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Arnica Herb Profile

Herb Market Report: 2014 Sales in US Up 6.8%

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Arnica

Arnica montana

Family: Asteraceae

INTRODUCTION

The genus *Arnica* comprises approximately 40 species,[1,2] of which *A. montana* is probably the most well-known. Arnica is an herbaceous perennial in the daisy family (Asteraceae) with leaves that form a basal rosette from which emerges a one- to two-foot stalk with orange-yellow flowers.[3] Though the flowers are the primary parts used medicinally, the dark brown, cylindrical rhizomes are also sometimes used.

Arnica montana is endemic to Europe, where it is relatively widespread, growing wild from Norway to the Balkans and from Spain to Ukraine.[4] Divided into two subspecies, *A. montana* ssp. *montana* grows in Scandinavia and Central Europe, while *A. montana* ssp. *atlantica* occurs in southern France, Spain, and Portugal. The material of commerce is obtained, for the most part, from wild collection in Romania (for example, in grassland areas of the Apuseni Mountains of Transylvania), where over half of the estimated annual global trade quantity is harvested,[5] followed by Spain (mainly in the northwestern region of Galicia and neighboring province of León), although Spain has recently become a less important source.[6] Arnica is also wild-harvested to some extent in Croatia,[7] as well as Ukraine, Bosnia and Herzegovina, Montenegro, Serbia, and the Former Yugoslav Republic of Macedonia.[8] There is some commercial cultivation, albeit not enough to satisfy market demand, occurring mainly in Germany, France, Italy, Switzerland, and Chile, especially due to the registration and approval in 1998 of the cultivar "Arbo" for field production. There are presently two cultivars approved and protected through the German *Bundessortenamt* (Federal Office of Plant Varieties, Federal Ministry of Food and Agriculture): the aforementioned Arbo (owned by Bayerische Pflanzenzuchtgesellschaft e.G. & Co KG; Freising, Germany) and "Arvita" (owned by Kneipp GmbH; Würzburg, Germany).[9]

Additional common names for *A. montana* include European arnica, leopard's bane, wolf's bane,*[10] and mountain tobacco.[10,11]

[Note: The flowers of *Arnica* species native to North America, which are not addressed in this article, are used in much the same way as *A. montana*. For more information on the use of North American species, see Michael Moore's books *Medicinal Plants of the Mountain West* (Museum of New Mexico Press, 2003) and *Medicinal Plants of the*

*The occasional common name wolf's bane employed for arnica should not be confused with another plant sometimes referred to as wolf's bane, i.e., monkshood (*Aconitum napellus*, Ranunculaceae).

Arnica *Arnica montana*
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Pacific West (2011). For Native American tribal use of North American species, see Daniel Moerman's Native American Ethnobotany database at http://herb.umd.umich.edu/.]

HISTORY AND CULTURAL SIGNIFICANCE

Arnica tinctures (hydroalcoholic extracts) and salves have been used externally for their anti-inflammatory,[10,11] bactericidal,[11,12] antineuralgic, antirheumatic, antiseptic, counterirritant,[13] and wound-healing[10] effects. Arnica preparations are also used topically to treat boils, bruises,[10,13] contusions, edema, hematoma, insect bites,[10,11,13] joint pain (including rheumatic conditions),[13] sprains,[10,13] phlebitis, thrombosis,[10] muscle pain,[11] alopecia neurotica (sudden hair loss after a disease or injury in which the nervous system was involved), and unbroken chilblains (painful inflammation of small blood vessels in the skin occurring in response to sudden warming from cold). Historically, a root plaster was used externally for tumors,[12] a foot bath containing the tincture relieved tender feet,[3] and rubbing the tincture into the scalp was believed to increase hair growth.[3,12] While arnica was also used in the past for canker sores and gingivitis,[13] it is now generally recommended that arnica not be used orally due to its potentially toxic helenalin content.[14]

In 1987, the German Commission E approved the external use of arnica flowers and preparations thereof for injuries and consequences of accidents, such as hematoma, dislocations, contusions, edema due to fracture, and rheumatic muscle and joint problems, as well as for inflammation of the oral and throat region, boils, inflammation caused by insect bites, and superficial phlebitis.[15]

Many sources emphasize the importance of using arnica preparations on unbroken skin.[14] Also, it should be noted that arnica contains chemical constituents, notably helenalin and its derivatives, that are allergenic and may cause topical dermatitis in some individuals.[16]

Historically, arnica had a number of internal uses that are rarely, if ever, implemented in modern phytomedicine due to the herb's toxic effects, including cytotoxicity (destructive to cells). For example, arnica was previously used internally as a cardiotonic, CNS stimulant,[10] expectorant, nervine, sedative, and to treat liver, stomach, and intestinal cancers, among other conditions.[12] Arnica homeopathic products are still used internally due to their high dilution, and thus extremely low concentration, of the herb's chemical components. The *Homœopathic Pharmacopœia of the United States* (HPUS) provides two arnica monographs for over-the-counter (OTC) and prescription uses: "Arnica Montana Radix HPUS" — which describes the 1X "mother tincture" (1:10) of the root for external use and the 3X attenuation level for OTC internal use† — and "Arnica Montana HPUS," which describes the same potency preparations but for the entire plant, including the root.[17]

In addition to its use in traditional European medical herbalism, arnica is widely used in two other European systems of medicine: anthroposophic medicine and homeopathic medicine. For its use as a traditional herbal medicine, the European Directorate for the Quality of Medicines (EDQM) provides quality standards monographs for arnica flower and arnica tincture in the *European Pharmacopoeia*,[18] while the European Medicines Agency (EMA) provides labeling standards monographs for prepared forms (tinctures and liquid extracts).[19] For use in anthroposophy, the whole fresh flowering plant, the fresh or dried inflorescence, the fresh or dried subterranean parts, and essential oil of the subterranean parts are described in the *Anthroposophic Pharmaceutical Codex*.[20] For arnica-based homeopathic preparations marketed in the European Union, quality standards monographs are provided in both the *French Pharmacopoeia*[21] and *German Homoeopathic Pharmacopoeia*.[22]

CURRENT AUTHORIZED USES IN COSMETICS, FOODS, AND MEDICINES

Arnica is used commercially in cosmetics, shampoos,[13,23] hair tonics, anti-dandruff products,[23] and bath products,[13] and arnica oil is used in perfumery.[12,23] The botanical has limited food use in very small quantities (0.02-0.08%) in baked goods, candy, gelatins, puddings, frozen dairy desserts, and beverages.[23]

In the European Union (EU), several defined arnica preparations — in particular, alcoholic tinctures of various strengths [1:5, ethanol 60% (v/v); and 1:10, ethanol 60% or 70% (v/v)] and liquid extract of fresh flowers [1:20, ethanol 50% (m/m)] — are regulated as traditional herbal medicinal products (THMPs) requiring registration and pre-marketing authorization. Registered preparations can be labeled and marketed for cutaneous (skin) use only and are indicated for the relief of bruises, sprains, and localized muscular pain.[19] For quality control, applicants must show that the herbal starting material complies with the "Arnicae flos PhEur" quality standards monograph of the *European Pharmacopoeia*, and that the resulting tincture conforms to the "Arnicae tinctura PhEur" monograph.[18]

EU Member States also have provisions for the authorization and marketing of herbal anthroposophic medicinal products as well as homeopathic medicinal products. In Germany alone, there are 843 registered medicinal products listing arnica as an active ingredient, of which 360 products are homeopathic medicines (e.g., "Arnica Oligoplex"®; Rottapharm SpA/Madaus; Monza, Italy) and 77 are anthroposophic medicines (e.g., "Arnica Planta Tota Rh D3 Augentropfen" [eye drops]; Weleda AG; Arlesheim, Switzerland). Many of the product registrations, however, are held by individual pharmacies for dispensing.[24]

For use in cosmetic products, the European Commission Health and Consumers Directorate lists three arnica preparations: "Arnica Montana Flower Oil" (essential oil obtained from distillation of the flowers) for perfumery, "Arnica Montana Flower Water" (aqueous solution of the steam distillate obtained from the flowers) as a skin conditioning ingredient, and "Arnica Montana Flower Extract" (extract of the dried flower heads) for masking, perfuming, and skin-conditioning functions.[25]

In the United States, preparations of arnica flower of several species (*A. montana*, *A. fulgens*, *A. sororia*, and *A. cordifolia*) are permitted for use as natural flavoring substances, although in alcoholic beverages only.[26] Most arnica products in the US market are regulated as nonprescription, OTC homeopathic drugs (e.g., Arniflora® Arnica Gel; Boericke & Tafel; Lehi, Utah), although some are prescription drug products (e.g., TranzGel®; Gensco Laboratories; Inverness, Florida). As such, the drug must be prepared according to the specifications of the General Pharmacy and relevant sections of the HPUS. The US Food and Drug Administration-issued National Drug Code (NDC) number must appear on the label of arnica prescription drugs, but it is not required to appear on labels of arnica OTC drug products.[27]

In Canada, arnica is regulated as an active ingredient of licensed natural health products (NHPs) requiring pre-marketing authorization from the Natural and Nonprescription Health Products Directorate (NNHPD). The authorized use for labeling of topical application arnica NHPs (infusion, tincture, or medicated oil) is "[traditionally] used in Herbal Medicine to help relieve pain and/or inflammation in muscles and joints (e.g., sprains, bruises, joint pain)." The quality of the starting material and resulting tincture must conform to their corresponding *European Pharmacopoeia* monographs.[28] With the same indications for use, a separate compendial monograph is provided for "Arnica – Semisolid Dosage Forms." The only acceptable dosage forms for compendial applications citing this monograph are semisolids such as creams, gels, ointments, and salves.[29] For use as a non-medicinal component of licensed NHPs, non-therapeutic dosages of arnica flower extracts are permitted for topical use as a fragrance ingredient or skin-conditioning agent.[30] At the time of this writing (July 2015), there were 482 arnica-containing licensed NHPs, of which 411 product licenses list arnica, in some form, as a medicinally active ingredient.[31]

MODERN RESEARCH

The chemical and pharmacological properties of *A. montana* are well-documented. Arnica chemical constituents include alkaloids, amines, carbohydrates, coumarins, flavonoids (e.g., eupafolin, patuletin, spinacetin), terpenoids (e.g., arnifolin, arnicolides, helenalin), volatile oils (e.g., thymol, ethers of thymol), phenolic acids, resins, bitters (arnicin), tannins, and carotenoids.[13,14,23] In vitro and animal studies have shown that some arnica extracts (but mostly homeopathic preparations) have anti-inflammatory[32-38] and antimicrobial[39] properties.

Human clinical studies have investigated topical and internal uses of *A. montana* herbal extracts and homeopathic products for their efficacy in treating various inflammatory conditions. Arnica extracts have been studied primarily for their topical use while studies on internal uses are limited to homeopathic products.

In 2010, a rater-blinded (i.e., a study in which rating scales are administered with no awareness of the participant's treatment assignment to limit scoring bias), randomized, controlled trial tested a 20% arnica ointment against three other ointments for reducing laser-induced bruising, a common side effect of dermatological procedures.[40] The arnica ointment, as well as a 5% vitamin K ointment, 1% vitamin K/0.3% retinol ointment, and a white petrolatum placebo, were prepared by a licensed compounding pharmacy. Healthy volunteers (n=16) who did not have a history of bleeding disorders and were not taking oral anticoagulants were provided a jar of each ointment labeled A, B, C, and D, applicators, and spot bandages to reduce cross-contamination or smearing of the ointments. Subjects then received four induced, standardized bruises that were randomized for treatment with one of the ointments. Bruises were photographed promptly after creation

Arnica *Arnica montana*
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† HPUS General Pharmacy. Liquid attenuations: "In the decimal scale the original quantity of medicine is divided progressively by ten so that the first decimal (1X) contains 1/10, the second decimal (2X) 1/100, and the third decimal (3X) 1/1000 of the original substance suspended in, and attenuated or expanded by, the diluent (alcohol, water, etc.)."

and at week two, and rated by a dermatologist who had no other involvement in the study. The 20% arnica ointment was significantly superior in its ability to reduce bruising compared to the 1% vitamin K/retinol and placebo oitments, but not the 5% vitamin K oitment.

A 2007 randomized, double-blind study investigated A. Vogel Arnica Gel® (containing 50 g *Arnica montana* fresh herbal tincture/100 g gel; 1:20 tincture ratio; supplied by Bioforce AG; Roggwil, Switzerland) versus Optifen® Gel (5% ibuprofen gel; Spirig Pharma Ltd.; Egerkingen, Switzerland) for treatment of osteoarthritis (OA) of the fingers.[41] A total of 204 patients with diagnosed osteoarthritis were randomized to receive treatment with the arnica gel (n=105) or ibuprofen gel (n=99) in 4 cm strip doses three times per day for three weeks. Improvement in all parameters was similar and clinically relevant, and neither patients nor doctors could distinguish between the two treatments. The authors stated that "arnica gel is not inferior to ibuprofen gel, regarding hand functional capacity, pain intensity, number of painful joints, duration and severity of morning stiffness, or paracetamol consumption."

An open-label, multi-center clinical study in 2005 investigated the safety and efficacy of an arnica gel (Rheuma-Gel AtroMed®; 500 mg tincture of organically grown fresh arnica flowers; 1:20, ethanol 58%; Bioforce AG; Roggwil, Switzerland). Patients (124 women, 80 men) diagnosed with rheumatic disorders of the musculoskeletal system applied a thin layer of gel to affected areas twice daily. Average baseline pain intensity was reduced significantly by nearly 50%. Efficacy was the same in patients with mild, moderate, and severe pain. Pain reduction was statistically significant in all three groups.[42]

An open, multicenter study, published in 2002, investigated the safety and efficacy of arnica gel (supplied by Bioforce AG; the same formula as in the study above) on OA of the knee.[42] Over a period of six week, 79 patients diagnosed with mild-to-moderate arthrosis/periarthropathy of at least one knee applied a thin layer of the gel to affected knee(s) morning and evening. Six of the 79 patients experienced localized reactions to the gel, a local symptom rate (7.6%) less than that experienced with topical nonsteroidal anti-inflammatory drugs (NSAIDs; approximately 10%).[43] Significant decreases in WOMAC Index (the Western Ontario and McMaster Universities Osteoarthritis Index, an accepted test for evaluation of OA of the knee) scores occurred at weeks three and six.[42] Additionally, pain, stiffness, and function were improved at visits two and three. Overall, the authors concluded that arnica gel treatment was comparable to treatment with diclofenac, an NSAID used to treat arthritis.

While there are a number of clinical studies on the topical use of homeopathic arnica preparations, they are, for the most part, not as positive in their outcomes as are studies on arnica extracts. One exception is a randomized, double-blind, placebo-controlled (RDBPC) study in which topical homeopathic arnica was applied after a downhill running protocol.[44] The participants in the homeopathic arnica group (n=20) reported reduced muscle tenderness, but the preparation did not affect performance markers of inflammation or muscle damage. More common are RDBPC studies that investigate homeopathic arnica cream for pain relief after eccentric exercise (pushing the muscles past their normal point of failure).[45] One such study found that, rather than experiencing decreased leg pain, subjects (n=20) reported increased leg pain 24 hours after extensive calf raises. In another RDBPC study (n=19) on a homeopathic arnica gel, there was no significant reduction in post-laser bruising.[46]

Internal homeopathic arnica preparations have not fared much better in clinical studies. A 2003 RDBPC study (n=64) with three parallel arms assessed the efficacy of arnica for the reduction of pain after elective carpal tunnel syndrome (CTS) surgery, wrist swelling, and use of pain medication.[47] No significant differences in the three arms were found in the arnica and placebo groups at day four. A 2002 randomized, double-blind comparison study (n=37) investigating the usefulness of arnica following CTS surgery had somewhat better results.[48] Compared to the placebo group, patients in the arnica group experienced no difference in grip strength or wrist circumference (swelling) one and two weeks after surgery, but the arnica group had significantly less pain after two weeks.

In a randomized, double-blind, parallel-group study, homeopathic arnica performed as well as diclofenac in relieving postoperative wound irritation and patient mobility following bunion surgery.[49] It was, however, inferior to diclofenac in relieving pain, and there were no significant differences in the two groups regarding postoperative use of analgesics.

Homeopathic arnica was investigated for post-tonsillectomy pain relief in a RDBPC study (n=190) and found to cause a small but significant drop in pain scores compared to placebo.[50] There was no difference in secondary outcomes (antibiotic use, analgesia use, visits to doctor or hospital, day on which swallowing returned to normal, and day on which patients returned to work) between groups.

FUTURE OUTLOOK

Romania is the main producer of wild-collected arnica flowers, exporting mainly to Germany, Italy, France and Switzerland.[51] Germany accounts for approximately 80% of Romania's arnica exports.

Estimates of market demand vary considerably. Nearly 20 years ago, Dagmar Lange, PhD — a professor in the Institute of Environmental Sciences at the University of Koblenz-Landau in Germany — estimated that 50 metric tons (MT) of dried arnica flowers (equivalent to 250,000-300,000 kg of fresh flowers) and hundreds of kilograms of dried roots were used annually in Europe.[52] More recently, Rolf Franke, PhD, and colleagues have suggested[8] that the demand in Germany alone is about 10 MT for the pharmaceutical sector and more than 10 MT for the cosmetics sector. In 2003, Kathe et al. reported that *A. montana* ranked as Romania's seventh top medicinal and aromatic plant export, with an estimated 28 MT per year for wild-collected herbs. In 2001, 20 MT were reportedly wild harvested in the Cluj region of Transylvania alone. However, Rosa Romero Franco, PhD — a professor at the University of Santiago de Compostela in Galicia, Spain — asserts that the annual demand for dried arnica flower is as high as 300 MT, although the source of her estimation is not cited.[53]

Natural populations of *A. montana* have been threatened by non-sustainable wild collection of the roots and flowers in southern and eastern Europe.[4] In northern Europe, the main threat comes from changes in land use (meadow to farm). Declining numbers of grazing animals and increased fertilization (to increase meadow fodder production) are factors contributing to a reduction in arnica habitat.

The conservation status of *A. montana* in Europe is subject to various EU policies, habitat directives, and wildlife trade regulations.[54] For example, *A. montana* is listed in Annex V of the European Commission's Council Directive on the conservation of natural habitats and of wild fauna and flora, meaning that it is a "plant species of community interest whose taking in the wild and exploitation may be subject to management measures."[55] *A. montana* is also listed on Annex D, the Council Regulation on the protection of species of wild fauna and flora by regulating trade therein.[56]

Furthermore, some European countries have their own protection measures. For example, *A. montana* is classified as "critically endangered" on the national red list of Luxembourg; as "vulnerable" on the red lists of Bosnia and Herzegovina, Croatia, and Germany; as "extinct" on the national red list of Hungary; and as "protected" under national laws in the Czech Republic, Lithuania, and Slovenia.[57] The International Union for Conservation of Nature (IUCN) recommends actions including better resource management where mowing of meadows occurs, providing land owners with financial support to graze, and controlling land use changes, i.e., converting meadows for agricultural use.

Arnica *Arnica montana*
Photo ©2015 Steven Foster

In Bavaria, where drastic declines in wild populations have been observed, the Government of Middle Franconia has implemented a botanical species protection program to manage and protect the last remaining populations from extinction, and to increase the population size in the region by targeted propagation and seeding.[58] In April 2015, the German Federal Ministry for the Environment, Nature Conservation, Building and Nuclear Safety (BMU) issued a joint press release with the German Federal Agency for Nature Protection (BfN) announcing a new project to protect *A. montana* in the State of Bavaria.[59] The organizations allotted approximately €140,000 ($154,000) to support the project, which aims not only to protect arnica habitats in Bavaria's mountain meadows, but also to demonstrate the benefits of investing in the protection of biological diversity and "ecosystem services" (i.e., benefits people obtain from ecosystems). BMU and BfN also hope to develop of a program for sustainable regional use and marketing of regional arnica products with geographical indication, and to raise public awareness about the importance of biodiversity.

In Romania, where the bulk of the arnica supply is wild-collected, considerable investment has been made towards sustainable collection and management of arnica habitats. A three-year project (2004-2007) — funded by the UK Darwin Initiative, WWF-UK in partnership with the

WWF Danube Carpathian Programme, the Agricultural and Veterinary University of Cluj, and the commune of Gârda de Sus — developed a model to strengthen capacity and economic incentives for arnica habitat conservation through sustainable wild collection and trade.[6,60] The company Weleda Germany was a project partner, providing information on processing and quality requirements and signing a five-year agreement to purchase the project's wild-collected arnica, which eventually obtained organic certification.

Weleda NZ Ltd. has also financially supported a project to cultivate the German cultivar Arbo in New Zealand under certified-organic conditions.[61] The project resulted in the publication of a grower's guide for commercial production of *A. montana*, prepared for the New Zealand Arnica Growers' Group.

There are also biotech projects aiming to develop cell culture techniques for indirect regeneration and biotechnological production of active ingredients of *A. montana*. Researchers involved in the ArnicActive Cell project, financed by the Rector's Conference of Swiss Universities, have hypothesized that standardized production of arnica's active constituents is possible, regardless of soil composition, climate and weather conditions, and agricultural practices.[62] They believe that this work will contribute to the sustainable protection and use of *A. montana* in the cosmetic, endurance sports products, and pharmaceutical products industries.

With significant efforts being made in Romania in recent years to implement sustainable wild-collection standards — coupled with the development of cultivars for field cultivation and, more recently, the development of innovative biotech methods for production of active principles — the commercial supply of *A. montana* raw materials should become more predictable for companies willing to pay fair prices that cover the costs of sustainable production.

Regarding substitution in the marketplace, professor emeritus Günter Willuhn, PhD, author of a chapter on *A. montana* in *Herbal Drugs and Phytopharmaceuticals* (CRC Press, 2004), has reported relatively frequent adulteration with Mexican arnica (*Heterotheca inuloides*, Asteraceae) in the past.[10] In addition, researchers from the Autonomous University of Tlaxcala in Tlaxcala, Mexico have reported that Mexican arnica was being exported in relatively large quantities, mainly to companies in the European Union and United States, for use as a substitute for *A. montana*.[63]

A European market survey carried out by the Centre de Desenvolupament Rural Integrat de Catalunya (Solsona, Spain) determined that most of the *Arnica* products in the Spanish market likely contained Mexican arnica. It was estimated that, in 2009, about 96% of the arnica consumed in Spain was Mexican arnica and less than 4% was *A. montana*. Reasons given by the respondent companies included an inability to obtain sufficient quantities of *A. montana*, its high cost compared to Mexican arnica, and that product companies did not include botanical names in their product specifications (only "arnica") in order to give them flexibility to use either European or Mexican arnica in formulations. Bulk wholesaler respondents expressed interest in returning *A. montana* to the market but stated that it would be difficult to get companies to switch back due to the significant price difference.[64]

In the meantime, the *Mexican Pharmacopoeia*, which includes quality standards monographs for both "Arnica, Flor" (*A. montana*) and "Arnica Mexicana, Flor" (*H. inuloides*), provides botanical identification assays that enable the detection of adulteration of *A. montana* with flowers of *A. chamissonis* ssp. *chamissonis*, *H. inuloides*, and/or *Calendula officinalis* (Asteraceae).[65]

In a recent US survey of nine botanicals that had previously been reported to be adulterated or were suspected to be at risk of adulteration, 10 samples labeled "*Arnica montana*" were purchased from separate vendors.[66] Of the 10 samples, six were *H. inuloides*. The authors opined that the substitution might be economically motivated as *H. inuloides* is larger and more abundant and accessible in its native habitat, Mexico. However, they admitted that honest confusion might also be responsible as *H. inuloides* is called "arnica" in Mexico, and is used similarly, e.g., for bruises. HG

—Gayle Engels and Josef Brinckmann

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dear *reader*

Members of the American Botanical Council Advisory Board — who provide expert peer review for *HerbalGram* articles, among many other essential tasks — hold a variety of esteemed positions around the globe. Earlier this year, ABC was pleased to discover that one such member had accepted a new type of position — a first for the Advisory Board. In June, Ameenah Gurib-Fakim was named president of the small Indian Ocean island republic of Mauritius; she is the first woman president of that country and probably the first medicinal plant scientist to hold this exalted position in any country.

This issue's cover photo of arnica reflects the herb profile by ABC's Gayle Engels and Traditional Medicinals' Josef Brinckmann on this popular herb that can be found most often in topical creams. Although the botanical rarely is used internally in modern phytomedicine, arnica is possibly the most widely used herb in homeopathic preparations.

We are always interested in clinical trials that attempt to document the safety and efficacy of various herbs and phytomedicines. Craig Hopp, a pharmacognosist at the US National Institutes of Health's National Center for Complementary and Integrative Health (NCCIH, formerly NCCAM) provides a general review of NCCIH/NCCAM-funded clinical trials on herbs, most of which have resulted in less-than-encouraging outcomes.

Despite some negative research findings (and there are many positive research studies, too), consumer and professional demand for herbal dietary supplements continued to grow in 2014. As discussed in our annual Herb Market Report, herbal supplement sales in the US increased by an estimated 6.8% last year, with sales growth in all channels. We are grateful to our colleagues at *Nutrition Business Journal*, SPINS, and IRI for their continued collaboration to produce what many consider to be the most comprehensive annual report on the sale of herbal supplements in the US, something we've been doing in *HerbalGram* for more than 15 years. And, interestingly, so far as we are aware, this is one of our most-cited articles.

