The placebo capsules were scented with 1/1,000 of the amount of lavender oil in the Silexan capsules to match the smell of Silexan (no other placebo contents were described).

The primary efficacy measure was the change in the investigator-rated HAMA and MADRS total scores from baseline to study end (10 weeks). For HAMA and MADRS, incidence of a favorable treatment response (defined as a 50% decrease in total score) and incidence of remission (defined as a decrease of more than 10 points on HAMA and 10 or more points on MADRS at study end) were secondary outcome measures. Other secondary outcome measures included the self-rated State-Trait Anxiety Inventory (STAI), the Hospital Anxiety and Depression Scale (HADS), Sheehan Disability Scale (SDS), the investigator-rated Clinical Global Impressions (CGI) scale and Short Form Health Survey (SF-36), adverse events (AEs), and safety parameters. For the CGI, a clinically relevant response was predefined as the number of patients with a reduction of illness severity in at least two categories (CGI item 1) and the number of patients assessed to be much or very much improved (CGI item 2). HAMA, MADRS, HADS, and STAI were assessed at baseline and weeks one, two, four, seven, and 10; CGI item 1, SDS, and SF-36 were assessed at baseline and week 10; and CGI item 2 was assessed only at week 10.

The majority (more than two-thirds) of the patients were women, and all but two patients were white. There were no significant differences between groups in demographic data or outcome measures at baseline. Based on CGI assessments, half of the patients in each group were at least moderately ill at baseline. Compliance was 99.6% in the Silexan group and 99.4% in the placebo group. One patient in the Silexan group and five patients in the placebo group were excluded from the per-protocol analysis due to unacceptable compliance (per-protocol analyses include only those who adhere to the study protocol). The frequency of AEs was similar between groups. Eructation (belching) was the only AE that occurred in the Silexan group markedly more frequently than in the placebo group (10% vs. 0%, respectively) and was considered potentially related to the treatment.

Anxiolytic Effect

The Silexan group had a significantly greater decrease in HAMA total scores than the placebo group at study end ($P = 0.008$, one-sided analysis of covariance [ANCOVA]). Silexan showed a statistically significant advantage over placebo from week four until treatment end. HAMA subscores indicated Silexan had a significant effect on both somatic and psychological anxiety ($P = 0.03$ for both subscales, two-sided t-tests). Responder and remitter rates were higher in the Silexan group (41.5% and 34.6%, respectively) than in the placebo group (34.6% and 28.8%, respectively). The Silexan group showed better improvement in anxiety than the placebo group, according to the STAI and HADS anxiety subscore (data not provided).

Antidepressant Effect

The Silexan group had a significantly greater decrease in MADRS total score than the placebo group at study end ($P < 0.001$, one-sided ANCOVA). Silexan showed a statistically significant advantage over placebo from week four until treatment end. Responder rates were higher in the Silexan group (40.3%) than in the placebo group (32.1%), and significantly more patients in the Silexan group (46.5%) than the placebo group (34%) were in remission ($P = 0.02$, two-sided chi-square test). HADS depression subscore decreased in both groups. Subgroup analyses of HAMA and MADRS scores revealed that patients with more severe symptoms at baseline had greater improvement with Silexan.

Significantly more patients in the Silexan group than the placebo group had a reduction of illness severity in at least two categories on the CGI ($P < 0.01$, two-sided chi-square test), and the number of patients assessed as much or very much improved on the CGI was significantly greater in the Silexan group ($P < 0.01$, two-sided chi-square test). Improvements in daily living skills were significantly more pronounced in the Silexan group than the placebo group based on SDS total score ($P < 0.01$, two-sided t-test), and all SDS subscores ($P < 0.05$, two-sided t-tests). SF-36 physical and mental health total scores were significantly more improved in the Silexan group than in the placebo group ($P = 0.01$ and $P < 0.01$, respectively, two-sided t-tests). The greatest benefits were observed in improving general health, vitality, role-emotional (i.e., limitations due to emotional problems), mental health, social functioning, and bodily pain ($P \leq 0.05$ for all, two-sided t-tests).

The authors concluded that "in patients suffering from MADD according to ICD-10 criteria, Silexan has an anxiolytic and antidepressant effect that leads to an improvement of impaired daily living skills and health-related quality of life and it was very well tolerated." The pre-determined standards for clinical relevance based on the CGI were met, indicating that Silexan had significant benefits in terms of reducing illness severity and global improvement. The homogenous ethnicity and age of the study population and the preponderance of female patients may limit the generalization of the results, as it is not clear whether this sample population was truly representative of patients diagnosed with MADD. Therefore, the study should be repeated with other populations. The degree to which illness severity at baseline may impact the efficacy of Silexan is unclear and should be explored in future studies as well.

This study fulfilled all of the Consolidated Standards of Reporting Trials (CONSORT) of herbal interventions criteria, with detailed reporting of all items except the chemical characterization of Silexan. HG

—Heather S. Oliff, PhD

Fenugreek Seed Extract Improves Symptoms of Androgen Decline, Sexual Function, and Testosterone Levels in Middle-aged and Older Males

Reviewed: Rao A, Steels E, Inder WJ, Abraham S, Vitetta L. Testofen, a specialized Trigonella foenum-graecum seed extract reduces age-related symptoms of androgen decrease, increases testosterone levels and improves sexual function in healthy aging males in a double-blind randomized clinical study. *Aging Male*. June 2016;19(2):134-142.

Editor's note: *The investigational products and study funding were provided by Gencor Pacific.*

The aging male syndrome (also known as andropause, partial androgen deficiency of the aging male, and late-onset hypogonadism) is characterized by a decrease in testosterone levels in men after age 40 in response to age-related physical changes such as weight gain, increased waist circumference, and deterioration of general health associated with chronic diseases such as diabetes, liver disease, and cardiovascular disease. Symptoms include weakness, increased abdominal fat, musculoskeletal changes and joint pain, hot flashes or sweating, sleep disturbances, insomnia, fatigue, depression, and low bone mineral density. Fenugreek (*Trigonella foenum-graecum*, Fabaceae) seed extract is reported to have a positive effect on male sexual health and promote anabolic and androgenic activity in younger men. This double-blind, randomized trial assessed the effect of a standardized fenugreek seed extract on symptoms of possible androgen deficiency, sexual function, and serum hormone concentrations in healthy aging males.

The study was conducted between February and November 2014 in Brisbane, Australia. Healthy male subjects (N = 120), aged 43 to 75 years, were recruited through a trial recruitment database and public media. The subjects underwent a comprehensive screening after an initial health assessment that included lifestyle questions, current medications, medical history, and a physical examination. The long list of exclusion criteria included any condition which, in the opinion of the investigator, made the subject unsuitable (e.g., any urogenital dysfunction, disease, abnormality, or surgery; medications affecting any of the measured parameters; major physical or psychiatric disorders, etc.).

The active treatment was Testofen (Gencor Pacific; Hong Kong, China), a standardized fenugreek seed extract, at a dose of 600 mg daily for 12 weeks. Testofen is a fenugreek extract standardized to 50% fenuside, described by Gencor Pacific as a proprietary matrix of saponin glycosides. The placebo contained maltodextrin.

The primary outcome measure was the change in the Aging Male Symptom (AMS) questionnaire, a measure of possible androgen deficiency symptoms. The AMS questionnaire, which includes 17 questions in three domains (psychological, somatic, and sexual), was completed at baseline, week six, and week 12. Secondary outcome measures were sexual function and serum testosterone. Sexual function was assessed using the Derogatis Interview for Sexual Functioning-Self Report (DISF-SR) questionnaire at baseline and at week 12. Serum levels of total testosterone, calculated free testosterone, sex hormone binding globulin (SHBG), dehydroepiandrosterone sulfate (DHEA-S), androstenedione, estradiol, and prolactin were measured from fasting blood draws at baseline, week six, and week 12. Serum lipids, electrolytes, and liver function were also assessed at baseline and week 12.

Fenugreek *Trigonella foenum-graecum*
Photo ©2016 Steven Foster

Of the 120 enrolled subjects, 111 completed the study (55 in the active treatment group and 56 in the placebo group). Five subjects in the placebo group discontinued treatment (two noted a lack of results and three gave no reason). In the fenugreek group, four subjects discontinued treatment (two for personal reasons and two because of adverse effects [AEs] including headache and dizziness). The remaining subjects in the treatment group ranged in age from 43 to 75 years (mean = 54.8 years); those in the placebo group were aged from 40 to 74 years (mean = 56.4 years).

No significant baseline between-group differences were seen in anthropometric measures, lifestyle factors, or lipid profiles. In both groups, the mean serum levels of total testosterone and free testosterone concentrations fell within the lower end of the healthy reference range for men in this age group. Correlations observed at baseline for all subjects were as follows: weak negative correlation between age and free testosterone, negative correlation between body mass index (BMI) and both total testosterone (P = 0.002) and free testosterone (P = 0.003), and total testosterone positively associated with high-density lipoprotein cholesterol (HDL-C) (P = 0.017) but not with total cholesterol or low-density lipoprotein cholesterol (LDL-C). No correlation between testosterone and the AMS score was observed except for the somatic subdomain (P = 0.001), and no correlations were seen between total or free testosterone levels and sexual function, sleep, or physical activity.

Fenugreek seed extract significantly improved total AMS score (P = 0.013) compared to placebo, with significant improvements in the somatic (P < 0.03) and sexual (P = 0.009) sub-scores. No treatment effect was seen for the psychological sub-score. Total score on the DISF-SR was improved significantly in the fenugreek group at week 12 compared with baseline (P = 0.006), with significant increases in the sexual arousal (P = 0.001) and sexual drive/relationship (P = 0.007) domains. No significant changes were seen in the placebo group.

At baseline, both groups reported an average of one erection weekly; this increased significantly to two to three weekly (P = 0.001) in the fenugreek group. Both groups at baseline reported sexual activity approximately one to two times monthly; by week 12, this increased significantly (P = 0.004) to almost once weekly in the fenugreek group. These results are consistent with the positive results reported in the AMS sexual function subdomain. No significant changes were seen in the placebo group. Between-group differences were not reported.

Small but significant increases were seen in total testosterone (P = 0.001) and calculated free testosterone (P = 0.002) levels from baseline to week 12 in the fenugreek group. These increases suggest a potential mechanism for the positive effects observed in somatic and sexual function. No significant changes were observed in any of the other hormones, liver function, or lipids in either group. No changes in BMI, waist-hip ratio, grip strength, sleep patterns, physical activity, or fatigue were observed in either group.

The fenugreek seed extract was well-tolerated, with no serious AEs reported. Of the five minor AEs reported, three occurred in the fenugreek group (headaches in two subjects and dizziness in one), and two occurred in the placebo group (nausea in one subject and increased asthma symptoms in another). The AEs were not attributed to the study medications.

The authors concluded that the fenugreek seed extract was safe and effective, reducing symptoms of possible androgen deficiency, improving sexual function, and increasing testosterone levels in healthy middle-aged and older men. A limitation of the study was the lack of between-group comparisons for two of the measures (number of erections and sexual frequency). HG

—Shari Henson

Meta-analysis Finds Curcumin to Be an Effective Adjunct Treatment for Major Depressive Disorder

Reviewed: Al-Karawi D, Al Mamoori DA, Tayyar Y. The role of curcumin administration in patients with major depressive disorder: Mini meta-analysis of clinical trials. *Phytother Res*. 2016;30(2):175-183.

Nearly 50% of patients with major depressive disorder (MDD) discontinue treatment due to adverse events. Therapies with better tolerability are needed to treat this chronic disease that negatively affects quality of life and increases morbidity. The antidepressant activity of curcumin, a chemical constituent of turmeric (*Curcuma longa*, Zingiberaceae) rhizome, has been evaluated in numerous clinical trials. This meta-analysis evaluated the safety and efficacy of curcumin in the treatment of MDD.

The search of the literature and presentation of the results followed the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). The following databases were searched from 1986 through 2016: PubMed, Scopus, PsycINFO, Evidence-Based Medicine Guidelines, DynaMed, JAMAevidence, and the Cochrane Library. The following key words were used: curcumin, depression, MDD, efficacy, and effect. Reference lists of identified papers were hand-searched. Included articles met the following criteria: (1) human study, (2) quantitative analysis, (3) intervention and control group, (4) curcumin was an independent intervention, (5) study addressed only MDD, (6) depression was measured with standardized scales, and (7) the study was published in English. The Quality Assessment Tool for Quantitative Studies was used to assess study quality and an overall rating of methodological quality was assigned. This rating system classifies studies as strong (no weak ratings), moderate (one weak rating), or weak (two or more weak ratings). For the meta-analysis, the data from all studies were converted into Hamilton Depression Rating Scale scores according to published methods. Small sample sizes were adjusted with the Hedges' adjusted *g* formulation of standardized difference in means. The random-effects model and generic inverse variance method were used to combine the results since the studies had different design characteristics.

Turmeric *Curcuma longa*
Photo ©2016 Steven Foster

A total of 1,757 studies were identified, and six met all inclusion criteria (four randomized controlled trials, one crossover study, and one open-label study).[1-6] The six studies included a total of 342 patients (n = 177, curcumin; n = 165, control). All patients received antidepressant therapy in addition to either curcumin (1,000 mg per day in five studies or 500 mg per day in one study) or placebo. In regard to methodological quality, five were rated as strong, and one was rated as moderate. The meta-analysis showed a significant reduction in MDD symptoms with curcumin treatment compared with control (P = 0.002). This outcome was not influenced by any single study. Several subgroup analyses were conducted with the following outcomes: (1) curcumin had a significant benefit in middle-aged patients (P = 0.002) but not older-aged patients (specific age ranges not described); (2) curcumin had a significant benefit in patients treated for more than six weeks (P = 0.001), but not patients treated for less than six weeks; (3) the 1,000 mg per day of curcumin had a significant benefit (P = 0.002), but the 500 mg per day did not; and (4) curcumin had a significantly greater benefit in patients with MDD only compared with patients with MDD plus comorbidities (P = 0.001).

In two of the studies,[4-5] researchers used BCM-95 (Arjuna Natural Extracts Ltd.; Aluva, Kerala, India), a standardized preparation of curcuminoids blended with the essential oil of turmeric. In three of the studies,[1-3] the curcumin treatment also contained piperine, a chemical constituent of black pepper (*Piper nigrum*, Piperaceae) fruit that has been shown to increase the bioavailability of curcumin. The authors of the meta-analysis provided no further descriptions of the curcumin preparations used in the six studies. Subgroup analysis showed that treatments containing piperine had smaller benefits than curcumin alone (P = 0.05). However, the authors note that two of these studies used a low (potentially subtherapeutic) dose of piperine, and the study that used a higher dose of piperine used a low dose of curcumin (which may have been too low to produce an effect). Therefore, the piperine meta-analysis should be viewed with caution.

The pooled data had minimal heterogeneity as assessed with the I^2 index. Funnel plot analysis showed no publication bias. Adverse events were digestive/gastrointestinal complaints (e.g., gastritis, nausea), tachycardia, flushing, and giddiness. Two of the six studies reported no adverse events; adverse effects in the placebo groups were not reported.

According to the authors, this is the first meta-analysis of the effect of curcumin on MDD. The authors conclude that curcumin is effective in reducing symptoms of depression in patients with MDD who are taking antidepressants. They also note that curcumin is more effective in middle-aged patients, at a dose of 1,000 mg per day, and when taken for more than six weeks. The authors acknowledge that the results should be interpreted with caution because only six studies were included and only two doses of curcumin preparations were evaluated. They also acknowledge that the dose of piperine and/or curcumin may not have been optimal, and that long-term outcomes were not assessed despite that MDD is a chronic condition.

The authors used rigorous methodology in conducting the meta-analysis. These encouraging results indicate that larger and longer-duration clinical trials of curcumin in the treatment of MDD are warranted. There were no conflicts of interest. HG

—Heather S. Oliff, PhD

References

1. Bergman J, Miodownik C, Bersudsky Y, et al. Curcumin as an add-on to antidepressive treatment: a randomized, double-blind, placebo-controlled, pilot clinical study. *Clin Neuropharmacol*. 2015;36(3):73-77.
2. Esmaily H, Sahebkar A, Iranshahi M, et al. An investigation of the effects of curcumin on anxiety and depression in obese individuals: a randomized controlled trial. *Chin J Integr Med*. 2015;21(5):332-338.
3. Panahi Y, SadeEi R, Karami GR, Sahebkar A. Investigation of the efficacy of adjunctive therapy with bioavailability-boosted curcuminoids in major depressive disorder. *Phytother Res*. 2015;29:17-21.
4. Lopresti AL, Maes M, Maker GL, Hood SD, Drummond PD. Curcumin for the treatment of major depression: a randomized, double-blind, placebo controlled study. *J Affect Disord*. 2014;167:368-375.
5. Sanmukhani J, Satodia V, Trivedi J, et al. Efficacy and safety of curcumin in major depressive disorder: a randomized controlled trial. *Phytother Res*. 2014;28(4):579-585.
6. Yu JJ, Pei LB, Zhang Y, Wen ZY, Yang JL. Chronic supplementation of curcumin enhances the efficacy of antidepressants in major depressive disorder: a randomized, double-blind, placebo-controlled pilot study. *J Clin Psychopharmacol*. 2015;35(4):406-410.

VALUE CHAINS OF BOTANICALS AND HERBAL MEDICINAL PRODUCTS:
A European Perspective

By Anthony Booker, PhD,[1,2] and Michael Heinrich, Dr. rer. nat. habil.[1]

[1] Research Cluster Biodiversity and Medicines/Centre for Pharmacognosy and Phytotherapy, University College London (UCL) School of Pharmacy, University of London

[2] Division of Herbal and East Asian Medicine, Department of Life Sciences, University of Westminster, London

Introduction

In recent years, the quality of botanicals has come under increased scrutiny. Despite the availability of numerous high-quality products from reputable companies, health care professionals, patients, and consumers are understandably concerned about questionable botanical ingredients in various consumer products. In Europe, this includes products that are generally unlicensed and unregistered supplements (also referred to as "botanicals"), which are often poorly regulated, or even totally unregulated, depending on the country of jurisdiction.*

This overview discusses the concept of value chains (some have referred to them as "value networks"[2]), emphasizing that it offers a framework for assessing the current quality problems with botanical raw materials and extracts with respect to their adulteration, and for developing strategies for best practices in the global botanical industry. We propose that some form of self-regulation, if it enforces good quality and follows best practices, will need to be linked to an understanding of value chains by those selling final products, irrespective of their regulatory status. Importantly, the concept of value chains also involves an understanding of the socioeconomic impact of different production systems on primary producers and other stakeholders.

The examples discussed here are based on studies of plant-based products sold in Europe (and, to a lesser degree, in North America) and compares regulated products with unregulated products, since such distinctions apply in Europe, per below.

The Need for Value Chains

An important difference between, for example, the United States and member states of the European Union (EU) is the level of regulation of plant-based products and the subsequent enforcement of the regulations. The European system offers an example of how quality assurance was introduced over the last 15 years. In the EU, traditional herbal registration (THR), as established by EU Directive 2004/24/EC,[3] has set minimum standards that aspire to guarantee the quality and safety of herbal medicinal products sold with medical claims for minor self-limiting diseases. The THR is one of several regulatory frameworks, and many European countries also regulate products under the Well-Established Use Directive[4] (Article 10(a) of EU Directive 2001/83/EC, as amended) or under national regulations that allow for full licensing as medicines.

THR is an example that highlights how consistent and high-quality herbal medicines can be produced by using such a regulatory framework. Alternatively, a company could go for a more rigorous and well-enforced self-regulation, driven by the relevant industry bodies. The introduction of more rigorous standards implemented at a global level results in a greater integration between some processors and primary producers, who are then able to ascertain better quality and to obtain more stable prices. Such standards could be based on a regulatory framework or on commonly agreed-upon principles of best practice, which are certified, for example, by an external agency.

A useful framework to achieve this improved quality is the concept of value chains, which for certain key food products (e.g., coffee [*Coffea arabica*, Rubiaceae], tea [*Camellia sinensis*, Theaceae], and cocoa [*Theobroma cacao*, Malvaceae]) have been investigated widely. However, value chains of medicinal botanicals have been largely ignored in the global research literature.[5,6] Analysis of the value chains of botanicals is important, since it is a critical part of understanding the quality and safety breakdowns that can occur along the chain — breakdowns that are likely to result in sub-standard or even unsafe finished products for consumers. While this is in no way a new problem (in fact, pharmacognosy as a scientific discipline has resulted, at least partially, from the need to identify adulteration and define best quality), it has become an evermore relevant problem with the rapid and dramatic globalization of trade in botanicals and herbal medicinal products.

*The American Botanical Council (ABC) has been actively bringing together stakeholders interested in educational efforts intended to help reduce the level of adulteration and contamination of ingredients used in such products.[1]

A value chain differs conceptually from a supply or commodity chain in that it is founded upon the insight that any company is more than a random assembly of machinery, people, and finance. Only if these things are arranged into definable systems will it become possible to produce a higher quality commodity for which customers are willing to pay.[7]

In our own research on botanicals and regulated phytomedicines, we have found that value addition can be introduced at various stages of production. This can occur, for example, through certified organic cultivation, use of superior extraction techniques, and/or through more stringent regulation, such as the European THR.[8-10]

For example, in the case of saw palmetto (*Serenoa repens*, Arecaceae) berry we found that regulated products manufactured using an extraction process with a soft gelatin capsule dosage form were typically of higher quality and more consistent than other products tested.[11] In the case of *Rhodiola rosea* (Crassulaceae) root products, we found that approximately one quarter of products that were marketed without a THR were of poorer phytochemical quality than those marketed with a THR as Traditional Herbal Medicines (THMs).[10] In addition, some of these products were adulterated with other species or did not meet their label specifications. This does not mean that all non-THR products were of poor quality. In fact, some sold as botanicals were comparable. One major problem with non-THR products is that it is practically impossible for consumers to differentiate high-quality products from low-quality products. Our data confirm that by choosing a THR product, the quality and safety are assured.

Benefits of Vertical Integration

We suggest that vertical integration, in which contracts are made directly with the farmers and primary processors, not only benefits those involved in primary production but also can lead to higher quality products for consumption in more economically developed countries. In such a value chain, a lead organization is responsible for two or more intertwined steps of the manufacturing or value chain process. Vertical integration, however, has been criticized as resulting in a high degree of dependence on the primary producers.[9]

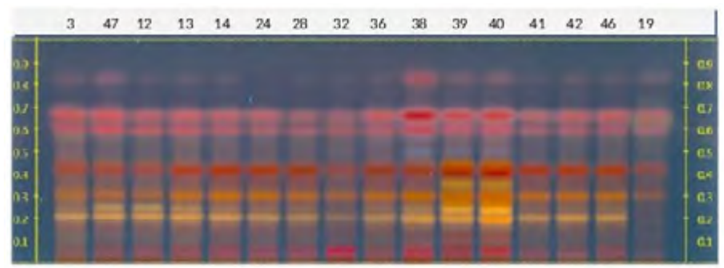
The product quality and economic benefits for a primary producer are highlighted in our work on turmeric (*Curcuma longa*, Zingiberaceae).[12] Looking at the production process of a multipurpose product containing turmeric root and rhizome, we found that turmeric derived from organically grown crops in India under contract from a European manufacturer retained more volatile phytochemical compounds. Such compounds are generally lost when turmeric is stored for long periods (e.g., when the market price is low). Moreover, we found that some products that were obtained through middlemen were the wrong species and thus did not meet the label claims (Figure 1).

Products derived from a vertically integrated value chain (VIVC) have obvious benefits for the consumer and, based on our assessment, the producers as well. The producers we evaluated in India, who were able to access the international market and agree to a quantity and price with the manufacturer prior to cultivation, were less susceptible to the price fluctuations and market shocks that can easily upset the smooth and expedient transfer of goods from one country to another.[12]

Value chains of botanicals and herbal medicinal products can be highly diverse. Vertical integration is not widespread throughout the industry, and free markets and middlemen are still the most common routes of supply. Supply chains for cultivated materials and wild-collected materials each have associated challenges, and the picture is further complicated by a lack of regulatory harmonization among different global regions and countries, including many that are within the EU.