Whether this continually growing demand will persist in 2015 is a question on many people's minds, particularly after the strongly negative media firestorm on herbal supplements that was generated by the New York Attorney General's (NY AG) unfortunate misuse of DNA testing technology. However, sales data for early 2015 are showing continued strong demand for herb products, particularly multi-herb formulations. (The AG's erroneous conclusions that the herb capsules he had tested from four major retailers were mislabeled — as misreported by the *New York Times* and other mainstream media outlets — were covered extensively in our previous issue.)

And yet, as we have been saying for many years, there *are* problems regarding the quality and identity of some herbal ingredients, despite the NY AG's botched and non-credible investigation. ABC members and long-time readers of this publication will recall that ABC has been managing a consortium of nonprofit organizations and others in the ABC-AHP-NCNPR Botanical Adulterants Program. We've previously published extensive reports in these pages about accidental and intentional adulteration of various herbs (bilberry fruit extract, black cohosh, so-called "grapefruit seed extract," and skullcap). Now the Program moves to another level, not only reporting on cases of adulterated herbs (stay tuned), but also providing resources and remedies for in-house and third-party laboratories: the Laboratory Guidance Documents (LGDs). These extensively peer-reviewed documents were created to help industry and third-party analytical labs save time and money in determining the suitability of various analytical methods to authenticate particular ingredients and detect potential adulteration. The Program's LGDs published thus far have summarized and evaluated literally dozens of methods (21 for skullcap and 39 for bilberry). This can really be a boon to industry members, and eventually, to consumers, health professionals, and researchers.

This issue also has an introductory article by Jahan Marcu on the endocannabinoid system to help readers better understand the growing positive clinical data on the health benefits of cannabis; a guest editorial from toxicologist Amy Roe about the lack of a common framework from which to gauge the need for herb-drug interaction studies in humans; and Karen Raterman's review of the recent BMPEA problem in which a few companies were selling an unapproved stimulant drug as an herbal extract, claiming it was derived from an acacia tree.

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St. John's Wort *Hypericum perforatum*
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44 Past and Future Research Priorities at NCCIH with Respect to Botanicals

By Craig Hopp, PhD

For the past 20 years, surveys have shown that Americans commonly use non-mainstream medical approaches as adjuncts — not alternatives — to conventional medical practices. In order to reflect this, the National Center for Complementary and Alternative Medicine (NCCAM) changed its name to the National Center for Complementary and Integrative Health (NCCIH) in December 2014. Although the name has changed, the Center's mission — to support the "research, training, and dissemination of information" on these practices — has not. After obtaining mostly negative results from large-scale human clinical trials on a variety of herbs, the Center was prompted to reexamine its research priorities. Today, as Craig Hopp, PhD, a program director at NCCIH, explains in this article, the Center has focused its efforts on improving study methodology and examining the complex interactions of natural products with other biological processes — two foundational aspects that are key to advancing this field of study.

52 Herbal Dietary Supplement Sales in US Increase 6.8% in 2014

By Tyler Smith, Mary Ellen Lynch, James Johnson, Kimberly Kawa, Hannah Bauman, and Mark Blumenthal

Total US retail sales of herbal dietary supplements saw a 6.8% increase in 2014, an upward trend that has continued for 11 years, according to data from *Nutrition Business Journal* and the market research firms SPINS and IRI. *HerbalGram*'s annual market report takes a comprehensive look at herbal supplement sales figures and trends from 2014: the mainstream, natural, and direct sales channels all showed an increase in sales, with Americans spending an estimated total of $6.4 billion on monopreparation and/or combination herbal supplements. Turmeric (*Curcuma longa*, Zingiberaceae) held on to the number-one spot in the natural channel, which it moved into for the first time in 2013, and horehound (*Marrubium vulgare*, Lamiaceae) continued to lead sales in the mainstream channel.

departments

On the Cover
Arnica *Arnica montana.*
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HerbDay at the Homestead: Plant Enthusiasts Join ABC in Celebrating 10th Annual HerbDay

While every day is "herb day" at the American Botanical Council (ABC), on May 2, 2015, the nonprofit opened its historic homestead in Austin, Texas, to hundreds of visitors in celebration of the official 10th annual HerbDay. The visitors ranged from professional herbalists and herbalism students to plant enthusiasts, laypeople interested in learning more about health options, children who enjoy cartwheels on a weedy lawn, and everyone else in between.

The day was filled with a variety of educational activities, including highly informative herb walks through more than 20 of ABC's lush, themed herbal gardens. Local herbalists Carlos Hernandez of BioStar Botanicals and Nicole Telkes of the Wildflower School of Botanical Medicine led guests on a journey of discovery of the potential uses, benefits, and methods of preparation of many of the herbs found in ABC's medicinal gardens. For some, it was the first chance to see herbs they've heard about for years — echinacea, ginkgo, even ephedra — in their natural state in a garden.

"HerbDay is an international celebration of herbs and herbal products, packed with events aimed at educating and sharing ideas about the many ways herbs bring joy and well-being into our daily lives," explained Gayle Engels, ABC's special projects director. "We celebrate herbs' use in food, beverages, medicine, beauty products, and crafts, along with the art of growing and gardening with herbs. HerbDay is a grassroots movement, and its events belong to everyone who chooses to participate."

Renowned herbalist, author, teacher, and nutritionist Brigitte Mars traveled to ABC from Boulder, Colorado, to give a lecture on "Natural Remedies for Mental and Emotional Health." Mars' insights ranged from ways to incorporate herbs into everyday health practices to ways to remove harmful or toxic elements from one's life with the goal of improving mental and emotional health. ABC's founder and executive director, Mark Blumenthal, broke out his constantly updated cache of health-oriented cartoons for an afternoon talk, effectively demonstrating the humor in how we approach health, drugs, diet, and lifestyle in the United States and around the world. Blumenthal's cartoon lecture not only educated but amused the audience gathered in ABC's annex building.

ABC's plant sale was, as always, a big hit with HerbDay attendees. Many of the plants were raised in ABC's greenhouse over the winter, or were offshoots of plants found in ABC's gardens. Attendees were also able to purchase books from Mars, Telkes, ABC, and others. For the kids and all those young at heart, the HerbDay celebration included a maypole dance, healthy snacks (generously provided by Peoples Rx Pharmacy, a local chain of compounding and natural pharmacies), and a "start your own plant and take it home" station.

The entire day was filled with music. Alternating between playing flute and guitar, local musician Deborah Ramaker entertained young and old as they lounged on the lawn, caught up with friends around the picnic tables, or just stopped with a glass of herbal tea to appreciate her musical stylings. We're sad to report that Ramaker passed away suddenly, soon after the event. ABC is grateful for and honored by the magical time she spent with us in celebration of herbs and their beneficial impact.

Overall, ABC's 10th annual HerbDay was a big success. "We are deeply grateful for the strongly positive turnout we've received from the Austin community," said Blumenthal.

While ABC is one of the main orchestrators of HerbDay, activities in celebration of HerbDay take place around the United States. According to the HerbDay Facebook page, Mountain Rose Herbs in Eugene, Oregon hosted an event at the Mount Pisgah Arboretum; The Dancing Herbalist had a full day of herbal activities, followed by camping for those interested, in Artemas, Pennsylvania; and the city of Brattleboro, Vermont, held its first HerbDay celebration with workshops, plant walks, and herbal crafts. HG

WHAT IS HerbDay?

HerbDay is a coordinated, nationwide series of independently produced public educational events celebrating the importance of herbs and herbalism. HerbDay was initiated by five nonprofit organizations with interests in herbs and herbalism to raise public awareness about the significance of herbs in the lives of millions of people worldwide, as well as the many ways herbs can be used safely and creatively for health, beauty care, and culinary enjoyment. *The HerbDay Coalition includes ABC, the American Herbalists Guild (AHG), American Herbal Pharmacopoeia (AHP), American Herbal Products Association (AHPA), and United Plant Savers (UpS). Find out more at http://herbday.org/.*

Top image: Visiting herbalist Brigitte Mars educates HerbDay attendees about using herbs, and other healthy practices, to improve mental and emotional health.

Bottom image: The Maypole dance, an annual event at ABC's HerbDay.

Photos ©2015 ABC

Austin herbalist Nicole Telkes of the Wildflower School of Botanical Medicine leads an herb walk through ABC's botanical gardens.

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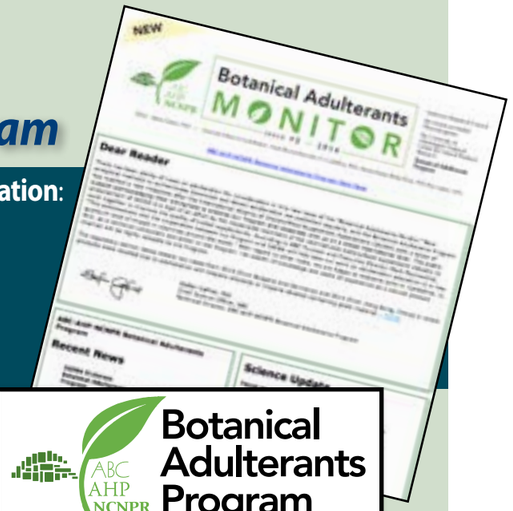

Botanical Adulterants Program

New "Laboratory Guidance Documents" Series Helps Industry Detect Potential Herb Adulteration

Botanical Adulterants Program's first two Lab Guidance Documents review analytical lab methods for skullcap and bilberry extracts

The ABC-AHP-NCNPR Botanical Adulterants Program (BAP) announces the publication of its new Laboratory Guidance Document (LGD) on bilberry (*Vaccinium myrtillus*, Ericaceae) fruit extract. This is part of the Program's new series of comprehensive, authoritative, extensively peer-reviewed, and up-to-date summaries and assessments of laboratory analytical methods for authentication of the identity of botanical ingredients and detection of the potential presence of known adulterants.

The Program's bilberry LGD is the second publication in its Laboratory Guidance Document series for botanical ingredients. It follows January's inaugural LGD publication on skullcap (*Scutellaria lateriflora*, Lamiaceae) herb. There is ample evidence from published and unpublished laboratory reports that both of these herbs are subject to adulteration in the US and international markets. These free documents — available at no cost thanks to the Program's underwriters and supporters — are intended for use by quality control personnel and lab technicians in the herbal medicine, botanical ingredient, and dietary supplement sectors to help them choose the most appropriate techniques and methods for their specific analytical needs.

The American Botanical Council (ABC)-American Herbal Pharmacopoeia (AHP)-National Center for Natural Products Research (NCNPR) Botanical Adulterants Program is an international consortium of nonprofit organizations, analytical laboratories, professional scientists, industry members, professional and trade organizations, and others that advises industry, researchers, health professionals, and the public about the various challenges related to adulterated herb and botanical ingredients sold in commerce. To date, more than 165 American and international parties financially support or otherwise endorse the Program.

"For the first several years of our Program, we published articles alerting members of the herb industry about adulteration of specific herbs," said Mark Blumenthal, founder and executive director of the American Botanical Council and director of the BAP. "Now, in addition to our soon-to-be-enhanced series of publications on adulterated herbs, we are offering technical resources to assist industry and third-party laboratories to detect adulteration and help prevent adulterated botanical ingredients and extracts from being processed into finished consumer products."

The ABC-AHP-NCNPR Laboratory Guidance Documents are intended to provide reliable, expert guidance on suitable methods to comply with the mandated requirements of testing for identity, purity, strength, and composition outlined in the United States Food and Drug Administration's current Good Manufacturing Practices (cGMPs) for dietary supplements, as well as government-mandated GMPs in other countries. Per the US cGMPs, it is the responsibility of the dietary supplement manufacturers to "conduct at least one appropriate test or examination to verify the identity of any component that is a dietary ingredient."[1]

The Program's LGDs provide information about suitable analytical methods for detection of certain adulterants and authentication of specific botanical materials in the form of whole, cut, or powdered raw materials, extracts, and essential oils. Conclusions are based on a thorough review of available analytical methods (e.g., from official and unofficial compendia, as well as the peer-reviewed literature) and input from peer reviewers from academia, government, and industry in multiple countries. The Bilberry Fruit Extract LGD was peer-reviewed by 16 such experts. The primary assessment of each method is based on its performance characteristics (i.e., suitability in detecting known adulterants, *if* they are present in a tested material); labor and analysis

Bilberry *Vaccinium myrtillus*
Photo ©2015 Steven Foster

time comprise the secondary evaluation criteria.

Stefan Gafner, PhD, ABC chief science officer and BAP technical director, emphasized the importance of having a solid analytical method to evaluate bilberry raw materials and finished products: "Based on comments from dietary supplement ingredient suppliers and manufacturers, the adulteration of bilberry extracts is a big concern in the herbal industry. Bilberries are a rich source of anthocyanins, naturally occurring blue-purple pigments with antioxidant and other beneficial properties found in many fruits and berries, but manufacturing a high-quality bilberry extract is very expensive due to the high cost of bilberries. People who intend to cheat have a number of cheaper anthocyanin sources available, making the discovery of adulteration sometimes challenging. Therefore, it is important to use an analytical method that is specific enough to detect the potential adulterants."

Dr. Gafner also shared his appreciation for everyone who participated in the extensive peer-review process for both LGDs. "I am grateful for the many analytical experts who took the time to peer-review the Skullcap and Bilberry LGDs. This process has led to numerous improvements in the papers and has ultimately resulted in documents that are helpful for those whose job it is to determine the authenticity of the products and the absence of adulterants."

The BAP's LGDs begin with a statement of purpose and scope in regard to the particular plant species covered, followed by a short overview of the botanical nomenclature of the species and its known adulterants. Also included are sections on analytical techniques (generally including macroscopic, microscopic, chemical, and genetic assays) and a phytochemical composition overview of the species and known adulterants. The LGDs conclude with a concise table of strengths and limitations of the various assays. Complete references are provided with links to original source documents.

The next LGD scheduled to be released by the ABC-AHP-NCNPR Botanical Adulterants Program is on the detection of black cohosh (*Actaea racemosa*, Ranunculaceae) adulteration.

For the bilberry extract LGD, 39 analytical methods were evaluated, including macroscopic analysis, botanical microscopy, HPTLC, HPLC/UHPLC, and UV/Vis spectrophotometry; the skullcap LGD reviewed 23 methods.

"The review is accurate and it is a valuable guidance on analytical methods to authenticate bilberry extracts and to detect adulteration," commented Roberto Pace, PhD, director of quality control at Indena S.p.A. in Milan, Italy, after reviewing the bilberry LGD. "I deem it will be one of the main references on the analytics of bilberry."

"We recently added a skullcap-based product to our line and the conclusions of the [Skullcap LGD] mirror our own," commented Katie Huggins, vice president of technical services at Traditional Medicinals, Inc., after reviewing the skullcap LGD. "I can say from experience that having such a document when evaluating a new ingredient for inclusion in a product and when writing specifications would be invaluable."

To date, the ABC-AHP-NCNPR Botanical Adulterants Program has published five extensively peer-reviewed and referenced articles on the history of adulteration, adulteration of the herbs black cohosh and skullcap, and adulteration of bilberry fruit extract and so-called "grapefruit seed extract." These open-access articles are available on the Program's webpage at http://cms.herbalgram.org/BAP/BotanicalAdulterantsIndex.html#AdulterationReports. The Program also publishes a quarterly e-newsletter, the "Botanical Adulterants Monitor," that highlights new scientific publications related to botanical authenticity and analysis to detect possible adulteration, recent regulatory actions, and Program news. HG

Reference

1. US Food and Drug Administration. Code of Federal Regulations Title 21, Volume 2, Part 111 (21CFR111): Current Good Manufacturing Practice in Manufacturing, Packaging, Labeling, or Holding Operations for Dietary Supplements. Available at: www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?CFRPart=111. Revised April 1, 2014. Accessed July 23, 2015.

AOAC INTERNATIONAL® Endorses the ABC-AHP-NCNPR Botanical Adulterants Program

International standards-developing organization offers support for botanical quality control initiative

The AOAC INTERNATIONAL® (formerly known as the Association of Official Agricultural Chemists) has endorsed the ABC-AHP-NCNPR Botanical Adulterants Program. The endorsement follows a unanimous vote by the AOAC Board of Directors in April.

Founded in 1884, AOAC INTERNATIONAL has grown from a US government agency establishing methods for chemical analyses for agricultural fertilizers to an international association of government, academic, and industry professionals encompassing a wide array of scientific disciplines. The work of the organization focuses on the creation, validation, and publication of reliable analytical test methods for food, beverage, dietary supplement, and ingredient safety and purity. AOAC's mission, as detailed on its website, is "to attain the vision of 'worldwide confidence in analytical results.'" The organization also publishes the bi-monthly *Journal of AOAC International*.

AOAC Board President Erik J.M. Konings, PhD, and Executive Director E. James Bradford, PhD, notified ABC Founder and Executive Director Mark Blumenthal of the organization's endorsement of the Program in a letter dated April 21, 2015. "AOAC International's industry partners represent a broad spectrum of interests, including dietary supplements and natural products," Drs. Konings and Bradford wrote. "As such, we encourage efforts which aim to strengthen the industry using responsible and science-based approaches in communication and education.

"AOAC supports the Botanical Adulterants Program's focus on educating industry, researchers, health professionals, regulators, and other interested parties with respect to the confirmation of types of adulteration and evaluation of analytical methods," they continued. "We look forward to a long relationship with the American Botanical Council and the ABC-AHP-NCNPR Botanical Adulterants Program."

"We are deeply grateful and highly honored to have AOAC's endorsement and participation in our Botanical Adulterants Program," said Blumenthal, who is also the general manager of the Program. "AOAC is one of the world's most highly respected standards-setting bodies, and their recognition of the goals and educational activities of our Program will help us move further towards increasing the international impact of our educational efforts."

"The endorsement by AOAC of the Botanical Adulterants Program [BAP] continues the global recognition by scientific bodies that this program has received," said James Neal-Kababick, director of Flora Research Laboratories and fellow of AOAC. "The pharmacognosy world

Continued on page 22

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These are just a few of the recent additions to the ABC catalog of expert books.

Ancient Pathways, Ancestral Knowledge: Ethnobotany and Ecological Wisdom of Indigenous Peoples of Northwestern North America by Nancy J. Turner, 2014. Turner, the preeminent ethnobotanist studying the First Nations of Canada, weaves together a complex understanding of the traditions of use and management of plant resources in this vast region. She follows Indigenous inhabitants over time and through space, showing how they actively participated in their environments, managed and cultivated valued plant resources, and maintained key habitats that supported their dynamic cultures for thousands of years, as well as how knowledge was passed on from generation to generation and from one community to another. To understand the values and perspectives that have guided Indigenous ethnobotanical knowledge and practices, Turner looks beyond the details of individual plant species and their uses to determine the overall patterns and processes of their development, application, and adaptation. Hardcover, Two volumes, 1056 pages. **$100.00 ($90.00 ABC Member Price)**

Botanicals: Methods and Techniques for Quality and Authenticity by Kurt Reynertson and Khalid Mahmood, 2015. Insight compiled from expert contributors addresses the challenge of identifying a botanical extract or preparation on the basis of its chemical content and includes a range of methods and techniques that can be used to help guide quality and authenticity determinations. Topics include metabolic profiling, authentication via morphology, and genetic methods of authentication; NMR, NIR, and HPTLC methods; and tools for building models for the authentication of materials. Hardcover, 332 pages. **$125.96 ($113.36 ABC Member Price)**

Essential Chinese Formulas: 225 Classical and Modern Prescriptions Organized by Clinical Category by Jake Paul Fratkin, 2014. Calling on the author's 35 years of clinical experience with Chinese herbal medicine, this book concisely summarizes existing information on 133 classical Chinese formulas, 83 modern formulas, and nine single herbs. It provides ingredient percentages, historical origins, TCM indications, commentary with clinical applications, and contraindications and cautions. Hardcover, 650 pages. **$65.00 ($58.50 ABC Member Price)**

The Herbalist's Bible: John Parkinson's Lost Classic Rediscovered by Julie Bruton-Seal and Matthew Seal, 2014. John Parkinson (1567-1650) was a practicing London apothecary, herbalist to the royal family, renowned gardener, and author. *The Herbalist's Bible* is a gorgeous presentation of 50 of the herbs addressed in Parkinson's *Theatricum Botanicum* of 1640, the main medical text of its day. Each reproduced page from Parkinson's herbal is set opposite a modern translation which includes therapeutic applications illustrated with color photographs. Hardcover, 256 pages. **$37.94 ($33.97 ABC Member Price)**

Handbook of African Medicinal Plants, 2nd ed. by Maurice M. Iwu, 2014. An overview of 2000 species of plants available in Africa as medicinal agents, with information about botany, chemistry, pharmacology, and usage, including traditional healing methods. Provides a pharmacognosy-based profile of 170 of the major herbs, with a brief description of the diagnostic features of the leaves, flowers, and fruits and monographs with botanical names, common names, synonyms, African names, habitat and distribution, ethnomedicinal uses, chemical constituents, and reported pharmacological activity. Hardcover, 506 pages**. $125.96 ($113.36 ABC Member Price)**

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AOAC continued from page 20

[has] a stake in the problems, [and] AOAC has been tapped to help address some selected clandestine adulteration in dietary supplements as well as economic adulteration…. Understanding how to ensure that adulterated material is not released into the food supply chain is critical and the BAP is making major inroads with its collaborative teamwork."

AOAC joins leading groups of medicinal plant research scientists that have already endorsed the Botanical Adulterants Program, including the American Society of Pharmacognosy, the Society for Medicinal Plant and Natural Product Research (GA), and the Natural Health Products Research Society of Canada.

"The endorsement by AOAC of the Botanical Adulterants Program continues the global recognition by scientific bodies that this program has received."

The Botanical Adulterants Program was also previously endorsed by US health practitioners groups including the Academy of Integrative Health and Medicine, the American Herbalists Guild, and the Integrative Healthcare Policy Consortium, as well as the American Association of Naturopathic Physicians. Recognizing the international nature of adulteration, several organizations outside the United States, including the Irish Register of Herbalists, the National Institute of Medical Herbalists, and the British Herbal Medicine Association, have also offered their support.

Endorsements from domestic and international industry trade associations include the Consumer Healthcare Products Association, the Council for Responsible Nutrition, the Natural Products Association, and the United Natural Products Alliance — all in the United States — as well as the International Alliance of Dietary/Food Supplement Associations, the Australian Self Medication Industry, Complementary Medicines Australia, the Australian Tea Tree Oil Association, and Natural Products New Zealand. HG

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For more details on joining the program, and access to the free publications produced to date, **please see www.herbalgram.org/adulterants or contact Denise Meikel at denise@herbalgram.org.**

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Cranberry *Vaccinium macrocarpon*. Photo ©2015 Steven Foster

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Medicinal Plant Scientist Becomes President of Mauritius

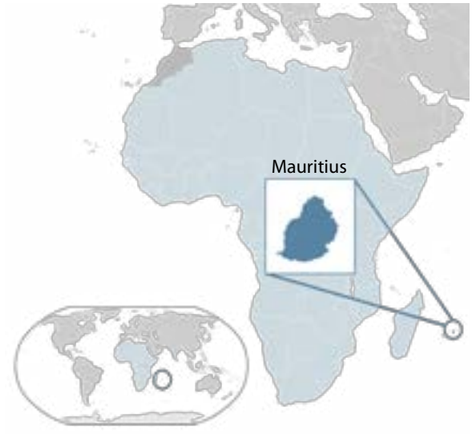
Ameenah Gurib-Fakim, noted author, professor, and ABC Advisory Board member, is first female president of small Indian Ocean island republic

The Republic of Mauritius, a small island nation off the coast of Madagascar, showcases a high level of biodiversity, making it particularly appealing for natural products chemists interested in exploring the possibilities among its flora for the supplement and cosmetics industries. Independent from British colonization since 1968, the republic's 1.3 million citizens enjoy one of the highest gross domestic products (GDPs) of an African nation, with a growing financial sector and tourism industry. On June 5, 2015, research scientist and American Botanical Council (ABC) Advisory Board member Ameenah Gurib-Fakim, PhD, was sworn in as the nation's first female president.


Ameenah Gurib-Fakim
Photo ©2014 TED Conference

Prior to her appointment as president, Dr. Gurib-Fakim served dual roles as researcher and academic. At her company, Centre for Phytotherapy Research (CEPHYR), she used her background in organic chemistry to perform clinical trials on pharmaceuticals, cosmetics, and dietary supplements, developing innovative ingredients from the abundance of plants unique to Mauritius. Over the course of her career, she has authored or co-authored several notable texts documenting the traditional knowledge of the area, including *African Herbal Pharmacopoeia* (AAMPS, 2010), *Medicinal and Aromatic Plants of the Indian Ocean Islands* (MedPharm, 2004), and *Novel Plant Bioresources: Applications in Food, Medicine and Cosmetics* (Wiley-Blackwell, 2014). She also served the University of Mauritius for 23 years, beginning as a lecturer for the faculty of agriculture and, from 2004-2010, holding the position of vice-chancellor for teaching and learning.