In our own investigations,[10-12] we found that a VIVC was conducive to the manufacture of organically grown products in which it is a requirement that traceability to the exact area of origin can be proved, and documented procedures for any primary processing are implemented (Figure 2).

Figure 1. HPTLC Chromatogram of Various Turmeric Root/Rhizome Samples and Powdered Products



More phytochemicals were present in the fresh rhizome samples 38, 39, and 40. The integrated chain powder samples 47, 12, and 13 displayed a strong zone at Rf 0.25, which was also observed for the fresh rhizome samples. The integrated chain samples and the fresh rhizome samples also displayed a stronger zone at Rf 0.83. Sample 19 displayed a different pattern, and the bisdemethoxycurcumin zone at Rf 0.2 was missing, which indicates that this sample was not *Curcuma longa*.

Figure 2. Cultivation and Primary Processing of Phytomedicines in an Integrated Chain

Photo A: Medicinal plants are harvested and put through a tiered wash cycle.

Photo B: After washing, the crops are dried in a covered area on designated racks.

Photo C: The dried material is cut into the required size at the factory.

Photo D: The dried material is then checked for foreign matter.

Photos ©2016 Anthony Booker

THR vs. Non-THR Products

Multiple factors differentiate products produced with a THR. Although there is no requirement for a THR product to be linked to any particular value chain, a company's commitment to and considerable financial investment in obtaining a THR constitutes a significant value addition to the product (Table 1), and it requires the establishment of robust systems of quality control, from good agricultural and collection practices (GACPS) to good manufacturing practices (GMPs) throughout the value chain.

THR products used to treat minor self-limiting conditions are now widely available within the EU. It is a legal requirement for any product that makes a medicinal claim, or any product that is deemed to have a significant pharmacological effect, to hold a registration before being placed on the market.[13] Such products can be readily identified by their unique THR number, and many also display the THR logo.

Food supplements (botanicals), however, are not yet required to have a THR before entering the market in Europe, and they remain widely unmonitored. Although regulations do exist, they are rarely cited or enforced. Food supplements are often mislabeled or make misleading claims, and the lack of effective enforcement in Europe has resulted in a large number of these products entering the market.

The value chains of food supplements typically are undisclosed, and it is only through careful analysis of the products that problems may be detected. In our unpublished investigation of milk thistle (*Silybum marianum*, Asteraceae) fruit extract and our analysis of ginkgo (*Ginkgo biloba*, Ginkgoaceae) leaf extract products,[14] carried out in collaboration with the BBC for its series *Trust Me, I'm a Doctor*,[15] we found widespread quality and adulteration problems. Approximately 40% of unregistered milk thistle products, sold legally as supplements in the EU, contained very low levels of the bioactive marker compounds collectively referred to as silymarin. Furthermore, after a detailed investigation, we found that more than 50% of ginkgo products either were not compliant with their label claims; contained high levels of flavonols, rutin, and/or quercetin; or were adulterated, one with a 5-hydroxytryptophan (5-HTP) derivative.

Wild-collected vs. Cultivated Material

The impact that different value chains have on botanicals and herbal medicinal products and their quality also can be linked to livelihoods and sustainability. Many rural communities and indigenous groups, particularly in Asia, depend on medicinal plant collection for their livelihoods.[16] A common pattern can be seen across different countries: As collected plants are depleted in the wild, their scarcity in the marketplace increases along with their economic value. This drives collectors to travel to isolated and potentially dangerous areas in order to find more of the raw material, or to use superficially similar material that can be sourced at lower cost. The collectors themselves, however, are often unaware of the true market value of the plants they collect and are prone to exploitation by middlemen.

The pressure to find more material may lead to adulteration of the crop with similar species (e.g., as with *Rhodiola* species) or adulteration further down the value chain. Another example is the adulteration of ginkgo products with lower-cost rutin derived from buckwheat (*Fagopyrum esculentum*, Polygonaceae). This is done in order to increase the flavonoid content of the product and to achieve a superficial similarity to some of the existing analytical standards that relate to ginkgo leaf extract. Clearly all such products, if they do not comply with the label claim, are put on the market illegally.

An integrated chain using cultivated material may provide a better alternative to these models, but a major drawback for many manufacturers and retailers is the cost. Cultivated material is typically more expensive than wild-collected material, especially when it is produced in more economically developed countries. This is particularly true for root crops that require a number of years of growth before they can be harvested, such as Asian ginseng (*Panax ginseng*, Araliaceae) and rhodiola. These crops are typically grown for four to six years before harvesting and incur considerable expenditure of both time and money. There are also concerns by some that cultivated material may be in some way inferior to wild-collected material, and that certain cultivated plant-based products may be less appealing to consumers.

Welfare Effects

Some companies, including manufacturers of food supplements containing botanical ingredients, have managed not only to find a way to cultivate their own crops, but also to use the VIVC model to their advantage. In doing so, they highlight to the general public the high quality of their products due to the tight controls employed along the chain, and raise awareness of the potential welfare effects that such chains can have on the primary producers in less economically developed countries (e.g., in India and Eastern European countries).[17] These welfare effects may not be sizeable in terms of hard cash but can help in some practical ways, and will be of longer-term benefit. For example, farmers can plan their crops based on definite orders, which can give farm workers and those involved in primary processing fixed terms of employment, rather than having to travel the country in search of farm labor or factory-based employment.

Rhodiola crenulata is collected at high altitude on the Chinese Sichuan-Tibet border. *Rhodiola crenulata* is used in the Chinese medicine industry, but based on the *European Pharmacopoeia*, for example, it is an adulterant. In other cases (if no specific label claims are made) it could be considered a substitute. Photo ©2016 Anthony Booker

The VIVC model has some obvious similarities to the Fairtrade approach.* However, in order to gain Fairtrade certification, farmers need to have a certain amount of infrastructure already in place. Consequently, it is not always a suitable partnership for the poorest farmers.[18] The partnerships that have been built between farmers and companies

Table 1. Comparing Benefits and Risks: THR Products vs. Non-THR Products

THR Products	Non-THR Products
Benefits	***Risks***
Cultivation & Collection Practices	
Quality from the source — *Controlled agricultural, cultivation, and collection practices.*	**Reliance on middlemen** — *Limited botanical knowledge may lead to misidentification of plant material.*
Primary Processing	
According to good manufacturing practices — *Batch integrity is maintained throughout processing. In-house quality control.*	**Variable standards followed** — *Poor controls, including container, packaging, and storage, can lead to spoilage.*
Manufacturing	
Standard operating procedures — *Tightly controlled processing leads to consistently high-quality products.*	**Manufacture may be poorly controlled** — *Lack of standard procedures can result in lower quality finished products.*
Retail	
Defined shelf-life based on extensive stability studies — *High confidence in product integrity during specified shelf-life.*	**Often lacking meaningful stability studies** —*Prolonged shelf-life can lead to deterioration of product due to spoilage.*
Consumers	
Purchases registered product — *Consumer has confidence that the product is safe and of good quality.*	**Purchases unregistered product** — *Variable quality and safety. Consumers are poorly informed about products.*

* Fairtrade (www.fairtrade.net) was established to support farmers and farm workers, mainly in less economically developed countries. The Fairtrade mark gives consumers the knowledge that workers have been paid a fair price and work under a set of agreed-upon working conditions.

producing both regulated and unregulated end products may offer an extra level of support for some of these poorest workers. Of course, a more informal fair-trade VIVC approach can also have its dangers without good governance. Some studies suggest that certain VIVCs, particularly ones that are dominated by a single powerful company, can lead to negative effects on the livelihoods of small producers.[19] Only through the establishment of mutual trust over a period of time (quasi-vertical integration) can these partnerships be successful and flourish.

A comparison of the different value chain approaches along with their main risks and benefits is given in Table 2. In comparing both tables, it becomes apparent that VIVCs and THR-driven supply systems have a number of similarities, most importantly as they relate to the possibility of ascertaining a consistent, high-quality end product.

Conclusion

Overall, to both producers and consumers, VIVCs appear to offer some distinct advantages over the reliance on middlemen that often occurs in a free-market system. However, in a market in which cost may still be the major driving force for most consumers of botanicals and herbal medicinal products, it is unlikely that VIVCs will become commonplace without sufficient consumer-driven demand for a specific group of products (e.g., demand for organically grown raw materials).

The examples presented here offer models for how to ascertain the best quality botanicals and herbal medicinal products. The research highlights not only the need for taking a broader approach with regard to quality control (including an understanding of best practices from source to consumer), but also that either regulation or self-regulation of the relevant industry is essential for quality assurance.

The lack of any government strategies for the effective cultivation, process-management, and regulation of wild-sourced medicinal or locally grown (often by smallholders) plant material — particularly plant material originating from less economically developed countries — is a major cause for concern for producers, manufacturers, and consumers of plant-based products. However, VIVC-based approaches, which encompass effective partnerships, ethical trading, and good governance, can help provide a more stable platform from which safe and high-quality products can be sustainably produced. HG

Acknowledgements

The initial research carried out on value chains and turmeric, which allowed the authors to develop the overarching concepts, was funded by The Leverhulme Trust (UK). Anthony Booker's research position is funded through a charitable donation by Dr. Willmar Schwabe GmbH & Co. KG, Karlsruhe, Germany.

Research on saw palmetto was partially funded by Bioforce AG, Switzerland. Intact and unopened ginkgo and milk thistle product samples were purchased with funds provided by the BBC. The authors express special gratitude to Deborah Johnston, PhD (School of Oriental and African Studies, University of London), for many discussions during the development of the concepts on value chains.

Anthony Booker, PhD, *is a senior lecturer in Chinese herbal medicine and medicinal plant science at The University of Westminster in London. In 2014, he received a doctorate from University College London in ethnopharmacy and pharmacognosy. His current post-doctoral projects at UCL investigate medicinal plant value chains and the quality of plant-based products. Email: anthony.booker.11@ucl.ac.uk.*

Michael Heinrich, Dr. rer. nat. habil., *is a professor at the Centre for Pharmacognosy and Phytotherapy, School of Pharmacy, University of London. Much of his research interest lies in ethnobotany, pharmacognosy, the quality of herbal medicinal products, and designing increased value for herbs along the supply chain. He is the co-author of a textbook on pharmcognosy and a member of the ABC Advisory Board. Email: m.heinrich@ucl.ac.uk.*

Table 2. Comparing Benefits and Risks: Vertically Integrated Value Chains vs. Free-Market Approach

Vertically Integrated Value Chains	Free-Market Approach
Benefits	***Risks***
Cultivation & Collection Practices	
Controlled agricultural, cultivation, and collection practices through on-site training and detailed customer requirements (e.g., organically grown).	*Impossible to control or influence collection and cultivation practices. Reliable traceability of defined batches often is lost along the chain.*
Primary Processing	
Company is in a stronger position to request and agree to primary processing procedures with the producers.	*How the harvested crop is initially processed (e.g., cutting and drying) is largely unknown.*
Producers	
Producer benefits from agreeing to known quantities of crops at fixed prices. Staff can benefit from training and input.	*Producer may reap greater financial benefits when prices are high but can experience big losses when market prices crash.*
Buyers (Retailers)	
Buyer is able to have some control along the length of the chain and plan for following years.	*Buyer maintains control of product only after it has been purchased. Buyer can be affected by price fluctuations and shortages.*
Consumers	
Good traceability back to the fields or collection areas. May be better quality.	*Often little or no traceability. May be lower-cost, but quality may be poorer.*

References

1. ABC-AHP-NCNPR Botanical Adulterants Program. Available at: http://cms.herbalgram.org/BAP/index.html. Accessed September 29, 2016.
2. Bewicke C. The global botanical supply chain: How it works & do we get what we pay for? — A supplier's viewpoint. Talk presented at: The UNPA Raw Materials & Supply Chain Summit; February 23-24, 2016; Salt Lake City, UT. Available at: www.slideshare.net/SandyHays/unpa-2016-the-global-botanical-supply-chain-by-cal-bewicke-eni. Accessed September 29, 2016.
3. European Parliament and the Council of the European Union. Directive 2004/24/EC of the European Parliament and of the Council of 31 March 2004 amending, as regards traditional herbal medicinal products, Directive 2001/83/EC on the Community code relating to medicinal products for human use. *Official Journal of the European Union*. April 30, 2004;L 136:85-90.
4. European Parliament and the Council of the European Union. Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use. *Official Journal of the European Union*. November 28, 2001;75(L 311):67-128.
5. Fullbright. Product chain study: Orthodox tea. Commercial agriculture development project. Vol Final Report. Nepal: Ministry of Agriculture and Cooperatives, Department of Agriculture; 2008:1-31.
6. Kaplinsky R. Competitions policy and the global coffee and cocoa value chain. United Nations Conference for Trade and Development (UNCTAD): United Nations; 2004.
7. Recklies D. The Value Chain. Management Models and Tools. Vol 2013. Recklies Management Project GmbH; 2001. Available at: www.themanager.org/Models/ValueChain.htm. Accessed July 31, 2016.
8. Booker A, Johnston D, Heinrich M. Value chains of herbal medicines — Research needs and key challenges in the context of ethnopharmacology. *J Ethnopharmacol*. 2012;140:624-633.
9. Shahidullah AKM, Haque CE. Linking medicinal plant production with livelihood enhancement in Bangladesh: Implications of a vertically integrated value chain. *J Transdisciplinary Environ Stud*. 2010;9:1-18.
10. Booker A, Jalil B, Frommenwiler D, et al. The authenticity and quality of *Rhodiola rosea* products. *Phytomedicine*. 2016;23:754-762.
11. Booker A, Suter A, Krnjic A, et al. A phytochemical comparison of saw palmetto products using gas chromatography and H1 NMR metabolomic profiling. *Journal of Pharmacy and Pharmacolgy*. 2014;66:811-822. doi:10.1111/jphp.12198.
12. Booker A, Johnston D, Heinrich M. The welfare effects of trade in phytomedicines: A multi-disciplinary analysis of turmeric production. *World Development*. 2016;77:221-230.
13. EMA. Uptake of the traditional use registration scheme and implementation of the provisions of Directive 2004/24/EC in EU member states. Patient Health Protection. London, UK: European Medicines Agency; 2013.
14. Booker A, Frommenwiler D, Reich E, Horsfield S, Heinrich M. Adulteration and poor quality of *Ginkgo biloba* supplements. *J Herbal Med*. 2016;6(2):79-87.
15. Do herbal supplements contain what they say on the label? *Trust Me, I'm a Doctor*. BBC Two website. Available at: www.bbc.co.uk/programmes/articles/4hX30rMYkMv9YjMTH38MY6/do-herbal-supplements-contain-what-they-say-on-the-label. Accessed October 4, 2016.
16. Alam G, Belt J. Developing a medicinal plant value chain: Lessons from an initiative to cultivate Kutki (*Picrorhiza kurrooa*) in Northern India. KIT Working Papers Series C5. Amsterdam: KIT; 2009.
17. van de Kop P, Alam G, de Steenhuijsen Piters B. Developing a sustainable medicinal plant chain in India. Linking people, markets and values. In: Ruben R, Slingerland M, Nijhoff H, eds. *Agro Food Chains and Networks for Development*. Vol 16. Netherlands: Springer; 2006:191-237.
18. Nelson V, Pound B. The Last Ten Years: A Comprehensive Review of the Literature on the Impact of Fairtrade. Natural Resources Institute (NRI); University of Greenwich: 2009.
19. van Niekerk J, Wynberg R. The trade in *Pelargonium sidoides*: Rural livelihood relief or bounty for the 'bio-buccaneers'? *Devel So Africa*. 2012;29(4):530-547.

Key Findings from UCL Investigations of Botanicals and Herbal Medicinal Products

In 2010, the research group of Michael Heinrich, Dr. rer. nat. habil, at the UCL School of Pharmacy in London initiated a series of investigations of the authenticity and identity of various herbal medicinal products and herbal food supplements sold in the United Kingdom and links to different value chains of such products.

In our initial project, we investigated value chains of turmeric, which is grown as a cash crop throughout India.[12] It is generally sold at auction, and the price can be variable from one year to the next. When the price is high one year, it encourages farmers to plant more, frequently resulting in an excess of crop the following year, which usually leads to a fall in the price. This is pure supply-demand economic dynamics. When the price is low, farmers may store the dried crop rather than sell it. The dried turmeric rhizomes can sometimes be stored for years in poor conditions, and farmers can rely on heavy use of pesticides and other chemicals to keep the material from degrading or perishing. Our analytical data suggested that this long-term storage also can result in the loss of therapeutically important, mainly volatile compounds (e.g., tumerone) that can evaporate over time.

We also investigated rhodiola products (i.e., herbal products made from roots of plants in the genus *Rhodiola*). These included both registered herbal products and unregistered food supplements used for the prevention or treatment of fatigue and widely used to improve sports performance. We looked at 39 products available in health food stores and on the internet and found that approximately 25% of these products were of poor quality.[10] The main problem was that an incorrect species had been used. Instead of the preferred *R. rosea* — the species of *Rhodiola* that has the most clinical research — the lower-cost Chinese species *R. crenulata* had been substituted in its place, even though 34 products claimed on the label to contain only *R. rosea*. Although *R. crenulata* is used medicinally in China, it does not contain the important compounds that give *R. rosea* its reputation as an effective adaptogenic medicinal product. More troublesome, a selection of the samples appeared to contain no *Rhodiola* species, and one was found to contain 5-HTP, a naturally occurring compound with reputed antidepressant properties. All of the THR products (n = 10) complied with their label specifications.

With ginkgo and milk thistle, we used a similar sampling strategy to rhodiola, using the internet, visiting high street supermarkets, pharmacies, and health food shops, and obtaining a reasonably representative sample of products available to UK consumers (ginkgo: n = 35; milk thistle: n = 18). Once again we found that 22% of all milk thistle products and 25% of all ginkgo products were of very poor quality when compared to the reference material or to THR products.[14] The quality problems included low concentrations of key compounds (with some being almost undetectable) when compared to reference products commonly used in intervention and clinical studies, and adulteration with other substances. Since the original work was done, we have looked more closely at the ginkgo samples and suggest that more than 50% contain low levels of ginkgo, and thus also are poor quality products. Some ginkgo samples appeared to have greater quantities of rutin than were detectable in the reference material. This suggests that they had been "spiked" — a process in which exogenous rutin is added to increase the total flavonoid content, making it appear that the samples are of acceptable quality. And again we found that one product contained a 5-HTP-related compound. This product was from the same company as the adulterated rhodiola product.

KRATOM

Medicine or Menace?

BY CONNOR YEARSLEY

In the United States, a proposed regulatory action on two compounds found in the Southeast Asian herb kratom (*Mitragyna speciosa*, Rubiaceae) has generated considerable public, professional, and media interest. In a notice of intent published in the *Federal Register* on August 31, 2016, the US Drug Enforcement Administration (DEA) announced the temporary listing of the kratom alkaloids mitragynine (MG) and 7-hydroxymitragynine (7-OH-MG) in Schedule I of the Controlled Substances Act (CSA) of 1970. The CSA defines Schedule I controlled substances, which include heroin, LSD, and marijuana (*Cannabis* spp., Cannabaceae), as "those that have a high potential for abuse, no currently accepted medical use in treatment in the United States, and a lack of accepted safety for use under medical supervision."[1-3]

The temporary scheduling, which would have taken effect on September 30, was "necessary to avoid an imminent hazard to the public safety," according to the DEA.[1] But backlash from the public and members of Congress prompted the DEA to announce on October 13 that it would withdraw its original notice of intent and allow for a public comment period through December 1, 2016. The DEA also stated that it would receive from the US Food and Drug Administration (FDA) a scientific and medical evaluation and scheduling recommendation for the compounds.[4,5]

After the public comment period, the DEA could decide to permanently place the compounds in a schedule of the CSA, which would require an additional period for lawmakers and the public to comment, or it could decide to move forward with the temporary scheduling that was originally proposed, which would not require an additional comment period.[4,5]

The proposed temporary scheduling would have lasted for two or three years. Under the CSA, a substance meeting the statutory requirements for temporary scheduling may be placed only in Schedule I.[1]

The placement of the compounds in Schedule I, in effect, would mean that possession and distribution of any preparations of kratom, a plant that has shown the potential to help wean recovering addicts off heroin and other addictive and dangerous opioids, would be illegal and could result in criminal prosecution.[6,7] Notably, cocaine and methamphetamine are currently listed in Schedule II, meaning that, unlike Schedule I substances, physicians can prescribe or administer these substances.[3,8]

Kratom is a tropical evergreen, broad-leafed tree native to peninsular Thailand, southeastern Myanmar, Malaysia, Borneo, Sumatra, the Philippines, and New Guinea. The herb is in the same family (Rubiaceae) as other economically and medicinally important plants, including coffee (*Coffea arabica*), gardenias (*Gardenia* spp.), and trees in the genus *Cinchona* (e.g., *C. officinalis* and *C. pubescens*).[9] Preparations of kratom leaves have been used for centuries in Southeast Asia for a wide range of purposes, including as an opium and alcohol substitute; to treat cough, diarrhea, and diabetes; to manage pain, opioid withdrawal, and sexual dysfunction; and to stave off fatigue.[6,10] In addition, the leaves have been applied to wounds and used as a vermifuge (an agent that expels parasitic worms), and as a local anesthetic.[9]

Leaf preparations of the plant, including powders and teas, act on the central nervous system. At low doses, they produce "cocaine-like" stimulant effects, while higher doses produce "morphine-like" sedative and intoxicating effects.[6] Therefore, some workers, such as seafarers, farmers, and rubber-tappers, in southern Thailand, northern Malaysia, and elsewhere chew the fresh leaves to increase work productivity and reduce fatigue during the day, and to relax after work.[9,11]

Kratom, which started gaining popularity in the United States within the last 15 years, has received increased media attention lately. Although some people have successfully used kratom to recover from opioid and alcohol addictions, there has been growing concern about the addictive potential of kratom itself. The DEA notice repeatedly refers to kratom's potential for abuse.[1]

The DEA's scheduling proposal comes in the midst of an unprecedented opioid epidemic in the United States. For example, in 2012, there were 12 states with more opioid prescriptions than residents. The ratio was the largest in Alabama, where there were 142.9 opioid prescriptions per 100 people, according to the Centers for Disease Control and Prevention (CDC).[12] Even worse, opioids, including both prescription pain relievers and heroin, were involved in 28,647 deaths in the United States in 2014 (an average of 78 deaths per day), more than any year on record. In addition, opioid overdoses quadrupled between 2000 and 2014.[13] In this context, it is obvious that solutions are needed, but there is disagreement about whether kratom is helping the problem or contributing to it.

Differing Perceptions of Kratom

At the time of the DEA's August 31 notice of intent, six US states (Alabama, Arkansas, Indiana, Tennessee, Vermont, and Wisconsin); Washington, DC; and at least 15 countries, including Thailand, had banned kratom. It had been included on the DEA's "Drugs of Concern" list since 2005.[1,9] After the notice, there was an outpouring of people who came to the defense of the plant. Within two weeks, a petition on We the People (petitions.whitehouse.gov) asking the White House to stop the scheduling had garnered nearly 125,000 signatures (and, at press time for this article, more than 143,000 signatures), surpassing the 100,000 necessary to receive a response.[14]

In the days leading up to the originally proposed scheduling date, 51 members of the House of Representatives, spurred by the Botanical Education Alliance, an organization whose stated mission is to preserve plant legality through education, formally requested that the DEA delay the scheduling.[15] Shortly thereafter, Senator Orrin Hatch (R–UT), the most senior Republican senator, wrote a letter asking the DEA "to allow both for a public comment period and sufficient time for the DEA to outline its evidentiary standards to the Congress regarding the justification for this proposed action."[16]

Days later, Senator Cory Booker (D–NJ), Senator Kirsten Gillibrand (D–NY), and Senator Ron Wyden (D–OR) wrote an emphatic letter to DEA Acting Commissioner Chuck Rosenberg in which they echoed Hatch's requests. They cited the eight-fold increase in US prison populations from the enforcement of "draconian drug laws," writing: "We should not, in haste and without adequate opportunity for comment and analysis, place substances in categories that may be inconsistent with their medical value and potential for abuse."[17]

Anecdotal Evidence

After the DEA notice, many news articles told the stories of people who claimed to have benefitted from kratom and who would personally be affected by its placement in

Schedule I. For example, one woman from Missouri named Margo Burton had been taking two teaspoons of an unspecified preparation of kratom every three hours to help her cope with pain caused by endometriosis, a condition in which uterine tissue grows outside the uterus. "I need it so I'm not hurting, so I can be a good mother," Burton is quoted as saying. When she heard about the DEA's plan to ban kratom, she sobbed.[18]

Susan Ash, founder of the American Kratom Association (AKA), a nonprofit that supports kratom users, started using kratom to manage pain caused by Lyme disease that went undiagnosed for years. In 2008, her condition became debilitating. "The pain was excruciating," Ash is quoted as saying. "It was in my joints. It would wake me up in the middle of the night. It would have me in the emergency room." Her doctors began prescribing drugs to treat the symptoms of the undiagnosed disease, and then began prescribing more drugs to treat the side effects of the other drugs.[18,19]

Ash was prescribed a cocktail of as many as 10 different prescription drugs and soon began suffering serious neurological effects. She was finally diagnosed with Lyme disease, but, by that point, she was addicted to painkillers. In 2011, she entered treatment and successfully detoxed, but she still felt chained to opioids.[19] "Life couldn't have been much worse at that point. I was not leaving the house at all. I was only leaving the house to see doctors," she said. Then, someone suggested that she try kratom and, although she was skeptical at first, she eventually did. "In a matter of two weeks, I had the energy, I had the pain relief, and I had the depression and anxiety relief I needed to become a productive member of society again. It was such a stark difference and such an immediate change in my life."[19]

In a video on YouTube, a US Army veteran, who says he suffered from terrible foot and lower back pain and migraine headaches, talks about his experience with kratom and his opinion of the DEA's proposed scheduling. "One of my best friends introduced me to this substance called kratom," he said. "I started taking it, and my pain went away…. I brew up some tea leaves, let it steep for 40 minutes or whatnot, have a cup of tea, I feel better." Later in the video, he continued: "I'm not talking about snorting cocaine, shooting up heroin. I'm not even talking about puffing a joint. I'm talking about brewing some tea, having a sip, and feeling better — being able to go for a run because my feet don't kill me after six years in the army."[20]

These are just some of the many anecdotal reports about the potential benefits of kratom. There are hundreds of testimonials on YouTube and elsewhere, some from military veterans using kratom to cope with post-traumatic stress disorder (PTSD), some from people using it to manage fibromyalgia and other painful conditions, and some from people using it to recover from alcoholism.[21] Testimonials like these and responses from members of Congress played a part in convincing the DEA to withdraw its original notice of intent and allow for public comment.

Testimonials from kratom users played a part in convincing the DEA to withdraw its original notice of intent and allow for public comment.

A Public Health Threat?

Still, some contend that kratom is dangerous. Dan Fabricant, PhD, CEO and executive director of the Natural Products Association (NPA), was the director of the Office of Dietary Supplement Programs at the FDA when the administration first took actions against kratom as an unapproved new dietary ingredient. In a recent NPA press release, he noted: "Kratom has been a public health target for almost five years, and its surging growth in use and availability is an unfortunate but real example of the federal government's unwillingness to use existing authorities to enforce the law. This [the DEA's scheduling] is a necessary and welcome step, but unless it is followed with real enforcement and penalties for those who are selling it in coffee bars, on the internet, and elsewhere, it will be toothless. Kratom is not an herbal supplement: it is addictive, harmful, and worse, it may be contributing to [the US's opioid] epidemic."[22]

The original DEA notice stated that there have been numerous deaths associated with kratom, beginning with a cluster of nine deaths in Sweden between 2009 and 2010 that were linked to a product called "Krypton."[1] According to other sources, kratom-containing products sold under the name "Krypton" were found to be adulterated with caffeine and synthetic *O*-desmethyltramadol (a metabolite of the prescription opioid tramadol), but the DEA notice does not mention this adulteration.[6,9]

According to the DEA notice, five other deaths related to kratom exposure were subsequently reported in the scientific literature, and autopsy/medical examiner reports for an additional sixteen deaths confirmed the presence of MG and 7-OH-MG in biological samples. Of these 21 deaths, 15 occurred between 2014 and 2016.[1]

A toxicologist was hired by the AKA to review the 15 deaths that occurred between 2014 and 2016, and in each case the toxicologist disputed the notion that kratom toxicity was the cause of death.[23] According to Ash, many of these deaths involved other drugs, and some likely involved pre-existing health conditions.

Adverse interactions have been reported involving kratom tea taken with substances such as carisoprodol (a muscle relaxant), modafinil (a wakefulness-promoting agent), propylhexedrine (a stimulant used as a nasal decongestant), or jimson weed (*Datura stramonium*, Solanaceae; a tropane alkaloid-containing plant with hallucinogenic and analgesic properties). In addition, a fatal case in the United States (presumably counted among the fatalities noted by the DEA) involved a mixture of kratom, fentanyl (a powerful synthetic opioid analgesic), diphenhydramine (a sedating antihistamine), caffeine, and morphine, which was mislabeled and illegally sold as an herbal product.[6]

Morphine-like Effects

MG and 7-OH-MG produce analgesic effects similar to those of morphine, the prototypical opioid, and the DEA notice and other sources classify them as opioids because of their binding affinity for the opioid receptors.[1]

The term "opioid" combines "opium" with the suffix "-oid," which means "like" or "resembling" and often implies an incomplete or imperfect resemblance to the preceding element. The term was originally proposed to describe drugs that have actions similar to, but chemical structures different from, morphine.[24] The term "opioid" should also be distinguished from "opiate," which is a narrower term that refers to naturally occurring alkaloids found in the opium poppy (*Papaver somniferum*, Papaveraceae), including morphine and codeine.[25]

According to the book *Kratom and Other Mitragynines* (CRC Press, 2015), substances are typically classified as opioids based on the following criteria: binding affinity for one or more of the major subtypes of opioid receptor, morphine-like in vivo effects (such as pain relief), miosis (excessive constriction of the pupil), constipation, respiratory depression, tolerance, cross-tolerance to a known opioid, development of dependence, and similarity of chemical structure to morphine or another opioid.[9] It has been

Kratom *Mitragyna speciosa*
Photo ©2016 GoldenJack

With anything, there are dangers of using too much.

shown that MG and 7-OH-MG meet most of these criteria, at least to some degree.

However, David Kroll, PhD, a pharmacologist, member of the American Botanical Council's (ABC's) Advisory Board, and medical writer who has written articles about kratom for *Scientific American* and Forbes.com, said that the pharmacological actions of MG and 7-OH-MG (see "In Depth: Botany and Pharmacology of Kratom" section) more closely resemble those of buprenorphine (a semisynthetic opioid with mixed opioid partial agonist/antagonist effects and that is used to treat opioid addiction) than those of other, more common opioids, such as morphine, hydrocodone, oxycodone, and heroin (email, October 16, 2016).

Kratom is one of a finite number of plants that have been found to produce compounds that have an affinity for opioid receptors, including *P. somniferum*; *P. bracteatum*, which produces thebaine, an opiate precursor to a variety of semisynthetic opioids, such as buprenorphine[26]; *P. orientale*, which also produces thebaine, in addition to oripavine, another opiate precursor to several semisynthetic opioids[27]; *Salvia divinorum* (Lamiaceae), which produces salvinorin A[9]; and *Dalea purpurea* (Fabaceae), which produces pawhuskin A, B, and C.[28]

Respiratory Depression

Perhaps the most significant way in which MG and 7-OH-MG differ from common opioids is that they have a much lower risk of producing respiratory depression.[21] (Notably, the misuse of the opioids fentanyl and carfentanil, a fentanyl analog that is approximately 10,000 times more potent than morphine, has resulted in an epidemic of overdose deaths caused by these respiration-depressing effects.[29]) At lower doses, common opioids reduce the amount of air passing into and out of the lungs in each respiratory cycle, and therefore depress respiration. At higher doses, opioids further decrease respiratory rate and impair respiratory rhythm. Opioid use also is associated with rigidity of the muscles used during respiration and decreased activity of these muscles during sleep.[9] This respiratory depression can starve the brain of oxygen and lead to permanent brain damage or death. The risk is heightened when opioids are taken with other depressants, such as alcohol, antihistamines, barbiturates, benzodiazepines, or general anesthetics.[30]

"It turns out mitragynine has a very low risk of respiratory depression," Kroll is quoted as saying. "It also appears that it's very difficult to at least get animals — get mice addicted to 'mitra,' either with the herb or with the pure chemical."[21] In addition, at higher doses, kratom induces vomiting, reportedly making it difficult to overdose.[23]

Kratom Use and Potential for Misuse

According to the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), a few grams of dried kratom leaves produce invigorating and euphoric effects within about 10 minutes, and these effects last for about one to one-and-a-half hours. Kratom users report increased alertness, sociability, and sometimes increased libido. Slight constriction of the pupils and blushing may occur. In one of the few human clinical experiments, a 50-mg oral dose of MG produced motor excitement, then giddiness, loss of motor coordination, and tremors of the extremities and face.[6]

Larger doses of dried kratom leaves (10-25 g) may initially cause sweating, dizziness, nausea, and dysphoria, but these effects are quickly replaced with euphoria, calmness, and a dreamlike state that can last for up to six hours. Miosis also occurs.[6]

Traditionally, when kratom is consumed as a tea, lemon juice is often added to encourage extraction of the alkaloids in the plant. Sugar or honey may be added to mask the bitterness of the tea. The dried leaves are also sometimes smoked. The veins of the leaves are usually removed before consumption, and salt may be added to prevent constipation. Kratom consumption is sometimes followed by drinking warm water, coffee, tea, or palm sugar syrup.[6]

"With anything, there are dangers of using too much," Walter C. Prozialeck, PhD, professor of pharmacology at Midwestern University and co-author of a review of the pharmacology of kratom, is quoted as saying.[19] "But the amount that a person has to take in to get any severe effects is ridiculously high. You're talking 10 to 15 grams of raw leaf. Most people who are using kratom for pain management don't take that much. Most people can't take that much."

In addition, according to Prozialeck, kratom doesn't produce much of a psychoactive high in low to moderate doses. "After researching the literature, I found that there were more positive aspects to kratom than there were negative," he is quoted as saying. "Additional studies are needed to explore potential benefits of kratom. Also, work is needed to look at toxicity, though."[19]

The original DEA notice pointed to data from poison control centers in the United States as evidence "that there is an increase in the number of individuals abusing kratom." Between 2000 and 2005, the American Association of Poison Control Centers identified two exposures to kratom. In the six-year period from January 2010 through December 2015, US poison centers received 660 calls related to kratom exposure. Though most (428 [64.8%]) of those involved kratom being used in isolation, some involved kratom being used with other substances, including ethanol, benzodiazepines, narcotics, acetaminophen, and other botanicals.[1] Compared to the more than 3.1 million calls received by the US's 55 poison centers in 2013 alone, calls involving kratom accounted for a tiny fraction.[31]

In addition, the DEA notice stated that it is especially concerning that "users have turned to kratom as a replacement for other opioids, such as heroin."[1] This is despite the fact that heroin was involved in more than 8,200 deaths in

Korthals, P.W. 1842. Kruidkunde. In *Verhandelingen over de Natuurlijke Geschiedenis der Nederlandsche Overzeesche Bezittingen. Botanie*, ed. C.J. Temminck, 1-259. Leiden.

Image courtesy of Peter H. Raven Library/Missouri Botanical Garden.

the United States in 2013, and the fact that heroin injection increases the risk of serious viral infections, including HIV and hepatitis B and C, and bacterial infections of the skin, bloodstream, and heart.[32] Furthermore, methadone, a synthetic opioid that is sometimes used to help wean recovering addicts off heroin, is involved in nearly 5,000 overdose deaths per year.[33] According to Kroll, buprenorphine (the pharmacological actions of which, again, resemble those of MG and 7-OH-MG) has been replacing methadone in opioid maintenance therapy for recovering opioid addicts. There is concern among kratom proponents that if the DEA criminalizes kratom, it will push some people back to abusing heroin and/or other opioids.[23] Perhaps time will tell.

Evidence suggests that kratom can be at least somewhat addictive. Mark Swogger, PhD, an assistant professor of psychiatry at the University of Rochester Medical Center and co-author of a qualitative analysis of 161 firsthand descriptions of human kratom use, is quoted as saying: "I think it's pretty safe to say that kratom has at least some addiction potential. The data is fairly strong on that, and our study also found that people are reporting addiction. Overall, we found that it's really mild compared to [common] opioid addiction and it didn't seem to last as long."[34]

In addition, tolerance has been observed. New kratom users typically need only a few leaves to feel an impact, but heavy users may need to chew the leaves between three and 10 times per day, and some users find that, over time, they need to increase the number of leaves chewed to between 10 and 30, or more, per day.[9] Furthermore, mice treated with 7-OH-MG developed tolerance, cross-tolerance to morphine, and withdrawal symptoms that could be brought on by administration of naloxone, a semisynthetic opioid receptor antagonist (i.e., an inhibitor of receptor activity) that is used to reverse the effects of opioids in cases of overdose or postoperative sedation.[6]

Regular kratom users may also become dependent. Human withdrawal symptoms are fairly mild and usually subside within a week. These symptoms include anxiety, restlessness, runny nose, muscle pain, weakness, lethargy, nausea, sweating, craving, jerky movements of the limbs, sleep disturbances, and sometimes hallucination.[6]

Prior Regulatory Actions

Before the DEA's notice of intent, kratom qualified as a dietary ingredient under the Federal Food, Drug, and Cosmetic Act (FDCA) of 1938 that could be used in dietary supplement products. However, under the Dietary Supplement Health and Education Act (DSHEA) of 1994, the FDA considers it a new dietary ingredient (NDI) because there is no information demonstrating that it was marketed as a dietary ingredient in the United States before October 15, 1994. If an ingredient is considered "new," then companies must meet certain additional regulatory requirements before using the ingredient in a supplement product.

The FDA did not believe that these regulatory requirements had been satisfied by any company that was marketing and selling kratom, and thus considered kratom and kratom-containing dietary supplements and bulk dietary ingredients to be adulterated under the FDCA. In February 2014, the FDA issued an import alert notifying field personnel that they could detain kratom-containing products listed in the alert without physical inspection.[35] In a separate alert, the FDA announced that other listed kratom products could be detained without physical inspection because these products were considered unapproved and/or misbranded drugs.[36] In these cases, importers and marketers were making unauthorized disease-treatment claims for their products. Between 2014 and the time of the DEA notice, products from 121 firms had been added to the two FDA import alerts.[1]

In September 2014, US Marshals, at the request of the FDA, seized more than 25,000 pounds of raw kratom material worth more than $5 million.[37] In January 2016, US Marshals, again at the request of the FDA, seized nearly 90,000 bottles of dietary supplements labeled as containing kratom.[38] And again, in August 2016, US Marshals, at the request of the FDA, seized 100 cases of products labeled as containing kratom.[39]

Kratom *Mitragyna speciosa*
Photo ©2016 Prachaya Roekdeethaweesab

Between February 2014 and July 2016, more than 55,000 kilograms (121,254 pounds) of kratom material was encountered at various ports of entry in the United States. In addition, at the time of the DEA notice, more than 57,000 kilograms (125,663 pounds) of kratom material offered for import at numerous ports of entry between 2014 and 2016 was awaiting an admissibility decision by the FDA. At the time of the DEA notice, the amount of kratom that had been seized or that was awaiting an admissibility decision was estimated to be enough to produce more than 12 million doses of kratom. According to the DEA, "such alarming quantities create an imminent public health and safety threat."[1]

The DEA's scheduling proposal came as a surprise to some. "While I'm not surprised that the FDA began to seize kratom as an unapproved drug…, I was surprised by the DEA's intent to place two of the alkaloids in Schedule I," Kroll wrote (email, September 19, 2016). "But I have to admit that it took me writing an article about kratom and getting reader comments before I realized people were overwhelmingly using the herb medically and not as a recreational psychotropic."

Impact on Research

Kroll also mentioned that two important kratom studies were only recently published: one by Kruegel et al. (from Columbia University) that was published in May 2016 in the *Journal of the American Chemical Society*[40] and one by Váradi et al. (from Memorial Sloan Kettering Cancer Center) that was published in August 2016 in the *Journal of Medicinal Chemistry*.[41] "So the DEA may not have been aware of the firm distinctions between *Mitragyna speciosa* alkaloids and strong, full agonist opioids [a full agonist binds to and activates a receptor, producing full activity at that receptor]," Kroll wrote. "What this tells me is that the DEA rushed to judgment based on the weak adverse [event] report record of the herb and/or its adulterants without fully investigating that its compounds were pharmacologically distinct from strong opioid agonists [e.g., morphine]."

Ash of the AKA is quoted as saying she "really believed that because of the progress medical marijuana has made through the states that the federal government was going to leave kratom alone and leave it to the states to decide whether it was appropriate to be legal."[42]

It is not entirely clear how the scheduling would impact research on kratom. Researchers will have to apply to the DEA for a Schedule I research license, which requires a fairly stringent collection of documentation and security protocols that can take time to implement, up to a year or more, wrote Kroll. "The researchers I've spoken to are more concerned about the availability of research amounts of raw plant material, since import restrictions on Schedule I substances are quite ornery," he wrote.

DEA spokesperson Russ Baer is quoted as saying, "As is the case with any controlled substance, the DEA will implement aggregate production quotas for kratom and make available an adequate and uninterrupted supply of research-grade material to accommodate valid scientists and researchers."[43]

It is possible this may be done through a federal supply contract similar to the marijuana farm at the University of Mississippi, which, until recently, supplied all of the medical cannabis used for DEA-approved research.[44]

According to Jahan Marcu, PhD, chief scientific officer for Americans for Safe Access, a medical cannabis advocacy organization, "it is unclear how long it would take the DEA to supply kratom, since it can take 20 years for a tree to reach maturity. A federal supply of kratom, produced in

Nomenclature and Taxonomy of Kratom

Mitragyna is a small genus that, depending on the taxonomic treatment, includes seven to 10 species. (A taxonomic treatment is a publication, or a section of a publication, that documents the features and/or distributions of a related group of organisms [i.e., a taxon] in ways that adhere to highly formalized conventions.[54]) According to one treatment, four *Mitragyna* species are found in Africa, while six are found in South and Southeast Asia. The Asian species are distributed between India and New Guinea.[9]

The Dutch botanist Pieter Willem Korthals (1807-1892) first described the genus. As a member of the Commission for Natural Sciences of the Dutch East India Company from 1830 to 1837, Korthals made important botanical discoveries and collections in the Malay Archipelago.[9] He named the genus *Mitragyna* because he thought the leaves and stigmas of the flowers of one of the specimens he observed resembled the shape of a bishop's mitre.[6] In 1839, Korthals published the genus and the species name *M. speciosa* in the same publication, but he didn't include a botanical description of *M. speciosa*, and that name is therefore considered a *nomen nudum* (a "naked name"). In 1842, Korthals transferred the species to the genus *Stephegyne*. Various authors subsequently renamed the species *Nauclea korthalsii*, then *Nauclea luzoniensis*, then *Nauclea speciosa*, before British naturalist George Haviland set the current accepted species name as *M. speciosa* in 1897.[9]

The common name "kratom" originates from Thailand,[9] but the plant has many common names (see Table 1). According to one source, "kratom" is likely derived from the Sanskrit *kadam*, a name that refers to *Neolamarckia cadamba* (Rubiaceae), a widespread tree that is sacred in Hinduism. Similar names are used for various related tree species in the region.[9]

Table 1: Common Names of *Mitragyna speciosa*[9]

Country	Common Names
Thailand	*ithang* (central), *thom* (peninsular), *bai krathom*, *gratom*, *kakuam*, *katawn*, *krathawm*, *kratom*, *kraton*
Malaysia	*biak*, *biak-biak*, *ketum*, *kutum*, *pokok biak*, *pokok ketum*, *sepat* (Sabah state)
Indonesia	*kadamba* (Kelantan state), *puri* (Batak Toba language, Sumatra), *keton*
Myanmar	*beinsa*, *bein-sa-ywat*
Philippines	*mambog* (Tagalog language), *lugub* (Mandaya people), *polapupot* (Ibanag language)
Vietnam	*giam d[ef]p*, *giam l[as] nh[or]*

the US, is 20 years away, leaving our [kratom] researchers to whither on the vine because they do not have access to their research tools" (email, October 13, 2016).

Schedule I study restrictions on kratom would undoubtedly "stall the scientific study of the herb at a time when our understanding of its molecular pharmacology has never been more advanced and promising," Kroll wrote. Additionally, he thinks the scheduling will hinder the study of semisynthetic analogs of the *M. speciosa* alkaloids that could lead to new FDA-approved drugs for pain and/or recovery from opioid and alcohol dependence.

Kratom in Thailand

Perhaps nowhere in the world does kratom have a longer and more interesting history than in Thailand. As in some other Southeast Asian countries, there are potentially toxic, kratom-containing admixtures used in Thailand, and various socioeconomic and political factors contribute to the perception of kratom misuse. Some of these factors may have some relevance to the current kratom debate in the United States.

In Thailand, chewing kratom leaves is a tradition that has been practiced for centuries, especially on the southern peninsula where the tree is more commonly found. According to one source, "In southern Thailand, traditional kratom use is not perceived as 'drug use' and does not lead to stigmatization or discrimination of users. Kratom is generally part of a way of life in the south, closely embedded in traditions and customs such as local ceremonies, traditional cultural performances, and teashops, as well as in agricultural and manual labor in the context of rubber plantations and seafaring."[53]

In some districts in southern Thailand, as much as 70% of the male population uses kratom on a daily basis (as of 2011), and many people consider it similar to drinking coffee. Some southern provinces, especially Pattani, Yala, and Narathiwat, are predominantly made up of Muslims who, because of the dictates of Islam, cannot consume alcohol. Kratom is an alternative that is not prohibited by the clergy, but it is controlled by the government.[53]

Kratom was banned in Thailand under the Kratom Act of 1943. Leading up to the ban, the Thai government had started levying taxes on opium users and retailers. Because opium started becoming more expensive, many users switched to kratom to help manage opium withdrawal. With the launch of the Pacific War (which debatably began in December 1941 when Japan invaded Thailand and attacked British possessions in the Pacific) and decreasing opium revenues, the Thai government took action to eliminate competition in the opium trade.[53]

In 1943, a government official was quoted as saying: "Taxes for opium are high while kratom is currently not being taxed. With the increase of those taxes, people are starting to use kratom instead and this has had a visible impact on our government's income."[53]

After World War II, the Kratom Act was not aggressively enforced, and kratom could be grown in moderation and consumed openly. In 1979, kratom was included in the least restrictive and punitive schedule of the Thai Narcotics Act. In the early 2000s, coinciding with a crackdown on illegal drugs that was initiated by the Thai government, the number of seizures and arrests related to kratom increased greatly. Shortly thereafter, in the mid-2000s, a kratom-containing cocktail called "4x100" started being used by some young people.[53] The cocktail involves boiling kratom leaves (15 to 100 at a time) to produce a tea, which is mixed with codeine- or diphenhydramine-containing cough syrup, a soft drink (usually Coca-Cola), and ice cubes.[9,53] Typically, the cocktail is prepared twice or more per day, depending on the availability and cost of the ingredients. 4x100 users are typically subject to some community discrimination, though not as much as *yaba* (methamphetamine) or heroin users.[53]

There have been concerns about reports of the cocktail being laced with additives "such as benzodiazepines, powder from fluorescent tubes, powdered mosquito coils, road paint, pesticides, ashes from dead bodies, and other substances found in the local environment to 'enhance' the effect of the cocktail." Apparently, little evidence to substantiate these claims has been found, and some contend these are exaggerations meant to vilify those who consume the cocktail, again, typically young people. One 4x100 user was quoted as saying: "We want to get high, not kill ourselves!"[53]

Because of these reports, however, authorities, with the stated intent of protecting young people, have been instructed to eradicate kratom trees and actively look for kratom and 4x100 users in certain communities (as of 2011). Beginning in the mid-2000s, several eradication campaigns in the southern provinces led to large numbers of kratom trees being cut down, either by law enforcement or by community groups (whether voluntarily or not). In Pattani, Yala, and Narathiwat provinces, few kratom trees are left in the wild. Authorities in Satun, Surat Thani, and Trang provinces are more lenient and tolerate a few trees in the community and up to one tree per household (as of 2011).[53]

According to one source, efforts to control kratom between the early 2000s and 2011 did little good. Kratom is still popular in the southern provinces and around Bangkok, though not among women (who usually prefer to chew betel nut [*Areca catechu*, Arecaceae] instead). The traditional chewers (as opposed to the 4x100 users) often own the land where kratom grows and are, therefore, usually the ones targeted by eradication campaigns. Younger 4x100 users sometimes resort to stealing from trees in the community, which has led some traditional chewers to set up barbed wire and other protection mechanisms around kratom trees. In addition, efforts to limit 4x100 use has almost exclusively focused on kratom, instead of trying to control cough syrup and benzodiazepines, the most potentially harmful components of the cocktail.[53]

Although kratom is technically illegal in Thailand, law enforcement has been uneven and many people continue to view kratom as a traditional medicine. According to some, kratom should be decriminalized, and community leaders should be empowered to control production and consumption of kratom. In addition, some argue that concerns surrounding 4x100 use have little to nothing to do with kratom.[53]

In Depth: Botany and Pharmacology of Kratom

Kratom grows in swamps and damp valley areas that are rich with humus, and forms "dense stands in the new alluvial substrate of ox-bow lakes and low muddy river banks that are frequently inundated."[9] The species is said to be a common riverside pioneer (i.e., a species that is the first to colonize previously disrupted or damaged ecosystems).