Dr. Gurib-Fakim gave a TED Talk in 2014 emphasizing the importance of preserving and actively conserving natural resources titled "Humble plants that hide surprising secrets."[1] In her talk, she highlighted five plants from Mauritius with documented traditional uses and possible pharmaceutical applications — but pointed out that Mauritius also was the home of the famously extinct dodo bird, and human interaction with the environment could precipitate similar tragedies in other delicate and diverse regions of the planet. She has been a passionate advocate for a proactive approach toward urbanization, climate change, and the study of natural products.



The road to the highest office of Mauritius, however, was an unusual one. "I did not choose politics," said Dr. Gurib-Fakim. "Politics chose me!" Her appointment to the role, which is largely ceremonial, followed the resignation of former president Kailash Purryag. Going into the recent election, leaders of her party, Alliance Lepep, approached her and asked if she would be willing to accept the position. "They wanted a person who was politically neutral," she explained, "a woman, and one who had some form of credibility. I had the scientific credibility and was known internationally. My name was proposed and the party won." The opposing party also approved her appointment, making the official parliamentary vote only a formality. Dr. Gurib-Fakim described politics as a "national sport" in Mauritius, with a population that is actively involved in the general elections. Voter turnout can be as high as 80% of the electorate. (As a matter of comparison, voter turnout for the 2012 US presidential election was estimated to be 57.5%.)

Her credibility is well-documented. Dr. Gurib-Fakim's work has international recognition, as she has lent her talents to a number of different organizations, including the following: International Council for Science (formerly the International Council of Scientific Unions), Mauritius Research Council, the Indian Ocean University, Pan-African Association of African Medicinal Plants, the Reference Group of the International Science Programme of Uppsala University in Sweden, and the International Foundation for Science in Stockholm. She has also served as a member of the Expert Panel on Infectious Diseases of the Special Programme convened by the United Nations Development Program, United Nations Children's Fund (UNICEF), the World Health Organization and World Bank, the Scientific Advisory Council of NTembi, the Nuclear Energy Commission of South Africa, the International Advisory Committee for the Cyclotron Project of the Indian Ocean based in La Réunion (a French island southwest of Mauritius), and American Botanical Council Advisory Board since 2010. She has used her education and passion for her country to build a reputation first as a scientist, then as an academic, and most recently as a political leader. She hopes that her current role will inspire other women to follow in her footsteps and emphasize the importance of science and conservation in education.

In a statement before parliament presenting the motion to elect Dr. Gurib-Fakim, Mauritian Prime Minister Sir Anerood Jugnauth called her "the perfect role model and a source of inspiration for our youth."

"Science, technology and innovation [STI] creates opportunities and improves the GDP," explained Dr. Gurib-Fakim. "If institutions build capacity, have a strong STI policy in place, and promote the entrepreneurial spirit among the young people, we will improve economic indicators and create opportunities and jobs." HG

—Hannah Bauman

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Systematic Review and Meta-analysis of the Antihypertensive Effects of Garlic

Reviewed: Rohner A, Ried K, Sobenin IA, Bucher HC, Nordmann AJ. A systematic review and metaanalysis on the effects of garlic preparations on blood pressure in individuals with hypertension. *Am J Hypertens*. March 2015;28(3):414-423.

One in three adults worldwide has high blood pressure.[1] The adverse effects of conventional antihypertensive medications often result in low compliance, poor blood pressure (BP) control,[2] and dissatisfied patients seeking alternative therapies. Garlic (*Allium sativum*, Amaryllidaceae) is one of the most popular herbal treatments for hypertension. The authors of this systematic review evaluated randomized clinical trials to assess the effect of garlic on BP in patients with hypertension and identified the risk of bias in the reported evidence.

The authors searched clinical trial registries of ongoing studies in addition to PubMed, Embase, Cochrane Library, and the Web of Science from inception through March 2014 using the terms "garlic" and "blood pressure" or "garlic" and "hypertension." Included in the systematic review were full-text, randomized, controlled trials of garlic preparations for the treatment of hypertension that reported BP values at baseline and after four or more weeks of treatment. There was no language restriction.

The authors identified nine trials (n=577 patients in total) that met the inclusion criteria. From the two trials that included both normal and hypertensive subjects, only data for the hypertensive subgroup (n=482) were included in the meta-analysis.

The included trials were heterogeneous in terms of subject naivety to hypertensive medication, medical diagnoses (hypertension or dyslipidemia), BP measurement methods (sitting or supine), type of garlic preparation (raw or aged dried extracts), dosage (240-2,400 mg/day), type of control (placebo or active treatment), and study duration (8-26 weeks).

The analysis of bias indicated that randomization and concealment of group allocation were adequate in five trials and unclear in four trials. The risk of performance bias was low in all trials, while detection bias was low in four trials and unclear in five trials. Only four trials included an intention-to-treat analysis. Although none of the trials explicitly reported industry funding, at least one study author in two of the trials was identified as an employee of the company producing the garlic preparation being investigated. The authors rated the risk of selective reporting bias for the trials as unclear because only two trials included study protocols.

The meta-analysis revealed that there was a significant reduction in both systolic BP (SBP) and diastolic BP (DBP) in patients treated with garlic compared to the controls; however, there was significant heterogeneity in the results. After restricting the analysis to higher-quality trials, the treatment effects were less pronounced but remained significant for garlic preparations compared to controls, with lower heterogeneity for SBP but not for DBP.

Garlic *Allium sativum*
Photo ©2015 Steven Foster

Addressing the heterogeneity of the study findings, the authors state, "It must be noted that different garlic preparations have variable effectiveness on BP." The different garlic preparations used in the trials, they continue, "may have contributed to the heterogeneous study findings and preclude an appropriate analysis of a dose relationship."

The adverse side effects associated with the garlic preparations were rare and mild. In two trials, patients taking garlic reported a higher incidence of bloating, flatulence, and reflux compared to control. Only three trials reported drop-outs in the garlic groups due to adverse gastrointestinal symptoms (a total of five out of 105 patients, or less than 5%).

Some of the study's strengths, according to the authors, were the comprehensive literature search and robust meta-analyses across subgroup and sensitivity assessments. Acknowledged limitations were as follows: the highly heterogeneous estimates of BP with large effect sizes and confidence intervals; small sample size of the included trials; overall quality of the included trials; lower significance of the results from trials with more rigorous methodologies; inconsistencies in the DBP data despite various sensitivity analyses; varied trial durations; and heterogeneity in the type and dosage of garlic preparations used. As one peer reviewer of this summary wrote, it is difficult to conduct a meta-analysis of trials using different commercial garlic products because each preparation contains different chemical constituents; for example, one product may contain more oil-soluble compounds and another may contain more water-soluble compounds (e.g., S-acetyl cysteine).

The authors conclude that the observed improvements are clinically relevant and that garlic preparations offer promise as an alternative treatment for reducing high BP. However, they note: "As of now, there is insufficient evidence to have confidence that garlic preparations are an effective alternative or complementary/adjunct herbal medication to conventional antihypertensive drugs."

Additional research is needed to understand the mechanisms of garlic's BP-lowering effects. As the authors conclude, after more than 25 years since the publication of the first randomized controlled trial of garlic for the treatment of hypertension,[3] "We still do not know whether garlic preparations lower BP in the long term. … A well-conducted, sufficiently powered long-term trial is needed to assess the BP-lowering capacities of a standardized form of a garlic preparation." HG

—Shari Henson

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Echinaforce® Hotdrink Is as Effective as Tamiflu® in Early Treatment of Influenza

Reviewed: Rauš K, Pleschka S, Klein P, Schoop R, Fisher P. Echinaforce Hotdrink versus oseltamivir in influenza: A randomized, double-blind, double dummy, multicenter, non-inferiority clinical trial [published online April 20, 2015]. *Curr Ther Res*. 2015. doi: 10.1016/j.curtheres.2015.04.001.

***Editor's note**: This study was sponsored by A. Vogel Bioforce AG, manufacturer of Echinaforce Hotdrink. One of the authors (Schoop) is an employee of the company.*

Influenza, commonly known as the flu, is a seasonal infectious disease with symptoms including cough, nasal congestion, headache, muscle pain, and fever that affects an estimated 25-50 million people each year in the United States alone. Complications occur frequently and can include life-threatening inflammatory events such as encephalitis, myelitis, myocarditis, septic shock, bronchitis, and pneumonia. The recommended medical treatment in early stages of the disease is the administration of neuraminidase inhibitors — e.g. oseltamivir (Tamiflu®; Hoffmann-La Roche; Basel, Switzerland) or zanamivir (Relenza®; GlaxoSmithKline; Philadelphia, Pennsylvania) — which has been shown in clinical trials to reduce flu duration and complications.

Echinacea *Echinacea purpurea*
Photo ©2015 Steven Foster

A total of 473 patients were enrolled in this randomized, double-blind, double-dummy, clinical trial carried out for 10 days at 29 general practices in the Prague area of the Czech Republic. Patients had been clinically diagnosed with influenza based on one or more respiratory symptom, systemic symptom, and a fever of at least 100°F (37.8°C), starting less than 48 hours prior to treatment. To be included in the study, participants were required to have good general health, a negative pregnancy test, body weight greater than 88 lbs (40 kg), and a signed consent form. Patients were excluded if they had been treated with antibiotics in the previous month; a flu vaccination; cardiovascular, liver, kidney, neurological, or endocrinological diseases; or allergies to acetaminophen, dextromethorphan, or plants in the family Asteraceae. The mean age of patients was 37 years. Also included in the study were nine children and adolescents between 12 and 17 years old.

A total of 237 patients received Echinaforce® Hotdrink syrup (A. Vogel Bioforce AG; Roggwil, Switzerland; containing 228 mg/ml *Echinacea purpurea* [Asteraceae] herb extract, 12 mg/ml *E. purpurea* root extract, 276.5 mg/ml *Sambucus nigra* [Adoxaceae] berry juice, and excipients) with oseltamivir placebo capsules. Patients in the second group (n=236) received Echinaforce Hotdrink placebo (containing the same excipients as the Echinaforce Hotdrink verum group plus colorants and flavors) and oseltamivir. Patients in the Echinaforce Hotdrink group received 5 ml syrup five times daily on the first three days, then 5 ml syrup three times daily for the remaining seven days of the study. At the same time, these patients received oseltamivir placebo capsules twice per day for each of the 10 days. In the oseltamivir verum group, the same regimen was followed with Echinaforce Hotdrink placebo and one capsule of oseltamivir twice daily (oseltamivir verum for the first five days, followed by oseltamivir placebo capsules for the next five days).

Treatment efficacy was evaluated using a symptom diary, in which patients recorded the severity of cough, nasal congestion, sore throat, fatigue, headache, muscle pain, feverishness, malaise, sweats, and/or chills using a scale from 0 to 3 (0=not present, 1=mild, 2=moderate, 3=severe). In addition, axillary body temperature was measured, and the occurrence of complications was recorded. The cumulative proportion of patients that recovered from influenza after one, five, and 10 days of treatment was chosen as the primary endpoint of the study. Recovery was defined as the first day when symptoms were mild in the evening or altogether absent. Other measured outcomes included days without sleep disturbance, duration until return to normal activity, use of rescue medication (acetaminophen or dextromethorphan), and additional contacts made to healthcare professionals. Patients and physicians also evaluated the tolerability and efficacy subjectively on a scale from 1 to 4 (1=very good, 2=good, 3=moderate, 4=poor).

Overall, both treatments were considered efficacious. After one, five, and 10 days, recovery was observed in 1.5% and 4.1%, 50.2% and 48.8%, and 90.1% and 84.4% of patients treated with Echinaforce Hotdrink and oseltamivir, respectively. There was no statistical difference in the clinical outcome between the two treatments, although the treatment failures after 10 days showed a non-statistically significant trend in favor of the patients receiving Echinaforce Hotdrink. There was also no significant difference in the efficacy judgement by physicians and patients.

The occurrence of complications and adverse side effects was higher in the oseltamivir group compared to the Echinaforce Hotdrink group. In the oseltamivir group, 14 complications were recorded, mainly of respiratory nature (pneumonia [n=2], sinusitis [n=4], bronchitis [n=2], and rhinopharyngitis [n=1]). The remaining five cases were gastrointestinal complications. Complications observed in the Echinaforce group (n=5) were all infections of the respiratory tract. A total of 44 adverse side effects occurred in patients treated with oseltamivir, while 31 adverse side effects were recorded in the Echinaforce Hotdrink group. The higher incidence of adverse side effects was mostly due to the occurrence of nausea and vomiting in the oseltamivir group. The exact nature of the adverse side effects other than gastrointestinal problems was not detailed in the publication, but the authors indicate that no serious adverse events were observed in either of the treatment groups. No limitations of the clinical study were reported.

In conclusion, the findings of this study suggest that the treatment outcomes of patients suffering from early influenza symptoms who are treated with oseltamivir or Echinaforce Hotdrink are equivalent in patients without concomitant diseases and who are not part of an "at-risk" population. The authors suggest that the lower incidence of complications and adverse side effects with Echinaforce Hotdrink make it an attractive alternative to standard treatment with neuraminidase inhibitors, and that the product's availability as a nonprescription medicine makes it a suitable choice for the very early treatment of symptoms, a central factor in the successful management of flu infections. HG

—Stefan Gafner, PhD

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Topical Lavender Cream Alleviates Anxiety, Stress, and Depression in Pregnant Women

Reviewed: Effati-Daryani F, Mohammad-Alizadeh-Charandabi S, Mirghafourvand M, Taghizadeh M, Mohammadi A. Effect of lavender cream with or without foot-bath on anxiety, stress and depression in pregnancy: a randomized placebo-controlled trial. *J Caring Sci*. 2015;4(1):63-73.

Editor's note: *Although the original journal article is marred with typographical and grammatical errors, the reported methodology is rigorous.*

Maternal anxiety, stress, and depression during pregnancy can have a negative effect on the health of both mother and child. Lavender (*Lavandula angustifolia*, Lamiaceae) flower essential oil has been shown to decrease anxiety, stress, and depression. Foot bathing has also been found to improve autonomic function, sleep quality, and relaxation. The purpose of this randomized, double-blind, placebo-controlled study was to compare the effects of lavender cream and foot bathing on anxiety, stress, and depression in pregnant women.

Healthy pregnant women (n=141, aged 18-40 years) at 25-28 weeks gestation participated in this study conducted at Tabriz University of Medical Sciences in Tabriz, Iran. Patients were excluded if they had a history of chronic disease; were taking medication (e.g., sedatives) that might interfere with the interventions; smoked; had a history of infertility; had a recent unwanted pregnancy; had allergic reactions to herbal medicines in the past; were obese (i.e., a body mass index ≥ 30); had inflammation at the site of cream application; were illiterate; worked a night shift; lived outside of Tabriz city; or had current severe depression, anxiety, or stress (defined by scores of ≥ 10 on the anxiety sub-scale, ≥ 17 on the stress sub-scale, or ≥ 14 on the depression sub-scale of the Depression Anxiety Stress Scales-21 [DASS-21]). The sample size was calculated to detect a reduction of at least 43% in mean anxiety scores and 40% in mean depression scores on the DASS-21.

Patients were randomly assigned to three groups as follows: placebo, lavender cream (Barij Essence Pharmaceutical Company; Kashan, Iran), and lavender cream plus foot bath. The lavender cream contained 1.25% lavender essential oil; the placebo was the base cream consisting of stearic acid, acetyl alcohol, Vaseline®, and glycerin. Patients were instructed to rub 2 g of lavender or placebo cream on their legs for 10-20 minutes, 1.5 hours before bedtime for eight weeks. The lavender-plus-foot-bath group was told to soak their feet in 40-42°C tap water, at a depth of 5 cm above the ankle, for 30 minutes after applying the cream. To facilitate blinding, patients only knew that the effect of an herbal cream was being investigated; the name of the plant was not mentioned.

Lavender *Lavandula angustifolia*
Photo ©2015 Steven Foster

The patients completed the DASS-21 questionnaire at baseline, week four, and week eight. Based on their responses, anxiety, stress, and depression sub-scores were calculated. To assess compliance, patients were asked to keep a daily diary of treatment application and to return cream tubes after four and eight weeks.

At baseline, the groups had similar characteristics. Compliance was comparable among all three groups. No serious side effects were reported. One patient in the lavender-plus-foot-bath group and three patients in the placebo group were lost to follow-up.

At four weeks, a significant improvement in stress and anxiety scores ($P<0.05$ for both) was observed in the lavender group compared to placebo. The lavender-plus-foot-bath group had significantly improved stress scores compared to placebo ($P<0.05$).

At eight weeks, there were significant improvements in anxiety, stress, and depression scores in the lavender group ($P<0.05$ for all), and in the lavender-plus-foot-bath group ($P<0.05$ for all), compared to placebo. There were no significant differences in DASS-21 scores between the lavender group and the lavender-plus-foot-bath group.

Acknowledged limitations of the study include the lack of a placebo-plus-foot-bath treatment arm, the lack of physiological measures of stress (e.g., saliva cortisol levels), and that the results cannot be generalized to pregnant women with psychological disorders. In addition, this study used only one instrument (DASS-21) to measure anxiety, stress, and depression.

The authors conclude that lavender cream with or without foot bathing for eight weeks significantly improved anxiety, stress, and depression in pregnant women. They recommend further studies to assess the effect of lavender on pregnant women with psychological disorders and women with postpartum depression. It is important to note that this study applies to the topical use of lavender essential oil. Future studies should consider the use of a natural carrier oil rather than a petroleum-based carrier. HG

—Heather S. Oliff, PhD

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Valerian Reduces Cognitive Dysfunction after Coronary Bypass Surgery

Reviewed: Hassani S, Alipour A, Darvishi Khezri H, et al. Can *Valeriana officinalis* root extract prevent early postoperative cognitive dysfunction after CABG surgery? A randomized, double-blind, placebo-controlled trial. *Psychopharmacology (Berl)*. March 2015;232(5):843-850.

One of the most commonly performed surgeries in the world is coronary artery bypass graft (CABG). A prevalent complication of the surgery is cognitive dysfunction, which occurs in 20-80% of patients. The authors of this article propose that such cognitive dysfunction is the result of brain damage caused by inflammation and other processes such as embolism (i.e., artery obstruction) and cellular debris picked up and reinfused by the cell salvage processing system. Sleep disruption is another risk factor for post-CABG cognitive dysfunction. Traditionally used as a sedative and anxiolytic, valerian (*Valeriana officinalis*, Caprifoliaceae) root has been shown to inhibit the inflammatory nuclear factor-kappa B (NF-κB) protein complex, stimulate serotonergic and cholinergic receptors, and improve sleep quality. Therefore, the authors hypothesized that valerian may prevent postoperative cognitive dysfunction in patients undergoing CABG surgery. This randomized, double-blind, placebo-controlled study evaluated the prophylactic effect of valerian root on the occurrence of cognitive dysfunction after CABG surgery.

Men and women aged 30-70 years who were undergoing elective CABG with cardiopulmonary bypass surgery participated in this study conducted at the Mazandaran University of Medical Sciences Mazandaran Heart Center in Sari, Iran. Patients were excluded if they required additional concurrent cardiac surgeries such as valve replacement; were undergoing reoperation; had a history of cerebrovascular disease, alcoholism, or known mental illness; used psychotherapeutic drugs in the previous three months, had hepatic failure, severe pulmonary insufficiency, acute renal failure, previous heart surgeries, or heart failure; were deaf, blind, or unable to speak; had sensitivity to valerian; or had a pH < 7.25 or serum base excess of < −6 mmol/L and coagulopathy (i.e., bleeding disorders).

Patients took capsules containing either placebo or 530 mg dried valerian root extract (Goldaru Company; Isfahan, Iran) every 12 hours, starting one day before surgery and continuing for 60 days post-surgery. The concentration and chemical characteristics of the valerian extract were not reported. The placebo capsules were prepared by emptying valerian capsules and refilling them with wheat (*Triticum* spp., Poaceae) flour to create a placebo with the same color, texture, taste, and odor as the valerian capsules. All patients had routine anesthesia and CABG with cardiopulmonary bypass surgery. The Mini-Mental State Examination (MMSE) was used to assess cognitive function before surgery, 10 days post-surgery, and two months post-surgery. Scores ≥ 25 were classified as normal, while scores of 21-24 were categorized as mild cognitive dysfunction. Of the 76 patients randomly assigned to receive valerian or placebo, seven in the valerian group and eight in the placebo group were lost to follow-up. No other measures (e.g., degree of inflammation) were obtained that could have provided evidence for alternate mechanisms of cognitive dysfunction.

Mean preoperative MMSE scores were within the normal range (-27) for both groups. In the valerian group (n=31), the mean MMSE score decreased slightly when assessed 10 days post-surgery (26.52) but remained within the normal range and returned to normal (27.45) after two months. In comparison, the mean MMSE score in the placebo group (n=30) decreased significantly when evaluated 10 days after surgery (24.0) and increased slightly to 24.83 after two months, indicating continuing mild cognitive dysfunction. There was a significant downward trend (P<0.05) in all MMSE scores in the placebo group, except for the attention and calculation domains. After adjusting for other variables, analysis using the generalized estimating equation indicated that valerian prophylaxis reduced the odds of cognitive dysfunction compared to the placebo group (odds ratio=0.108; 95% confidence interval [CI], 0.022-0.545). It should be noted that the MMSE is greatly affected by education level and is not very sensitive to mild cognitive impairment.

In summary, the valerian group had a significantly lower incidence of cognitive dysfunction and a greater improvement in cognitive function during the eight weeks after CABG surgery compared to the placebo group (as measured by the MMSE). The authors suggest that patients undergoing CABG surgery may also benefit from the reported anticoronaryspastic, antihypertensive, and antibronchospastic properties of valerian.

Acknowledged limitations of the study were the use of a single subjective instrument to assess cognitive function (completed only once per day), and the relatively small sample size. The authors conclude that "the use of *V. officinalis* root extract may prevent early postoperative cognitive dysfunction after on-pump CABG surgery.… However, further robust randomized, blinded studies with large sample sizes are required.…" More specific cognitive tests and additional measures (e.g., of inflammation) should have been used as well. HG

—Heather S. Oliff, PhD

Valerian *Valeriana officinalis*
Photo ©2015 Steven Foster

Valerian *Valeriana officinalis*
Photo ©2015 Steven Foster

The Biochemical System Controlling the Effects of Cannabis – An Introduction

By Jahan Marcu, PhD

In every human there are complex biological systems working to keep physiological functions in order. When these biochemical systems are functioning properly, they help maintain optimal mood, appropriate levels of immunity, digestion, sleep, brain function, etc. The housekeeping properties of these systems have an important role in modulating health and disease. One of these systems is the endocannabinoid system (ECS), which is built out of G protein-coupled receptors (called CB_1 and CB_2 receptors) and the endocannabinoids that bind to them. The ECS maintains normal cerebral and physiological function.[1]

Human clinical trials and animal studies show that stimulating this biochemical system can have highly beneficial health effects with limited negative side effects.[2,3] Basic research experiments with genetically modified mice, which are created without CB_1 or CB_2 receptors, have shown that without this biochemical system, the animals (and, presumably, humans) would die at birth.[4-7] Studies in both humans and animals demonstrate that blocking this biochemical system can result in dreadful consequences, including, but not limited to, depression, stress, nausea, vomiting, diarrhea, anxiety, and even increased tendency for suicide.[8-11] The only antagonist drug ever to be marketed to humans that blocked the cannabinoid receptors — Acomplia* (rimonabant; Sanofi-Aventis; Paris, France) — was quickly withdrawn from the market due to its negative health consequences.[12]

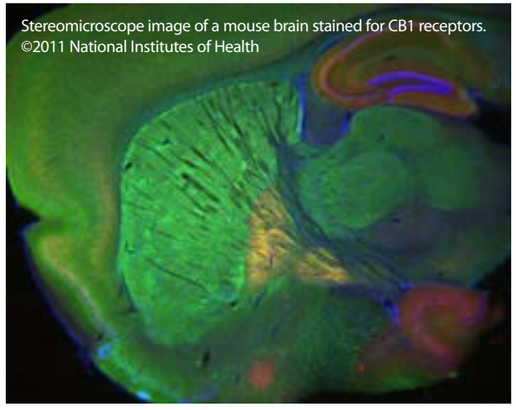
How Medical Cannabis Works

Cannabis (*Cannabis* spp.*, Cannabaceae; common name marijuana, among others) has been used for centuries to treat neurological and neurodegenerative disorders such as epilepsy and spastic disorders. The medieval Arab writer Ibn al-Badri documented the use of hashish or a cannabis concentrate to cure a neurodegenerative disorder (probably epilepsy) afflicting the son of the chamberlain of the Caliphate Council in Baghdad.[2] Centuries later, Western physicians, including W.B. O'Shaughnessy and other British neurologists of the 19th century, confirmed the benefits of cannabis concentrates (hashish, hash oil, and tinctures) in the treatment of spasticity, convulsions, and related neurodegenerative disorders.[13,14] However, it was not until the discovery of the ECS in 1994 that scientists could explain these observations.