According to one source, the tree can grow to 4-16 meters (13-52 feet) tall with a spread of more than 15 feet.[6,45] According to *Kratom and Other Mitragynines*, it can grow to 25 meters (82 feet) in height and two to three feet in diameter. The trunk is usually straight. The outer bark is smooth and gray, and the inner bark is pinkish.[9] The leaves are oval or ovate-lanceolate and dark green.[6] They are 14-20 centimeters long and 7-12 centimeters wide.[9] The veins of the leaves are either greenish-white or red. Leaves with greenish-white veins are said to be more potent. The average weight of a fresh leaf is about 1.7 grams, while the average weight of a dried leaf is about 0.43 grams. The tree produces yellow and globular flowers that can bear up to 120 florets. The fruit is a capsule that contains several small, flat seeds.[6]

Alkaloid Chemistry and Composition

The tree contains more than 40 structurally related alkaloids, in addition to several flavonoids, saponins, polyphenols, and glycosides. Kratom is the only species known to produce the indole alkaloids MG and 7-OH-MG, two of the main psychoactive components in the plant.[6] At least three other alkaloids found in kratom (speciogynine, paynantheine, and speciociliatine) have been shown to have some opioid receptor affinity.[46]

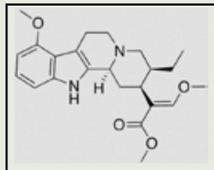
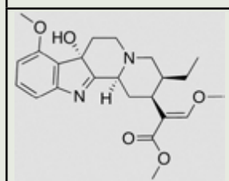
The chemical profile of kratom varies depending on several factors: the variety and age of the plant, the environment, and the time of harvest. The total alkaloid concentration in dried leaves typically ranges from 0.5% to 1.5%.[6]

MG is structurally similar to yohimbine (a compound derived from the African tree yohimbe [*Pausinystalia johimbe*, Rubiaceae]),[10] and it is typically the most abundant alkaloid in the leaves,[9] although it has also reportedly been found in the fruits and stembark of kratom.[47] MG was first isolated in 1921, and its structure was determined in 1965.[9]

The amount of MG that kratom yields depends on geography and the maturity of the leaves.[9] For example, MG accounted for 66% of the crude base of alkaloids extracted from young leaves of a specimen from Thailand, while the compound accounted for only 12% of the alkaloids extracted from mature leaves of a specimen from Malaysia.[47] It is possible that, in this case, geography, not leaf maturity, accounted for the difference, since, according to *Kratom and Other Mitragynines*, MG is typically much more abundant in older plants than younger ones, and much more abundant in Thai plants than Malaysian ones. Interestingly, the predominant alkaloid found in a kratom specimen grown at the University of Mississippi was the oxindole-type mitraphylline (at 45% of the total alkaloids), not MG.[9] Mitraphylline is also found in the bark of cat's claw (*Uncaria tomentosa*, Rubiaceae).[48]

7-OH-MG is a minor alkaloidal constituent of kratom. It accounted for just 2% of the crude base of alkaloids extracted from young leaves of a specimen from Thailand. A 2004 study using guinea pigs showed that 7-OH-MG was almost 50-fold more potent than MG and more than 10-fold more potent than morphine.[47] Another study using guinea pigs, however, showed that 7-OH-MG was 30-fold more potent than MG and 17-fold more potent than morphine.[46] It is thought that 7-OH-MG is more potent than morphine because it is more lipophilic (i.e., able to combine with or dissolve in fats) than morphine and distributes more quickly across the blood-brain barrier, a diffusion barrier that impedes the influx of most compounds from the blood into the brain.[9,49] However, 7-OH-MG is less lipophilic than MG, and it is thought that it is more potent than MG because of tighter receptor binding to the mu-opioid

Table 2: Properties of Mitragynine and 7-hydroxymitragynine

 Mitragynine (MG)[6,9,10,40,48,52]	• Structurally similar to yohimbine • Can cross the blood-brain barrier • Soluble in organic solvents • Partial agonist of the MORs • Antagonist of the KORs and DORs • Stimulates alpha-2-adrenergic receptors • Activates descending serotonergic and noradrenergic pathways in spinal cord • Blocks stimulation of 5-hydroxytryptamine$_{2A}$ receptors. These receptors may play a role in the pathogenesis of depression • Blocks neuronal Ca^{2+} channels • Does not recruit beta-arrestin-2 protein
 7-hydroxymitragynine (7-OH-MG)[9,10,40,46]	• Oxidation product of MG • Found by one animal study to be 30-fold more potent than MG and 17-fold more potent than morphine • More lipophilic and can diffuse more quickly across blood-brain barrier than morphine, but less lipophilic than MG • Potency and quick-acting characteristics attributed to hydroxyl group (-OH) not present in MG • Only a trace constituent in some kratom specimens • Does not recruit beta-arrestin-2 protein

receptors (MORs), which is associated with 7-OH-MG's hydroxyl group (-OH) at the C7 position, a structural feature not present in MG.[9,40]

MG and mitraphylline have also been shown to be able to diffuse across the blood-brain barrier in vitro. In addition, MG and 7-OH-MG were found by one study to be unstable in simulated gastric fluid (which could account for why some of the 7-OH-MG [23%] was converted to MG), but both were found to be stable in simulated intestinal fluid.[48] MG is not soluble in water, but it is soluble in conventional organic solvents (i.e., solvents that contain carbon atoms).[6]

Receptor Activity and Mechanisms of Action

According to the study conducted by researchers at Columbia University, both MG and 7-OH-MG are partial agonists of the MORs, and MG was shown to have about 34% of the maximal effect of a full agonist. This study was conducted using human kidney cells that had been genetically modified to express the human versions of each opioid receptor subtype. MORs are located in the brain, spinal cord, and gastrointestinal tract, and MOR agonists (like morphine) are the "gold standard" of pain therapy. But, in addition to producing analgesia, MOR activation can produce serious adverse side effects, including constipation, sedation, nausea, itching, and, as previously mentioned, respiratory depression. In addition, the euphoria produced by MOR agonists makes them widely subject to misuse.[40]

Kroll proposed three explanations for why MG and 7-OH-MG cause less-to-no respiratory depression, compared with other MOR agonists. "First, they are partial agonists at the MORs, meaning that the maximal effect is lower than the maximal effect of a full agonist like morphine," he wrote. "What this means is that no matter how much MG or 7-OH-MG you put in the system, you'll never get to the same effect as the maximum effect of morphine."

"Second, the *Mitragyna speciosa* alkaloids all appear to be 'biased' toward the G-protein signaling pathway and away from the beta-arrestin-2 pathway," Kroll continued. "This is a relatively new and often confusing concept, even to some pharmacologists. When a receptor sitting on the cell surface is bound by a drug, it can either do nothing (as with a blocker, or antagonist), or it can transduce a signal to the inside of the cell that triggers a cascade of events. MORs can signal through a so-called G-protein and/or the beta-arrestin-2 protein. Beta-arrestin-2 seems, at least in part, to mediate respiratory depression (as well as tolerance, accounting for why patients and addicts all require progressively more opioids over time to produce the same effect)."

According to Kroll, a possible third reason "is that MG and 7-OH-MG are both antagonists at kappa-opioid receptors [KORs], albeit with less potency than as partial MOR agonists. The overall effect is that you can get pain-killing approaching that of morphine with much less respiratory depression."

KOR antagonists, such as MG and 7-OH-MG, have shown the potential to help promote stress resilience, which may help treat certain types of anxiety, depression, and addiction disorders, all of which are exacerbated by hypersensitivity to stress.[50] The Columbia University study also showed that MG and 7-OH-MG are antagonists of the delta-opioid receptors (DORs).[40] Animal studies suggest that DORs control rewarding or addictive properties of drugs that act on the MORs or other non-opioid receptor sites. Therefore, DOR antagonists may have the ability to block morphine reward and tolerance.[51]

Interestingly, the Thai strain of kratom used by the Columbia University researchers yielded only trace quantities of 7-OH-MG that were too small to isolate. "Therefore," the researchers wrote, "it is doubtful that this alkaloid is a universal constituent of all *Mitragyna speciosa* preparations and is unlikely to generally account for the psychoactive properties of this plant." They were, however, able to prepare 7-OH-MG through photochemical oxidation of MG, which, according to Kroll, indicates that "growing and storage conditions may dramatically affect the overall potency of the botanical material."[40]

In addition, the study found that paynantheine, speciogynine, and speciociliatine (which, together, accounted for a percentage of the total extracted alkaloids that was approximately equal to the percentage accounted for by MG) all exhibited antagonist activity at the MORs that competed with the agonist activity of MG. The researchers, therefore, concluded that "the gross psychoactive effects of crude plant material are likely to represent a complex interplay of competing agonist and antagonist effects at the opioid receptors."[40]

Kratom's unusual and paradoxical stimulant/sedative effects are not fully understood. "Some opioids have a paradoxical stimulating effect in some patients, particularly in elderly folks," Kroll wrote. "But the *Mitragyna speciosa* alkaloids have some other receptor effects (e.g., alpha-2-adrenergic) that may or may not be relevant for the amounts of kratom people consume. From anecdotes, the [stimulating] effect does sound like it's real but it hasn't been systematically studied in humans or attributed to a specific compound or neuroreceptor system."

One guinea pig study showed that MG may produce analgesic effects through the blockade of neuronal calcium ion (Ca^{2+}) channels.[52] And another source suggests that MG's analgesic effects may involve the activation of serotonergic and noradrenergic pathways that descend down the spinal cord. In addition, kratom seems to have anti-inflammatory properties.[10]

Conclusion

Kratom is a complicated plant that is not fully understood, either by the scientific community or by the global community. It is likely that language has played a part in shaping perceptions about kratom, with some sources referring to it as an opium "substitute" and other sources referring to it as an opium "remedy."[9] Different perceptions of the plant have led some to celebrate it for its medicinal potential and others to malign it for its abuse potential.

At a time when the United States needs safer alternatives to opioids more than ever, the DEA's placement of the kratom alkaloids in Schedule I would force those who were successfully using the plant for pain management, opioid withdrawal, and other therapeutic purposes to become criminals, seek alternatives that may be more dangerous, or simply do without. Detractors point to the fact that kratom users may become addicted to, dependent on, and tolerant of kratom over time. Proponents emphasize that the kratom alkaloids produce less constipation and, more importantly, less-to-no respiratory depression, compared to other common opioids.

However, proponents, and even some detractors, agree that more research is needed, on both the potential benefits and the potential dangers of kratom. DEA scheduling would make this research more difficult.

"I think that the best kratom researchers should get together and write a couple of clinical trial protocols to the National Center for Complementary and Integrative Health (NCCIH) to investigate a well-characterized, analytical and GMP[good manufacturing practice]-verified kratom product to investigate pharmacokinetics of each compound and metabolite, and efficacy in pain and substance dependence recovery, while also assessing adverse effects, including dependence on the kratom itself," Kroll wrote.

As far as the individual compounds, Kroll believes that MG, 7-OH-MG, the fermentation product mitragynine pseudoindoxyl, and semisynthetic analogs of each should be investigated as single-entity drugs. "But the semisynthetic analogs will likely be required, not just for intellectual property purposes, but for improved half-life and dosage formulation," Kroll wrote. "Users have told me they need to dose with kratom tea up to four or five times in a day, and there is some published data that MG's half-life [i.e., the time it takes for half of the administered amount to be eliminated from the bloodstream] is on the order of an hour."

Though according to some it is not legally realistic to expect kratom to remain unregulated, there is interest within the scientific community about the potential for new therapeutics derived from the plant (either single compounds or whole-plant preparations) to become safer and better pain-relievers and opioid recovery aids. "At a time when the opioid dependence issue is at its greatest national awareness," Kroll wrote, "I think we need any tool — pharmacological, psychological, [mindful] meditation, yoga, etc. — that can relieve people of the burden, pain, and potential lethality of substance dependence." HG

Kratom *Mitragyna speciosa*. Photo ©2016 Frank600 iStockPhoto.com

References

1. Schedules of Controlled Substances: Temporary Placement of Mitragynine and 7-Hydroxymitragynine Into Schedule I. *The Federal Register*. Available at: www.federalregister.gov/documents/2016/08/31/2016-20803/schedules-of-controlled-substances-temporary-placement-of-mitragynine-and-7-hydroxymitragynine-into. Accessed September 14, 2016.
2. Part 1308.11 Schedule I. Drug Enforcement Administration website. Available at: www.deadiversion.usdoj.gov/21cfr/cfr/1308/1308_11.htm. Accessed September 14, 2016.
3. Controlled Substances Act. Food and Drug Administration website. Available at: www.fda.gov/regulatoryinformation/legislation/ucm148726.htm. Accessed September 15, 2016.
4. Withdrawal of Notice of Intent to Temporarily Place Mitragynine and 7-Hydroxymitragynine Into Schedule I. *The Federal Register*. Available at: www.federalregister.gov/documents/2016/10/13/2016-24659/withdrawal-of-notice-of-intent-to-temporarily-place-mitragynine-and-7-hydroxymitragynine-into. Accessed October 13, 2016.
5. Ingraham C. The DEA is withdrawing a proposal to ban another plant after the internet got really mad. *The Washington Post* website. October 12, 2016. Available at: www.washingtonpost.com/news/wonk/wp/2016/10/12/the-dea-is-reversing-its-insane-decision-to-ban-the-opiate-like-plant-kratom-for-now. Accessed October 18, 2016.
6. Kratom (*Mitragyna speciosa*) drug profile. European Monitoring Centre for Drugs and Drug Addiction website. Available at: www.emcdda.europa.eu/publications/drug-profiles/kratom. Accessed September 14, 2016.
7. The Controlled Substances Act (CSA): Overview. FindLaw website. Available at: http://criminal.findlaw.com/criminal-charges/controlled-substances-act-csa-overview.html. Accessed September 15, 2016.
8. Part 1308.12 Schedule II. Drug Enforcement Administration website. Available at: www.deadiversion.usdoj.gov/21cfr/cfr/1308/1308_12.htm. Accessed September 14, 2016.
9. Raffa RB, ed. *Kratom and Other Mitragynines: The Chemistry and Pharmacology of Opioids from a Non-Opium Source*. Boca Raton, FL: CRC Press; 2015.
10. Prozialeck WC, Jivan JK, Andurkar. Pharmacology of kratom: An emerging botanical agent with stimulant, analgesic and opioid-like effects. *J Am Osteopath Assoc*. 2012;112(12):792-799. Available at: http://jaoa.org/article.aspx?articleid=2094342. Accessed September 14, 2016.
11. Cinosi E, Martinotti G, Simonato P. Following "the roots" of kratom (*Mitragyna speciosa*): The evolution of an enhancer from a traditional use to increase work and productivity in Southeast Asia to a recreational psychoactive drug in western countries. *Biomed Res Int*. 2015;2015:968786. doi: 10.1155/2015/968786.
12. Paulozzi LJ, Mack KA, Hockenberry JM. Vital Signs: Variation Among States in Prescribing Opioid Pain Relievers and Benzodiazepines — United States, 2012. CDC website. Available at: www.cdc.gov/mmwr/preview/mmwrhtml/mm6326a2.htm. Accessed September 14, 2016.
13. Injury Prevention and Control: Opioid Overdose. CDC website. Available at: www.cdc.gov/drugoverdose/data/statedeaths.html. Accessed September 14, 2016.
14. Please do not make Kratom a Schedule I Substance. White House website. Available at: http://petitions.whitehouse.gov/petition/please-do-not-make-kratom-schedule-i-substance. Accessed September 30, 2016.
15. Ault A. Congress Members Call for Halt on DEA Kratom Ban. Medscape website. September 28, 2016. Available at: www.medscape.com/viewarticle/869402. Accessed September 30, 2016.
16. DiSalvo D. Kratom Has the Senate's Attention, and the DEA's Schedule I Date May Shift. Forbes website. September 29, 2016. Available at: www.forbes.com/sites/daviddisalvo/2016/09/29/kratom-now-has-the-senates-attention-and-the-deas-schedule-i-date-may-shift. Accessed September 30, 2016.
17. Kroll D. DEA Delays Kratom Ban, More Senators Object to Process and "Unintended Consequences." Forbes website. September 30, 2016. Available at: www.forbes.com/sites/david-kroll/2016/09/30/dea-delays-kratom-ban-more-senators-object-to-process-and-unintended-consequences. Accessed October 18, 2016.
18. Boodman E. Hidden Network of Kratom Devotees Tries to Keep the Supplement Safe — and Legal. Stat News website. September 2, 2016. Available at: www.statnews.com/2016/09/02/kratom-devotees-fight-for-supplement/. Accessed September 15, 2016.
19. Wing N. Some Say Kratom is a Solution to Opioid Addiction. Not if Drug Warriors Ban It First. Huffington Post website. March 3, 2016. Available at: www.huffingtonpost.com/entry/kratom-ban-drug-policy_us_56c38a87e4b0c3c55052ee3f. Accessed September 19, 2016.
20. Soldier of the Year Speaks Out on Soldiers for Change on Kratom. YouTube website. September 2, 2016. Available at: www.youtube.com/watch?v=7VwKcTH2nik. Accessed September 19, 2016.
21. Silverman L. Kratom Advocates Speak Out Against Proposed Government Ban. NPR website. September 12, 2016. Available at: www.npr.org/sections/health-shots/2016/09/12/493295493/kratom-advocates-speak-out-against-proposed-government-ban. Accessed September 16, 2016.
22. DEA Kratom Change "Toothless" Without United States Government Enforcement, Says NPA [press release]. Washington, DC: Natural Products Association; August 31, 2016. Available at: www.npainfo.org/App_Themes/NPA/docs/press/PressReleases/Kratom%20Classification.pdf. Accessed September 19, 2016.
23. Nelson S. DEA's Sudden 'Herbal Heroin' Ban Triggers Stiff Resistance from Kratom Community. US News website. September 1, 2016. Available at: www.usnews.com/news/articles/2016-09-01/deas-sudden-herbal-heroin-ban-triggers-stiff-resistance-from-kratom-community. Accessed September 19, 2016.
24. Opium and opioids: a brief history. Available at: www.scielo.br/scielo.php?pid=S0034-70942005000100015&script=sci_arttext&tlng=en. Accessed September 21, 2016.
25. Levine B, ed. *Principles of Forensic Toxicology*. Washington, DC: AACC Press; 2003.
26. Seddigh M, Jolliff GD, Calhoun W, Crane JM. *Papaver bracteatum*, potential commercial source of codeine. *Economic Botany*. 1982;36(4):433-441.
27. Shafiee A, Lalezari I, Nasseri-Nouri P, Asgharian R. Alkaloids of *Papaver orientale* and *Papaver pseudo-orientale*. *Journal of Pharmaceutical Sciences*. 1975;64(9):1570-1572. doi: 10.1002/jps.2600640937.
28. Belofsky G, French AN, Wallace DR, Dodson SL. New geranyl stilbenes from *Dalea purpurea* with in vitro opioid receptor affinity. *J Nat Prod*. 2004;67(1):26-30.
29. Emerging Trends and Alerts. National Institute on Drug Abuse website. Available at: www.drugabuse.gov/drugs-abuse/emerging-trends-alerts. Accessed October 18, 2016.
30. What Are the Possible Consequences of Opioid Use and Abuse? Drug Abuse website. Available at: www.drugabuse.gov/publications/research-reports/prescription-drugs/opioids/what-are-possible-consequences-opioid-use-abuse. Accessed September 22, 2016.
31. American Association of Poison Control Centers. AAPCC website. Available at: www.aapcc.org/. Accessed September 26, 2016.
32. Today's Heroin Epidemic. CDC website. Available at: www.cdc.gov/vitalsigns/heroin/. Accessed September 26, 2016.
33. Prescription Painkiller Overdoses. CDC website. Available at: www.cdc.gov/vitalsigns/methadoneoverdoses/. Accessed September 26, 2016.
34. Szalavitz M. Why Banning the Controversial Painkiller Kratom Could Be Bad News for America's Heroin Addicts. Vice website. January 20, 2016. Available at: www.vice.com/read/why-banning-the-controversial-painkiller-kratom-could-be-bad-news-for-americas-heroin-addicts. Accessed September 26, 2016.
35. Import Alert 54-15. Food and Drug Administration website. Available at: www.accessdata.fda.gov/cms_ia/importalert_1137.html. Accessed September 26, 2016.
36. Import Alert 66-41. Food and Drug Administration website. Available at: www.accessdata.fda.gov/cms_ia/importalert_190.html. Accessed September 28, 2016.
37. US Marshals seize botanical substances kratom from southern California facility [press release]. Silver Spring, MD: Food and Drug Administration; September 25, 2014. Available at: www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm416318.htm. Accessed September 26, 2016.
38. US Marshals seize dietary supplements containing kratom [press release]. Silver Spring, MD: Food and Drug Administration; January 6, 2016. Available at: www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm480344.htm. Accessed September 26, 2016.
39. Kratom seized in California by US Marshals Service [press release]. Silver Spring, MD: Food and Drug Administration; August 4, 2016. Available at: www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm515085.htm. Accessed September 26, 2016.
40. Kruegel AC, Gassaway MM, Kapoor A, et al. Synthetic and receptor signaling explorations of the *Mitragyna* alkaloids: Mitragynine as an atypical molecular framework for opioid receptor modulators. *J Am Chem Soc*. 2016;138(21):6754-64. doi: 10.1021/jacs.6b00360.
41. Varadi A, Marrone GF, Palmer TC, et al. Mitragynine/corynantheidine pseudoindoxyls as opioid analgesics with mu agonism and delta antagonism, which do not recruit beta-arrestin-2. *J Med Chem*. 2016;59(18):8381-8397. doi: 10.1021/acs.jmedchem.6b00748.
42. Wing N. Feds Declare War on Herb Touted as a Solution to Opioid Addiction. Huffington Post website. August 30, 2016. Available at: www.huffingtonpost.com/entry/dea-kratom-schedule-i_us_57c5c263e4b0cdfc5ac98b83. Accessed September 21, 2016.
43. Boodman E. Kratom Ban Will Hinder Studies of the Plant for Treating Pain or Addiction, Researchers Say. Stat News website. September 8, 2016. Available at: www.statnews.com/2016/09/08/kratom-ban-hinders-research/. Accessed September 28, 2016.
44. Halper E. DEA Ends Its Monopoly on Marijuana Growing for Medical Research. *Los Angeles Times*. August 11, 2016. Available at: www.latimes.com/politics/la-na-marijuana-dea-20160811-snap-story.html. Accessed September 28, 2016.
45. Kratom (*Mitragyna speciosa* Korth). Drug Enforcement Administration website. Available at: www.deadiversion.usdoj.gov/drug_chem_info/kratom.pdf. Accessed September 28, 2016.
46. Horie S, Koyama F, Takayama H, et al. Indole alkaloids of a Thai medicinal herb, *Mitragyna speciosa*, that has opioid agonistic effect in guinea pig ileum. *Planta Medica*. 2005;71(3):231-236. doi: 10.1055/s-2005-837822.
47. Takayama H. Chemistry and pharmacology of analgesic indole alkaloids from the Rubiaceous plant, *Mitragyna speciosa*. *Chem Pharm Bull*. 2004;52(8):916-928.
48. Manda VK, Avula B, Ali Z, Khan IA, Walker LA, Khan SI. Evaluation of in vitro absorption, distribution, metabolism, and excretion (ADME) properties of mitragynine, 7-hydroxymitragynine, and mitraphylline. *Planta Medica*. 2014;80(7):568-576. doi: 10.1055/s-0034-1368444.
49. Ballabh P, Braun A, Nedergaard M. The blood-brain barrier: an overview: structure, regulation, and clinical implications. *Neurobiol Dis*. 2004;16(1):1-13.
50. Chavkin C. The therapeutic potential of κ-opioids for treatment of pain and addiction. *Neuropsychopharmacology*. 2011;36:369-370. doi:10.1038/npp.2010.137.
51. Pradhan AA, Befort K, Nozaki C, Gaveriaux-Ruff C, Kieffer BL. The delta opioid receptor: an evolving target for the treatment of brain disorders. *Trends Pharmacol Sci*. 2011;32(10):581-590. doi: 10.1016/j.tips.2011.06.008.
52. Matsumoto K, Yamamoto LT, Watanabe K, et al. Inhibitory effect of mitragynine, an analgesic alkaloid from Thai herbal medicine, on neurogenic contraction of the vas deferens. *Life Sciences*. 2005;78(2):187-194.
53. Tanguay P. Kratom in Thailand: Decriminalization and Community Control? Transnational Institute website. Available at: www.tni.org/files/download/kratom-briefing-dlr13.pdf. Accessed October 3, 2016.
54. Agosti D. What is a treatment? Biosyscontext website. Available at: http://biosyscontext.blogspot.com/2011/02/what-is-treatment-on-way-to-define-or.html. Accessed October 6, 2016.

Kratom *Mitragyna speciosa*. Photo ©2016 Ninoninos iStockPhoto.com

NBTY Signs Agreement with New York Attorney General Regarding DNA Testing of Herbs

NY AG finds no evidence for non-compliance with cGMPs

By Stefan Gafner, PhD

On September 20, 2016, NBTY, Inc., the largest dietary supplement manufacturer in the United States, signed an agreement with the Office of the New York Attorney General (NY AG) to develop and incorporate enhanced herbal authentication methods, including DNA barcoding, into its quality control procedures.[1,2]

The agreement comes more than 18 months after an investigation initiated by the NY AG in February 2015 alleged that four out of five herbal dietary supplement products sold at retailers GNC, Walgreens, Walmart, and Target did not contain ingredients listed on the label. The allegations were based on the results of a controversial DNA barcoding approach, which suggested that only five of the 24 commercial products analyzed contained DNA of the labeled species. These results led the NY AG to demand that the four retailers remove the products from their shelves in the state of New York.[3]

The accuracy of the results, however, was immediately questioned by experts in the field of botanical ingredient authentication.[4,5] Although details of the method used were not released, these experts indicated that because the majority of the products were made from herbal extracts, which contain plant DNA that is frequently fragmented or degraded, DNA barcoding was unlikely to provide useful or definitive results upon which to base regulatory action. The investigation reported finding DNA from species in the following genera: *Oryza* (found in 19 samples), which includes rice (*O. sativa*, Poaceae); *Allium* (in nine samples), which includes garlic (*A. sativum*, Amaryllidaceae) and onion (*A. cepa*); and *Dracaena* (Asparagaceae; found in seven samples), which includes popular non-medicinal houseplants. These findings strongly suggest that the DNA barcoding results were due to cross-contamination. In addition, one valerian (*Valeriana officinalis*, Caprifoliaceae) sample allegedly contained saw palmetto (*Serenoa repens*, Arecaceae) DNA, again raising the question of cross-contamination.[6]

The results of the investigation and subsequent cease-and-desist orders issues by the NY AG were publicized in national newspapers, including *The New York Times* and *The Washington Post*.[7-9] Despite the apparent use of an inappropriate and inadequate test method, some news organizations did not question the results and were highly critical of the dietary supplement industry. A widely distributed Associated Press article published shortly after the NY AG's initial announcement did attempt to cover the growing controversy surrounding the NY AG's reliance on only the DNA barcoding analytical method.[10] A detailed review on the investigation by the NY AG was published in *HerbalGram* issue 106.[11]

NBTY, which had contract-manufactured herbal supplements sold at Walgreens and Walmart under the retailers' respective brands, responded to and fully cooperated with the NY AG's investigation, providing documentation confirming that the supplements in question were produced and labeled in accordance with current good manufacturing practices (cGMPs), as required by federal law (i.e., none of the supplements were found to be deficient, adulterated, mislabeled, or a potential hazard to public health, as initially alleged by the NY AG).[3,7,8]

On March 27, 2015, in a highly publicized development, supplement retailer GNC signed an agreement with the NY AG to implement DNA-barcoding testing methods on all botanical ingredients in its dietary supplements before such ingredients were processed into extracts.[12]

While NBTY maintains that there are currently no scientifically valid testing methods for DNA barcoding-based identification of botanical ingredients, it has agreed to incorporate DNA barcoding into its quality control testing procedures no later than September 20, 2017, for at least 12 distinct botanical species (the 12 herbs are not named in the agreement). Also, as part of the agreement, NBTY will implement DNA barcoding authentication of all botanical ingredients for which scientifically valid methods exist* no later than September 20, 2018.

In addition, NBTY pledged to invest $250,000 to foster genetic authenticity research and education, to partner with academic institutions (e.g., Cornell University) to improve transparency and traceability of botanical dietary supplements, to work with industry organizations in the development of supplier cGMPs,** and to have their manufacturing facilities audited by a third-party accreditation body. Also included in the agreement is a commitment to allergen labeling and a campaign to improve consumer information, similar to the requirements outlined in the agreement between the NY AG and GNC from March 2015.[12]

The agreement terminates the investigation by the NY AG into NBTY's supplement manufacturing processes, and it will cease to be in effect 36 months from the date of the agreement. A resolution between the NY AG and Target still appears to be pending.

Many members of the botanical dietary supplement industry have shown their willingness to embrace new analytical techniques for improved quality control processes as long as they are fit for the intended purpose, with the goal to provide the highest quality product for consumers. While DNA-based authentication is a promising technology, the uncritical use of DNA barcoding has led to an unfortunate situation in which regulatory action has been based on erroneous results. This investigation is an example of a lack of understanding by regulatory agencies of the manufacturing processes involved in the production of botanical dietary supplements and of scientifically valid testing methods. HG

References

1. A.G. Schneiderman Announces Major Nationwide Agreement with NBTY, Herbal Supplement Maker for Walgreens and Walmart [press release]. Albany, NY: New York State Attorney General's Office; September 28, 2016. Available at: http://ag.ny.gov/press-release/ag-schneiderman-announces-major-nationwide-agreement-nbty-herbal-supplement-maker. Accessed October 11, 2016.
2. Albany, NY: New York State Attorney General's Office; September 20, 2016. Available at: https://ag.ny.gov/sites/default/files/nbty_agreement.pdf. Accessed October 12, 2016.
3. A.G. Schneiderman Asks Major Retailers to Halt Sales of Certain Herbal Supplements as DNA Tests Fail to Detect Plant Materials Listed on Majority of Products Tested [press release]. Albany, NY: New York State Attorney General's Office; February 3, 2015. Available at: www.ag.ny.gov/press-release/ag-schneiderman-asks-major-retailers-halt-sales-certain-herbal-supplements-dna-tests. Accessed October 11, 2016.
4. Harbaugh Reynaud DT, Mishler BD, Neal-Kababick J, Brown PN. *The Capabilities and Limitations of DNA Barcoding of Botanical Dietary Supplements* [white paper]. Richmond CA: AuthenTechnologies; March 2015. Available at: https://gallery.mailchimp.com/2d47ec72fa1542de734a46f71/files/Reynaud_DNA_Barcoding_White_Paper.pdf. Accessed October 11, 2016.
5. Is DNA barcode testing appropriate for the conclusions reached by the New York Attorney General? Here's what some of the experts say... . Council for Responsible Nutrition website. Available at: www.crnusa.org/NYAG/quotes.html. Accessed October 11, 2016.
6. Parveen I, Gafner S, Techen N, Murch SJ, Khan IA. DNA barcoding for the identification of botanicals in herbal medicine and dietary supplements: strengths and limitations. *Planta Med*. 2016;82(14):1225-1235. DOI:10.1055/s-0042-111208. Available at: www.thieme-connect.com/products/ejournals/pdf/10.1055/s-0042-111208.pdf. Accessed October 12, 2016.
7. O'Connor A. New York Attorney General targets supplements at major retailers. *New York Times*. February 3, 2015. Available at: http://well.blogs.nytimes.com/2015/02/03/new-york-attorney-general-targets-supplements-at-major-retailers/. Accessed October 11, 2016.
8. O'Connor A. What's in those supplements? *New York Times*. February 3, 2015:A1. Available at: http://well.blogs.nytimes.com/2015/02/03/sidebar-whats-in-those-supplements/. Accessed October 11, 2016.
9. Kaplan S. GNC, Target, Wal-Mart, Walgreens and accused of selling adulterated 'herbals'. *Washington Post*. February 3, 2015. Available at: www.washingtonpost.com/news/morning-mix/wp/2015/02/03/gnc-target-wal-mart-walgreens-accused-of-selling-fake-herbals/. Accessed October 11, 2016.
10. Esch M. Supplements industry derides NY attorney general's DNA tests. February 10, 2015. *Seattle Post-Intelligencer* website. Available at: www.seattlepi.com/news/medical/article/Supplements-industry-derides-NY-attorney-6069689.php. Accessed March 9, 2015.
11. Smith T. The Supplement Saga: A Review of the New York Attorney General's Herbal Supplement Investigation. HerbalGram. 2015;106:44-55. Available at: http://cms.herbalgram.org/herbalgram/issue106/hg106-FEAT-NYAG.html. Accessed October 12, 2016.
12. A.G. Schneiderman Announces Agreement with GNC to Implement Landmark Reforms for Herbal Supplements [press release]. Albany, NY: New York State Attorney General's Office; March 30, 2015. Available at: www.ag.ny.gov/press-release/ag-schneiderman-announces-agreement-gnc-implement-landmark-reforms-herbal-supplements. Accessed October 11, 2016.

* According to the agreement, existing scientifically valid DNA barcoding methods are those that meet one or more of the following criteria:

- DNA barcoding methods that are incorporated in a monograph associated with the relevant ingredient by the United States Pharmacopeia or the American Herbal Pharmacopoeia.
- The US Food and Drug Administration accepts or endorses the use of DNA barcoding, either as a standalone method or part of a multi-method protocol, as a scientifically valid method for confirming the identity of the relevant ingredient.
- Any US industry group in which NBTY is a corporate member identifies DNA barcoding as a valid or appropriate method for confirming the authenticity of the relevant ingredient, as either a standalone method or part of a multi-method protocol.
- Upon review of scientific literature and industry practice, NBTY or its Herbal Authenticity Program independently recognizes that reliable and scientifically valid DNA barcoding is available for that ingredient.

** cGMPs pertain to manufacturers and distributors of dietary supplements but not to the producers and suppliers of the ingredients used in the production of finished products. Several recent herb and dietary supplement industry initiatives have focused on creating guidelines for manufacturers to require of suppliers in the absence of federally mandated practices for ingredient suppliers.

QUALITY CONTROL

Adulteration of Pomegranate Products — A Review of the Evidence

By John H. Cardellina II, PhD, and Mark Blumenthal

***Editor's note**: This article was produced as part of the ABC-AHP-NCNPR Botanical Adulterants Program's continuing coverage of adulteration-related issues.*

Introduction

Pomegranate (*Punica granatum*, Lythraceae) fruit juice has enjoyed considerable market growth and commercial success as a popular beverage in the United States and internationally for more than a decade. The consumption of pomegranate juice in the United States went from roughly 75 million eight-ounce servings in 2004 to about 450 million servings in 2008 — a 500% increase.[1] One review indicates that sales of pomegranate juice grew dramatically from $84,500 in 2001 to $66 million in 2005.[2] According to 2014 estimates, 150,000-200,000 metric tons of fresh pomegranates and 3.7 million gallons of pomegranate juice concentrate are sold annually (A.R. Rejaei, director of clinical regulatory affairs at POM Wonderful, email to M. Blumenthal, April 7, 2015).

As the popularity of pomegranate has increased, many suppliers of herbs and other plant-based materials have begun to produce a variety of dried pomegranate materials (e.g., dried juice concentrates and extracts) for use as ingredients with health-promoting properties in the burgeoning global market for natural products.* These concentrates and extracts are produced by various means from pomegranate juice, whole pomegranate fruit, or selected parts of the fruit.

Many manufacturers produce botanical extracts standardized to a chemical compound or a class of compounds (marker compounds) for quality control purposes and/or to help ensure consistent, reproducible biological activity. Following this trend, some manufacturers of pomegranate fruit extracts (PFEs) are standardizing their PFEs to ellagic acid (EA), a common phenolic compound widely distributed in nature. EA has a number of reported beneficial physiological activities, with much work focusing on the compound's antioxidant activity.[3] (EA was recently found to have pro-oxidant properties as well.) The antioxidant activities of EA metabolites formed in the intestinal tract ("colonic metabolites," such as urolithin A) are thought to be responsible for the therapeutic effects attributed to EA.[4,5]

A number of PFEs are marketed with claims of high levels of EA (ca. 40-70%), but industry experts have questioned the practice of standardizing PFEs to such high levels of EA. A concern raised by some experts — and a central question in this paper — is whether such high EA levels are endogenous in the pomegranate fruit source of these extracts, or if they are the result of added, non-pomegranate-sourced (i.e., exogenous) EA.

Other pomegranate products have been the subject of adulteration reports as well. A 2009 article describing pomegranate juice adulterated with other fruit juices suggests that there may be several forms of adulteration that exist in the marketplace.[6]

This article briefly reviews the chemistry and reported health benefits of pomegranate, the evidence for adulteration of pomegranate juice and extract, the pharmacology and safety of EA, and the issues surrounding standardizing PFEs to EA content.

Pomegranate *Punica granatum*
Photo ©2016 Steven Foster

* Natural products may be referred to as functional foods, dietary supplements (in the United States), natural health products (in Canada), therapeutic goods (in Australia), or food supplements (in Europe), depending on where they are sold.

Background

Pomegranate is believed to have originated in an area encompassing what is now Iran, Afghanistan, and northern India. Pomegranate played a prominent role in Greek mythology, symbolism, and ceremonies, as well as in numerous religions, including Zoroastrianism, Buddhism, early Christianity, Hinduism, and Islam.[7,8] All parts of the pomegranate plant (root, bark, leaves, flowers, and fruit) have been used in Ayurvedic medicine in India for a variety of purposes, including as an antiparasitic agent and blood tonic, and for the treatment of ulcers, canker sores, and diabetes.[7] The antitumor, antidiabetic, cardioprotective, antioxidant, and antimicrobial properties of pomegranate preparations have taken on a more prominent role in current use.[2,9-12]

The chemistry of pomegranate is dominated by phenolic compounds of differing complexity, including benzoic and cinnamic acid derivatives, flavonoids, ellagitannins, and anthocyanins.[10] Lignans were reported in pomegranate for the first time in 2009, adding to the family of phenolics found in this species.[13] Two analyses of pomegranate juice using ultra high-performance liquid chromatography-mass spectrometry (UHPLC-MS) have cataloged 67 and 75 different secondary metabolites, respectively, most of them phenolics.[14,15] Triterpenes have also been reported in pomegranate.[16] Pomegranate seed oil contains phytosterols and has a fatty acid profile dominated by punicic acid, an omega-5 linolenic acid isomer with the carbon-carbon double bonds at positions 9, 11, and 13.[17]

The majority of pomegranate dietary supplements are reportedly manufactured from dried extracts. The materials of commerce discussed in this review are all derived from the fruit, whether from the seed, juice, or rind/husk/peel.[18] Pomegranate dietary supplements are typically produced from either dehydrated pomegranate juice (also known as juice concentrate, not an extract) or compounds extracted from pomegranate fruit and/or fruit parts by using a solvent (e.g., water, ethanol, methanol, or combinations thereof), often after the juice has been removed by mechanical pressing. Depending on the methods used and the desired chemical profile of the finished material, manufacturers often try to preserve the bioactive phenolic compounds[19] of pomegranate that have been the subject of numerous chemical, pharmacological, and clinical studies.

As a conventional food, pomegranate juice remains a popular beverage for its antioxi-

dant activity. A recent review summarizing the impact of processing on the bioactive constituents, flavor, and aroma of pomegranate juice noted that temperature, pH, pressure, and time all affect the final concentration and ratios of different juice constituents.[20]

Evidence of Adulteration

At least three different forms of adulteration have been reported in pomegranate products in the global marketplace: pomegranate juices made with juice(s) from other fruits; pomegranate extracts spiked with additional EA or polyphenols; and products made mostly from unknown or unidentified source materials, with little to no pomegranate constituents.

Juice

Increased demand for an agricultural commodity in relatively fixed supply usually drives up the cost of the raw material, which can tempt less scrupulous suppliers and manufacturers to dilute or substitute the actual commodity with lower-cost, more readily available materials. The addition of lower-cost, readily available juices to more expensive juices in limited supply has been an issue in the food and beverage industry for some time.[21] Both pomegranate juice and extracts thereof appear to have been subject to this form of economically motivated adulteration.

In 2009, Zhang et al.[6] evaluated 45 juice samples from 23 US manufacturers, all purchased in local markets. First, they adapted criteria for determining the identity of genuine pomegranate juice from the databases of Krueger Food Laboratories, Inc., and the Association of the Industry of Juices and Nectars of the European Economic Community.[22-24] After examining the profiles of anthocyanins, ellagitannins, sugars, and acids in those juice samples, they found that only approximately 35% of the tested juices had complete profiles appropriate for or representative of pomegranate juice. (The researchers also tested the samples for mannitol and tartaric acid content, and used stable isotope ratio analysis [SIRA] to test for any added sugars.) This seminal study established that adulteration of pomegranate juice was pervasive at the time, and offered a multi-parameter profile to determine if juice products are adulterated.

Numerous methods and criteria have been used previously to identify adulterated juice products. In 2011, concern about fruit juice adulteration led the Grocery Manufacturers Association to conduct an HPLC-MS analysis of various fruit juices, including pomegranate, apple (*Malus* spp., Rosaceae), orange (*Citrus sinensis*, Rutaceae), red grape (*Vitis vinifera*, Vitaceae), white grape (*V. vinifera*), and cranberry (*Vaccinium macrocarpon*, Ericaceae), to determine their levels of tartaric, quinic, malic, and citric acids.[25] The researchers used the unique ratio of acids in each juice to determine if other juice(s) were present. This study also confirmed the presence of low levels of tartaric and quinic acids in pomegranate. A group in Spain subsequently evaluated pomegranate juice to measure the contents of organic acids, sugars, minerals, proline, and volatile flavor/aroma compounds. The analyses revealed adulteration with varying amounts of grape or peach (*Prunus persica*, Rosaceae) juice.[26] Furthermore, Tezcan et al. in Turkey used a chiral micellar electrokinetic chromatography laser-induced fluorescence (MEKC-LIF) method to develop a fairly complete amino acid profile of pomegranate juice. The results suggested that asparagine (L-Asn) could serve as an effective indicator of adulteration with apple juice, since it is six- to 13-fold more abundant in juices made from certain varieties of apples.[27]

Borges et al. used HPLC with multiple detectors in two studies of products advertised to contain "100% pomegranate juice." In one study,[28] HPLC coupled with a photodiode array and tandem mass spectrometers (HPLC-PDA-MS^2) was used to analyze the polyphenolic profiles of 36 commercially sold juices, including six labeled to contain 100% pomegranate juice and 20 pomegranate juices blended with other fruit juices. (The remaining 10 juices were composed of other fruits.) Three of the "pure" pomegranate juices exhibited typical pomegranate profiles and the highest ellagitannin contents of the tested juices, but only one of these contained significant concentrations of anthocyanins. The other three juices advertised as "pure pomegranate juice" displayed aberrant HPLC profiles relative to the expected pomegranate fingerprint, which suggested blending with other fruit juices or the addition of exogenous polyphenols.

In the second study by Borges et al., fluorescence detection (FD) was combined with the previously used HPLC-PDA-MS method to compare the polyphenolic profiles of a known pure pomegranate juice to red wine and three other juices claiming to be pure pomegranate juice.[29] The red wine and the authentic pomegranate juice both exhibited the expected anthocyanin profiles and were readily distinguished by the analytical methods used (pomegranate juice also produced peaks for its ellagitannins, while the red wine, in contrast, gave peaks for flavan-3-ol monomers and procyanidin dimers and trimers). Notably, the three supposedly pure pomegranate juices had the expected ellagitannins, but they also exhibited anthocyanin profiles indicative of a mixture of both source fruits (pomegranates and grapes), as well as the procyanidins and flavan-3-ols seen in grape-derived juices. These results suggested that grape juice might be used to dilute more expensive pomegranate juice, while maintaining an appropriate color.

Krueger Food Laboratories followed up its aforementioned work[22,23] with a three-year study of more than 500 juice samples.[30] With this large dataset, researchers were able to use an iterative statistical analysis to reduce the sample set to a group of compositionally consistent juices. This was accomplished by calculating a mean and standard deviation of various juice components for the whole set of samples, then excluding any samples that were three or more standard deviations from the mean. The process was repeated on the remaining samples until a stable set of 263 juices was obtained — the presumptive authentic pomegranate juice samples. The report includes a table of 14 pomegranate juice components, mostly sugars and organic acids (with mean content and standard deviation), and a representative HPLC-UV profile of the anthocyanins. A number of patterns of adulteration were observed, including the addition of up to seven fruit juices, sugars, anthocyanin colorants from many natural sources, and artificial colors. Ten references are provided for the analytical methods used, six of which are official AOAC International methods.

In 2016, researchers from Italy demonstrated the use of a DNA-based method, Sequence Characterized Amplified Regions (SCAR), to detect as low as 1% adulteration of pomegranate juice by 10 other botanical sources of anthocyanins reported as potential adulterants of pomegranate products. The SCAR marker selected as a positive control for pomegranate, designated ScPg$_{231}$, correctly identified eleven different accessions** of *P. granatum*. The marker also identified pomegranate in four product mixtures: two herbal teas containing 2% and 20% pomegranate, respectively; a jam containing pomegranate, lemon (*Citrus limon*, Rutaceae), agave (*Agave* spp., Agavaceae), and pectin; and a juice mix containing 3.5% pomegranate juice concentrate. These results indicate that relatively short-length SCAR markers may be highly useful for identifying pomegranate components with partially degraded DNA.[32]

Extracts

While pomegranate juice adulteration is generally the result of addition of other fruit juices, adulteration of pomegranate extracts predominantly involves the addition of exogenous polyphenolic material. Pomegranate extracts not standardized to a particular marker, but instead to a non-specific estimation of antioxidant capacity or total phenolics, may be particularly prone to the addition of inexpensive polyphenols (e.g., EA) or tannins to increase antioxidant activity, or to the addition of anthocyanins to adjust color. In an extreme case, a non-pomegranate-based material could be similarly augmented with polyphenols to resemble a pomegranate-derived product.