The progression of diseases such as multiple sclerosis, Parkinson's disease, amyotrophic lateral sclerosis (ALS; Lou Gehrig's disease), and other neurodegenerative diseases is mediated by neuroinflammation and neurodegeneration (brain cell death).[15] Cannabis can have a positive effect on these and related disorders in a number of ways. Tetrahydrocannabinol (THC) from the cannabis plant stimulates CB_2 receptors, which decreases neuroinflammation by inhibiting the movement, growth, and activity of immune cells. Basically, the stimulation of the ECS by constituents from the cannabis plant results in decreasing the migration and activation of the immune cells that maintain the environment of neurodegenerative disorders, thereby disrupting the signals that sustain inflammation and cell death.[16]

Another important aspect of neurodegenerative disorders is the irreversible death of neurons leading to progressive dysfunction. Excessive glutamate receptor activity is known to cause neuronal cell death by damaging cells and creating reactive oxygen species (ROS). The CB_1 receptors found in the brain have a direct effect on neurons by limiting glutamate release when stimulated at the presynaptic nerve terminals. (Glutamate is a key neurotransmitter, derived from glutamic acid, an amino acid.) Cannabis compounds are also potent antioxidants, reducing oxidative damage and blocking the activities of inflammatory signaling molecules like TNFα (tumor necrosis factor-alpha). Stimulation of the ECS also has pro-survival effects on brain cells.[17,18]

At the present time, the evidence of the ECS as an appropriate target to treat neurodegenerative and other diseases does not come solely from the limited approved studies on marijuana from the US National Institute on Drug Abuse (NIDA). The information comes from a wealth of new information about stimulating this biological system



Stereomicroscope image of a mouse brain stained for CB1 receptors. ©2011 National Institutes of Health

***Editor's note:** There is disagreement in the scientific community regarding* Cannabis *nomenclature and taxonomy. Readers interested in this topic can find more information in Clarke and Merlin's* Cannabis: Evolution and Ethnobotany *(University of California Press, 2013), among other authoritative sources.*

Cannabis *Cannabis sativa*
Photo ©2015 Miran Rijavec

and the mechanisms explaining the central role of this system in health. The ECS is inherent to proper human functioning; in fact, every physiological system that has been studied is positively modulated by it.[19] Recent reports suggest that cannabis, cannabis extracts, and mixtures of the plant's active ingredients are useful for treating epilepsy (e.g., Dravet syndrome), traumatic brain injury, cancers, post-traumatic stress disorder (PTSD), human immunodeficiency virus (HIV), wasting, glaucoma, Crohn's disease, multiple sclerosis, autism, and other diseases and symptoms.[20]

Since the isolation and structure elucidation of THC in the 1960s, several research groups have explored THC and other cannabinoids for therapeutic effects (e.g., anti-epileptic effects and palliative care) in adults and children.[21-23] In the same period, more than 100 other plant cannabinoids have been documented.[24-29] The efficacy of THC can be increased with other phytocannabinoids and plant compounds such as cannabidiol (CBD) and various terpenes, respectively.[30-34] THC and CBD are both psychoactive but have very different therapeutic mechanisms of action; THC directly stimulates CB_1 and CB_2 receptors, while CBD appears to interact with receptors of other important neurotransmitters such as serotonin and adenosine.[33,35] When the distinct mechanisms of THC and CBD are combined, they can trigger an enhancement of activity. For example, experimentally derived combinations of THC and CBD have been documented to synergistically inhibit cancer cell growth in Petri dish experiments of human grade-IV glioma cells by increasing activity in a specific molecular pathway when co-applied.[34] When a 1:1 combination is used clinically, it proves effective at treating multiple sclerosis without causing intoxication.[36-38]

In mammals, the ECS is modulated during disease or injury; for example, CB_2 receptor density is increased during inflammation or bone injury.[39-42] This upregulation or modulation during disease or injury is associated with increases in both levels of endocannabinoids and the expression of the cannabinoid receptors on the cell membrane.[1,43,44] Modulation of the ECS may be an attempt by the body to reduce or abolish unwanted effects or to slow the progression of various disorders. There is evidence supporting a modulation of this biochemical system in a number of disease models.[2] Additionally, a number of genetic mutations and polymorphisms of the ECS (e.g., CB_1 and/or CB_2 receptor mutations) in the human genome are associated with human diseases such as anorexia, bulimia, migraines, chronic pain, gastrointestinal disorders, mental disorders, alcoholism, and other treatment-resistant conditions.[45-50] A mutation or fault in the ECS that may underlie a disease or condition has been coined the "Clinical Endocannabinoid Deficiency Syndrome."[47]

Conclusion

In addition to anecdotal reports and more than 30,000 basic scientific studies with cannabinoids, there are also over 100 published clinical studies that have looked at the effect of a variety of cannabis-based medicines (including inhaled whole-plant material, oral THC capsules, and cannabis extracts) on the treatment of a wide range of disorders.[3,36,51]

The data generated from these clinical trials suggest that cannabis and its various preparations interact with the ECS to result in improvements in spasticity, muscle spasms, pain, sleep quality, tremors, appetite, and the patient's general condition.[3,51] Most of these clinical trials have focused on THC as the primary therapeutic ingredient, or a 1:1 ratio of THC to CBD, but there is a paucity of clinical studies examining pure CBD for a therapeutic outcome.

Animal and human research also demonstrates a potential for synergizing or enhancing certain therapeutic effects when cannabinoids and/or terpenes are applied in an appropriate combination. The therapeutic rationale for combining THC and CBD, and other cannabis plant components in fixed ratios, can result in a decrease in unwanted side effects and an enhancement of therapeutic benefits.[33,37] HG

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Cannabis *Cannabis sativa*
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GUEST EDITORIAL

Assessing Potential Herb-Drug Interactions in the Use of Herbal Dietary Supplements: Need for a Common Framework Approach

By Amy Roe, PhD

Health professionals and others have expressed varying degrees of interest and concern regarding the potential for clinically relevant interactions between conventional pharmaceutical medications and dietary supplements, including herbal products.[1,2] Considerations such as history of safe use (within the context of traditional versus modern usage), literature data from pharmacology and toxicity studies, and constituent quantities in supplements provide some guidance on whether to assess herb-drug interactions (HDIs) experimentally. The scientific literature is replete with pre-clinical reports of various herbal extracts and constituents as potent inhibitors of drug-metabolizing enzymes (Table 1).[3-6] However, without the use of appropriate analytical methods for herbal product characterization and quantitation of constituents, dose performance analysis, or in vitro testing in physiologically relevant models to allow some prediction of bioavailability of key constituents, extrapolating these reports to determine whether human testing is necessary to identify clinically relevant HDIs is difficult. This lack of a clear determination of risk hinders clinicians and consumers from making informed decisions about the safety of taking herbal products with conventional medications. A suitable framework is needed that describes a flexible approach for assessing when human HDI studies are warranted, as well as an outline of standard methods when HDI testing is conducted.

Herbal product usage in Western countries continues to increase across all age groups.[7,8] Individuals in these countries also have ready access to conventional medications, and significant polypharmacy is often observed, particularly in women and older adults.[8,9] Many patients are reticent to disclose herbal product usage to their healthcare providers, and many providers still do not inquire about such usage. In addition, many healthcare professionals are now recommending herbal products to counteract side effects of some conventional drugs.[10] Thus, the potential for both HDIs and drug-drug interactions is frequently ignored in clinical practice because of the complexity of the problem. The net result is that the opportunity for clinically significant HDIs exists and should be evaluated in a systematic manner.

Although dietary supplements and herbal products in most countries are not subject to the same regulatory guidelines for pre-market testing as conventional drugs, there is an increasing focus by many regulatory agencies on the potential for HDIs. Likewise, consumers have an increased awareness of HDIs as a result of numerous media reports. Providing accurate information on potential HDIs facilitates informed decision-making by consumers and healthcare providers alike.

There are an increasing number of scientific papers related to the field of HDIs. However, most studies utilize simple in vitro metabolic systems (e.g., liver microsomes), and the results often are too unreliable to provide meaningful assessment of clinically relevant HDI potential. The in vitro exposure to the complete phytochemical complexity of an herb or herbal extract does not represent the systemic exposure to the ingested and altered phytochemical matrix or its limited absorption and variable distribution. Thus, most of these reports are preliminary and often do not attempt to define the clinical relevance of such findings. There is little follow-up work conducted in more complex in vitro systems such as whole-cell hepatocytes with fully functional transporter and metabolizing enzymes, or the use of physiologic-based pharmacokinetic (PBPK) models to extrapolate to in vivo relevance. Won et al. recently reviewed a number of dietary substance-drug interactions in which both in vitro and clinical data exist, and in many cases there was no correlation of findings.[11] In addition, there is sometimes poor analytical characterization of the botanical materials used, contributing in large part to inconsistent findings across studies.

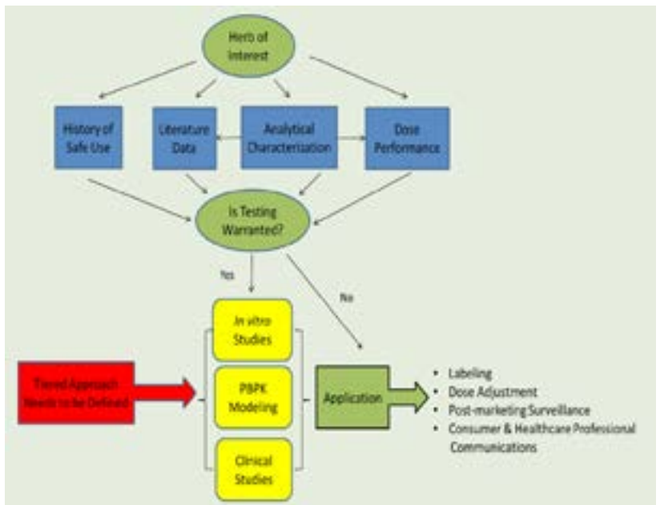

Figure 1. A summary of the key components that should be included in a common framework for assessing potential herb-drug interactions

In the prescription medicine world, there is clear guidance on how to assess potential drug-drug interactions.[12,13] Because there is no standard/systematic regulatory guidance on testing for HDI potential, there is an opportunity in the scientific community to lead the way in establishing such a framework.

From a dietary supplement industry perspective, an ideal framework approach for assessing HDI potential would include the following criteria (summarized in Figure 1):

- A screening approach that can encompass a pipeline (i.e., "higher throughput");
- Cost and resource efficiency;
- Readily transferable to external partners (e.g., contract research organizations) since many companies do not have the internal expertise and/or testing facilities;
- Consistent application across the industry;
- Inclusion of a decision tree to determine when more in-depth studies may be warranted (e.g., a tiered approach);
- Guidance on how to design and interpret studies; and
- Guidance on how to apply HDI information to dose adjustment, labeling, and/or post-marketing surveillance strategy.

Furthermore, there are a number of important considerations that should be included within each component (Table 2). Follow-up studies may be warranted in situations where there is an inconsistent history of safe use or insufficient literature data on HDI potential, e.g., if there is no data available on cytochrome P450 (CYP450)/transporter inhibition/induction potential, or literature data reporting potent in vitro inhibition of CYP450/transporters. When testing is necessary, one can refer to the drug-drug interaction guidances of the US Food and Drug Administration and European Medicines Agency.[12,13]

In summary, there is a need to form an academia/industry/regulatory-wide expert working group to develop a framework for assessing HDI potential. Expertise is needed in diverse areas including in vitro metabolism/transporter studies, PBPK modeling, clinical pharmacokinetics, analytical chemistry, biopharmaceutics, and risk assessment. The goal would be to develop a comprehensive strategy that incorporates these key components into an overall HDI risk assessment that facilitates informed decision-making by consumers and healthcare providers.

The topic of assessing HDI potential was highlighted at the 41st Annual Summer Meeting of the Toxicology Forum in July 2015. A plenary presentation, titled "Assessing Potential Natural Product-Drug Interactions: Need for a Common Framework Approach," was given by a number of experts in this field that further described the concepts captured herein. Details related to this meeting can be found at: http://toxforum.org/next_meeting. HG

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Table 1. Examples of potent in vitro CYP450 and/or transporter inhibition by herbal extracts or constituents as reported in the scientific literature with no current follow-up as to clinical relevance

Herb and Plant Part / Individual Constituent(s)	CYP450/Transporter Inhibited	Reference
Frankincense tree resin (*Boswellia serrata*, Burseraceae) extract	CYP1A2, 2C8, 2C9, 2C19, 2D6, 3A4	3
β-Boswellic acid, 11-keto-β-Boswellic acid	CYP2C8, 2C9, 3A4	3
Acetyl-11-keto-β-Boswellic acid	CYP2C9, 3A4	3
Acetyl-β-Boswellic acid	CYP2C9	3
Schisandra (five-flavor-fruit; *Schisandra chinensis*, Schisandraceae) fruit extract	CYP3A4	4
Gomisin C, Gomisin B, Gomisin G	CYP3A4	4
Gomisin N, Gomisin A	CYP2C19, 3A4	4
Rhodiola (golden root; *Rhodiola rosea*, Crassulaceae) root extract	CYP3A4, P-glycoprotein (P-gp)	5
Cat's claw (*Uncaria tomentosa*, Rubiaceae) herb extract	CYP3A4	6

Table 2. Important considerations that warrant inclusion in a framework for assessing potential herb-drug interactions.

History of Safe Use:

- How do geography and culture of historical use compare to the proposed product market?
- Is the historical use the same as the proposed product use?
- Is the same form (whole plant vs. plant part vs. single ingredient) used?
- What is known about the targeted audience (acute vs. chronic use, underlying disease/conditions, co-medications, age group)?

Literature Data:

- Pharmacokinetic studies on constituents provide understanding of which constituents are readily absorbed and what relevant concentrations to use in in vitro assays
- Which drug-metabolizing enzymes/transporters are affected may guide the need to do additional studies (e.g., potent inhibition of CYP3A4 would likely be more concerning than moderate inhibition of CYP1A2)
- Are there clues in the clinical chemistry and/or histopathology from animal toxicity studies that may indicate potential effects on drug-metabolizing enzymes or transporters (e.g., increases in bilirubin, cholestasis, increased liver weight, etc.)?

Incorporation of Analytical Characterization:

- Useful for assessing toxicity potential, but can also be applied to assessing HDI potential
- Enables further data mining of literature for HDI information
- Are there any structure-activity relationship (SAR) alerts for individual constituents of the herbal extract/constituent?
- Quantitation of individual constituents can be useful in predicting potential exposure levels, designing in vitro studies, and determining whether additional testing is necessary (cost effective).

Dose Performance:

- Disintegration of dose form
- Dissolution of constituents
- Physical-chemical data on constituents
- Solubility information on extract/constituents

Disclosure

The Procter & Gamble Company is a distributor of dietary supplement products.

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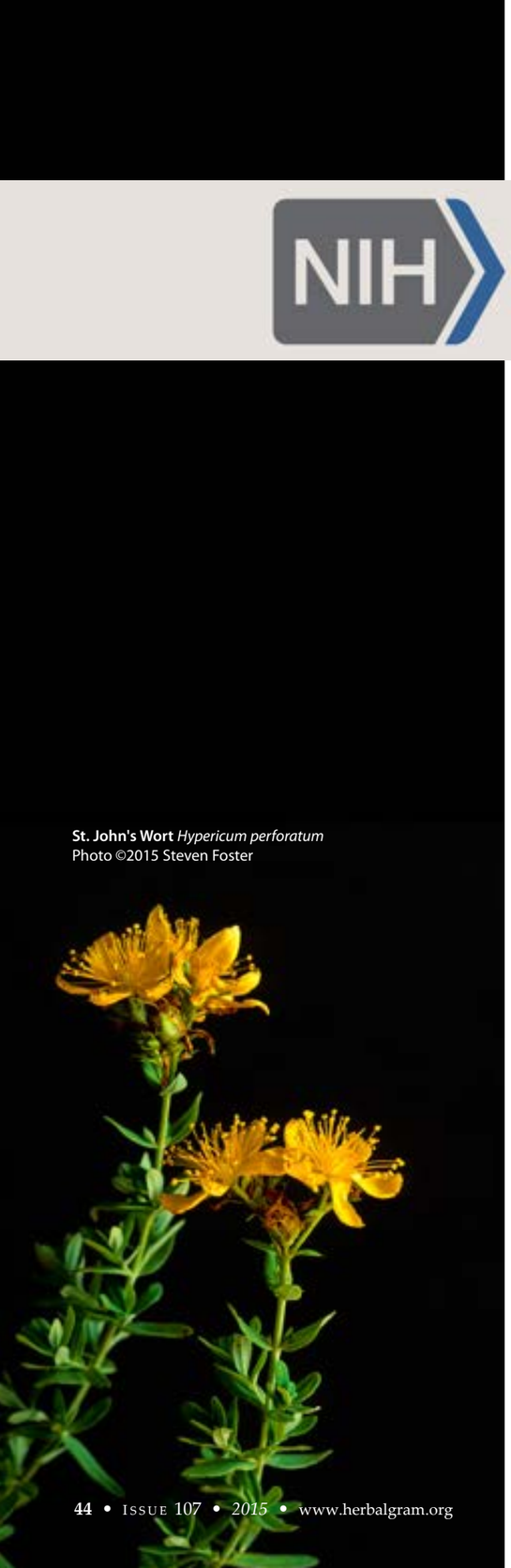
Frankinscense Tree *Boswellia serrata*
Photo ©2015 Michael Wolf

Rhodiola *Rhodiola rosea*
Photo ©2015 Michael Wolf

Past and Future Research at National Center for Complementary and Integrative Health

With Respect to Botanicals

By Craig Hopp, PhD



St. John's Wort *Hypericum perforatum*
Photo ©2015 Steven Foster

History of NCCIH Botanical Research Funding

The National Center for Complementary and Alternative Medicine (NCCAM) was established in 1998 by Public Law 105-277 for the purpose of supporting research, training, and the dissemination of information on a diverse collection of health practices considered to be outside of mainstream medicine. Importantly, in that legislation, the Center's director was also given the charge to study the integration of these modalities with the practice of conventional medicine. During the last 20 years, national surveys have consistently shown that most Americans use dietary supplements or other complementary health approaches in conjunction with (i.e., integrative) rather than in lieu of (i.e., alternative) conventional care.[1] In December 2014, NCCAM's name was changed to the National Center for Complementary and Integrative Health (NCCIH*) by Public Law 113-235. Notably, although the name changed, the mission has remained the same, and the new name now more accurately reflects the research NCCIH supports.

While NCCIH's overall mission has remained unchanged for the past 17 years, its research priorities have evolved. When the Center was first established, its natural products research portfolio was organized into two main areas. The first was a set of large, NCCIH-initiated phase III clinical trials testing the efficacy of a number of botanical products for a variety of different conditions (Table 1). These trials included studies of St. John's wort extract for depression, echinacea extract and herb for upper respiratory tract and rhinovirus infections, ginkgo extract for memory and dementia, saw palmetto extract for benign prostatic hyperplasia, and milk thistle extract for hepatitis C. (See Table 2 for more information about the botanicals mentioned in this article.) The second area of the natural products research funding supported a wide variety of research initiated by academic investigators. This research, spanning in vitro, in vivo, and clinical projects, involved a diverse collection of natural products for an equally disparate set of conditions. The reason for supporting such an assortment of projects stemmed from a realization that research in this field was still in its infancy and there were so many products with such limited evidence that the Center did not have sufficient data upon which to base decisions regarding a particular research focus.

*For simplicity, the Center is referred to as NCCIH throughout the remainder of this article, even though some of the events described took place before the name change.

Over time, the natural product clinical studies were completed and the findings published. For the most part, the results failed to support the hypothesized benefits of the botanical products. However, once the studies were published, their designs were criticized by some for failing to use what critics considered the optimal product formulation and/or dose. Furthermore, for most of the products, the mechanisms of action by which they exerted their hypothesized activity was unclear, making it difficult to make definitive statements about the biological activity of the products even at the conclusion of the studies. Consequently, the Center chose not to initiate additional large clinical studies for natural products unless the mechanistic underpinnings of their hypothesized activity were clearly established.

Without the large investment in NCCIH-targeted clinical studies, the academic investigator-initiated portion of the Center's research portfolio began to account for an increasing percentage of its budget. Because of the diffuseness of that portfolio, it became difficult to articulate clear priority areas or adequately describe a research niche NCCIH supports that did not overlap with other parts of the National Institutes of Health (NIH).

Establishing Research Priorities

Recently, the Center has undertaken a critical evaluation of its natural products research funding to better understand past and current investments. This included an analysis of the NIH-wide investment in botanical research to determine where resources could have the most impact. The Center also organized a series of workshops, convened an expert panel, and had numerous informal conversations over the past two years to solicit advice and input from experts in the field. NCCIH reached the conclusion that its investments in natural products have supported a large number of groups conducting high-quality research. Because of limited resources, the Center also recognized the need to concentrate efforts into more focused areas that are aligned with NCCIH research interests in order for investments to produce a meaningful impact on this field of science.

Importantly, this led to the decision that NCCIH would consider research focused on disease treatment a low priority. The reasons for this were twofold. First, many other branches of NIH focus specifically on individual diseases (e.g., National Cancer Institute, National Institute of Neurological Disorders and Stroke [NINDS], National Institute of Diabetes and Digestive and Kidney Diseases [NIDDK], etc.). Second, surveys consistently show that for those people who take dietary supplements, their primary reason for doing so is not for disease management but for general health promotion.[2-4]

What has emerged from this intensive effort is a reshaped natural products research agenda that focuses NCCIH funding into a handful of scientific areas that are closely aligned with its research priorities; these areas are not well represented at other parts of NIH, and they offer the potential to yield impactful research that will advance the field. The first major research focus is on improved methodology across all aspects of natural products research. The second major focus is on exploration of the ways in which natural products, either as complex mixtures or as isolated ingredients, interact with biological systems.

Red Clover *Trifolium pratense*
Photo ©2015 Steven Foster

NCCIH has initiated a new program that focuses on providing clear guidance to the research community on best practices for conducting research on natural product/drug interactions.

Methodology

There is a sense among some in the research community that the techniques and methodologies employed to conduct natural products research have remained largely unchanged for the last 20-30 years. Compared to the rapid advances in the biological sciences as a whole, progress in natural products research has not kept pace. As a result, natural products researchers continually struggle with the same bottlenecks. Therefore, to make major advances, improved methods are needed across the board, including those related to chemical characterization, biological characterization, and biological manipulation.

There is continued reliance on traditional chromatographic methods to fractionate and purify the milligram quantities of natural products needed for NMR (nuclear magnetic resonance)- and MS (mass spectrometry)-based dereplication and structure elucidation. This generally requires relatively large amounts of material and time. Improvements in chemical characterization will allow for improved quality control procedures in the dietary supplement industry while also providing a means to more rapidly determine if a particular extract contains interesting compounds worth pursuing. Efforts are currently underway using bioinformatics to compare the chemical profiles, based on NMR or MS spectra, of large numbers of extracts to ascertain similarities and differences among them. Depending on the context, an "outlier" may represent a batch of product that does not meet established specifications, or it may represent a promising lead for new natural product discovery.

Improvements in biological characterization will allow for a more comprehensive approach to identifying bioactive compounds and describing their overall biological activities. The existing paradigm is to assay isolated natural products in highly specific mechanism-based assays. However, it is well known that complex mixtures may contain multiple active compounds and that individual natural products often have pleiotropic effects mediated by activity at numerous targets. For example, curcumin, a component of turmeric, has been reported to modulate dozens of different genes and proteins. Conversely, a combination of berberine and specific flavonoids in goldenseal has been shown to act synergistically through different mechanisms to produce the antibacterial activity present in this plant. By moving toward more phenotypic assays (e.g., whole-cell or animal rather than single-enzyme), it will be possible to identify bioactive compounds without stipulating a priori the mechanism of action. Furthermore, this will make it possible to capture activity when more than one compound is responsible for the phenotypic response or when multiple mechanisms of action are involved.