An analysis of the ellagitannin content and antioxidant capacity of 27 commercially available pomegranate extracts found that only five extracts contained significant amounts of punicalin and punicalagins (pomegranate-specific ellagitannins). Seventeen of the samples contained mostly EA, currently the most used marker compound for standardization of these extracts, while the remaining five had little or no EA or ellagitannins and weak antioxidant activity.[33]

Another analysis of 19 commercially available pomegranate extracts by a different research group provided similar results.[34] Qualitative analysis indicated that only seven of the 19 tested extracts produced polyphenolic profiles indicative of pomegranate, while 13 of the extracts had EA levels exceeding what should be found in the arils (seed coverings) and rind of pomegranate, and six of those had little or no pomegranate ellagitannins present. The extracts that contained some pomegranate ellagitannins but no pomegranate anthocyanins, the authors noted, were likely produced by extraction of the press cake (rinds and arils) after juice production. Two possible explanations were presented for the extracts with high levels of EA but no pomegranate ellagitannins: (1) The extraction and/or associated processing methods were so harsh that the ellagitannins were all decomposed, or (2) no pomegranate was present, and exogenous EA was added.

In addition to the HPLC analyses described above, thin-layer chromatography (TLC) may also be helpful in determining whether an unknown sample matches authentic pomegranate reference samples.

Pomegranate *Punica granatum*
Photo ©2016 Steven Foster

** According to the US Department of Agriculture, an accession is "a genetically unique plant sample from a particular geographic location."[31]

QUALITY CONTROL

Pomegranate *Punica granatum*
Photo ©2016 Steven Foster

Ellagic Acid

EA Standardization

The issue of standardizing PFEs to EA content is complex, sometimes even problematic, for a number of reasons, discussed below.

1. Free EA is not the most abundant phenolic compound in pomegranate.[19] Table 1 summarizes the EA content of various pomegranate parts from several geographic regions, illustrating that EA yields from experimental pomegranate extracts are not likely to exceed 10%. Furthermore, the data suggest that considerable variation of EA (and other polyphenols) may be observed in different varieties of pomegranate, as well as in accessions of the fruit from different ecological niches and geographic regions. Further complicating the matter is the fact that different processing methods for the juice or extracts can result in partial hydrolysis of EA esters (ellagitannins), leading to higher observed levels of free EA in the resulting extract. Considering the experimental conditions used in various publications cited in Table 1, it would be exceedingly difficult, if not practically impossible, to achieve the high levels of EA (40-70%) advertised in products claiming to contain only pomegranate fruit.

One report has described the preparation of a processed extract of pomegranate rinds containing a remarkable 90% EA, as measured by HPLC analysis.[35] The process was described as a triple extraction with hot 50% ethanol, followed by boiling those extracts in hydrochloric acid (HCl) for six hours, and drying the resulting reaction mixture solids. An extract processed in this manner could be used to augment the EA content of pomegranate extracts and products derived therefrom. However, extracts produced using these methods would be unlikely to retain the chemical fingerprint of pomegranate polyphenols.

2. EA is also available in substantial quantities from other sources of ellagitannins (e.g., chestnut [*Castanea* spp., Fagaceae] bark or fruit[36] or gall nuts), offering a potentially lower-cost alternative source for "enhancing" pomegranate extracts. Moreover, the last dozen years have seen a surge of interest in producing free EA through the biotransformation of tannins (i.e., the enzymatic degradation of complex polyphenols to EA by microbial cultures).[37-41]

3. EA is not the primary or foremost bioactive compound in pomegranate. In fact, the compounds responsible for many of the pharmacological benefits attributed to pomegranate have not been adequately identified. It is possible, even likely, that different compounds may be associated with various bioactivities.

Punicalin and punicalagins A and B are more abundant than EA in pomegranate and have been reported to account for 89% of the antioxidant activity of pomegranate juice.[19,42] Although standardizing PFEs to EA content may be convenient from an analytical chemistry standpoint, it would be more logical to standardize PFEs to punicalin and punicalagins A and B, which are more abundant and distinctive markers for pomegranate. The availability of high-quality reference standards to analyze for these potential markers might be a short-term issue, but there is clearly a market need for such reference standards.

4. EA is poorly soluble in aqueous media, particularly under acidic conditions, and it is not significantly bioavailable when consumed as the free acid.[43,44] However, hydrolysable ellagitannins (e.g., punicalin and the punicalagins) not only are more soluble than EA in physiological media, but also yield bioavailable EA during metabolism in the human gut.[44] Ironically, higher EA content in various commercial products would thus seem likely to result in lower blood levels of EA, relative to the complex of authentic, unaltered pomegranate polyphenolic compounds.

EA Bioavailability

A single human volunteer, after fasting overnight, took a dose of 180 mL of pomegranate juice containing 25 mg of EA and 318 mg ellagitannins. Blood samples were drawn prior to dosing and at 30 minutes, one, two, three, four, and six hours after dosing, and they were processed and analyzed by HPLC. The peak EA concentration, 31.9 ng/mL (0.106 µM), was observed in the one-hour sample, and EA was undetectable by the fourth hour. The ellagitannins were not detected at any time point.[52]

In another small pharmacokinetic study, 11 human volunteers consumed 45 g of freeze-dried black raspberries (*Rubus* spp., Rosaceae) each day for seven days. Blood and urine samples were collected and analyzed for four anthocyanins and free EA.[53] The research team found that less than 1% of the compounds of interest were absorbed and eliminated in urine. Maximum levels of the anthocyanins and EA occurred between one and two hours after dosing, while the highest levels in urine were found up to four hours after consumption. No adverse effects were noted.

In a different study, 11 volunteers fasted overnight before consuming two capsules, each containing 400 mg of pomegranate extract. The combined dose contained 21.6 mg of EA and 330.8 mg of ellagitannins. Blood was drawn at 30 minutes, one, two, four, six, eight, and 24 hours after dosing, and subsequently analyzed by HPLC-MS. Significant variation in blood levels was observed among the 11 subjects, but the average peak EA concentration, 33.8 ng/mL, was recorded at the one-hour time point.[54] These results compare remarkably well with the one-person study reviewed above,[52] even though the pomegranate products used were in different dosage forms (juice vs. capsule) and were produced by different manufacturers.

An additional study involved 16 adults who consumed, sequentially, eight ounces of pomegranate juice from a first-press squeezing of whole fruit, a teaspoon of a concentrated liquid extract of the fruit material left after first press squeezing in eight ounces of water, and a capsule containing 1,000 mg of a dried powder obtained by a solid phase extraction of the concentrated liquid extract described

Table 1. Ellagic Acid Content of Various Pomegranate Samples

Variety/Source	Plant Part	Extraction Method	EA Content[a]	Analytical Method
Chelfi/Tunisia[45]	dried peel	80% methanol	0.01	HPLC
Gansu, China[46]	dried peel	50% methanol	1.1	HPLC, CE[b]
		80% methanol with 1.2M HCl	12	HPLC, CE[b]
Yunnan, China[47]	dried peel	Methanol	5.8	HPLC
		95% methanol	7.1	HPLC
		90% methanol	7.7	HPLC
		85% methanol	6.8	HPLC
		80% methanol	6.2	HPLC
Not specified/Peru[48]	pressed whole fruit	Juice	4.6-7.2 mg/L	HPLC
	arils	Juice	2.1 mg/L	HPLC
	peel	80% methanol with 0.1M HCl	0.06	HPLC
	mesocarp	80% methanol with 0.1M HCl	0.02	HPLC
Wonderful/Canary Islands[49]	fruit pulp	Water	0.8	HPLC
	fruit pulp	Ethanol	3.9	HPLC
	pressed whole fruit	Juice	121 mg/L	HPLC
	commercial product	Juice	95 mg/L	HPLC
Mollar de Elche/Spain[50]	fresh rind	80% methanol with 1% acetic acid	0.25	HPLC
	dried rind	80% methanol with 1% acetic acid	0.11-0.2	HPLC
	fresh arils	80% methanol with 1% acetic acid	0.006	HPLC
	dried arils	80% methanol with 1% acetic acid	0.001-0.006	HPLC
Various: Spain, Italy, Iran, Israel, Tunisia, Turkey[51]	fresh arils	Juice	140-490 mg/L	HPLC-UV-MS

[a] Percent dry weight, unless otherwise indicated
[b] CE = capillary electrophoresis

above. Consumption of each of these doses was separated by a one-week washout phase. Blood samples were drawn prior to dosing and at 30 minutes, one, two, three, four, six, and 24 hours after dosing. The three test materials had similar gallic acid equivalent values, but no analyses for punicalagins or EA were provided in the paper. The times to maximum concentration (T_{max}) of EA for the juice and extract dissolved in water were similar to previously reported times, roughly one hour. The T_{max} for the encapsulated dry powder was considerably longer, about 2.6 hours, but this may have been related to dissolution time of the gelatin capsule. All three dosage forms gave similar areas under the curve (i.e., integration of the plot of EA concentration vs. time after dosing).[55]

EA Safety

A search of the scientific and toxicological literature revealed no reports of adverse effects or significant toxicity associated with EA. The poor bioavailability of EA likely makes establishing a lowest-observed adverse effect level (LOAEL) for EA difficult.

In an effort to determine an LD_{50} level (a measure of acute toxicity that is based on the lethal dose that produces mortality in 50% of test animals) in mice, the animals were given a single dose of 25-1,500 mg/kg of EA orally or 25-1,000 mg/kg intraperitoneally and observed for 14 days. No animals died within 24 hours, meaning that an LD_{50} was not reached. No animals died after 14 days, nor were any irreversible signs or symptoms observed in the test animals.[56]

In a subchronic toxicity study, rats were given an EA oral dose of 10, 30, or 100 mg/kg. Thirty days after dosing, hematological and biochemical tests were conducted on blood samples and histopathological profiles were observed for vital organs. The only deviation from normal observed was reduced uric acid levels at the 30 and 100 mg/kg doses. Thus, this study found that free EA exhibited quite low toxicity.[56]

In another, longer subchronic toxicity study, rats were fed a powder basal diet for 90 days that included EA at dose levels of 0, 1.25, 2.5, and 5% (0, 9.4, 19.1, 39.1 g/kg body weight, respectively, in males, and 0, 10.1, 20.1, 42.3 g/kg body weight, respectively, in females).[57] No mortality, histopathological changes, or treatment-related clinical signs were observed, except for decreased weight gain in female rats fed the three actual doses of EA. From these results, the authors calculated an estimated no-observed adverse effect level (NOAEL) dose for EA in females of 3,254 mg/kg/day and estimated no-observed effect level (NOEL) values in males (3,011 mg/kg/day) and females (778 mg/kg/day).

This relatively small but consistent pool of data, along with the widespread presence of EA in the human diet and the low bioavailability of EA, suggest that high levels of EA in a supplement may not be a safety issue, but rather a possible regulatory, efficacy, and/or ethical matter.

Conclusion

The evidence reviewed above indicates that some pomegranate juice products are adulterated by blending with other fruit juices and/or colorants. Furthermore, some pomegranate juice concentrates and extracts (and resulting products) are likely adulterated by the addition of non-pomegranate EA sources. In either case, the consumer may not receive the expected benefits of consuming pure, high-quality pomegranate juice or extracts.

Suppliers, buyers, and manufacturers of finished products need to be aware of this issue and should take steps to ensure that their materials are not adulterated. This report indicates that a single analytical method will most likely not be able to determine all of the possible adulterants (and approaches to adulteration) of pomegranate juice, juice concentrate, and extract, but there is an array of available methods that can be applied for quality control purposes. Ongoing research in various laboratories will likely provide additional tools and methods in the near future. HG

References

1. Packer R. Pomegranate juice adulteration. *Food Safety Magazine*. February 2013.
2. Johanningsmeier SD, Harris GK. Pomegranate as a functional food and nutraceutical source. *Annu Rev Food Sci Technol*. 2011;2:181-201.
3. Tomás-Barberán FA, García-Conesa MT, Larrosa M, et al. Bioavailability, metabolism, and bioactivity of food ellagic acid and related polyphenols. In: *Recent Advances in Polyphenol Research.* Vol 1. Daayf F, Lattanzio V, eds. Hoboken, NJ: Blackwell Publishing Ltd.; 2008:263-267.
4. Espin JC, Larrosa M, Garcia-Conesa MT, Tomas-Barberan F. Biological significance of urolithins, the gut microbial ellagic acid-derived metabolites: the evidence so far. *Evid Based Complement Alternat Med*. 2013(2013):270418. doi:10.1155/2013/270418.
5. Saha P, Yeoh BS, Singh R, et al. Gut microbiota conversion of dietary ellagic acid into bioactive phytoceutical urolithin A inhibits heme peroxidases. *PLoS One.* 2016;11:e0156811. doi:10.1371/journal.pone.0156811.
6. Zhang Y, Krueger D, Durst R, et al. International multidimensional authenticity specification (IMAS) algorithm for detection of commercial pomegranate juice adulteration. *J Agric Food Chem*. 2009; 57:2550-2557.
7. Bhandari PR. Pomegranate (*Punica granatum* L). Ancient seeds for modern cure? Review of potential therapeutic applications. *Int J Nutr Pharmacol Neurol Dis*. 2012;2:171-184.
8. Ruis AR. Pomegranate and the mediation of balance in early medicine. *Gastronomica*. 2015;15:22-33.
9. Miguel MG, Neves MA, Antunus MD. Pomegranate (*Punica granatum* L.): A medicinal plant with myriad biological properties — A short review. *J Med Plants Res*. 2010;4:2836-2847.
10. Jasuja ND, Saxena R, Chandra S, Sharma R. Pharmacological characterization and beneficial uses of *Punica granatum*. *Asian J Plant Sci*. 2012;6:251-267.
11. Katz SR, Newman RA, Lansky EP. *Punica granatum*: Heuristic treatment for diabetes mellitus. *J Med Food*. 2007;10:213-217.
12. Jurenka J. Therapeutic applications of pomegranate (*Punica granatum* L.): A review. *Alt Med Rev*. 2008;13:128-144.
13. Bonzanini F, Bruni R, Palla G, Serlataite N, Caligiani A. Identification and distribution of lignans in *Punica granatum* L. fruit endocarp, pulp, seeds, wood knots and commercial juices by GC-MS. *Food Chem*. 2009;117:745-749.
14. Calani L, Beghe D, Mena P, et al. Ultra-HPLC–MS*n* (poly)phenolic profiling and chemometric analysis of juices from ancient *Punica granatum* L. cultivars: A nontargeted approach. *J Agric Food Chem*. 2013;61:5600-5609.
15. Mena P, Calani L, Dall'Asta C, et al. Rapid and comprehensive evaluation of (poly)phenolic compounds in pomegranate (*Punica granatum* L.) juice by uHPLC-MS*n*. *Molecules*. 2012;17:14821-14840.
16. Jiang HZ, Ma QY, Fan HJ, et al. Fatty acid synthase inhibitors isolated from *Punica granatum* L. *J Brazilian Chem Soc*. 2012;23:889-893.
17. Kaufman M, Wiesman Z. Pomegranate oil analysis with emphasis on MALDI-TOF/MS triacylglycerol fingerprinting. *J Agric Food Chem*. 2007;55:10405-10413.
18. Gardner Z, McGuffin M, eds. *American Herbal Products Association's Botanical Safety Handbook.* 2nd ed. Boca Raton, FL: CRC Press; 2013:155-159.
19. Gil MI, Tomás-Barberán FA, Hess-Pierce B, Holcroft DM, Kader AA. Antioxidant activity of pomegranate juice and its relationship with phenolic composition and processing. *J Agric Food Chem.* 2000;48:4581-4589.
20. Nuncio-Jáuregui N, Calín-Sánchez A, Vázquez-Araújo L, Pérez-López AJ, Frutos-Fernández MJ, Carbonell-Barrachin AA. Processing pomegranates for juice and impact on bioactive components. In: *Processing and Impact on Active Components in Food.* Preedy VR, ed. Amsterdam, Netherlands: Elsevier Inc.; 2015:629-636.
21. US Food and Drug Administration Guide to Inspection of Foods, Section 10, Orange and Other Juices. Available at: www.fda.gov/ora/Inspect_ref/igs/foodspa.html. Accessed September 22, 2016.
22. Krueger DA. Composition of commercial pomegranate juice. Abstracts, 122nd Annual Meeting of the AOAC, 2008.
23. Krueger DA. Composition of pomegranate juice. *J AOAC Int*. 2012;95:163-168.
24. Association of the Industry of Juices and Nectars from Fruits and Vegetables of the European Economic Community (AIJN). Draft Reference Guideline for Pomegranate Juice, Code of Practice for Evaluation of Fruit and Vegetable Juices. March 18, 2008.
25. Ehling S, Cole S. Analysis of organic acids in fruit juices by liquid chromatography-mass spectrometry: An enhanced tool for authenticity testing. *J Agric Food Chem.* 2011;59:2229-2234.
26. Nuncio-Jauregui N, Calin-Sanchez A, Hernandez F, Carbonell-Barrachina AA. Pomegranate juice adulteration by addition of grape or peach juices. *J Sci Food Agr*. 2014;94:646-655.
27. Tezcan F, Uzaşçi S, Uyar G, Oztekin N, Erim FB. Determination of amino acids in pomegranate juices and fingerprint for adulteration with apple juices. *Food Chem.* 2013;141:187-1191.
28. Borges G, Mullen W, Crozier A. Comparison of the polyphenolic composition and antioxidant activity of European commercial fruit juices. *Food Funct*. 2010;1:73-83.
29. Borges G, Crozier A. HPLC-PDA-MS fingerprinting to assess the authenticity of pomegranate beverages**.** *Food Chem*. 2012;135:1863-1867.
30. Krueger Food Laboratories. Composition of pomegranate juice. *J AOAC International*. 2012;95(1):163-168. Available at: www.kfl.com/pom.html. Accessed June 2, 2016.
31. Definitions: What is an accession? United States Department of Agriculture – Agricultural Research Service website. Available at: www.ars.usda.gov/plains-area/fort-collins-co/center-for-agricultural-resources-research/plant-germplasm-preservation-research/docs/ncgrp-faq/. Accessed October 10, 2016.
32. Marieschi M, Torelli A, Beghé D, Bruni R. Authentication of *Punica granatum* L.: Development of SCAR markers for the detection of 10 fruits potentially used in economically motivated adulteration. *Food Chem*. 2016;202:438-444.
33. Zhang Y, Wang D, Lee RP, Henning SM, Heber D. Absence of pomegranate ellagitannins in the majority of commercial pomegranate extracts: implications for standardization and quality control. *J Agric Food Chem*. 2009;57:7395-400.
34. Madrigal-Carballo S, Rodriguez G, Krueger CG, Dreher M, Reed JD. Pomegranate (*Punica granatum*) supplements: Authenticity, antioxidant and polyphenol composition. *J Funct Food*. 2009;324-329.
35. Yoshimura M, Watanabe Y, Kasai K, Yamakoshi J, Koga T. Inhibitory effect of an ellagic acid-rich pomegranate extract on tyrosinase activity and ultraviolet-induced pigmentation. *Biosci Biotechnol Biochem*. 2005;69:2368-2373.
36. Vekiari SA, Gordon MH, Garcia-Macias P, Labrinea H. Extraction and determination of ellagic acid content in chestnut bark and fruit. *Food Chem*. 2008;110:1007-1011.
37. Vattem Dam Shetty K. Ellagic acid production and phenolic antioxidant activity in cranberry pomace (*Vaccinium macrocarpon*) mediated by *Lentinus edodes* using a solid-state system. *Proc Biochem*. 2003;39:367-379.
38. Shi B, He Q, Yao K, Huang W, Li Q. Production of ellagic acid from degradation of valonea tannins by *Aspergillus niger* and *Candida utilis*. *J Chem Technol Biotechnol.* 2005;80:1154-1159.
39. Juang W, Ni J, Borthwick AGL. Biosynthesis of valonia tannin hydrolase and hydrolysis of valonia tannin to ellagic acid by *Aspergillus* SHL 6. *Process Biochem*. 2005;40:1245-1249.
40. Robledo A, Aguilera-Carbó A, Rodriguez R, Martinez JL, Garza Y, Aguilar CN. Ellagic acid production by *Aspergillus niger* in solid state fermentation of pomegranate residues. *J Ind Microbiol Biotechnol*. 2008;35:507-513.
41. Sepúlveda L, Ascacio A, Rodríguez-Herrera R, Aguilera-Carbó A, Aguilar CN. Ellagic acid: Biological properties and biotechnological development for production processes. *African J Biotechnol*. 2011;10:4518-4523.
42. Tzulker R, Glazer I, Bar-Ilan I, Holland D, Aviram M, Amir R. Antioxidant activity, polyphenol content, and related compounds in different fruit juices and homogenates prepared from 29 different pomegranate accessions. *J Agric Food Chem*. 2007;55:9559-9570.
43. Lei F, Xing D-M, Xiang L, et al. Pharmacokinetic study of ellagic acid in rat after oral administration of pomegranate leaf extract. *J Chromatogr B*. 2003;796:189-194.
44. Seeram NP, Henning SM, Zhang Y, Suchard M, Li Z, Heber D. Pomegranate juice ellagitannin metabolites are present in human plasma and some persist in urine for up to 48 h. *J Nutr*. 2006;136:2481-2485.
45. Ben Nasr C, Ayed N, Metche M. Quantitative determination of the polyphenolic content of pomegranate peel. *Z Lebensm Unters Forsch*. 1996;203:374-378.
46. Zhou B, Wu Z, Li X, Zhang J, Hu X. Analysis of ellagic acid in pomegranate rinds by capillary electrophoresis and high-performance liquid chromatography. *Phytochem Anal.* 2008;19:86-89.
47. Panichayupakaranant P, Issuriya A, Sirikatitham A, Wang W. Antioxidant assay-guided purification and LC determination of ellagic acid in pomegranate peel. *J Chromatogr Sci*. 2010;48:456-459.
48. Fischer UA, Carle R, Kammerer DR. Identification and quantification of phenolic compounds from pomegranate (*Punica granatum* L.) peel, mesocarp, aril and differently produced juices by HPLC-DAD–ESI/MS*n*. *Food Chem*. 2011;127:807-821.
49. Jimenez Del Rio M, Ramazanov A, Sikorski S, Ramazanov Z, Chkhikvishvili I. A new method of standardization of health-promoting pomegranate fruit (*Punica granatum*) extract. *Georgian Medical News*. 2006;140:70-77.
50. Calín-Sánchez Á, Figiel A, Hernández F, Melgarejo P, Lech K, Carbonell-Barrachina ÁA. Chemical composition, antioxidant capacity, and sensory quality of pomegranate (*Punica granatum* L.) arils and rind as affected by drying method. *Food Proc Biotechnol*. 2013;6:1644-1654.
51. Gómez-Caravaca M, Verardo V, Toselli M, Segura-Carretero A, Fernández-Gutiérrez A, Caboni MF. Determination of the major phenolic compounds in pomegranate juices by HPLC-DAD-ESI-MS. *J Agric Food Chem*. 2013;61:5328-5337.
52. Seeram NP, Lee R, Heber D. Bioavailability of ellagic acid in human plasma after consumption of ellagitannins from pomegranate (*Punica granatum* L.) juice. *Clin Chim Acta*. 2004;348:63-68.
53. Stoner GD, Sardo C, Apseloff G, et al. Pharmacokinetics of anthocyanins and ellagic acid in healthy volunteers fed freeze-dried black raspberries daily for 7 days. *J Clin Pharmacol*. 2005;45:1153-1164.
54. Mertens-Talcott SU, Jilma-Stohlawetz P, Rios J, Hingorani L, Derendorf H. Absorption, metabolism, and antioxidant effects of pomegranate (*Punica granatum* L.) polyphenols after ingestion of a standardized extract in healthy human volunteers. *J Agric Food Chem*. 2006;54:8956-8961.
55. Seeram NP, Zhang Y, McKeever R, et al. Pomegranate juice and extracts provide similar levels of plasma and urinary ellagitannin metabolites in human subjects. *J Med Food*. 2008;11:390-394.
56. Beserra AMSS, Souza MdC, Colodel EM, et al. Toxicological evaluation of ellagic acid in rodents. *Rev Bras Farm*. 2010;91:16-24.
57. Tasaki M, Umemura T, Maeda M, et al. Safety assessment of ellagic acid, a food additive, in a subchronic toxicity study using F344 rats. *Food Chem Toxicol*. 2008;46:1119-1124.

‘Strengths and Limitations of DNA Barcoding’ Article Published in *Planta Medica*

ABC Chief Science Officer Co-authors Review of DNA Barcoding Analysis

Editor’s note: *American Botanical Council (ABC) Chief Science Officer Stefan Gafner, PhD, co-authored the* Planta Medica *article with Iffat Parveen, PhD, Natascha Techen, PhD, and Ikhlas Khan, PhD, all researchers at the internationally respected National Center for Natural Products Research (NCNPR) at the University of Mississippi (a US Food and Drug Administration [FDA]-funded Center of Excellence in the area of medicinal plant analysis), and Susan Murch, PhD, an expert in the analysis of botanical ingredients at the University of British Columbia in Canada. Interested parties are encouraged to obtain the original article from the journal.*

Background

In July 2016, the respected, peer-reviewed medicinal plant journal *Planta Medica* published an online paper[1] written by various experts in medicinal plant analysis. The paper reviews the strengths and limitations of DNA barcoding analytical methods — a subject that has received significant global attention since the New York attorney general’s (NY AG’s) now-infamous and highly flawed DNA analysis of various herbal dietary supplements, which was covered by *The New York Times* and other major news outlets in 2015.

Based on the DNA analysis, the NY AG took regulatory action against four major retailers for allegedly selling mislabeled herbal supplements. (The products produced and sold by retailer GNC were later deemed by the NY AG to be compliant with state and federal regulations and allowed back onto retail shelves in New York; actions against Target, Walgreens, and Walmart are still pending.) The NY AG has been criticized for relying solely on DNA barcoding analysis as the basis for his regulatory actions. These criticisms have come from a variety of sources: from plant analytical experts in academia, government, and industry, to industry sources and ABC publications.

As noted in the paper, DNA barcoding methods should not be used as the sole analytical method to determine the identity of botanical ingredients in finished herbal formulations (e.g., dietary supplements). Rather, DNA barcoding should be used as part of a larger array of methodologies, including microscopic and chemical methods.

Article Summary

The authors of the *Planta Medica* article begin with an overview of DNA barcoding and discuss the steps (extraction, amplification, and sequencing) involved in the technology, as well as its strengths and limitations for plant identification.

DNA barcoding, which involves the use of short genomic regions to distinguish species of animals, plants, fungi, bacteria, and other organisms, has become an increasingly popular technology to determine the authenticity of botanical ingredients in herbal medicines and dietary supplements. Plant DNA barcoding, initially used predominantly in academia to determine the relationship among species (phylogeny), is now used by many groups, including dietary supplement manufacturers, contract analytical laboratories, government agencies (e.g., the FDA), and, as noted previously, the office of the NY AG. The outcome of DNA barcoding varies depending on the method of DNA extraction, primer choice, amplification, and sequencing. In addition, the success of the technology depends on the presence of high-quality DNA and the absence of interfering compounds in the material analyzed.

A number of extraction methods are used in practice. The choice of the method depends on the material to be analyzed. Different plant parts (DNA is more difficult to obtain from bark or root compared to leaves or flowers) and metabolite compositions (e.g., presence of polysaccharides or polyphenols) will affect the extraction efficiency. The choice of the genomic region is crucial for the successful outcome of the approach. Some regions are difficult to amplify in certain plants (e.g., *matK*) or have a low resolving power (i.e., they do not adequately distinguish among certain species). Others, like the widely used ITS region, may differentiate plants readily, but there may be several copies with varying DNA sequences within the same plant (e.g., in valerian [*Valeriana officinalis*, Caprifoliaceae] and related species). For example, ITS regions from fungal species that may be present as an endophyte (living within the plant) or ectophyte (living at the surface of the plant) may be preferentially amplified.

The quality of DNA present in botanical material is highly dependent on the various steps used to process the material (e.g., drying, grinding, sterilization, storage, extraction, etc.). In many cases, DNA is degraded or absent altogether. The universal primers used for DNA barcoding are designed to amplify the target genomic region of as many plant species as possible, but variations in the sequence in which the primers anneal (bind) may introduce an amplification bias (i.e., in a mixture of botanically derived ingredients, one material is amplified preferentially over the other). The presence of plant polyphenols, such as tannins, in the amplification step also may be problematic, since these metabolites inhibit the polymerases that amplify the DNA.

DNA barcoding, which involves the use of short genomic regions to distinguish species of animals, plants, fungi, bacteria, and other organisms, has become an increasingly popular technology to determine the authenticity of botanical ingredients in herbal medicines and dietary supplements.

The final step in DNA barcoding is the sequencing of the DNA. The Sanger sequencing method has been the method of choice in the past, and works well in cases in which a single botanical ingredient is present. Drawbacks of the Sanger sequencing method include the difficulty of obtaining accurate results for mixtures of ingredients, the low throughput, and the need for greater amounts of DNA compared to next-generation sequencing (NGS). NGS allows simultaneous analysis of multiple DNA fragments (e.g., when multiple plant species are present, such as in herbal preparations used in traditional Chinese medicine or Ayurvedic medicine).

There are, however, some notable advantages to using DNA barcoding compared to other methods of plant species identification. While botanical taxonomy remains the basis of plant classification when a whole plant can be examined in its natural habitat (or as a pressed herbarium species), botanical ingredients are predominantly sold in cut, powdered, or extracted form. For cut or powdered crude raw material, DNA barcoding offers a reliable way to authenticate samples in addition to methods such as organoleptic evaluation, botanical microscopy, and chemical analysis, especially in cases in which species distinction may be challenging.

For materials with fragmented DNA, the amplification of shorter genomic regions, so-called mini-barcodes, may enable identification of the plant material. In order for mini-barcoding to be successful, the analyst has to design species-specific primers resulting in a much shorter amplicon (the piece of DNA that is amplified) compared to the universal barcoding. To apply mini-barcoding, the analyst has to have an idea of the composition of the material, and by using species-specific primers may fail to detect adulterant material. Some plant materials may not be suitable for the design of mini-barcodes (i.e., a small amplicon may not contain sufficient sequence variation to distinguish among species).

The main limitations of current DNA barcoding techniques are the possibility of erroneous results when DNA is degraded (or when large amounts of DNA from other species is present), the reliance on databases in which the material from which the DNA sequence was obtained may not have been authenticated properly, and its inability to distinguish plant parts, which is a legal requirement specified in the FDA’s current good manufacturing practices (cGMPs) for dietary supplements.

As with every analytical method used for quality control of botanical ingredients, DNA barcoding methods need to be properly validated in order to ensure that the results are accurate and reproducible. Validation requirements specific to DNA barcoding of plant ingredients are a matter of debate, and the establishment of guidelines to validate such methods is much-needed.

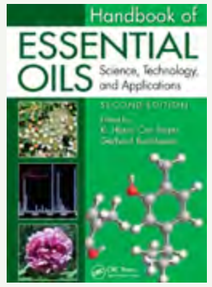
Overall, DNA barcoding is a helpful tool to determine the authenticity of botanical material in whole, cut or powdered form. However, based on its inherent limitations, it should be used in combination with other identification methods, such as microscopic, macroscopic, organoleptic, and chemical methods of analysis. HG

—Stefan Gafner, PhD

Reference

1. Parveen I, Gafner S, Techen N, Murch SJ, Khan IA. DNA barcoding for the identification of botanicals in herbal medicine and dietary supplements: strengths and limitations [published online July 8, 2016]. *Planta Med.* 2016. doi:10.1055/s-0042-111208. Available at: www.thieme-connect.com/products/ejournals/pdf/10.1055/s-0042-111208.pdf. Accessed August 10, 2016.

BOOK REVIEWS



Handbook of Essential Oils: Science, Technology, and Applications, 2nd ed., by Gerhard Buchbauer and K. Hüsnü Can Başer, eds. Boca Raton, FL: CRC Press; 2016. Hardcover; 1,109 pages. ISBN: 978-1-4665-9046-5. $199.95.

The second edition of *Handbook of Essential Oils: Science, Technology, and Applications* is a collective work, written by top scientists and led by two eminent specialists in medicinal and aromatic plants: Gerhard Buchbauer, PhD, and K. Hüsnü Can Başer, PhD.

This text is 1,109 pages of pure interest on essential oils, and it provides a crucial compilation of information related to their development, use, and marketing, with a particular focus on their chemistry, pharmacology, and biological activities.

No topic is left out: history and production, chemical analysis and quality control, toxicity and adulteration, pharmacognosy and medical use, pharmacodynamics and biotransformation by the living, galenic and industrial use, trade and legislation. Each topic has its own chapter(s), well-documented, with an extensive bibliography.

Whether it be researchers, professors, professionals and industrials, herbalists, or simply curious individuals, this work is of considerable interest to essential oils enthusiasts, thanks to its large knowledge base, which is supported by up-to-date data.

If I could borrow from Woody Allen, I would name this book *Everything You Always Wanted to Know about Essential Oils but Were Afraid to Ask*.

Compared to the first edition, this book presents new chapters on the natural variability of components occurring in essential oils, and on the natural processes that cause adulteration of essential oils; revisions, updates, and expansions of previous chapters; and a split of the previous chapter on biological activities and antioxidative properties of essential oils.

The book is divided into several large sections:

Part I describes the sources, production, and natural variability of essential oils. This part is a beautiful study, precisely integrating the concept of "chemotype," which is essential for the understanding of aromatherapy.

Part II concerns chemistry. These chapters lead to the understanding of the biosynthetic pathways of aromatic compounds, discuss the most relevant analytical methods for quality control, describe adulteration, and lay the foundations for the safe use of aromatic molecules and essential oils.

Part III focuses on pharmacology, toxicology, and biological activity of essential oils, with two very important chapters describing the metabolism of terpenoids in animal models and humans, as well as encapsulation and other programmed released techniques for essential oils and volatile terpenes.

Part IV describes the biotransformation mechanisms of terpenoids in microorganisms, fungi, green algae, insects, mammals, and other living things. This is timely now that ecotoxicology is becoming more and more important.

Part V discusses the use of essential oils in aromatherapy, veterinary medicine, agriculture, and cuisine.

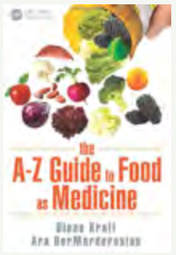
Part VI describes the trade, storage, labeling, and transport of essential oils.

Part VII reviews the recent European Union legislation update on flavors and fragrances and its impact on essential oils.

This "handbook" will assist anyone working on or interested in essential oils. The first edition never leaves me, nor will the second. The quality of this book definitely outshines its price, considering the amount of knowledge it provides. HG

—Francis Hadji-Minaglou, PharmD
Scientific Director, BOTANICERT
Grasse, France

The A-Z Guide to Food as Medicine by Diane Kraft and Ara DerMarderosian. Boca Raton, FL: CRC Press; 2016. Softcover, 347 pages. ISBN: 9781498735230. $69.95.



The A-Z Guide to Food as Medicine had me hooked by the time I read the foreword, which was written by Penny Kris-Etherton, PhD, RD, the Distinguished Professor of Nutrition at Penn State University. She said it all, in that this book "will serve as an expedient resource for quickly accessing fact-based information about foods and phytochemicals in a manner that obviates the need to spend unnecessary time hunting down reputable information in the literature."

These were the objectives of the authors, and they achieved them in spades. I particularly appreciated that one author is a dietitian with clinical experience (Kraft), and one is a scientist with expertise in pharmacology and medicinal chemistry (DerMarderosian). So often, overtaxed health care providers are asked by patients whether a certain food or nutrient is "good." This book answers those probing questions satisfactorily and from an unbiased, scientific stance. This balanced, honest approach is refreshing. Many books in this space have "agendas," but this text is fact-based with literature citations at the end of each letter of the alphabet.

The chapters cover a variety of food items, including plants, such as asparagus (*Asparagus officinalis*, Asparagaceae), açaí (*Euterpe oleracea*, Arecaceae), and pomegranate (*Punica granatum*, Lythraceae); non-plant foods, such as eggs and dairy foods; and selected vitamins and minerals, such as calcium, selenium, and riboflavin. Lastly, phytochemicals such as anthocyanins, astaxanthin, and kaempferol were presented. Each profile includes the following sections: (1) item name, definition, and common use; (2) scientific findings; (3) bioactive dose; and (4) safety data.

The approach for presenting the information was excellent. The definition and common use sections were interesting and often evoked an "I didn't know that." For example, I learned that the high calcium content (344 mg per cup) of rhubarb (*Rheum rhabarbarum*, Polygonaceae) is poorly absorbed, and that melatonin is naturally found in corn (*Zea mays*, Poaceae), rice (*Oryza sativa*, Poaceae), barley (*Hordeum vulgare*, Poaceae), and ginger (*Zingiber officinale*, Zingiberaceae). I also learned that the ugli fruit (*Citrus paradisi* × *reticulata*, Rutaceae) is a hybrid of a grapefruit (*C.* × *paradisi*) and a tangerine (*C. reticulata*). I could go on.

The scientific findings pertaining to each item were thorough but succinct. The authors included primary research from high-quality journals, but they also occasionally referred to the Natural Medicines Comprehensive Database, which was created by the California-based Therapeutic Research Center (an independent evidence-based research organization).[1] For example, when discussing the effect of yeast-derived beta-glucan fiber on lowering blood cholesterol, the authors simply cited the database. My colleagues and I conducted that research, which was published in the *American Journal of Clinical Nutrition*.[2] In addition, the database was cited to support the statement that consuming more than three grams of dietary fish oil may decrease platelet aggregation. Again, we have published a clinical study in *Nutrition* on this topic, which was not cited.[3] Nevertheless, the spirit of the information cited in the book obtained from the database accurately reflects the primary studies.

Bioactive doses were not included for each food. Despite the availability of high-quality research data on many food items, bioactive doses were listed mainly for essential nutrients, such as vitamins and minerals, with the exception of riboflavin.

The safety section for each food focused on risks associated with excess consumption by healthy people and consumption by those who are pregnant. I wish the risks for children had been highlighted as well; perhaps this will be included if there is a new edition. Many adults use the substances reviewed in this book for their children, thinking of them as "little adults," which is not true, physiologically speaking.

I spotted only a couple of minor errors or omissions. Linoleic acid does not convert to eicosapentaenoic acid (EPA); only linolenic acid does. The only scientific study cited on beta-carotene and lung cancer supported a role for risk reduction. It would have been nice to cite another study that shows this is not true for smokers (in fact, the opposite effect occurs).[4]

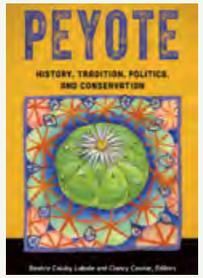
In summary, the book is a helpful reference guide that will meet the needs of a busy clinician. Information was easy to find, well-written, and factual. I would recommend this book to any health care practitioner. The items included are precisely the sorts of things that my patients ask about. I am grateful that I now have this book to use as a reference. HG

—Stacey J. Bell, DSc, RDN
Chief Science Officer, Nutrient Foods
Reno, Nevada

References

1. Natural Medicines Comprehensive Database. Therapeutic Research Faculty. Available at: http://naturaldatabase.therapeuticresearch.com/Content.aspx?page=aboutdbhtml&xsl=generic&AspxAutoDetectCookieSupport=1. Accessed August 24, 2016.
2. Nicolosi R, Bell SJ, Bistrian BR, Greenberg I, Forse RA, Blackburn GL. Plasma lipid changes after supplementation with β-glucan fiber from yeast. *Am J Clin Nutr*. August 1999;70(2):208-212.
3. Swails WS, Bell SJ, Bistrian BR, et al. Fish-oil-containing diet and platelet aggregation. *Nutrition*. 1993 May-Jun;9(3):211-217.
4. The Alpha-Tocopherol Beta Carotene Cancer Prevention Study Group. The effect of vitamin E and beta carotene on the incidence of lung cancer and other cancers in male smokers. *N Engl J Med*. 994;330:1029-103

Peyote: History, Tradition, Politics, and Conservation by Beatriz Caiuby Labate and Clancy Cavnar, eds. Santa Barbara, CA: Praeger; 2016. Hardcover, 280 pages. ISBN: 978-1-4408-3400-4. $60.00.



This book is a welcome addition to scholarly publications regarding the spineless psychoactive cactus peyote (*Lophophora williamsii*, Cactaceae). The editors, Beatriz Caiuby Labate, PhD, and Clancy Cavnar, PsyD, have assembled a dozen essays by scholars, legal specialists, and a Native American Church leader on a range of topics. Readers with an interest in botanical entheogens (i.e., compounds that alter consciousness), indigenous North American spiritual practice, and native peoples' religious rights will find a close reading of these essays rewarding.

Unlike previous publications in this field, these authors hail from several disciplines and illuminate distinct aspects of the human/cactus relationship. However, it must be mentioned that the book's subtitle, "History, Tradition, Politics, and Conservation," does not spell out the essayists' primary concerns. A more accurate subtitle might be "History, Law, and Tourism." The reader can easily find a wealth of information on peyote tradition from the classic studies on peyote use by Native Americans described in *People of the Peyote: Huichol Indian History, Religion, and Survival* by Stacy Schaefer, PhD, and Peter Furst, PhD (University of New Mexico Press, 1997). However, in the present book only one chapter, "From Solid to Frothy: Use of Peyote in the Cora and Huichol Easter in Western Mexico," is concerned with "tradition."

While several chapters explore the intricate and prolonged struggle for legal religious use by native peoples in the United States and Mexico, these processes are discussed from the perspective of court rulings, and the politics of supporting and opposing constituencies are discussed only in passing. In their instructive introduction, James Bauml, PhD, and Schaefer draw attention to the issue of conservation and raise an alarm regarding declining peyote populations in the Texas borderlands, apparently resulting from "improper

harvesting techniques," as well as habitat degradation resulting from "mining, agriculture, raising cattle, oil developments, and construction of wind farms."

Kevin Feeney, JD, in his chapter "Peyote, Conservation, and Indian Rights in the United States," addresses legal aspects of potential cultivation to reduce pressure on remaining peyote populations in this country. Bob Prue, PhD, offers insight into Native American Church members' attitudes toward cultivation as a response to diminishing supply in his chapter, "Protecting the Peyote for Future Generations." These authors are understandably preoccupied with the approach of a drastic shortfall in the supply of a sacramental substance crucial to spiritual practice, healing, and community for thousands of Native American Church members in the western United States and Canada. Reading between the lines, it seems clear that interested parties, many of whom are familiar with the myriad factors at play, have yet to generate a plan for the recovery of peyote populations in the United States and the protection of endangered Mexican populations.

The three chapters by Mexican specialists indicate that the cactus has been overharvested in that portion of its extensive range in the central deserts of northern Mexico known as Wirikuta, a complex landscape sacred to the Huichol people who reside far from peyote habitat in the Sierra Madre Occidental of western Mexico. This overharvesting is the result of sustained enthusiasm for an authentic experience by non-indigenous seekers, both Mexican and international, and from entrepreneurs' extraction of "organic mescaline" for the recreational drug trade. A chapter on conservation from the biological perspective would have been illuminating and would justify, for plant-oriented readers, the use of the term "conservation" in the subtitle.

Readers not familiar with the existing literature will find brief but useful introductions to peyote biology, history, and Native American Church and Huichol peyote practices. Those versed in the basics will find new tales of the cactus's adventures in humanland. For example, a chapter by Erika Dyck, PhD, "Peyote and Psychedelics on the Canadian Prairies," not only documents the little-studied arrival of peyote ceremonialism in Canada but also brings to light the strategic and serendipitous confluence of Canada's early psychedelic research scientists and the nascent Canadian Native American Church, then facing stiff government repression.

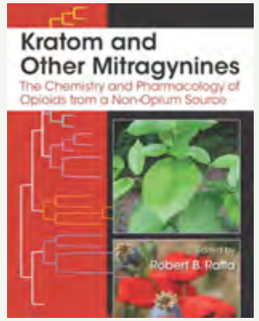
Also outstanding are three chapters on legal history and legal status of Native American peyote use in the United States: "Peyote, Christianity, and Constitutional Law" by Varun Soni, PhD, JD; "State and Federal Legal Protections for Peyote Use in the United States" by John P. Forren, PhD; and Feeney's "Peyote, Conservation, and Indian Rights in the United States." The Native American Church's legal travails and victories have been detailed in previous publications, but these chapters, which are mostly accessible to non-specialist readers, uncover broader implications for Native American rights and the practice of minority religion in general.

This focus on legal aspects of peyote continues with Labate and Feeney's chapter, "Paradoxes of Peyote Regulation in Mexico," an exhaustive and groundbreaking account of international treaties, national legislation, and regulations pertaining to the protection and use of peyote. The authors highlight the "lack of recognition of mestizo folk uses, as well as of contemporary hybrid ceremonies." They find this lack especially deplorable because of Mexico's history of exchange and fusion between local and European cultural traditions. In their introduction, Bauml and Schaefer point to a corresponding discrepancy north of the border, questioning "whether or not it makes sense to have our governments continue to police racial boundaries as they did in the past." Non-native use, either medical or spiritual, outside of recognized religious context is the elephant in the courtroom.

Perhaps the most notable contribution to peyote literature is made by Vincent Basset, PhD, and Mauricio Genet Guzman Chavez, PhD. Their chapters address issues arising from burgeoning international guided spiritual and cultural tourism in Wirikuta (the focus of Huichol pilgrimage) and from the embrace of practices derived from Huichol pilgrimage, and based in Huichol sacred landscape by Mexicans seeking connection with ancestral roots. The authors refrain from disparaging the aspirations and ceremonies of guides, tourists, and culture seekers, but make it clear that neither cactus nor Huichol pilgrims can sustain this attention. HG

—Bret Blosser, PhD
Moab, Utah

Kratom and Other Mitragynines: The Chemistry and Pharmacology of Opioids from a Non-Opium Source by Robert B. Raffa, ed. Boca Raton, FL: CRC Press; 2015. Hardcover, 366 pages. ISBN: 978-1482225181. $139.95.



Though not clear from the title, this book is mostly about opioids (compounds that bind to the opioid receptors) that come from the leaves of the tree commonly known as kratom (*Mitragyna speciosa*, Rubiaceae), as well as other interesting analgesic and psychoactive alkaloids from other plants. The editor, Robert B. Raffa, PhD, notes that the book evolved from a course taught at Temple University School of Pharmacy in Philadelphia, Pennsylvania. The predominant viewpoint of this collection of essays seems to be one of medicinal chemistry and, as such, can be heavy on chemical structures and their specific activities. The book chapters are not so much defined topics in an ordered sequence but rather reflect the interest and expertise of the faculty of pharmacy and other chapter authors. There are also chapters on other plant species including the opium poppy, *Papaver somniferum* (Papaveraceae). The most notable effect of the opiates (and other opioids), of course, is powerful analgesia. Alkaloids from both plant species bind to these specific receptors in the brain, and affect our perception of pain.