Improvements in biological manipulation have the potential to drastically expand the pool of accessible natural products in two ways. First, they will allow access to the vast number of unculturable microorganisms that represent perhaps more than 95% of the microorganisms on

Table 1. Select NCCIH-Supported Herb/Botanical Clinical Trials

Focus of Clinical Study	Pub. Year	NIH Grant Support	Institution	Author Conclusions†
St. John's wort for major depression of moderate severity[13]	2002	NIMH, NCCIH‡	Duke University	This study fails to support the efficacy of *H. perforatum* extract in moderately severe major depression. The result may be due to low assay sensitivity of the trial, but the complete absence of trends suggestive of efficacy for *H. perforatum* is noteworthy.
Evaluation of the effects of unrefined echinacea on cold symptoms[14]	2002	NCCIH	University of Wisconsin-Madison	Compared with placebo, unrefined echinacea capsules provided no detectable benefit or harm in these college students who had the common cold.
Echinacea in treating upper respiratory tract infections (URTIs) in children[15]	2003	NCCIH	University of Washington	Dried, pressed *E. purpurea* juice (of the aboveground parts), as dosed in this study, was not effective in treating URTI symptoms in patients 2-11 years old, and its use was associated with an increased risk of rash.
Evaluation of echinacea in experimental rhinovirus infections[16]	2005	NCCIH	University of Virginia School of Medicine, Charlottesville	The results of this study indicate that extracts *of E. angustifolia* root, either alone or in combination, do not have clinically significant effects on infection with a rhinovirus or on the clinical illness that results from it.
Herbal alternatives (HALT) for menopause study: black cohosh for vasomotor symptoms[17]	2006	NIA, NCCIH	Center for Health Studies; Group Health Cooperative, Seattle	Black cohosh extract used in isolation, or as part of a multi-botanical regimen, shows little potential as an important therapy for relief of vasomotor symptoms.
Saw palmetto trial for enlarged prostates (STEP): Saw palmetto extract in benign prostatic hyperplasia (BPH)[18]	2006	NIDDK, NCCIH	Northern California Institute for Research and Education; UCSF	In this study, saw palmetto extract did not improve symptoms or objective measures of BPH.
Comparing effects of three sources of garlic on serum lipids[19]	2007	NCCIH, NCRR (now NCATS)	Stanford University	None of the forms of garlic used in this study, including raw garlic had statistically or clinically significant effects on LDL cholesterol or other plasma lipid concentrations in adults with moderate hypercholesterolemia.
Ginkgo evaluation of memory (GEM) study for the prevention of dementia[20]	2008	NCCIH, ODS, NIA, NHLBI, NINDS	University of Pittsburgh	In this study, *G. biloba* extract at 120 mg twice per day was not effective in reducing either the overall incidence rate of dementia or Alzheimer's disease incidence in elderly individuals with normal cognition or those with mild cognitive impairment.
GEM study analysis of ginkgo for prevention of cognitive decline[21]	2009	NCCIH, ODS, NIA, NHLBI, NINDS	University of Pittsburgh	Compared with placebo, the use of *G. biloba* extract, 120 mg twice daily, did not result in less cognitive decline in older adults with normal cognition or with MCI.
GEM study analysis of ginkgo for reduction of risk of cardiovascular events[22]	2010	NCCIH, ODS, NIA, NHLBI, NINDS	University of Pittsburgh	There was no evidence that *G. biloba* extract reduced total or cardiovascular disease (CVD) mortality or CVD events. *G. biloba* cannot be recommended for preventing CVD. Further clinical trials of peripheral vascular disease outcomes might be indicated.
GEM study analysis of ginkgo for reduction of high blood pressure (BP)[23]	2010	NCCIH, ODS, NIA, NHLBI, NINDS	University of Pittsburgh	Our data indicate that *G. biloba* extract does not reduce BP or the incidence of hypertension in elderly men and women.
GEM study analysis of ginkgo for reduction of cancer risk[24]	2010	NCCIH, ODS, NIA, NHLBI, NINDS	University of Pittsburgh	Overall, these results do not support the hypothesis that regular use of *G. biloba* extract reduces the risk of cancer.
Black cohosh and red clover for management of vasomotor symptoms[25]	2009	ODS, NCCIH, NIGMS, ORWH	University of Illinois, Chicago	Compared with placebo, black cohosh and red clover extracts did not reduce the number of vasomotor symptoms. Safety monitoring indicated that chemically and biologically standardized extracts of black cohosh and red clover were safe during daily administration for 12 months.
Complementary and alternative medicine for urological symptoms (CAMUS): effect of saw palmetto on BPH-associated urinary symptoms[26]	2011	NIDDK, NCCIH, ODS	Massachusetts General Hospital	Increasing doses of a saw palmetto fruit extract did not reduce lower urinary tract symptoms more than placebo.
Study of cranberry juice for the prevention of recurrent urinary tract infection[27]	2011	NCCIH	University of Michigan	Daily cranberry prophylaxis to prevent recurrent urinary tract infections may be beneficial in some populations of women.
Pharmacotherapy for minor depression: study of St. John's wort or citalopram[28]	2011	NIMH, NCCIH	Cedars-Sinai Medical Center; University of Pittsburgh; Massachusetts General Hospital	This study suggests that neither St. John's wort extract nor citalopram treatment has a clinically or statistically significant benefit for acute treatment of minor depressive disorder when compared to placebo treatment. These findings were clearly due to a consistently high placebo response rate on all outcome measures.
Silymarin in nonalcoholic steatohepatitis (NASH) and C hepatitis (SyNCH): study of silymarin for hepatitis C virus (HCV)[29]	2012	NCCIH, NIDDK	University of North Carolina, Chapel Hill	Higher than customary doses of silymarin did not significantly reduce serum ALT levels more than placebo in participants with chronic HCV infection unsuccessfully treated with interferon-based therapy.

NIMH (National Institute of Mental Health); NIA (National Institute on Aging); NCRR (National Center for Research Resources, now National Center for Advancing Translational Sciences [NCATS]); ODS (Office of Dietary Supplements); NHLBI (National Heart, Lung, and Blood Institute); NIGMS (National Institute of General Medical Sciences); ORWH (Office of Research on Women's Health); UCSF (University of California – San Francisco)

† The author conclusions are derived from each article's PubMed abstract; the wording was edited per *HerbalGram* style. If the herbal material was an extract, as is the case with most of the trials, such wording has been added to the author's original summary.

‡ The term NCCIH is used throughout this table, but the Center's name was NCCAM when most of this research was funded.

Table 2. Latin Binomials, Plant Families, and Plant Part Used of Herbs Mentioned

Common Name	Latin Binomial	Plant Family	Plant Part Used in NCCIH Research*
Black Cohosh	*Actaea racemosa*	Ranunculaceae	Root/rhizome
Cranberry	*Vaccinium macrocarpon*	Ericaceae	Fruit
Echinacea	*Echinacea* spp.	Asteraceae	Root
Garlic	*Allium sativum*	Amaryllidaceae	Bulb
Ginkgo	*Ginkgo biloba*	Ginkgoaceae	Leaf
Goldenseal	*Hydrastis canadensis*	Ranunculaceae	Root
Milk Thistle	*Silybum marianum*	Asteraceae	Fruit (seed)
Red Clover	*Trifolium pratense*	Fabaceae	Herb
Saw Palmetto	*Serenoa repens*	Arecaceae	Fruit
St. John's Wort	*Hypericum perforatum*	Hypericaceae	Herb
Turmeric	*Curcuma longa*	Zingiberaceae	Root/rhizome

*In most cases, extracts of the plant parts were used in clinical trials. In some cases, the extracts are leading commercially available extract preparations on which previous clinical research has been conducted.

Cranberry *Vaccinium macrocarpon*
Photo ©2015 Steven Foster

Saw Palmetto *Serenoa repens*
Photo ©2015 Steven Foster

Garlic *Allium sativum*
Photo ©2015 Steven Foster

earth, thus increasing the likelihood of discovering novel compounds.[5,6] The second way is by uncoupling the relationship between natural products and their sources. Researchers are just beginning to develop techniques that allow the biosynthetic machinery of natural product production to be transferred from the original producing organism into a more sustainable host. This approach has the potential to protect valuable natural resources while also providing researchers with a reliable source of natural product compounds.

Interactions

Natural products have the ability to interact with biological systems in a wide variety of ways. Recent advances in the various "omics" technologies now make it possible to capture these interactions in ways that were not imaginable a few years ago. NCCIH has an interest in exploring these interactions in a few selected contexts, including drug interactions, network pharmacology, the microbiome, and genetics/epigenetics.

The American public is prescribed an ever-increasing number of pharmaceutical medications.[7] About one-third of adults who are taking prescription drugs report also taking one or more dietary supplements.[8] This suggests there is a widespread risk of natural product/drug interactions. Current literature and publicly available resources provide varying accounts of just how prevalent and significant such interactions may be.[9,10] Many warnings are based on animal studies, case reports, or purely theoretical arguments, which has led to confusion among consumers and healthcare providers. NCCIH has initiated a new program that focuses on providing clear guidance to the research community on best practices for conducting research on natural product/drug interactions. The expectation is that this will ultimately lead to improvements in reporting of such interactions and allow for better healthcare management.

Some natural products have been shown to have a high degree of selectivity and specificity for individual biological targets. More commonly, however, the same natural products are found to modulate multiple targets. When this is extended to a complex mixture as found in medicinal plants, the number of possible interactions is staggering. The term *network pharmacology* has been coined to describe the sum of these biological interactions. NCCIH is interested in studying the ability of natural products, either individually or collectively, to modulate biological systems through these networks. To do so will require the application of powerful bioinformatics tools to the study of natural products.

Over the last several years, there has been an explosion of interest in the human microbiome. Researchers are only beginning to fully understand the myriad of ways in which the microbiome influences human health. The trillions of microbial cells in the human body are known to metabolize phytochemicals in ways that the human metabolic machinery cannot. NCCIH has a keen interest in better understanding how natural products interact with the human microbiome, including what metabolites are produced, how they are distributed throughout the body, and what activity, if any, they possess. This will involve careful study regarding the intricacies of human/microbiome co-metabolism of natural products to fully understand the biological implications of this interaction.

Recent NCCIH-funded research has shown that individuals with a genotype common in people of African descent metabolize fatty acids differently than individuals with a genotype common in people of European descent; this difference may make the "Western diet" even more unhealthy for those with the genotype of African origin.[11] The implications are potentially enormous for the field of personalized nutrition. Similarly, natural products can influence a person's genome through tailoring modifications known as epigenetics.[12] These changes can have lasting impacts long after consumption of the natural product. As a result, natural products can not only produce short-term pharmacologic responses, but also change individuals' genotypes and influence their future health and that of their children. NCCIH seeks to better understand how individuals' genetic backgrounds can influence their biological response to certain natural products and how natural products might modulate health through epigenetic modifications.

Product Integrity Policy

NCCIH's natural product integrity policy is foundational to all aspects of its natural products research portfolio. This policy was established to ensure that the natural product materials studied through NCCIH funding are rigorously evaluated in terms of their identity and composition. This is critically important to allow for proper interpretation of research results and to maximize the reproducibility of research. The requirements of the NCCIH policy operate on a graduated scale depending on the complexity of the product and its intended use. For herbal extracts, NCCIH asks for information not required for pure compounds. Similarly, additional information is required for human research that is not necessary for cell culture or animal studies.

NCCIH has made efforts to align its policy with relevant US Food and Drug Administration (FDA) guidance. For example, the policy requires documentation that the product was manufactured in accordance with current Good Manufacturing Practices (cGMP) if it was obtained from a commercial source. Also, there is a requirement for independent confirmation of any specifications declared on a certificate of analysis. This is especially important for confirming the identity of plant material, relative concentrations of important marker compounds, and purity of isolated ingredients. Similarly, any investigator proposing clinical research must consult with the FDA to determine if an Investigational New Drug (IND) application is needed for the study. It is important to recognize that this is a regulatory decision that NCCIH cannot adjudicate. This is a source of much confusion on the part of some investigators based on the incorrect assumption that any clinical trial involving a product with GRAS (Generally Recognized As Safe) status does not require an IND. The IND status of a product is predicated

The NCCIH has made efforts to align its policy with relevant US Food and Drug Administration (FDA) guidance. For example, the policy requires documentation that the product was manufactured in accordance with current Good Manufacturing Practices (cGMP) if it was obtained from a commercial source.

Milk Thistle *Silybum marianum*
Photo ©2015 Steven Foster

Turmeric *Curcuma longa*
Photo ©2015 Steven Foster

Goldenseal *Hydrastis canadensis*
Photo ©2015 Steven Foster

Black Cohosh *Actaea racemosa*
Photo ©2015 Steven Foster

on the design of the study and not the nature of the product. For example, if a GRAS product is being investigated for its ability to stabilize blood sugar in diabetics, then, from FDA's perspective, it is being studied as a drug rather than a dietary supplement and therefore likely will require an IND designation.

Summary

The priority areas outlined herein were chosen because they are well-aligned with the overall mission of NCCIH, fit research gaps not currently addressed by other parts of NIH, and are well-integrated with each other. For example, it is not difficult to imagine how advances in natural products methodology could help better unravel complex interactions or how a better understanding of the ways in which natural products interact with the microbiome could potentially lead to a more complete understanding of the network pharmacology of natural products. The objectives of reshaping the NCCIH natural products portfolio are to concentrate the limited resources of the Center into areas that build on prior investments, align with overall priorities, and have the potential to yield impactful results that will move the field forward. Through NCCIH's continued emphasis on product integrity, the results of NCCIH-funded research can be expected to reflect the high standards held by the Center and meet expectations regarding reproducibility of the scientific conclusions reached. HG

Craig Hopp, PhD, *obtained his doctorate in pharmacognosy from Purdue University in 1997. He joined the National Center for Complementary and Integrative Health (NCCIH) in January 2009 as a program director. At NCCIH, one of his primary responsibilities is the administration of the product integrity policy, which involves evaluating proposed study materials to ensure they are safe and properly characterized. Additionally, he is the coordinator for the Botanical Research Centers Program and oversees other natural products projects supported by NCCIH. Dr. Hopp uses his expertise and experience in the field of natural products to help shape priorities at NCCIH.*

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Herbal Dietary Supplement Sales in US Increase 6.8% in 2014

Retail sales total more than $6.4 billion in 11th consecutive year of growth

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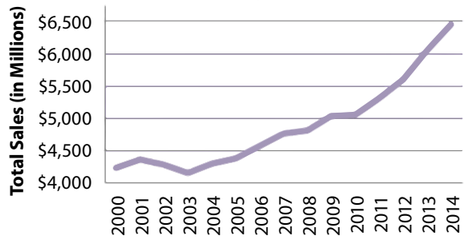
Introduction

Total retail sales of herbal dietary supplements in the United States increased by an estimated 6.8% in 2014 marking the 11th consecutive year of growth. This increase is slightly less than 2013's 7.9% increase, which was the greatest percentage sales jump since the late 1990s.[1] Sales of herbal supplements have been increasing steadily since 2002-2003 when the market experienced a brief, two-year dip in total sales (Figure 1 and Table 1). Last year, American consumers spent roughly $6.4 billion on herbal supplements — over $1 billion more than was spent in 2011 and $400 million more than 2013 — according to aggregated market statistics provided by the *Nutrition Business Journal* (NBJ).

The data in this report correspond to retail sales of herbal supplements in three distinct market channels — mainstream, natural, and direct sales (Table 2) — as defined by NBJ and the Chicago area-based market research firms SPINS LLC and IRI (Information Resources, Inc.). Herbal supplement sales estimates do not include herbal teas, plant-based natural cosmetic products ("cosmeceuticals"), or over-the-counter (OTC) medications with US Food and Drug Administration (FDA)-approved botanical ingredients such as psyllium (*Plantago ovata*, Plantaginaceae) or slippery elm bark (*Ulmus rubra*, Ulmaceae).

In 2014, for the sixth year in a row, sales increased in each of these three channels (Table 3). Herbal supplement sales from natural and health food stores experienced the strongest estimated growth of 7.7%, while mainstream and direct sales increased by 5.0% and 6.7%, respectively, from the previous year.

Figure 1. Total Estimated Herb Retail Sales in All Channels, 2000-2014



Fenugreek *Trigonella foenum-graecum*
Photo ©2015 Steven Foster

Table 1. Total Estimated Herb Retail Sales in All Market Channels in US

Year	Total Sales (in Millions)	% Change (from Previous Year)
2000	$4,225	2.8%
2001	$4,361	3.2%
2002	$4,275	-2.0%
2003	$4,146	-3.0%
2004	$4,288	3.4%
2005	$4,378	2.1%
2006	$4,558	4.1%
2007	$4,756	4.3%
2008	$4,800	0.9%
2009	$5,037	5.0%
2010	$5,049	0.2%
2011	$5,302	5.0%
2012	$5,593	5.5%
2013	$6,033	7.9%
2014	$6,441	6.8%

Source: Nutrition Business Journal (NBJ). NBJ primary research includes NBJ surveys of supplement manufacturers, distributors, MLM firms, mail order, internet, and raw material and ingredient supply companies, as well as numerous interviews with major retailers (Walmart, Costco, etc.), manufacturers, suppliers, and industry experts. Secondary sources include Information Resources Inc., SPINSscan Natural, ACNielsen, *Natural Foods Merchandiser*, Insight, The Hartman Group, company data, and other published material.

Table 2. Definitions of Retail Market Segments

	Per SPINS/IRI	Per *Nutrition Business Journal*
Mainstream Multi-Outlet/ Food, Drug, and Mass-Market (FDM) ("Mainstream Channel")	Includes supermarkets, drugstores, mass-market retailers, military commissaries, select buyer's clubs, and so-called dollar stores. The mainstream channel, as defined by SPINS/IRI, does *not* include convenience store sales.	Includes food and grocery stores, mass-merchandise and club (e.g., Sam's Club and Costco) retailers, and drug and convenience stores.
Natural and Health Food ("Natural Channel")	Includes co-ops, independent and chain natural product retail stores. Does *not* include sales from natural foods retail giant Whole Foods Market (which does not report its herbal supplement sales to SPINS or other market tracking firms).	Includes specialty retail outlets (with Whole Foods Market estimates), GNC, sports nutrition stores, etc.
Direct Sales Channel		Includes sales from Internet, mail order, catalog, direct mail, and direct-response TV and radio outlets; healthcare practitioners; and multilevel or network marketing firms (e.g., Advocare, Herbalife, Nature's Sunshine, NuSkin (Pharmanex), Nutrilite (Amway), Shaklee, USANA, etc.).

Mainstream Retail Channel

Sales of herbal dietary supplements in the mainstream channel alone totaled $815,970,645 in 2014, as determined by SPINS and IRI. This figure represents a 2.1% increase over 2013 sales in this channel, which totaled just under $800 million (Table 4). NBJ — which includes convenience store data in its mass-market channel — estimated slightly higher sales of $1.12 billion.

Since 2013, SPINS and IRI have collaborated to produce a combined data set for mainstream retail sales; previously, *HerbalGram* included separate tables that reflected the firms' different methods for coding herbal products. (The SPINS-IRI collaboration resulted in a restatement of previously published 2013 and 2014 sales. Though the data are identical in most cases, small discrepancies remain, as some of the sales figures are sometimes modified subsequent to their initial publication. Year-over-year trends should be referenced within the same published report.)

Horehound was the top-selling herbal dietary supplement in mainstream outlets for the second year in a row with sales of $105,880,497 — almost twice that of the second top-selling herb, cranberry. Traditionally, horehound has been used as an expectorant and to treat respiratory symptoms, often in the form of a bitter tea[2]; today, the herb is commonly found in multi-herbal combination lozenges (e.g., Ricola® Natural Herb Cough Drops).

Many popular and well-known botanicals kept their place on 2014's list of top-selling herbal supplements in mainstream retail outlets. Ginkgo, garlic, valerian, and milk thistle ranked among the 20 top-selling herbs; total sales for these supplements were also some of the least changed from 2013 suggesting their continued mainstream acceptance.

Several herbs experienced significant sales increases in 2014. For the first time, ivy leaf made *HerbalGram*'s top-40 list in the mainstream market channel with estimated total sales of $8,086,029 — a whopping 379% increase from 2013. The German Commission E approved ivy leaf for the treatment of respiratory inflammation, and the herb has been a popular component of cough-relieving formulas in Europe for years.[3] (According to Pizzorno and Murray's *Textbook of Natural Medicine*,[4] "more than 80% of herbal expectorants prescribed in Germany [in 2007] comprised ivy extract….") Although the authors of a 2010 systematic

Table 3. Total Herbal Supplement Sales (in Millions) by Channel in US

	2012	2013	2014	% Increase (from 2013)
Mass Market	$987	$1,063	$1,116	5.0%
Natural & Health Food	$1,864	$2,029	$2,186	7.7%
Direct Sales	$2,742	$2,941	$3,139	6.7%
Total	**$5,593**	**$6,033**	**$6,441**	**6.8%**

Source: *Nutrition Business Journal*, www.nutritionbusinessjournal.com

Table 4. The 40 Top-Selling Herbal Supplements in the US Mainstream Multi-Outlet Channel in 2014[a]				
	Herbal Supplement[b]	**Latin Name**	**Total Sales**	**% Change (from 2013)**
1	Horehound[c]	*Marrubium vulgare*	$105,880,497	-1%
2	Cranberry	*Vaccinium macrocarpon*	$56,366,811	16%
3	Echinacea[d]	*Echinacea* spp.	$50,733,344	79%
4	Black Cohosh	*Actaea racemosa*	$42,463,816	-8%
5	Flaxseed/Flaxseed Oil	*Linum usitatissimum*	$25,503,596	-10%
6	Valerian	*Valeriana officinalis*	$23,188,457	-1%
7	Yohimbe	*Pausinystalia johimbe*	$20,019,154	-11%
8	Bioflavonoid Complex[e]		$19,769,553	21%
9	Saw Palmetto	*Serenoa repens*	$17,990,612	-17%
10	Ginger	*Zingiber officinale*	$17,539,955	8%
11	Aloe Vera	*Aloe vera*	$17,044,331	-8%
12	Milk Thistle	*Silybum marianum*	$16,350,627	0%
13	Garlic	*Allium sativum*	$15,182,227	4%
14	Cinnamon	*Cinnamomum* spp.	$14,263,836	-3%

Table 4 continued on following page

Turmeric *Curcuma longa*
Photo ©2015 Steven Foster

Ivy Leaf *Hedera helix*
Photo ©2015 Steven Foster

review[5] concluded that there was "no convincing evidence" that ivy leaf is effective for treating upper respiratory tract infections, at least two recent studies[6,7] have suggested that the herb may be beneficial for respiratory conditions in children under the age of 12. According to SPINS, the ivy leaf product with the highest mainstream sales in 2014 was, in fact, a pediatric formulation.

In addition to ivy leaf, three other botanicals were new to 2014's list of 40 top-selling herbal supplements in the mainstream channel. Sales of rhodiola, guarana, and grass (wheat or barley) supplements earned these herbs rankings of 15th, 21st, and 40th, respectively. These products replaced bromelain, artichoke, slippery elm, and acai, each of which was on 2013's list of 40 top-selling herbs in this channel.

Coconut oil continues to enjoy booming sales in the mainstream channel. Mass-market retailers sold an estimated $9,239,429 of the botanical product in 2014, a remarkable 210% jump from the previous year. The increased sales were enough to make coconut oil the 22nd top-selling herb in 2014 in the mainstream channel, up significantly from its ranking of 40th in 2013. Dr. Mehmet Oz, MD, first touted the health benefits of this "miracle fat that fights fat" in 2012 on his daytime television program,[8] claiming that the product can help with weight loss, skin conditions, and ulcers. Rich in saturated fat and medium-chain triglycerides, coconut oil became even more

Table 4 (continued). The 40 Top-Selling Herbal Supplements in the US Mainstream Multi-Outlet Channel in 2014[a]				
15	Rhodiola	*Rhodiola* spp.	$14,188,978	-20%
16	"Horny Goat Weed"	*Epimedium* spp.	$12,492,718	-17%
17	Ginkgo	*Ginkgo biloba*	$11,147,066	-3%
18	Plant Sterols[f]		$11,087,439	33%
19	Red Yeast Rice	*Monascus purpureus*	$11,046,789	-8%
20	Elderberry	*Sambucus nigra*	$9,964,444	64%
21	Guarana	*Paullinia cupana*	$9,958,189	9%
22	Coconut Oil	*Cocos nucifera*	$9,239,429	210%
23	Senna[g]	*Senna alexandrina*	$8,798,808	-10%
24	Ivy Leaf	*Hedera helix*	$8,086,029	379%
25	Chia Seed/Chia Oil	*Salvia hispanica*	$7,418,456	26%
26	Turmeric[h]	*Curcuma longa*	$7,079,791	60%
27	Maca	*Lepidium meyenii*	$6,589,177	36%
28	Fenugreek	*Trigonella foenum-graecum*	$6,575,986	85%
29	Isoflavones[i]		$6,160,410	-29%
30	Ginseng[j]	*Panax* spp.	$5,687,836	-13%
31	St. John's Wort	*Hypericum perforatum*	$5,577,820	-3%
32	Green Tea	*Camellia sinensis*	$4,699,286	-11%
33	Fennel	*Foeniculum vulgare*	$4,668,874	18%
34	Horsetail	*Equisetum* spp.	$4,603,098	-20%
35	Tribulus	*Tribulus terrestris*	$4,144,491	-20%
36	White Kidney Bean	*Phaseolus vulgaris*	$3,975,546	15%
37	Evening Primrose Oil	*Oenothera biennis*	$3,924,130	-3%
38	Kelp	*Laminaria digitata*	$3,166,024	-26%
39	Gymnema	*Gymnema sylvestre*	$2,762,736	28%
40	Grass (Wheat or Barley)	*Triticum aestivum* or *Hordeum vulgare*	$2,351,642	9%
Subtotal: Top-40 Herbs			$627,692,008	
Subtotal: All Other Herbs			$174,607,041	
Total Herb Sales			**$802,299,049**	**2.1%**

[a] *Source: SPINSscan Natural and IRI, 52 weeks ending December 28, 2014.*
[b] Herb coded as primary ingredient.
[c] Horehound is the primary ingredient in many throat lozenges that may contain other herbs and other non-herbal ingredients.
[d] Echinacea collectively refers to supplements made from roots and/or aerial parts of plants from three species in the genus *Echinacea*: *E. angustifolia*, *E. pallida*, and *E. purpurea*.
[e] Bioflavonoids are present in citrus fruits. Many bioflavonoid supplements are extracted and manufactured from citrus fruits, e.g. *Citrus reticulata* and *C. aurantium*.
[f] This category does not include policosanol, beta sitosterol, or octacosanol.
[g] All supplements currently being captured with senna as the primary ingredient in the herbal dietary supplement category are representative of herbal senna. SPINS does capture sales of OTC stimulant laxative drugs containing senna's active compounds, sennosides, as well, but uses a separate ingredient tag so as to avoid crossover; accordingly, OTC laxative drugs containing senna are not included in these data.
[h] Standardized turmeric extracts with high levels of curcumin, as well as proprietary turmeric-containing herbal combination Zyflamend®, are included under the primary ingredient turmeric.
[i] Isoflavones are a type of phytoestrogens found in legumes and other foods.
[j] Excludes *Eleutherococcus senticosus*, formerly referred to as "Siberian ginseng."

popular in 2013 when adopters of the Paleo diet — which encourages the consumption of so-called "healthy" fats — embraced the product. In 2014, celebrity endorsements[9] of coconut oil for "oil pulling" (an Ayurvedic folk tradition in which oil is swished around the mouth to improve oral and general health) helped increase its visibility once again. Despite popular claims that coconut oil has benefits ranging from teeth-whitening to heart disease risk reduction, there are few high-quality scientific studies that support such assertions.[10-12]

Compared to 2013 data, total mainstream channel sales increased significantly for a number of other herbs including fenugreek (+85%), echinacea (+79%), elderberry (+64%), and turmeric (+60%). Mainstream echinacea sales in 2014 resulted in the herb moving from the 8th top-selling herb in 2013 to the 3rd top-selling in 2014; increased sales of fenugreek bumped the supplement's ranking from #36 to #28 in the same time period.

Two plant-derived compounds saw mainstream sales increases in 2014 as well. Sales of plant sterols in 2014 increased 33% from the previous year, and bioflavonoid supplement sales increased by 21%. However, sales of isoflavones — the only other isolated plant compound-based supplement on the list — resulted in the largest percentage decrease (-29%) of any of the 40 top-selling products in the mainstream channel.

Other notable sales declines in 2014 include kelp (-26%), rhodiola (-20%), horsetail (-20%), and tribulus (-20%).

Sales figures for the categories "Chinese herbs" and "whole food concentrate" were not included in *HerbalGram*'s top-40 mainstream channel rankings due to their relative broadness. Had they remained on the list, Chinese herbs would have been the 2nd top-selling supplement and whole food concentrate would have ranked 39th in this channel. Individual formulations not primarily derived from botanicals — such as biotin, a B vitamin found in some plants, and beta glucans, derived from yeast — also were excluded. As the only branded supplement on the list, Relora® (Next Pharmaceuticals, Salinas, California; purchased by InterHealth Nutraceuticals Inc., Benicia, CA), a proprietary blend of magnolia (*Magnolia officinalis*, Magnoliaceae) and phellodendron (*Phellodendron amurense*, Rutaceae) bark extracts, was removed as well.

Table 5. The 20 Top-Selling Herbal Dietary Supplements in the Natural Channel in the US in 2014 (per SPINS)*

	Herbal Supplement†	Latin Name	Total Sales	% Change (from 2013)
1	Turmeric‡	*Curcuma longa*	$26,288,705	**30.9%**
2	Grass (Wheat and/or Barley)	*Triticum aestivum* or *Hordeum vulgare*	$21,945,643	**7.8%**
3	Flaxseed and/or Oil	*Linum usitatissimum*	$16,496,598	**-4.3%**
4	Aloe Vera	*Aloe vera*	$13,709,869	**2.9%**
5	Spirulina Blue Green Algae	*Arthrospira* spp.	$10,789,938	**1.7%**
6	Milk Thistle	*Silybum marianum*	$9,192,317	**1.3%**
7	Elderberry	*Sambucus nigra*	$8,785,801	**9.4%**
8	Maca	*Lepidium meyenii*	$7,425,180	**15.2%**
9	Echinacea§	*Echinacea* spp.	$7,185,402	**5.4%**
10	Oregano§§	*Origanum vulgare*	$6,433,051	**12.4%**
11	Saw Palmetto	*Serenoa repens*	$6,363,119	**-1.0%**
12	Chia Seed and/or Oil	*Salvia hispanica*	$5,637,501	**-1.2%**
13	Valerian	*Valeriana officinalis*	$5,563,897	**7.3%**
14	Garlic	*Allium sativum*	$5,302,449	**5.2%**
15	Echinacea/Goldenseal Combo	*Echinacea* spp.-*Hydrastis canadensis*	$5,116,708	**6.1%**
16	Chlorophyll/Chlorella**	NA/*Chlorella vulgaris*	$4,812,341	**2.8%**
17	Cranberry	*Vaccinium macrocarpon*	$4,254,478	**10.3%**
18	Ginkgo	*Ginkgo biloba*	$4,076,228	**2.2%**
19	Stevia	*Stevia rebaudiana*	$4,037,603	**-12.3%**
20	Red Yeast Rice	*Monascus purpureus*	$3,852,079	**-5.1%**
Subtotal: Top-20 Herbs			$177,268,907	
Subtotal: All Other Herbs			$152,749,192	
Total Herb Sales			**$330,018,099**	**5.2%**

*Source: SPINSscan Natural, 52 weeks ending December 28, 2014. Does not include Whole Foods Market sales. (SPINS permits *HerbalGram* to publish the 20 top-selling herbs, whereas IRI customarily has provided *HerbalGram* with sales data on all herbs sold in the mainstream multi-outlet channel, hence the listing of 40 top-selling herbs in the latter channel as ranked in Table 4.)
†Herb coded as primary ingredient.
‡Standardized turmeric extracts with high levels of curcumin, as well as proprietary turmeric-containing herbal combination Zyflamend®, are included under the primary ingredient turmeric.
§Echinacea collectively refers to supplements made from roots and/or aerial parts of plants from three species in the genus *Echinacea*: *E. angustifolia*, *E. pallida*, and *E. purpurea*.
§§Includes oregano oil as well as oregano leaf tinctures.
**Coding for this category includes chlorophyll or chlorella single or combination products.

Natural Channel

The natural channel saw a 5.2% increase to $330,088,019 in estimated total sales over 2013 (Table 5), a healthy yet significantly smaller gain compared to 2013's 9.9% increase[1] and 2012's impressive 14.7% increase.[13] (These data do not include sales from Whole Foods Market, which does not report its supplement sales to market tracking firms.) Sales in the natural channel tend to come from what marketers call "core shoppers," who are committed to a more natural lifestyle, including natural-health modalities. So-called "peripheral shoppers," who have less of a personal commitment to a natural-health philosophy, are more likely to purchase dietary supplements in the mainstream channel.

Consumers in the natural channel also are showing an increasing interest in issues of transparency, traceability, and sustainability, often choosing supplements that are ethically sourced, organically grown or wild-crafted, part of a fair trade initiative, etc.

After taking the first slot in the natural channel in 2013, turmeric sales remained strong with an almost 31% increase, totaling $26,288,705 in 2014. This is a continued increase from 2013, in which turmeric saw 26.2% growth in the natural channel. Recent research on turmeric and its primary active constituent curcumin garnered a great amount of attention, with a growing list of purported benefits. PubMed, the research database run by the National Center for Biotechnology Information (part of the National Institutes of Health), lists almost 8,000 studies on curcumin as of July 2015.[14] Originally gaining interest for its anti-inflammatory effects as a natural COX-2 inhibitor, turmeric and curcumin currently are being investigated for their cancer-fighting properties,[15] protection against heavy metal toxicity,[16] and relief of symptoms of depression,[17] among many other potential uses.

The top 20 herbs in the natural channel remained the same from 2013, though some swapped rankings. Maca and oregano showed high growth at 15.2% and 12.4%, respectively; stevia, now a popular non-caloric sweetener, saw the largest drop of 12.3%. (Sales of stevia as a supplement do not reflect sales of stevia as a food product and use as a sugar alternative; previously, before the FDA approved stevia as a safe food ingredient, it was sold legally in the United States only as a dietary supplement.)

Maca's popularity in 2014 surprised the Peruvian farmers that cultivate the crop, and increasing demand from both the United States and China caused the price for fresh and dried maca to skyrocket. The adaptogenic herb is prized for its use against aging, declining sexual health, and depression, and allegations of biopiracy and Chinese maca smuggling has been reported.[18] Despite high prices and suspected adulteration, Peruvian-sourced maca continues to draw consumers.

Oregano supplements, which SPINS defines as oregano essential oil and supplements as well as oregano leaf tinctures, experienced double-digit growth in 2014. Marketers claim that oregano supports the immune system and has antifungal, antibacterial, and antiviral properties. In late September 2014, the FDA issued warning letters to several companies that made exaggerated and unsubstantiated claims regarding their oregano oils in regards to the Ebola virus epidemic.[19]

Direct Sales

In 2014, the direct sales channel saw a growth of 6.7%, or almost $200 million more than 2013. Direct channel sales of herbal dietary supplements include multi-level marketing companies (also known as network marketing companies) such as Advocare, Herbalife, Nature's Sunshine, Nu Skin/Pharmanex, Nutrilite (Amway), Shaklee, USANA, and similar competitors. This channel also encompasses mail and Internet order sales companies, direct response TV and radio sales, and sales by health practitioners.

Single vs. Combination Supplements Sales

According to NBJ, sales of single-herb dietary supple-

Oregano *Origanum vulgare*
Photo ©2015 Steven Foster

ments in all channels increased by 4.4%, and sales of combination formulas rose 10.7% (Table 6). Combination formulas generally use a blend of herbs that are marketed for a specific benefit, including maintaining healthy blood sugar and/or blood lipid levels, and easing the effects of menopause, among others. As shown in Table 6, herbal combination supplements have been growing in popularity for the past few years, consisting of 36.2% of total herb sales in 2012 and currently representing 39.2% of sales. Consumer knowledge of herbs and their benefits continues to become more sophisticated, and as sales of whole herb preparations maintain their growth, a more educated population emerges. Consumer awareness of the benefits of whole herbs versus their isolated constituents may also play a role in the increasing sales for combination supplements. Herbal blends, such as those used in traditional Chinese medicine, have a long history of traditional use and modern research continues to explore their efficacy.[20,21]

Table 6. Herb Retail Sales (in Millions) by Category in All Market Channels in US: Singles (Monopreparations) vs. Combinations

2012	Total Sales	% Total Sales	% Increase*
Total Single Herbs	$3,567	63.8%	2.7%
Total Combination Herbs	$2,026	36.2%	10.8%
Total Herbs	**$5,593**		**5.5%**
2013			
Total Single Herbs	$3,749	62.2%	5.1%
Total Combination Herbs	$2,284	37.8%	12.7%
Total Herbs	**$6,033**		**7.9%**
2014			
Total Single Herbs	$3,914	60.8%	4.4%
Total Combination Herbs	$2,527	39.2%	10.7%
Total Herbs	**$6,441**		**6.8%**

*Growth is expressed in percentages over previous years. Source: *Nutrition Business Journal*

Conclusion

For the 11th consecutive year, American consumers spent more on herbal dietary supplements than they did in the previous year. Since 2011, estimated herbal supplement sales in all channels have increased by more than $1 billion; in 2014, US consumers spent roughly $400 million more on plant-based supplements than in 2013. These figures suggest a clear trend: Americans are continuing to rely on botanical products for various aspects of their wellbeing and other personal needs.

The sales data presented in this report reflect consumer preferences that are similar to those of previous years. In 2014, retail sales of combination herbal supplements and total supplement sales in natural and health food stores increased faster than other herbal supplement products and channels, respectively.

Despite more than a decade of increased total annual sales of herbal dietary supplements, some members of the natural products community have expressed concern that 2015 sales could be impacted by recent negative press surrounding herbal products — namely, the New York Attorney General's herbal supplement investigation that began in February 2015.[22] However, as detailed in a recent NutraIngredients-USA article,[23] SPINS data show that sales of herbal formula (combination) supplements for the 52 weeks ending in mid-July 2015 are up 12.6% from the same period a year earlier. Interestingly, single-herb supplements have not fared as well. Total sales, calculated by SPINS in four-week segments, increased for single-herb products until March 22, but since then, sales of these products have steadily declined. Still, overall sales of herbal monopreparations in the US remained fairly constant between mid-July 2014 and mid-July 2015, with a total increase of just 1.1%.

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Horehound *Marrubium vulgare*
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LEGAL & REGULATORY

BMPEA/*Acacia rigidula* Controversy Fuels Further Criticism of Botanicals

by Karen Raterman

A little-known and somewhat scrappy shrub native to Texas and Mexico is at the heart of one of the more recent controversies surrounding dietary supplements with botanical ingredients. *Acacia rigidula* (Fabaceae), sometimes used in weight-loss and sports performance products, was implicated in a study from Harvard University Medical School, which found that products listing *A. rigidula* on the label contained beta-methylphenylethylamine (BMPEA), a synthetic isomer of amphetamine.[1] After three weeks of swirling publicity that included criticism of the US Food and Drug Administration's (FDA's) alleged inaction on regulating products containing synthetic and unapproved stimulant ingredients, alleged conflicts of interest between FDA and industry, and statements from three US senators calling for FDA to remove BMPEA-containing products from the market, the agency sent warning letters to five companies and banned the sale of BMPEA, noting potential health issues.[2,3]

(In a related development, FDA later took action on April 24, sending warning letters to companies selling DMBA, a different unapproved stimulant, after the ingredient was found in supplements tested in a 2014 study from Harvard.[4,5])

Though this might have been a fairly standard procedural event in which FDA dealt with marketers' not filing a New Dietary Ingredient (NDI) notification, or citing companies for use of a banned substance, it followed on the heels of the New York Attorney General's investigation into private-label herbal dietary supplement products that reportedly failed DNA barcode tests for identity at four major retailers in New York state.[6,7] As a result, the BMPEA/*A. rigidula* issue has become the latest log on a fire that is fueling the increasingly negative consumer perception of dietary supplements in general, and herbal supplements in particular. It has some industry experts concerned that these ongoing controversies and misinformation in the media are increasing the "vulnerability" of supplement companies and may even generate a "national referendum" on the Dietary Supplement Health and Education Act of 1994 (DSHEA).

While FDA's announcement banning the sale of BMPEA was not unexpected and was supported by several industry groups, many say the current atmosphere remains dynamic. Lead author of the Harvard study on BMPEA and *A. rigidula*, Pieter Cohen, MD, who has been both an outspoken critic of supplements and FDA's enforcement of DSHEA, called FDA's action a step in the right direction, albeit a small one. "This only addresses those products that openly listed BMPEA on the label – a clear violation of DSHEA," he wrote (e-mail, April 27, 2015). "What is much more insidious are the products that list only *Acacia rigidula* or other botanical ingredients, but are actually spiked with drugs like BMPEA."

Acacia rigidula
Photo ©2015 D Carlson

What FDA did not deal with in this latest action is the legal status of *A. rigidula*. The wording of the FDA letters calling the products "misbranded" rather than adulterated, which would be more typical in this type of scenario, was interesting, according to industry veteran Loren Israelsen, president of United Natural Products Alliance, an industry trade group. "It is clear that FDA is responding to external pressure. They moved quickly to get the letters out, and as far as I am concerned, they are doing their job. But it is an interesting dynamic," he wrote (e-mail, April 25, 2015).

"I think the action is significant and appropriate," said Daniel Fabricant, PhD, CEO of the Natural Products Association, an industry trade association (oral communication, April 29, 2015). "The agency has to be very thoughtful and metered when they do these things. Their experts have to be court-ready. So the language they use would depend on their evidence. If it is a labeling issue, then that is likely the legal theory they would advance. That doesn't mean they can't tack on an adulteration charge after further testing."

Regarding the legal standing of *A. rigidula*, Fabricant added that the herb could qualify as a dietary ingredient, but what is in question is whether the stimulant compound BMPEA is a constituent of acacia. "The science in general probably does not support inclusion of this ingredient as an extract of the plant," Fabricant said.

A Tale of Two Compounds

To understand how *A. rigidula* became linked with an amphetamine-like stimulant requires a quick review of the history of the plant's use as a supplement. The current *A. rigidula*/BMPEA issue began with the release of the Harvard study in early April, noting that 11 of 21 products tested that claimed to contain *A. rigidula* on their labels contained BMPEA, a compound that was first synthesized in 1931 as a potential replacement for amphetamine but never approved for human consumption. BMPEA has not been studied for safety and efficacy in humans and was known primarily as a research chemical, according to Dr. Cohen's paper in *Drug Testing and Analysis*.[1]

It has, however, been used in some products sold as dietary supplements since 2010.[8] The Harvard researchers also revealed that a 2012 study by FDA, published in the *Journal of Pharmaceutical and Biomedical Analysis* in 2014, had similar findings, yet the agency failed to act or warn consumers about supplements that contained the compound.[9]

Following three weeks of discourse, the agency sent warning letters to five companies: Hi-Tech Pharmaceuticals, Inc.; Tribravus Enterprises, LLC; Train Naked Labs, LLC; Better Body Sports, LLC; and Human Evolution Supplements, Inc.[10] (One of those companies, Hi-Tech Pharmaceuticals, of Norcross, Georgia, has filed a libel and slander suit against the Harvard team, seeking both punitive and compensatory damages.[11] The company is also involved in a legal battle with FDA over products containing another stimulant, 1,3-dimethylamylamine [DMAA], that is also banned in dietary supplements.[12])

The first association between *A. rigidula* and BMPEA, however, likely dates back to research in the 1960s, and then the 1990s, which recorded large amounts of compounds, including methamphetamine, mescaline, and others that would become classified as controlled substances, in *A. rigidula*.[13,14] According to James Neal-Kababick, director of Flora Research Laboratories, LLC in Grants Pass, Oregon, aggressive extraction technology, coupled with old analytical technologies, likely led to misidentification of compounds in these early papers, which may have informed some use of the plant in supplement products. More recent studies, including the 2012 analysis by FDA, used more advanced analytical techniques and researchers were able to conduct characterizations of botanical materials. "The later results suggest some fairly significant errors in the earlier work," said Neal-Kababick (oral communication, April 23, 2015).

FDA's study found that "many of the ingredients noted in the earlier papers did not show up in *A. rigidula,* or were at such low levels it would take tons of raw materials to make one product run," added Neal-Kababick. "It doesn't add up. And you can't spend 10 or 20 times as much on a product as you can sell it for. It doesn't calculate economically."

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Further, Neal-Kababick noted that it is unlikely that such a common plant in the Southwestern United States would contain an "armada of Schedule 1 controlled substances" without attracting more attention (email, May 18, 2015). "If methamphetamine and mescaline were really in those leaves at any appreciable level to render them a source of those substances, the DEA would have an army of agents spraying herbicides or ripping out plants."

There also may have been poor quality peer review of the earlier papers, he added. "Reviewers have to have enough depth to catch things of concern, and, a lot of times, they are not able to dive in, or [they] have limited understanding and accept certain things as fact." At the time of some of these publications, he continued, there was a peer-review desert that still exists somewhat today. Due to time constraints, many scientists are very limited in what they can fact-check. "Journals had a hard time getting reviewers, and reviewers often did not dive in too far. This resulted in a lot of erroneous or inadequate papers in the 1990s and early 2000s."

History aside, the Harvard study on BMPEA triggered a second round of negative publicity about dietary supplements and the industry that produces them. Such media coverage followed ongoing headlines regarding the separate New York AG investigation, and included calls from Senators Charles Schumer (D-NY), Dick Durbin (D-IL), and Richard Blumenthal (D-CT) urging FDA to ban BMPEA[2,3], and a *New York Times* editorial[15] alleging industry conflicts of interest at FDA, as well as multiple other media reports on the poor quality and inadequate regulation of supplements. And then, on May 12, Cohen and his team released a new case report noting that a hemorrhagic stroke in a 53-year old woman was likely caused by exercise in combination with the use of a BMPEA-containing supplement.[16]

Although the timing of these developments may be coincidental, the recent issues have at least some industry stakeholders questioning motivations of key players in the overall drama. This is the same argument and the same players that have criticized DSHEA from the beginning, Israelsen noted (e-mail, April 20, 2015). "There are some people who would say that the New York AG investigation, and continuance of non-GMP compliance [by some companies], all point to the same thing — an underlying fault in the law. Change the law and the problem goes away."

Dr. Cohen calls his latest research nothing more than a continuation of his ongoing work to push FDA to enforce DSHEA. "In my recent paper on BMPEA, I emphasize two main themes: the presence of this new stimulant in supplements and the FDA inaction. I do not venture a guess as to why FDA has been so slow to move against the ingredient, which has no role in dietary supplements and poses potential health risks," he said (e-mail, April 22, 2015).

Although Dr. Cohen has argued for aggressive enforcement of DSHEA and sees the law as an excellent framework for the sales of vitamins and minerals, he does note that

it is less appropriate for other ingredients, like botanicals, probiotics, and glandular extracts. "Many physician-critics of the supplement industry believe we should regulate botanicals like drugs. I disagree," he stated. "I think there is a compromise solution, in which regulations should be tailored to the special challenges of providing access and high-quality botanical supplements to consumers." Some of the changes he would consider recommending would be to require disclosure of known adverse events on the label, make reports of these events publicly available, and create a more robust system to detect adverse effects from supplements.

The FDA Dilemma

Regulatory experts believe that DSHEA provides FDA with adequate tools, but the agency may be hampered by too many priorities and limited resources. The problem, Israelsen added, is that FDA continues to struggle with the job of taking effective leadership with dietary supplements. And that issue is not likely to improve, considering the current lack of resources and expertise at FDA. "It is hard to see at the moment how FDA can be a clearly focused regulator that industry can work with. But that is the way it is at the moment," said Israelsen.

Neal-Kababick noted that one FDA agent told him that for every criminal case the agency pursues, there are many more that they do not go after due to limitations of budget and resources. "I personally feel from my some two decades of interaction with FDA that if they are properly funded to enforce the cGMP regulations, then we would see the rogue products nipped in the bud and companies with deficiencies would more quickly be brought to compliance," he said.

"I can't answer the question about FDA's lack of action other than it is a resource priority," said Dr. Fabricant. "We know that one of every four dollars is spent on some kind of packaged good [that comes under the FDA regulatory purview]. So it is a tall path they have to follow, and I understand the issue legally. But I think there was not really a public health hook [with BMPEA], so there has not been a great need to act immediately."

What may be more concerning is that the New York AG situation has made the industry much more vulnerable to reports like the one on BMPEA and *A. rigidula*, noted Steve Mister, president and CEO of the Council for Responsible Nutrition (CRN), an industry trade association (oral communication, April 18, 2015). "It makes this seem like a mainstream problem, but the [BMPEA] issue is very limited in terms of products with *Acacia rigidula*. However, coming on the heels of the New York investigation and the focus on retail, it makes this seem like a much more widespread issue."

Mister added that in CRN's conversations with members of New York AG Eric Schneiderman's staff, he seems to be taking the position that even if the DNA tests that prompted all of this are erroneous, they know there is activity taking place in the industry that shouldn't occur. "Maybe they pointed their finger in the wrong direction, but they got consumers concerned and that is good enough," Mister said.

Regardless, Dr. Fabricant pointed out that "the industry has a perception challenge right now and needs to meet that challenge, such that we are not always in reactive mode. We need to be more proactive and start painting organizations and industry in a good light."

Mister believes that FDA is smart enough to see the difficulty of what is happening, but he also reiterated that it is a pivotal time for the industry. "Companies will need to be much more careful in addressing their critics and the media, in light of these recent actions. Retailers need to know what is on their store shelves, and they need to step up and be smart about the vendors they are dealing with," he said.

These issues have definitely been taken out of proportion and perspective, Neal-Kababick agreed. He added: "Companies that are doing the right thing have to unfairly compete with those who are not doing things right. If FDA doesn't stop them, it will be very hard for good companies to compete."

"Too many companies," Neal-Kababick continued, "are doing high production, without the heart of traditional pharmacognosy in their organization, and they don't have botanical practitioners involved in designing their products. It's a big issue."

Beyond the negative media, these issues are creating new problems and unrealistic expectations of industry. As an example, Neal-Kababick noted GNC's settlement with the New York AG following their citation by the office after some of their products reportedly failed the DNA barcode tests. The settlement, he said, was perceived as if the Attorney General was whipping GNC into shape, when the company actually admitted no wrongdoing but did agree to use DNA testing on raw materials.[17] "I know it was an economic decision for their shareholders, but it doesn't benefit industry. Many small companies are not able to mandate such requirements to their suppliers of botanical extracts who are often middle brokers and not the manufacturers. Even if [the companies] could, how can they confirm the data is from the actual product being purchased after changing hands?" he questioned. "This is where chromatographic techniques and microscopy become extremely critical as they must test what they use."

The Upside of Controversy

While some people in the natural products industry have had a tendency to point fingers at others in the wake of these problems, Dr. Fabricant believes that companies also need to shoulder some of the blame for the current status quo. "It is never a bad idea to hold up a mirror and get your house in order, and this is providing that opportunity," he said. "As an industry we have become too apathetic politically. We need to get people more involved and that means joining associations, giving to PACs [political action committees], and sending letters to Congress saying 'I am an industry member, I vote, I provide jobs, and this situation seems motivated by political agendas rather than scientific fact.'"

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CRN's Steve Mister says these problems should be a wake-up call for industry, starting with companies in the high-risk categories of weight-loss, sports performance, and sexual enhancement. "They should be doing appropriate tests and not spiking their products with things that should not be there."