Thus, in the second chapter, Raffa et al. discuss how morphine, codeine, and related opiates are not the only potent analgesics from plants. The primary analgesic alkaloids in kratom leaves are mitragynine (MG; typically the most prevalent) and 7-hydroxymitragynine (7-OH-MG; the most potent). 7-OH-MG may be 10 times stronger than morphine, so even though its concentration in kratom is much smaller than MG, it may be responsible for a significant part of the total plant properties. Other species or varieties may have varying alkaloid contents, however. With long-term, heavy use, the addictive effects that may result are similar to those of opiates (and other opioids), and a withdrawal syndrome can be observed in animals after injection of the opioid antagonist naloxone. Other animal studies suggest that the kratom compounds are less toxic than the opiates and have some other behavioral differences that will require much more research to better understand.

Chapter 3 explores the pharmacology of other psychoactive indole alkaloids and Chapter 4 is about salvinorin A, a non-alkaloid opioid from the hallucinogenic plant *Salvia divinorum* (Lamiaceae), with considerable focus on chemistry and structure-activity relationships. Chapter 5 deals with the botany and taxonomy of *M. speciosa* and related species in the genus. The effects seen with a common traditional method of consumption (chewing the leaves while working in the fields) are different from the effects produced by opium poppy, however. The reasons for this are not entirely clear but probably relate to the degree of absorption of the alkaloids during the chewing process. Taste may also be a factor as many alkaloids are extremely bitter.

The chemistry of *M. speciosa* is dealt with in detail in chapters 6 to 9, while the chemistry and structure-activity relationships of the opioids are discussed in Chapter 10. Chapter 11 is a discussion of how the active compounds in *M. speciosa* are related to its use and abuse. Chapter 12 deals with metabolism of these compounds, and Chapter 13 describes the analgesic properties of the compounds and their analogs. Non-analgesic CNS properties of kratom are discussed in more detail in chapters 14 and 15. In addition to pain-relieving properties, kratom also will suppress coughs and cause constipation but perhaps less so than the classic opioids. Even very high doses of MG in rodents did not show as much emesis (vomiting) or respiratory depression as codeine.

Chapter 16 presents firsthand experiences with kratom and discusses indigenous use and abuse. The authors quote from postings by kratom users at Erowid, a non-profit educational website dealing with information on various psychoactive and other, usually plant-based, substances. The effects from chewing the leaves of kratom are actually more reminiscent of the indigenous use of coca (*Erythroxylum* spp., Erythroxylaceae) leaves, and result in a mild stimulation with increased energy and reduced hunger. Clearly, as with coca, there are others who use it for other reasons and in much higher doses. Higher doses of kratom are generally associated with the analgesic and euphoric properties. Had leaf-chewing been the only use of these plants, it is unlikely they would ever have come to the attention of the authorities.

The toxicology of indole alkaloids is discussed in Chapter 17 but seems off-subject in many respects and is without reference to the compounds' chemistry or pharmacology and how these would relate to toxicity. On the other hand, Chapter 18 concerns itself with adverse effects of opioids other than those found in kratom. Toxicity of compounds found in kratom is discussed in Chapter 19. Here, it is mentioned that there are no verified reports of kratom causing death when used alone. There are kratom products adulterated with synthetic drugs, however, some of which appear to be considerably more toxic. Many of the studies dealing with kratom's toxicity are obviously done with animals. Chapter 20 deals specifically with animal behavioral models used to measure tolerance, dependence, and abuse potential. These are clearly limited in what they can deliver, and more work from other disciplines needs to be integrated for a better understanding.

Chapter 21 concerns the epidemiology, abuse, and legal status of kratom, and it provides a background in which to understand the plant. Very little controlled human data are available. One interesting point is that the MG content in kratom extracts varies significantly by geographic origin. Use was exclusive to Southeast Asia until around 1990, when the internet made it easy to order from anywhere in the world. In Southeast Asia, kratom is widely used as a stimulant to increase work production and for the treatment of opioid withdrawal symptoms.

In the United States, the legal status of kratom is obviously undergoing a major upheaval at the time of writing (October 2016), with regulatory agencies proposing (and then temporarily withdrawing that proposal) to classify two of the active alkaloids in kratom as Schedule I substances, which would, in effect, criminalize kratom possession and distribution. The US public will have to wait until the dust settles before it knows if, and in what form(s), kratom might be legally available. HG

—Jerry Cott, PhD
Senior Pharmacologist
Silver Spring, Maryland

Martin Wedel
1954-2016

Martin Wedel, the managing director of purchasing and procurement at the Martin Bauer Group and grandson of company founder Martin Bauer, died on September 21, 2016, at the age of 62, after a battle with cancer. Wedel had been involved with the Martin Bauer Group from a young age, inspired by the examples of his grandfather and his father, Hans Wedel. According to a press release issued by the Martin Bauer Group on September 23, 2016, Martin Wedel "was well known not only for his good sense of humor but for his social involvement as well."[1]

Wedel was born in 1954 in Vestenbergsgreuth, Germany, the first child of Hans and Sofie Wedel-Bauer. During his childhood, he often accompanied his father on trips to the Balkan Peninsula to visit suppliers of the botanicals used by the Martin Bauer Group, which has grown to become the leading botanical supplier in the world. This early exposure to the business allowed him to learn the intricacies of the tea industry, leaving him well positioned to join his father and grandfather's business in 1978. Later, his younger brother, Adolf, joined him.

As the focus of the company shifted from herbal raw materials to medicinal tea formulations and standardized extractions, Wedel stayed innovative throughout the changing demands in supply. He helmed the purchasing and procurement department as it sought new supply regions and markets, and diversified its growing range of products to meet the needs of clients. Under his leadership, the Plantextrakt subsidiary developed the company's first line of plant extracts in 1980, followed by phytopharmaceutical extracts in 1989. The Martin Bauer Group processes tens of thousands of tons of raw materials from more than 50 countries, but some of that production occurs near its headquarters in Vestenbergsgreuth. Wedel's extracts divisions (which now include the Finzelberg company, a maker of phytomedicinal extracts) promote sustainability among their raw material suppliers, and they now represent a key success area for the company.

In addition to his dedication to his business, Wedel was deeply involved with his local community. He was the chairman of his father's charity, the Hans Wedel Foundation, which promotes employment in Vestenbergsgreuth and the conservation of Christuskirche, the local Lutheran church, which was built in 1959. He also served as a member of the town council for more than 30 years. On Wedel's 60th birthday, Mayor Helmut Lottes personally honored Wedel with a certificate of honorary citizenship. A press release from the Martin Bauer Group issued on April 16, 2014, noted that the community was "particularly appreciative of Martin Wedel's humor, with which he could relax some difficult situations, and his uncomplicated way, [which] he has always maintained despite his position."[2] He was also an honorary member of the local soccer club, TSV Vestenbergsgreuth, which was founded by his father. Wedel earned recognition on a national stage, as well. In 2015, he received the Order of Merit of the Federal Republic of Germany in honor of his long and successful career and his service to the community and botanical industry.

Wedel is survived by his wife Anita, sons Martin, Viktor, and Jochen, daughter Sofie, and brother Adolf, who still serves as managing director at the Martin Bauer Group. HG

—Hannah Bauman

References

1. Following a long and serious illness, Martin Wedel, successful entrepreneur and a recipient of the Order of Merit of the Federal Republic of Germany, has died at the age of 62 [press release]. Vestenbergsgreuth, Germany: Martin Bauer Group; September 23, 2016.
2. Martin Wedel celebrating his 60th birthday and is an honorary citizen of Vestenbergsgreuth [press release]. Vestenbergsgreuth, Germany: Martin Bauer Group; April 16, 2014. [translated from German]

Philippe Rasoanaivo
1946-2016

Renowned phytochemist Philippe Rasoanaivo, PhD, passed away on July 13, 2016, at the age of 69, after a heart attack. Rasoanaivo dedicated his professional career to bioprospecting the rich plant life of his native Madagascar for new plant-based medicines, particularly for malaria, and co-founded the Association for African Medicinal Plants Standards (AAMPS). At the time of his death, he was the research director at the Malagasy Institute of Applied Research (IMRA) and a professor at the University of Antananarivo (UA) in Antananarivo, Madagascar.

Rasoanaivo was instrumental in building up the natural products research industry in Madagascar and established collaborative connections throughout Africa. After earning his doctorate at UA, he pursued his post-doctoral studies with Norman R. Farnsworth, PhD, at the University of Illinois at Chicago as a Fulbright Scholar. He returned to Madagascar to continue his research on ethnomedicinal plant use for malaria and neurological diseases, working as a researcher at the National Centre for Applied Pharmaceutical Research. Upon joining the faculty at UA, he supervised more than 30 doctoral dissertations and mentored many young researchers.

"Philippe was not only a friend to many of us, but also one of the founding fathers of the [AAMPS]," wrote Thomas Brendler, CEO of Plantaphile (email to M. Blumenthal, August 22, 2016). "He was a major contributor to the African Herbal Pharmacopoeia and other AAMPS publications."

The International Foundation for Science (IFS) awarded Rasoanaivo a total of four grants in the 1970s and 1980s, first in 1975 for his research on the wound-healing properties of *Ilex mitis* (Aquifoliaceae). From this work, clinical trials were performed on an extract called Fanaferol, which later became available for clinical use. Following a resurgence in malaria cases in Madagascar, Rasoanaivo switched his focus to traditional malaria remedies. He analyzed remedies used by rural populations, which led him to study alkaloids from *Strychnos myrtoides* (Loganiaceae) as an adjuvant therapy to chloroquine, an antimalarial drug. The combination therapy was more effective than chloroquine alone. In 2001, IFS awarded Rasoanaivo the sixth Sven Brohult Award. Named after the first president of IFS, the Sven Brohult Award recognizes excellence in research in developing countries, and is awarded every three years.

As the research director at IMRA, Rasoanaivo sought to balance modern techniques with local knowledge to keep treatments affordable and attainable. His approach to bioprospecting native plant remedies promoted economic development in Madagascar, where he also worked to sustain wild populations and biodiversity.

In 2002, Madagascar's Ministry of Health established the Department of Traditional Medicine and Pharmacopoeias. There, Rasoanaivo worked closely with officials to create a regulatory framework that encouraged the use of traditional remedies while combating the ever-present threat of biopiracy. He also worked with international research and academic centers to collect more than 800 plant specimens over a period of seven years. This cooperative arrangement resulted in improved laboratories and equipment for UA, and the university continues to play a key role in the extraction of compounds from medicinal plants.

Rasoanaivo received numerous awards, grants, and other recognitions for his long and fruitful career. He was an invited professor at institutions in Italy and France, and served as an advisor for a World Health Organization initiative that promoted traditional medicine in Africa. He published more than 100 papers and held seven patents.

He received the Prize of the Malagasy Academy and a research prize awarded by the Ministry of Higher Education in Madagascar, as well as international honors from Cape Town, South Africa, to an entrepreneurship prize in Malaysia. In June 2016, he was awarded the prestigious Olusegun Obasanjo Prize for Scientific Discovery and Technological Innovation, which is bestowed by the African Academy of Sciences every two years to individuals whose scientific discoveries and innovations have helped improve their societies. The award was given in recognition of Rasoanaivo's work on plant-based treatments for psychiatric and sleep disorders, convulsions, and male sexual dysfunction. When speaking of the award, Rasoanaivo was quoted as saying, "African problems require African solutions."[1]

Rasoanaivo is survived by his wife and five daughters. HG

—Hannah Bauman

Reference

1. Ackbarally N. Plant medicine research makes scientist win science prize. SciDev.net. July 13, 2016. Available at: www.scidev.net/sub-saharan-africa/medicine/news/plant-medicine-scientist-win-science-prize.html. Accessed September 21, 2016.

Götz Harnischfeger
1939-2016

Götz Harnischfeger, PhD, died on April 26, 2016, at the age of 77. Harnischfeger was a botanist, chemist, and pharmacist who expanded the fields of plant biochemistry and medicinal plant research as both an educator and a member of the German phytomedicine industry. He spent most of his career at Schaper & Brümmer, a German company that developed the world's leading clinically studied black cohosh (*Actaea racemosa*, Ranunculaceae) extract.

Harnischfeger studied pharmacy at the University of Frankfurt in Germany before earning his PhD in the United States at Florida State University. He returned to Germany to complete his post-doctorate studies at the University of Göttingen in 1976, after which he served as a professor of botany for the university. In 1982, he was appointed as a professor of plant biochemistry.

After leaving academia, Harnischfeger joined the phytopharmaceutical industry in a variety of management and research positions, focusing his efforts on improving standardization of phytomedicines and embracing the challenge of staying ahead of rapidly evolving analytical methods. His reputation as an expert on natural product research grew, and he co-authored and assisted in the development of several landmark publications on the subject, including *Stabilitätsprüfung in der Pharmazie* ("Stability Testing in Pharmaceutics") and an updated edition of Hermann Hager's *Handbook of Pharmaceutical Practice*.

"I met Professor Harnischfeger in 1991 when I joined the natural product research-oriented pharmaceutical company Schaper & Brümmer, where he was manufacturing/production manager," wrote Eckehard Liske, PhD, who was the head of the international medical department at Schaper & Brümmer (email to M. Blumenthal, June 27, 2016). "In the following years we had numerous discussions on central issues of rational phytotherapy regarding plant extraction, whole extract versus single marker substances, active ingredients, and quality control. Pretty soon I realized that Professor Harnischfeger was a world-renowned expert in this research field. Looking back, I must say that he made me familiar with the philosophy of rational phytotherapy resulting in evidence-based herbal medicine. I am very grateful to him for these discussions."

Mark Blumenthal, founder and executive director of the American Botanical Council, recalled the first time he met Harnischfeger. "I met Dr. Harnischfeger through the late Professor Varro E. Tyler, with whom he had formed a professional relationship and friendship over the years," he said. "As a key scientist at Schaper & Brümmer, he made an excellent (and entertaining) presentation at one conference on his company's production of black cohosh extract. He was instrumental in developing a unique program in which the company grew its own black cohosh in Germany — probably the first commercial-scale cultivation of this indigenous wild eastern North American medicinal plant outside of the United States — thereby reducing pressure on wild populations."

Harnischfeger's commitment to the safety and quality of herbal medicinal products drew him to a number of professional committees. He was a member of Gesellschaft Deutscher Chemiker (German Chemical Society), Deutsche Botanische Gesellschaft (German Botanical Society), and Gesellschaft für Arzneipflanzen- und Naturstoff-Forschung (GA; Society for Medicinal Plant and Natural Product Research). He also served as an elected member of the Deutscher Arzneibuch Ausschuss Pharmazeutische Biologie (German Pharmacopeia Committee on Pharmacognosy) from 1992 to 2005, and a member of the expert group on phytochemistry for the European Pharmacopoeia for 15 years. In recognition for his work relating to public health, he was awarded the Order of Merit of the Federal Republic of Germany in 1999.

"The internationalization of GA is … due [in part] to his never-ending activities to promote this society to a global acceptance and impact," noted Gerhard Franz in his remembrance of Harnischfeger for the July 2016 GA newsletter. "He attended all the annual member meetings and his criticism was feared by many members and even some presidents of the GA."

In his personal life, Harnischfeger was a deeply devout Catholic and served as an archivist and church historian for his parish. He was also a member of the German Association of the Holy Land and was awarded the Star of the Order of the Holy Sepulchre in Jerusalem in 1996. He is survived by his wife Jeanne. HG

—Hannah Bauman

Publications

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

Australian Journal of Herbal Medicine: 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, P.O. Box 696, Ashfield, NSW 1800, 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.

American College of Healthcare Sciences: ACHS.edu is a DEAC accredited, fully online college offering Graduate and Undergraduate degrees, diplomas, and career-training certificates in holistic health and herbal medicine. ACHS is committed to exceptional online education and is recognized as an industry leader in holistic health education worldwide. Federal financial aid available to those who qualify. Educational resources available to the public include: ACHS Health and Wellness Blog, Master Lecture Webinar Series, and eBooks. For more information: visit www.achs.edu, call (800) 487-8839, or stop by the College campus located at 5005 SW Macadam Avenue, Portland OR 97239.

Other

Interns, get hands-on experience before you graduate! If you're a future pharmacist or dietitian, you can choose a rotation through ABC's internship program. You'll get a comprehensive introduction to phytomedicines, researching the medicinal, culinary and cosmetic uses of herbs, answering ABC members' questions, working with medicinal plants in ABC's 2.5 acres of herbal gardens, and preparing herbal salves, tinctures or meals. For more information, call 512-926-4900x114 or e-mail education@herbalgram.org.

Herb/Berry/Vegie farm seeking assistance with cultivation, processing, landscaping, web work, and GMP certification. Agri-Tourism startup. Work not hard but steady. Profit Sharing. Starting immediately in the Virginia Blue Ridge, Zone 7. hootinanney@yahoo.com.

Stock Photography that doesn't look like Stock: Steven Foster Group, Inc. Photography, Consulting, Publications. Specializing in medicinal and aromatic plants, along with the places they grow, our stock photo files include more than 120,000 images shot around the world for over 30 years. Contact us at our location in the heart of the Ozarks in Eureka Springs, Arkansas. Visit our website: www.Stevenfoster.com or email: sfoster@Stevenfoster.com.

Considering supplying herbal products in Europe? Ann Godsell Regulatory can offer consulting advice on regulatory strategy, and data requirements. Services for dossier preparation & submission also available. For more information email regulatoryinfo@anngregulatory.eu.

Tea Business Development: 60 years combined experience supporting new and existing tea ventures from start-ups to Fortune 500 companies. Original recipes, flavor and functionality enhancements, raw materials sourcing, production trouble-shooting, regulatory, scientific substantiation, and more. Former Whole Foods and Celestial Seasonings blendmasters, R&D / Q.C. Tea Bags, loose teas, RTD. Advisory services for wholesale, branded consumer products, and retail operations. Email us with your information and needs: sage@sagegroupnetworks.com.

Montana YewTip™ products, the natural Taxane source, Pacific Yew (*Taxus brevifolia*). Sustainably wildcrafted and manufactured exclusively by Bighorn Botanicals, Inc., Noxon, Montana. Capsules, tea, powder, tincture, oil, salve, lotion, soap, and lip balm. To review our products, go to www.bighornbotanicals.com. For more information, including ethnobotany, sustainable harvest protocols, safety, and biological activities, click on the "Plant Profile." Order online or call toll-free 1-888-847-1223.

Yarrow
Achillea millefolium, Asteraceae

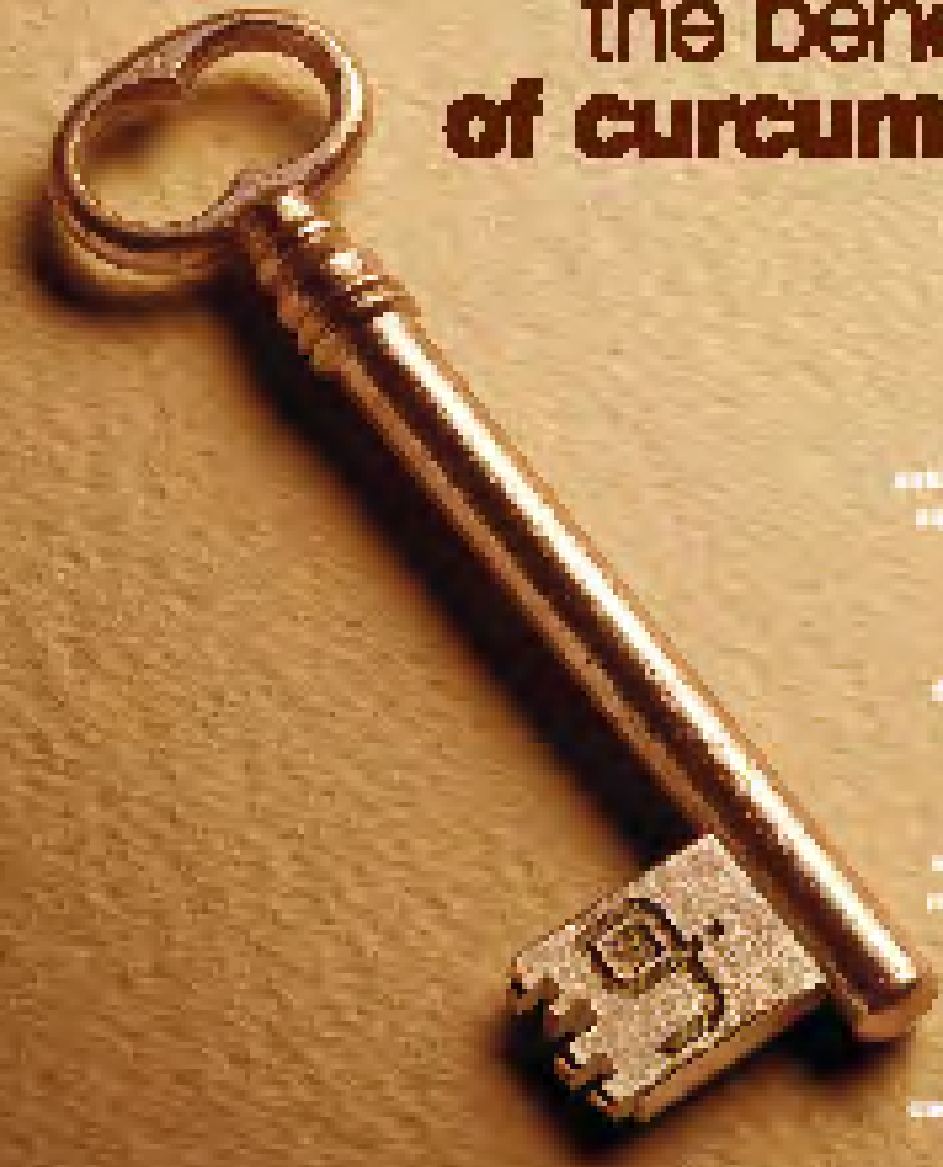
Photo taken by Petar Milošević in Anthemideae, Slovenia with a Panasonic Lumix DMC-GM1 at f8, 1/1000sec, ISO 200.

Yarrow (*Achillea millefolium*, Asteraceae) is a perennial, low-growing plant that has been used in traditional medicine preparations for a variety of both external and internal ailments. The flower, stem, and leaf are the most commonly used parts of the plant.[1] Traditional European uses for yarrow include as a decoction for colds and fevers (especially for children), for menstrual disorders, and as a poultice for bleeding wounds. Native tribes across North America used yarrow in many different ways, including for headaches, as an infusion for earaches, as an analgesic, and as an insomnia remedy.[2] The community herbal monograph by the European Medicines Agency approves yarrow as a traditional herbal medicinal product for the symptomatic treatment of mild, spasmodic gastrointestinal complaints (e.g., bloating and flatulence), for temporary loss of appetite, for the symptomatic treatment of minor spasms associated with menstrual periods, and externally for the treatment of small, superficial wounds.[3,4]

References

1. Grieve M. *A Modern Herbal*. Vol. 2. New York, NY: Dover Books; 1971.
2. Moerman D. NAEB Text Search: *Achillea millefolium*. Native American Ethnobotany Database. Available at: http://naeb.brit.org/uses/search/?string=achillea+millefolium. Accessed October 18, 2016.
3. Committee on Herbal Medicinal Products. Community herbal monograph on *Achillea millefolium* L., herba. London, UK: European Medicines Agency; 2011.
4. Committee on Herbal Medicinal Products. Community herbal monograph on *Achillea millefolium* L., flos. London, UK: European Medicines Agency; 2010.

How **Meriva** unlocks the benefits **of curcuminoids**



Curcumin, endowed with powerful antioxidant activity, has been shown to support joint mobility and eye health. Unfortunately, the bioavailability of the natural form is low. Which is why Indena developed Meriva®, a curcuminoid formulation that uses the exclusive, patented Phytosome system to increase bioavailability of the natural active principles. Meriva® improved the resident walking performance of subjects by more than 200% in just two months. Furthermore, Meriva® showed a significant improvement in individuals with eye challenges. To discover more about how Meriva® unlocks the benefits of curcuminoids, visit indena.com today.

Indena®

NATURE IS OUR NATURE

MERIVA®

BIOAVAILABLE CURCUMIN