This is also a reminder that the New Dietary Ingredient process is not optional just because the industry is waiting on the next draft of the guidance, said Mister, referring to the NDI requirement in Section 8 of DSHEA, which stipulates that a company notify FDA 75 days prior to marketing any "new" ingredient in a dietary supplement that was not sold in the United States prior to October 15, 1994, provide safety data for that ingredient, and obtain FDA consent for the marketing of the ingredient. The FDA has not yet issued final guidance on this process or the criteria for having to file the notices.

"It is a fundamental requirement that companies with New Dietary Ingredients must give FDA a 75-day notice, and that goes back to 1994," Mister said. "So even though we are still arguing about the nuances of the process, the process still needs to be followed, and that was not done in the case of BMPEA."

While the world as dietary supplement companies know it may be somewhat altered, the situation may not be as dire as some believe it to be. As witnessed by its April 23 announcement, FDA does have procedures to keep unsafe products off store shelves. And although some critics have urged Congress to enact sweeping changes to DSHEA, Israelsen sees no real clues that this kind of scenario is imminent. "Although you can never be certain, it appears now that given the schedule and issues facing Congress, we are not seeing the conditions necessary for a successful attempt to amend DSHEA."

That said, he noted that things feel different than before, with the change in industry's historic leadership and its unique political legacy, along with the current willingness of the national press to be a bull horn to communicate accusations against dietary supplements. The debate to come, Israelsen added, may be to "consider a middle ground that is both practical and doable to achieve the jointly held view of quality products with compliant research, and yet preserve broad access for US consumers."

But first, he continued, "we need to square up to and answer questions about how to do this by addressing proper enforcement of DHSEA. Until we see what a fully engaged

Acacia rigidula
Photo ©2015 Texas Agricultural Experiment Station

BMPEA Timeline[8]

2010
- BMPEA first reported in dietary supplements
- Athletes in European Union (EU) test positive for BMPEA

2012
- Supplements labeled as containing *Acacia rigidula* first purchased for FDA study

2013
- FDA presents paper "Determination of biogenic amines at *A. rigidula* and it dietary supplements using LC-MS/MS methods"[18]

2014
- FDA paper published online in the *Journal of Pharmaceutical and Biomedical Analysis*[9]
- Pawar et al. recognized by FDA Center for Food Safety and Applied Nutrition (CFSAN) for the study identifying *A. rigidula* or its extracts in weight-loss supplements as a noteworthy accomplishment in 2013
- EU experts say *A. rigidula* is not food
- Researcher from Harvard/UCSF purchase *A. rigidula* product for study

2015
- Health Canada recall of *A. rigidula* products
- Cohen's Harvard study published online Oct. 8, 2014, "A Synthetic stimulant never tested in humans, 1,3-dimethylbutylamine (DMBA), is identified in multiple dietary supplements"[5]

and enforced DSHEA looks like, it is premature to change the law.… We can only do so much. FDA has to do the rest." HG

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Acacia rigidula Herb Profile

Commonly known as blackbrush, blackbrush acacia, chaparro prieta, catclaw or gavia, *Acacia rigidula* is a spiny, thicket-forming shrub with stiff branches that is native to the Rio Grande plain in Texas and northern Mexico. The perennial tree grows 3-15 feet tall and has aromatic pale white to golden yellow flowers that bloom from March to June. The bark of the shrub is a whitish color and its leaves are dark green, glossy, and crowded[1]. A member of the Fabaceae family, *A. rigidula* produces a legume-type fruit. Its native habitat is prairie, plains, meadows, pastures, savannahs, and chaparral and brush country.[2] The plant grows on limestone hillsides, is adaptable to a variety of soil types, drought tolerant, and hardy to 20º F (-6.7º C).[3]

While it is known that Native Americans and Hispanic peoples made numerous therapeutic preparations from North American acacias,[4] there is little information about indigenous uses of *A. rigidula* and few reports of its use as a traditional medicine. That said, there is some record that the people of the Mexican Kickapoo tribe drank a decoction of *A. rigidula* leaves, or a combination of *A. rigidula* and *A. farnesiana* roots, for treatment of severe diarrhea with blood in the stool.[4] Other species of *Acacia*, notably *A. farnesiana*, are more often mentioned in literature as being used in traditional treatments for ailments, ranging from headache and respiratory disorders to rheumatism and a treatment for conjuntivitus.[4]

In current times, *A. rigidula* or its extracts are often listed as ingredients in weight-loss supplements that claim to provide stimulant and appetite-suppressing properties.[5] These products frequently contain other botanical extracts such as hoodia (*Hoodia gordonii*, Apocynaceae) and bitter orange (*Citrus aurantium*, Rutaceae). Although no serious problems have been documented regarding the consumption of *Acacia* legumes, there are some reported cases of sheep and goat poisonings related to consumption of *A. berlandieri* and *A. rigidula* foliage and fruit.[6] Consumption of the plants by these animals was associated with development of locomotor ataxia, also known as "limber leg," in which the animals develop a wobbling in the hind legs that leads to stumbling, falling, and prostration, and sometimes causes death.[4,6] The condition is attributed to the appreciable levels of toxic alkaloids in the plant, which can be a significant part of the diet for these grazing animals in times of drought. The overconsumption of *A. rigidula* and *A. berlandieri* also has been linked to poor reproductive health in cattle.[6,7]

More than 50 species of the *Acacia* genus have been reported to contain various amines and alkaloids.[5] In studies looking specifically at *A. rigidula*, researchers in the 1960s reported that the plant contained the phenethylamine-type compounds *N*-methyl-β-phenethylamine, *N*-methylphenethylamine (N-MePEA), and *N*-methyltyramine (N-MeTYR).[8] In the 1990s, a study of acacia plant material gathered in spring and late season, reported trace amounts of compounds that reserachers identified as amphetamine and methamphetamine, especially in plant material from the fall.[6,7] Later research by Pawar et al. has noted that amphetamine is a synthetic compound and the only time it has been reported naturally was from the papers noted above.[5] The research concluded that, in contrast to the earlier reports, they found only fairly low amine levels in authenticated *A. rigidula* materials. The study also demonstrated that β-methylphenethylamine (B-MePEA), a synthetic compound apparently added to *A. rigidula* extracts, can be misidentified as amphetamine when using LC-MS methods. They suggested that particular care must be taken to separate isomers chromatographically when using these methods.[5]

—Karen Raterman

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New Plant-Derived Drugs from Traditional Chinese Medicine Discussed at UN Conference

ILSC's conference highlights safety and benefits of natural products

By Erika L. Kurt, LLB, BCL

On June 1, 2015, the Institute for Life Sciences Collaboration (ILSC) hosted a conference — "Sustainable Development Healthcare Delivery: Nutraceuticals & Natural Products" — as part of the "United Nations at 70" non-governmental organization series. The event took place at the United Nations (UN) Church Center in New York City and highlighted natural product (particularly medicinal plant) breakthroughs and new resources. The UN conference series convenes leading experts to uncover the mechanisms of action of natural products, identify and promote recent progress and developments in healthcare, and improve global healthcare delivery through evidence-based approaches. This series advances ILSC's mission to make meaningful and measurable improvements in the global healthcare landscape.

Herbal Breakthroughs and Updates

Several speakers presented updates in their efforts to incorporate natural products and traditional Chinese medicine (TCM) into mainstream American medical therapy. This included significant progress in treating people with asthma, food allergies, non-alcoholic fatty liver disease (NAFLD), gastrointestinal and inflammatory side effects of chemotherapy, and inflammatory bowel disease (IBD).

Asthma and Food Allergies

Xiu-Min Li, MD, the director of the Center for Integrative Medicine for Allergies and Wellness at Mount Sinai Hospital's Icahn School of Medicine, shared two novel treatments that her team is developing for asthma and food allergies using TCM.

Reishi Mushroom *Ganoderma lucidum*
Photo ©2015 Steven Foster

The first treatment addresses asthma, which results in the deaths of 3,000-4,000 Americans annually and $56 billion in medical costs and indirect costs (e.g., missed work).[1,2] Currently, the most effective treatments involve conventional pharmaceutical steroid drugs, which are not curative or advised for long-term use due to undesirable side effects. Thus, there is a strong need to develop better treatments for asthma.

Dr. Li's team has created a safe and effective therapy for moderate-to-severe asthma. Anti-Asthma Simplified Herbal Medicine Intervention (ASHMI) is made from three herbs of the 14-herb formula MSSM-002. It consists of capsules of dried water extracts of 63% *ling zhi* (reishi mushroom; *Ganoderma lucidum*, Ganodermataceae) fruiting body, 28% *gan cao* (licorice; *Glycyrrhiza glabra, G. uralensis*, Fabaceae) root, and 9% *ku shen* (*Sophora flavescens*, Fabaceae) root.

In mouse models and human clinical trials, ASHMI has been shown to have long-lasting therapeutic benefits, unlike other treatments, and to be effective as a stand-alone therapy for moderate-to-severe asthma. Its effects were comparable to the conventional pharmaceutical steroid drug prednisone in improving lung function and reducing levels of serum immunoglobulin E (IgE; an antibody involved in allergenic diseases); but, unlike prednisone, it did not exhibit adverse side effects.[3] In a four-week clinical study of adults, ASHMI normalized Th1 immune functioning (i.e., the part of the immune system that protects against microbial and viral infections, which is often deficient in highly allergic patients) and moderated Th2 function, which is associated with allergies. It also reduced reliance on beta-2 agonists such as inhaled bronchodilator drugs that are used to relax the muscles lining the airways during asthma attacks. Further, cortisol levels remained normal unlike with steroid use, which causes adrenal suppression. Phase I human clinical trials showed positive safety and tolerability. In children with asthma, with or without allergic rhinitis, a combination therapy of ASHMI and inhaled steroids was found to be safe and more effective than steroids alone. It is well-established that asthma is a heritable condition, influenced by the environment, and modified by in utero exposures and aging. Interestingly, animal models have shown that desensitizing an asthmatic mother with ASHMI may provide transgenerational benefits and reduce the risk for allergic asthma in offspring.[2,4]

Dr. Li's team has also developed the first botanical Investigational New Drug (IND) for food allergies and carried out the first clinical trial of a therapy directed at *multiple* food allergies. Food Allergy Formula 2 (FAHF-2) is made from 46% reishi mushroom, 20% Chinese plum (*Prunus mume*, Rosaceae), 6% gold thread (*Coptis chinensis*, Ranunculaceae) root, 6% Asian ginseng (*Panax ginseng*, Araliaceae) root, 6% ginger (*Zingiber officinale*, Zingiberaceae) root/rhizome, 6% angelica (*Angelica sinensis*, Apiaceae) root, 4% Amur cork tree (*Phellodendron amurense*, Rutaceae), 4% true cinnamon (*Cinnamomum verum*, Lauraceae) bark, and 2% prickly ash (*Zanthoxylum simulans*, Rutaceae) peel.[5]

In animal models, FAHF-2 completely blocked anaphylaxis in mice. Moreover, it provided persistent protection for 50 weeks after treatment versus the 2-4 week protection provided by conventional pharmaceutical drug therapy. In human studies, it was shown to be safe and have immunomodulatory effects on T cells and suppress basophil activation. However, due to the large dose requirement of this formula, nearly 50% of patients reported poor compliance. To ease compliance, the research team used butanol purification to concentrate the active compounds in an extract, resulting in B-FAHF-2. The modified formula reduced the required daily dose by 80% to just six pills and was nine times more potent than FAHF-2 in suppressing IgE production by human B cells. Dr. Li and colleagues discovered that berberine (BBR; a key isoquinolone alkaloid found in gold thread root) is a key compound that inhibits IgE production by human B cells; the team would like to create a formula composed of specific bioactive components, enhance BBR bioavailability and absorption, and use nanotechnology to encapsulate BBR — all of which would reduce dosage requirements.

Dr. Li has found that if she can connect the classical TCM formulas with pathology recognized by Western physicians, she may get a head start on finding cures. Before she had the idea to test Chinese herbs for food allergies, she had tested at least 10 different types of immunotherapy. Since the symptoms of food allergies overlap with those of parasites, Dr. Li made the leap to try an herbal formula for parasites. Each of the ingredients was tested individually, but it was revealed that the whole package was more effective than any lesser combination and that it acted on multiple cells involved in the allergic response. While it is possible to follow these herbal treatments under the care of a professional or individually, both ASHMI and B-FAHF-2 have 8-10 more years ahead of them until they are approved as new drugs.

Non-alcoholic Fatty Liver Disease

Peikwen Cheng, MBA, and Yung-Chi Cheng, PhD — in conjunction with Yale University and Shwu-Huey Liu, PhD — founded the biotechnology company Yiviva to develop evidence-based botanical products to address aging-associated diseases. One of the diseases that Yiviva is tackling is non-alcoholic fatty liver disease (NAFLD), which is common in metabolic syndrome and affects one in three people in the United States. It is the most common liver disease in the United States, Europe, and Asia, and it is a gateway condition to serious chronic diseases. Currently, there are no approved pharmaceuticals for NAFLD. Yiviva has developed an herbal formulation, YIV001 (the contents of which are confidential), that has been shown in preclinical studies to significantly reduce fat and inflammation in the liver. In vitro and in vivo studies are currently underway. Since it is being developed as a dietary supplement, YIV001 will likely get to market in one year instead of the 12 years on average that drug approval requires.

Gastrointestinal & Inflammatory Side Effects of Chemotherapy

In a separate effort, Dr. Yung-Chi Cheng tested an herbal mixture that has been used more than 1,800 years as the basis for PHY906 to reduce the gastrointestinal side effects of chemotherapy while enhancing the effects of cancer treatment. The proprietary pill consists of four herbs — Chinese skullcap (*Scutellaria baicalensis*, Lamiaceae) root, Chinese licorice root, Chinese peony (*Paeonia lactiflora*, Paeoniaceae) root, and Chinese date tree (*Ziziphus jujuba*, Rhamnaceae) fruit — based on an ancient recipe called *Huang Qin Tang* traditionally used to treat nausea, vomiting, and diarrhea. In a Phase I study funded by the US National Institutes of Health's (NIH) National Cancer Institute (NCI), mice undergoing chemotherapy that were given PHY906 lost less weight and experienced more anti-tumor activity than mice not given the formula. The herbal formula reduced chemotherapy toxicity by inhibiting inflammation and promoting creation of new intestinal cells. Of probably little surprise to those who are experts in the use of herbs and medicinal plants in therapy, the plants in the formula were found to have a synergistic effect that diminished if any one herb was removed.[6] Thanks to an NCI grant, PHY906 is currently in Phase II clinical trials at Yale University and the University of Pittsburgh for people undergoing irinotecan chemotherapy for colorectal cancer.* The study's primary outcome measures the effect of PHY906 on irinotecan toxicity, with the goal of achiev-

* There may be future development or off-label usage, given the strong Phase I clinical trial data for PHY906 and other indications and therapies, including PHY906+Xeloda and PHY906+Nexavar for hepatocellular carcinoma, as well as PHY906+Xeloda and PHY906+Gemzar for advanced pancreatic cancer.

Licorice *Glycyrrhiza glabra*
Photo ©2015 Steven Foster

ing a 30% reduction in the overall incidence of grade 2-4 toxicity.†

Koraljka Gall Troselj, MD, PhD, senior research associate at Croatia's Rudjer Boskovic Institute, spoke about the potential use of curcumin, a group of polyphenols derived from the turmeric (*Curcuma longa*, Zingiberaceae) rhizome, for combined cancer therapy. Dr. Gall Troselj acknowledged that much recent research has documented that curcumin has many activities related to cytokines, has been shown to be a strong inhibitor of NF-kappaB activity (a mediator of inflammatory reactions), and often leads to cellular apoptotic response (normal, programmed cell death). It also exhibits antibacterial, antioxidant, and anti-arthritic properties, has hepato-, uro-, neuro-, and cardio-protective effects, and is thrombosuppressive. There is a strong link between inflammation and cancer, mediated by NF-kappaB, including human papilloma virus (HPV) and cervical cancer, smoking and lung cancer, and microbial infections. Signaling pathways activated by NF-kappaB commonly result in cellular proliferation. Further, the link extends into the area of cancer treatment with chemotherapy-induced cellular damage and the consequential inflammatory reaction, which may lead to resistance to cytostatic agents. As shown in various cell line models, curcumin can, through its inhibitory effect on NF-kappaB, synergistically add to the antiproliferative action of the cytostatic agent. However, the effect strongly depends on timing. In the majority of in vitro studies, this effect takes place only if curcumin is administered several hours before the cytostatic agent. If given in the reverse order, the effect is antagonistic. In a review of current research, Dr. Gall Troselj has found that the animal studies are promising but highly variable.

Inflammatory Bowel Disease

Longgui Wang, MD, executive director of Natrogen Therapeutics International, took a TCM formula (*Danggui Longhui Wan*) that reduces symptoms of chronic myeloid leukemia and — using what he considers its primary active herbal component, *qing dai* (*Indigo naturalis*‡) — developed a formula known as Natura-alpha. According to Dr. Wang, Natura-alpha is a derivative of indiribin, a compound found in *qing dai*. At high concentrations, Natura-alpha inhibits cyclin-dependent kinases (cdks). At low concentrations, Natura-alpha selectively blocks phosphorylation, thereby inhibiting pro-inflammatory cytokine expression and stimulating the anti-inflammatory cytokine IL-10. Dr. Wang believes that Natura-alpha may have other applications, including for use in inflammatory bowel disease (IBD). Currently, Natura-alpha is in Phase II trials for the treatment of ulcerative colitis, which is the most common form of IBD.

Importance of Natural Products

Eric Patridge, PhD, founder of ChemStats, discussed the importance of natural products in developing new antibiotics. While Dr. Patridge was a research associate at Yale's Natural Products Lab, he was part of a team that examined all 14,053 new molecular entities (NMEs) that were FDA-approved and not reformulated as of the end of 2013.[7] This is important because, even as the problem of antimicrobial resistance expands, the cumulative number of FDA-approved antibiotic NMEs on the market has been decreasing. Only 62% of these NMEs are currently available as fewer antibiotics are being approved and more are exiting the market. Further, many pharmaceutical companies have abandoned this space, including Pfizer, Eli Lilly, Bristol-Myers Squibb, Johnson & Johnson, Bayer, and AbbVie, as antibiotics are not as lucrative as drugs for chronic conditions. Yet, as multiple reports confirm, "[t]he true cost of antimicrobial resistance would be $100 trillion and 300 million premature deaths if no action was taken between now and 2050."[8]

As Dr. Patridge pointed out, natural products, and microbes in particular, may be the key to developing a new pipeline of antibiotics. Specifically, since 2000, 77% of FDA-approved antibiotics have been natural products derived from microbes. In looking toward the ancient origins of bioactive natural products, it is interesting to note that some of the first antibiotics were derived from fermented soybean curd and early African Sudanese beer fermented with *Streptomyces* fungi. One innovative model in this arena is the Small World Initiative (www.smallworldinitiative.org), a crowdsourcing program that aims to develop new antibiotics from soil microbes that was formulated at Yale in 2012 and is now being managed by ILSC.

New Guidelines and Information

Pudupakkam K. Vedanthan, MD, president and founder of Global Chest Initiatives, covered his experience treating asthma and allergy patients and training doctors in the developing world. Through this work, he often sees patients taking natural remedies and speaks of the need to educate both patients and providers. In particular, he cautioned that just because something is natural and works on a specific condition does not mean that it can be safely used. He also highlighted a new source of information — the Traditional Knowledge Digital Library (www.tkdl.res.in) — which contains 1,200 herbal formulations selected from the classical texts of Ayurveda, Unani, and Siddha traditional systems of medicine. This library, offered in five languages, was undertaken as a collaborative project between the Indian Council of Scientific & Industrial Research and the Department of Ayurveda, Yoga & Naturopathy, Unani, Siddha and Homeopathy (AYUSH). In addition, India's National Center for Complementary and Alternative Medicine is funding three Centers of Excellence to explore TCM therapies.

Gary Deng, MD, PhD, at Memorial Sloan Kettering Cancer Center discussed how, over the last 13 years, he has worked to incorporate natural products into a general approach to oncological care. After overcoming resistance from mainstream physicians, he has worked to disseminate evidence-based knowledge on natural products to doctors and patients. Since many patients with cancer are interested in complementary and alternative medicine, Dr. Deng stressed the importance of providing accurate information. For example, popular natural products used by patients may inadvertently detox chemotherapy treatments, increase bleeding tendencies, or heighten estrogenic effects. For these reasons, Dr. Deng has been generating a natural products database based on pharmocokinetic and pharmacodynamic effects matched with prescribed treatments. As a result, he provides information to doctors and patients about what helps and what might be counterproductive. In addition, his team developed a website of educational materials[9] to share knowledge on dietary supplements, the "About Herbs" app, and three clinical practice guidelines backed by the NIH Clinical Practice Guidelines Clearinghouse.

Improvements Needed for TCM

Several speakers tackled the challenges of bringing TCM into Western medicine. In particular, they highlighted the issues of quality control (QC) and determining mechanisms of action.

Dr. Yung-Chi Cheng stressed the importance of ensuring product QC, including that the right high-quality species is used, there is no adulteration with other substances or contamination with heavy metals, and a standard procedure for harvesting and preserving herbs is employed. As covered extensively by the American Botanical Council in response to the New York Attorney General's recent investigation, the use of the DNA barcoding method to test herbal dietary supplements, particularly botanical extracts, is problematic.[10] A novel approach is required to determine what to measure and how to measure it. To assess quality, Yiviva has created its own patented QC platform, Phytomics, which integrates unique chemical and biological fingerprints. The fingerprint technology measures more than 100 parameters to ensure consistency even for complex botanical mixtures. A simplified analysis could occur once chemicals relevant to the pharmacological activity are determined. According to Peikwen Cheng, Phytomics has allowed Yiviva to achieve more than 90% consistency in its herbal preparations over a 10-year period.

To develop novel solutions from TCM and gather evidence-based information, Yiviva has also developed its own proprietary database — STAR (Signal Transduction, Action and Response) Discovery Platform — and screened over 250 herbal formulations across 30 signal transduction pathways. This has provided Yiviva's team with greater insight into how different botanicals affect biological responses, including inflammation, immunomodulation, and hormones, and the team is using bioinformatics to mine this database. A challenge in determining the mechanism of action in TCM is that Western medicine tends to follow a single target/single chemical reductionist approach while TCM goes after a multiple target/multiple herb polychemical and herbal interaction approach. Drs. Cheng and Li believe that multiple targets should be entertained more often in Western medicine as one herb can make another herb more effective and can affect the larger immune system. By looking at them one at a time, Dr. Li cautioned that researchers may be missing out.

While there are limited financial incentives or regulatory requirements to study dietary supplements, Dr. Cheng stressed the importance of additional studies to determine proper dosages, schedules, and durations of treatment; ensure safety; and examine potential interactions with other treatments. Furthermore, studies are needed to determine the microbiota impact on herbs and vice versa, mechanisms of action of herbal formulas for each indication, and determination of active compounds. This will help traditional

† NCI has developed Common Terminology Criteria for Adverse Events, which are reported by grade on a scale of 1 to 5 (1=mild, 2=moderate, 3=severe [hospitalization required], 4=life-threatening [urgent intervention required], 5=death related to adverse event).

‡ *Qing dai* (pharmaceutical name: *Indigo naturalis*) is a preparation of five botanicals: *Baphicacanthus cusia* (Acanthaceae), *Polygonum tinctorium* (Polygonaceae), *Indigofera tinctoria* (Fabaceae), *Isatis indigotica* (Brassicaceae), and *I. tinctoria*.[13]

medicine advance from being experience-based and often vague to evidence-based and more information-rich medicine. To this end, Dr. Cheng chairs the Consortium for the Globalization of Chinese Medicine (CGCM) to bring government, academia, and industry together to advance the field of Chinese medicine.

Regulatory Issues — Dietary Supplements vs. Drugs

A panel on regulatory issues brought together the expertise of Target Health Inc.'s team. Target Health is a full service contract research organization dedicated to all aspects of drug and device development. Its president, Jules Mitchel, PhD, highlighted a new online database of country-specific clinical research regulatory information that the NIH's National Institute of Allergy and Infectious Disease (NIAID) is developing to save time and effort in planning and implementing clinical research (https://clinregs.niaid.nih.gov/index.php).

Glen Park, PharmD, Target Health's senior director of clinical and regulatory affairs, defined the well-known differences between dietary supplements and drugs. For a botanical to become a drug and gain marketing approval via the US Food and Drug Administration's (FDA) Botanical Drug Approval process, all safety and efficacy requirements must be met on a pre-market approval basis. However, initial human studies do not require animal toxicology studies if the botanical has extensive use as dietary supplement. Due to cost and time, only two botanical drugs have so far been approved by the FDA (e.g., Veregen® [sinecatechins], an extract of dried green tea [*Camellia sinensis*, Theaceae] leaves for the topical treatment of external genital and perianal warts, and Fulyzaq® [crofelemer], derived from red sap of the *Croton lechleri* [Euphorbiaceae] tree bark to relieve symptoms of diarrhea in patients with HIV/AIDS taking antiretroviral drugs).

One of Target Health's regulatory affairs experts, Mary Shatzoff, provided examples to demonstrate how similar products may fall into different categories. For example, capsaicin, the active component in chili pepper (*Capsicum annuum*, Solanaceae), can be regulated as a dietary supplement, an over-the-counter (OTC) drug, or a prescription drug. If the product is in oral form, it can be regulated as a dietary supplement as long as there are no therapeutic claims. However, if the capsaicin product is in topical form, it is regulated as an OTC drug at concentrations below 0.25% and as a prescription drug at concentrations above 0.25%. The 8% topical concentration is approved only for the management of neuropathic pain associated with postherpetic neuralgia. Shatzoff also described how digestive enzymes are regulated based on the source of the compounds and the evidence of historical safety and label claims. Digestive enzymes of animal origin are considered drugs and regulated according to a *Federal Register* announcement[11] in 2004 and the FDA Exocrine Pancreatic Insufficiency Drug Product FDA Guidance.[12] On the other hand, enzymes of bacterial, fungal, or plant origin are considered dietary supplements and regulated per DSHEA. HG

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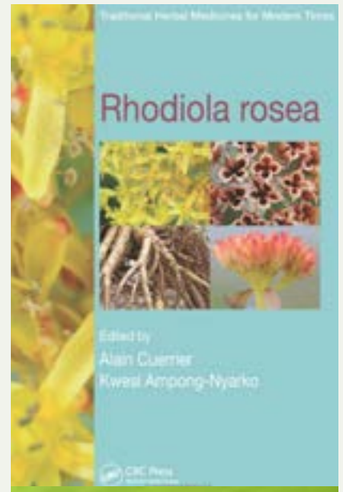

Available in the ABC Online Bookstore

Over the past 35 years, many once-obscure herbs have become well known and gained popularity in the marketplace. Herbs such as echinacea (*Echinacea* spp., Asteraceae), saw palmetto (*Serenoa repens*, Arecaceae), turmeric (*Curcuma longa*, Zingiberaceae), black cohosh (*Actaea racemosa*, Ranunculaceae), St. John's wort (*Hypericum perforatum*, Hypericaceae), and milk thistle (*Silybum marianum*, Asteraceae) have become familiar to people worldwide and are readily available. Occasionally, a little-known regional herb will break through and join the ranks of major medicinal plants. In the last decade, maca (*Lepidium meyenii*, Brassicaceae), reishi mushroom (*Ganoderma lucidum*, Ganodermataceae), holy basil (*Ocimum tenuiflorum*, Lamiaceae), cat's claw (*Uncaria tomentosa* and *U. guianensis*, Rubiaceae), ashwagandha (*Withania somnifera*, Solanaceae) and the northern circumpolar adaptogen *Rhodiola rosea* (Crassulaceae; also known as rose root due to the root's odor, which is reminiscent of rose geranium [*Pelargonium graveolens*, Geraniaceae]) all have gained significant prominence.

One commonality that several of these herbs share is that they are considered to be adaptogens. Adaptogens are herbs that enhance the body's ability to better cope with a wide range of non-specific stressors including psychological, noise, temperature, exercise, or environmentally induced stress. Human and animal research suggests that rhodiola (as well as ashwagandha, holy basil, and reishi) has many of these functions. It is no wonder that in our overly busy, action-packed lives this type of herb would find broad acceptance.

Each of these herbs has a long history of use by native peoples and in traditional systems of medicine. The roots of several species of rhodiola have been used for millennia in traditional Chinese, Tibetan, Russian, Central Asian, and Scandinavian medical practices. Modern clinical, phytochemical, horticultural, animal, and laboratory research on various *Rhodiola* species is voluminous and, until recently, was scattered throughout many journals and often not written in English. The only two books solely focused on rhodiola were popular books that, while useful for introducing this "new" herbal medicine to a wider audience, had limitations. The first, *Arctic Root (Rhodiola Rosea): The Powerful New Ginseng Alternative* by Germano and Ramazanov (Kensington Publishing, 1999), lacked the scientific rigor and depth to be a highly useful text. The second, *The Rhodiola Revolution* by Brown and Gerbarg (Rodale Books, 2005), is much more informative but is almost 10 years old, written for a lay audience, and focuses solely on medicinal usage of this plant (the authors are psychiatrists who are familiar with rhodiola research and use rhodiola supplements in their clinical practices). For professionals needing an authoritative text, clinicians, phytochemists, herb growers, pharmacognosists, and botanists, the wait is now over.

The editors of this volume are well qualified for this task. Alain Cuerrier, PhD, is a botanist and ethnobotanist who has published widely on the use of plants by native Canadian peoples.[1] He also has a special interest in rhodiola and has beautiful specimens growing at the Jardin Botanique de Montréal, with which he is associated. Kwesi Ampong-Nyarko has for many years worked with Alberta Agriculture and Rural Development creating the technology and expertise needed to develop commercial cultivation of rhodiola. This has led to a new high-value agricultural product for Canada. Other contributors include Richard Brown, MD, and Patricia Gerbarg, MD, authors of *The Rhodiola Revolution*, the most comprehensive and best of the popular accounts on rhodiola and an extensive cover story on rhodiola in *HerbalGram* 56 in 2002[2]; John T. Arnason, PhD, an authority on natural products chemistry and biopharmaceutical sciences; and Alexander Panossian, PhD, and Georg Wikman, two of the world's leading researchers on adaptogenic plants and the clinically tested proprietary extract Rhodiola SHR-5, and co-authors of numerous clinical trials and related research on rhodiola. (Gerbarg, Arnason, and Panossian are members of the American Botanical Council [ABC] Advisory Board.)

The book is divided into 12 chapters, with in-depth discussions of rhodiola taxonomy, ethnobotany, conservation, phytochemistry, cultivation in Europe, Canada and Alaska, diseases affecting rhodiola, biotechnology, pharmacological activities of the plant, research on Rhodiola SHR-5, the use of rhodiola in psychiatry and medical/herbal practice, its toxicology and safety, and the commercial development of this medicinal herb. No matter which topics you find of interest, the well-written chapters will provide the reader with detailed and up-to-date information, impossible to find in any other single text.

As a clinician, I was immediately drawn to the chapters on ethnobotany, medicinal uses of rhodiola, and its toxicology. Even though I am well acquainted with this herb and its uses, I still found information that was new to me. The use of rhodiola extract in toothpaste to treat gum disease and an adjunctive treatment for ADHD, PTSD, and cancer is not well known. Also of interest was the discussion of the use of

rhodiola as a selective estrogen receptor modulator (SERM) to enhance fertility in women in their 40s for whom in vitro fertilization techniques have failed.

In rose root's far northern habitat, it is a slow-growing and overharvested plant. As this botanical gains popularity and commercial success, it is imperative that large-scale cultivation replace wild-harvested roots. While I have never grown this herb, the chapters on cultivation of rhodiola (which include common diseases of the plant, soil requirements and amendments, methods to enhance crop yields, effective propagation practices, and proper harvesting and drying techniques) are a detailed primer for the successful growing of a high-quality medicinal product.

My only criticisms of this excellent book are minor. I would have liked a few color photographs of healthy fresh and dried rhodiola roots (there is a color picture of a diseased root). A chapter on the pharmacognosy of rhodiola with macroscopic and microscopic details would have been highly useful for organoleptic analysis of dried rhodiola, helping manufacturers to determine whether they actually have *R. rosea* or another related species. In addition, a chapter on the human and animal research that has been conducted on other rhodiola species (*R. crenulata*, *R. imbricata*, *R. kirilowii*, etc.) would have been appropriate, as these studies are only briefly mentioned in the ethnobotany section. My last issue, one that is common with scientific publishers, is with the cost of the book ($129.95). The publisher offers a 10% discount on the title if purchased from their website (the same discount applies to ABC members when purchased via the ABC eStore), but it still is rather expensive for the researcher or clinician who does not have the resources or funding to purchase the book.

It is always possible to do more, to add another last-minute reference or additional chapter, or to have another authority to look over the proofs. The nature of book publishing is there are deadlines, budget constraints, and sometimes word limits. Even with the reality that is commercial publishing, this book succeeds in almost every way and will be an essential text for anyone wanting to use, research, or grow this remarkable plant. HG

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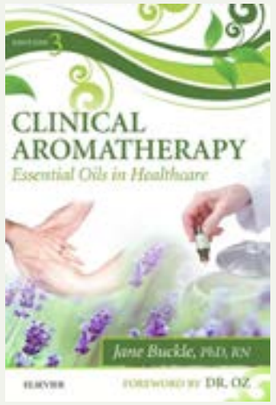
Clinical Aromatherapy: Essential Oils in Healthcare, 3rd ed., by Jane Buckle. St. Louis, MO: Churchill Livingstone, an imprint of Elsevier, Inc.; 2015. Paperback, 418 pages. ISBN: 978-0-7020-5440-2. $66.95.



This is the first peer-reviewed, evidence-based book on clinical aromatherapy and includes reviewers from around the world. The wide-ranging applications of essential oils, from beauty aids and pharmaceuticals to cleaning products and beverage ingredients, explains why these plant extracts were a billion-dollar industry in 2013. Jane Buckle's, PhD, RN, third edition of this book (which includes additional tables, updated citations, and new chapters) is evidence of the popularity and importance of this subject. The book's foreword by Mehmet Oz, MD, confirms an interest from the integrative medical community, and may encourage others to take another look at essential oils as viable phytotherapeutic agents in integrative and, perhaps, primary health care.

The author provides an excellent overview of how essential oils can contribute to a healthier medical system, enhancing patient care and lowering medical costs at a critical time in this community. Nurses have been the champions of aromatherapy in healthcare settings, as demonstrated by the many studies conducted by Dr. Buckle's students, but this book may encourage physicians to take a closer look at the potential of essential oils as a viable option in some primary-care situations, especially when antibiotics fail. This text examines issues within conventional and integrative medical practices with applications relevant to a variety of settings and circumstances. Rigorously cited with an impressive number of references, even the harshest skeptic will be convinced by the author's thorough research and personal clinical experience that there is no better authoritative voice to bring forth this important information that is pertinent for our time.

The book is divided into three sections:

"Section I: Overview" provides basic historical background on the emergence of aromatherapy in different cultures up to modern times, and it parses out the three main segments of aromatherapy practice in aesthetic, holistic, and clinical care. Chapters in this section include: "The Evolution of Aromatherapy," "How Essential Oils Work," "Basic Plant Taxonomy, Basic Essential Oil Chemistry, Extraction, Biosynthesis, and Analysis," "Essential Oil Toxicity and Contraindications," "Aromatherapy and Integrative Healthcare," and "The 'M' Technique®" (a hands-on technique for persons who cannot receive conventional massage, or for those not adequately trained in massage). By reporting on the pharmacokinetics of essential oils, the author helps clarify the misunderstood theories and misuse of dermal and respiratory absorption; in addition, Dr. Buckle expounds on the involvement and role that the brain plays in the effects and applications of aromatherapy in physiological and psychological health. Section I even tackles the much-maligned and misconstrued subject of internal uses via oral, vaginal, and rectal applications.

The chapter on taxonomy, essential oil chemistry, extraction methods, and analysis includes information on how to assess and obtain high-quality oils. Some practitioners may consider this topic irrelevant to medical practice, but Dr. Buckle makes a clear case for the need to understand this material in order to use aromatherapy to its fullest potential. The toxicity and contraindication chapter provides readers with details on how to cultivate a healthy respect for the power of these very concentrated, (mostly) distilled extracts and their safest applications.

As a nurse, the author's many years of experience come to bear in Chapter 5, in which she discusses the various ways of incorporating aromatherapy into an integrative model of health care. Outlining the many instances of this integration, Dr. Buckle provides copious examples of healthcare systems in a variety of states in America and countries throughout the world that have adopted an integrative model for incorporating essential oils in patient care. The chapter includes a discussion on how a practitioner might go about bringing this modality to a more skeptical organization, as well as a detailed guide of how to create a hospital clinical aromatherapy policy. Dr. Buckle's extensive research is apparent in the explanation of her own registered method of gentle touch for fragile, distressed, or dying patients known as the "'M' Technique," a new subject for this edition, and the dozens of facilities using it.

"Section II: Clinical Use of Aromatherapy" covers a broad range of evidence-based applications for essential oils in a medical setting, which includes efficacy data and chapters on infections, insomnia, nausea and vomiting, pain and inflammation, and stress and well-being. The data on drug-resistant pathogens is particularly relevant in this era of the situational failing of antibiotics. The author has paid explicit attention to this subject in Chapter 7, "Infection," an extremely well-referenced section that contains more than 200 citations — a significant increase from the previous edition. The subsection, "Evolutionary Pharmacology," at the end of this chapter discusses a topic familiar to most clinical aromatherapists: that of non-standardized essential oils (NSEOs). The author makes a good case for using whole essential oils, foregoing isolates or fractions sometimes known as standardized essential oils (SEOs). Isolating what some consider "active" ingredients dismisses the synergy of other constituents that may contribute to how and why essential oils are less susceptible to pathogenic resistance than SEOs, a topic with which many phytotherapists are familiar for various reasons.

"Section III: Aromatherapy in Clinical Specialties" spotlights the clinical potential of aromatherapy within specific medical departments and addresses elder care, intensive care, dermatology (viruses, fungi, and acne), mental health, oncology, pediatrics, respiratory care, women's health, and palliative, hospice, and end-of-life care, many of which are new to this edition. The numerous citations go beyond animal studies and reference clinical research, which she establishes is available more often than is perceived.

Despite the excellent overview of Section I, this is not a beginner's book; it contains no *materia medica* or detailed formulas. It is, however, an excellent review of how essential oils are being used currently in medical facilities and their potential for incorporation into a wider range of clinical settings. While simply reading this information is not enough to qualify one as a skilled practitioner, it certainly will help to expand a reader's understanding of the current scope and future prospects of the practice of aromatherapy and advance further investigation of the great potential of one of the most powerful and misunderstood forms of phytotherapy available today.

Even the most conservative of medical professionals cannot deny the body of evidence compiled in this book and the relevance for clinical aromatherapy to take its rightful place in the therapeutic arsenal against a wide variety of human ailments. Dr. Buckle makes this complex subject easy to understand, whether the reader is exploring for the first time the viability of essential oil use or is experienced with these particular plant distillates. The third edition of *Clinical Aromatherapy* is an excellent guide for the clinically inclined aromatherapist, and it will enrich the role of healthcare professionals in their exploration, development, and understanding of the value of aromatic oils and their extensive benefits in primary, integrative, and palliative care, or in any holistic setting. It is thoughtfully laid out, very well organized, and of great value for forward-thinking pharmacists and anyone interested in expanding their use of phytotherapy.

I highly recommend this book, both as a resource and a highly informative read; the compilation of bibliographic citations alone is significant. Some of the most useful summaries for quick-scanning data are the "Chapter Assets" on chapter title pages, where tables and page numbers offer accessible, organized, and relevant information. A broader range of essential oil suppliers for the United States may have been useful for American readers (the book was written in the United Kingdom), but these are also available through mining some of the other US resources provided. HG

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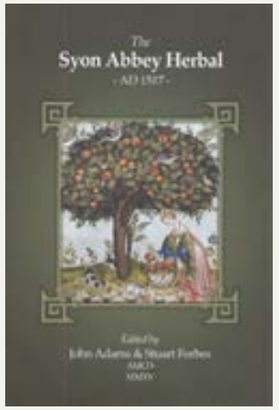
BOOK REVIEWS

The Syon Abbey Herbal — AD 1517: The Last Monastic Herbal in England by John Adams and Stuart Forbes, eds. London, UK: AMCD Publishers; 2015. Hardcover, 376 pages. ISBN: 978-1897762-69-1. $54.00.



That the 2015 publication date of this book coincides with the 600th anniversary of the founding of Syon Abbey in the United Kingdom is no coincidence. Both editors of this book are research associates at the abbey, where extensive archaeological and historical studies are attempting to reveal the details of a wealthy monastic establishment that was suppressed and completely leveled by King Henry VIII in 1539. Now home to the Duke and Duchess of Northumberland, the property is open to the public and supported by an active Syon Abbey Society.

The history of the abbey and its library is detailed throughout the book, albeit in chunks that can be difficult to follow. The authors attempt to create a coherent history, but the reader soon learns that the title of this book, as well as the dust cover illustration, is somewhat misleading.

The dust cover features a garden scene with a pomegranate (*Punica granatum*, Lythraceae) tree, clearly suggesting an herbal. However, just like the handwritten 1517 original, the book itself has no plant illustrations. The cover image actually comes from an Austrian medical manuscript dated a century earlier. In Appendix 3, the editors speculate that botanist William Turner, who stayed at the abbey not too long after the monastery's dissolution, may have encountered such a tree on the grounds. As Adams and Forbes explain, "Turner may have found still growing at Syon plants which had been generally in the monastic medical repertoire." They surmise one such plant might have been a pomegranate tree, which could have survived until Turner's stay. The connection is a stretch, and a good deal of the appendix is tenuously linked to the famous botanist. Although Turner can be linked to the location of the monastery itself, very little, if any, of his work can be directly linked to the monastery, its library, or its garden.

It is not easy to accept what Adams and Forbes call the "Syon Abbey Herbal" as an actual monastic herbal. Instead, the book so titled contains excerpts from a personal notebook compiled over time by the librarian at Syon Abbey, Thomas Betson, a priest who at age 45 retired there to live out the rest of his life. What the editors call the "herbarium" is simply a list of medicinal plants that they couple to a random, unassociated group of herbal remedies. Also included with them is a section entirely in Latin on use of urine for diagnoses. Middle English is also used in the text, and for the many readers unfamiliar with either language, translations would have been most welcome for everything, not just for the plant list. Some translations are provided for Middle English terms, but very few for Latin. Because of this issue, the book will be challenging for the general reader, to whom this volume seems to be aimed, though the intended audience is not apparent.

As far as the list of plants and unassociated remedies is concerned, the editors say they have found no clue as to why, when, or where Betson wrote them down. No link can be established to the monastery garden, its medicinal plants, or any medical treatments used at the monastery or in an infirmary. As the editors write, "We have in fact no evidence that Betson, or any other member of the Syon Abbey community, male or female, had any practical knowledge of herbalism, botany or medicine." It is interesting that the editors often use the term "notebook" to describe Betson's compilation. It would have been much better to use the term "notebook" instead of "herbal" in this book's title, because that is exactly what it is, and no more.

The way in which Betson's plant list, or herbarium, is presented is also misleading, since the tabular format suggests actual correlations between texts and terms. The editors hypothesize that Betson may have used the numerous medical texts in the abbey library to compile his plant and remedies lists, as supposedly detailed in Appendix I. Unfortunately, the list is nowhere to be found — a shame, as it would have been of great interest to medical historians. This is the list one would expect to be cited in the table.

Instead, the editors located a work called the *Synonyma de nominibus herbarum* by John Bray (spelled *Synonoma* by Betson) in the British Library's Sloane Manuscripts Compendium 282, from ca. 1381, which they claim to be the basis for Betson's plant list, though it was never at Syon Abbey. They say Betson used it and, for this reason, present it beside Betson's plant list in the form of a table. Do they offer any proof that Betson ever saw the *Synonyma*? Well, no, not exactly, and one wishes they had provided such evidence. Because none of the plants in the table can be linked to the abbey, to the remedies Betson had in his notebook, or to any garden at all, the postulated source is rather irrelevant, other than that it may have been of some interest to Betson. The translations of the plant names provided as the third element in the "herbarium" table (using Tony Hunt's cited works) give it an authoritative look, but to what end?

Truth be told, the content of Betson's notebook might have been more valuable to historians if it were published in its entirety under that name, including — with translations into modern English — the study of a sad love affair at the abbey (not titled "Mental Health and Syon"!), notes about mirrors, canon law, jokes, astrology, and so forth. Such a book could be accurately considered a compendium of topics of interest around the year 1500, one of them being medicinal herbs and health. HG

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University of New Mexico

New Book Profiles

Medicinal Plants of Texas by Nicole Telkes. Cedar Creek, Texas: Wildflower School of Botanical Medicine Publishing; 2014. Softcover, 191 pages. ISBN: 9780615767567. $35.73.

Founder and director of the Wildflower School of Botanical Medicine, Nicole Telkes has compiled a collection of short profiles to form a *materia medica* of native medicinal plants found in Texas. Taking the unique Texas growing seasons into account, Telkes draws upon 15 years of personal experience and harvesting to describe 140 common wild plants, including their traditional uses, peak harvesting period, and the medicinal components of each plant. The monographs are consistently laid out and include color photographs of each plant as well as warnings for toxic or potentially toxic herbs, such as jimsonweed (*Datura wrightii*, Solanaceae) and chinaberry (*Melia azedarach*, Meliaceae). The back material contains a glossary of botanical and medicinal terms, additional resources for further research, references, and an index with both common names and Latin binomials.

A Practical Approach to the Science of Ayurveda: A Comprehensive Guide for Healthy Living by Acharya Balkrishna. Haridwar, India: Divya Yog Mandir Trust; 2013. Softcover, 359 pages. ISBN: 978-8189235888. $35.00.

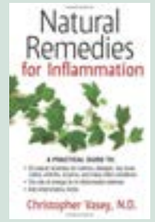
A Practical Approach to the Science of Ayurveda highlights the basic principles of one of the world's oldest medicine systems. The text allows the reader to understand his or her constitution, ailments in the body, and ways to eradicate such ailments. In 10 chapters, the author introduces the fundamental principles of Ayurveda, including the five basic elements, three biological humors, and how they interact with the body as a whole. In addition, the text covers diet and nutrition, diseases and examinations, treatment methods, and the importance of yoga in therapy. The back material contains an appendix and glossary, which lists the botanical names of the medicinal plants mentioned in the chapters. The text is in full color, with tables, figures, and beautiful art plates that help clarify, organize, and illustrate the information presented.

My Tata's Remedies (Los Remedios de Mi Tata) by Roni Capin Rivera-Ashford. El Paso, Texas: Cinco Puntos Press; 2015. Hardcover, 40 pages. ISBN: 978-1-935955-91-7. $17.95.

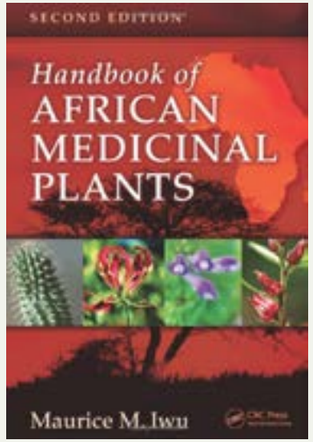
This illustrated children's book introduces readers to herbal remedies and the healing traditions of the American Southwest. With text in English and Spanish, the book is about a young boy named Aaron who learns herbal remedies from his grandfather, or Tata. Tata is known around town as a healer, and he treats a wide variety of simple conditions, including bee stings, toothaches, and burns, with common herbs such as arnica (*Arnica montana*, Asteraceae), aloe (*Aloe vera*, Xanthorrhoeaceae), and mullein (*Verbascum thapsus*, Scrophulariaceae). Both herbal remedies and Mexican culture are celebrated in this book, which is suitable for children ages eight and above.

Natural Remedies for Inflammation by Christopher Vasey. Rochester, Vermont: Healing Arts Press; 2014. Softcover, 192 pages. ISBN: 978-1-62055-323-7. $14.95.

Natural Remedies for Inflammation, previously published in French, has now been translated for the English-speaking market. Christopher Vasey, ND, a naturopathic physician, offers a guide to natural remedies for 50 of the most common inflammation-related ailments such as allergies, arthritis, eczema, and sciatica. The book contains chapters on 18 herbs and 15 other natural products with anti-inflammatory properties. Each herb has its own subsection that contains information on plant parts used, its history of use, healing properties, and dosage. Dr. Vasey emphasizes the importance of omega-3 fatty acids and their role in defending the body against inflammation, and discusses their plant and animal sources. The book, which also includes a chapter on hydrotherapy, is intended to be a guide for readers who choose to eschew conventional pharmaceutical anti-inflammatory medications.



Handbook of African Medicinal Plants, 2nd ed., by Maurice M. Iwu. Boca Raton, Florida: CRC Press; 2014. Hardcover, 506 pages. ISBN: 978-1-4665-7197-6. $139.95.



African traditional medicine has been studied and documented during colonial times; two outstanding examples of books published on this subject in the last century include *The Useful Plants of West Tropical Africa* by Burkill (Royal Botanic Gardens, Kew, 1937) and *Medicinal and Poisonous Plants of Southern and Eastern Africa* by Watt and Breyer-Brandwijk (E & S Livingstone, 1962). The few, more recent publications, such as *Medicinal Plants in Tropical West Africa* by Oliver-Bever (Cambridge University Press, 1986), *Medicinal Plants of West Africa* by Ayensu (Reference Publications, 1978), *Medicinal Plants of East Africa* by Kokwaro (University of Nairobi Press, 1976), and the unfortunately hapless attempt to create an African pharmacopoeia (the first volume of the *Pharmacopée Africaine* was published by the Organization of African Unity in 1985 and the project was subsequently abandoned) remain local or hard to find.

The first edition of the *Handbook of African Medicinal Plants*, published by CRC Press in 1993, constituted a milestone and caused something of a paradigm shift, as it was one of the first publications to expose African traditional medicine to a mainstream academic audience, establish interest, and trigger research for decades to come. Others with similar impacts followed closely on its heels: Neuwinger's *Afrikanische Arzneipflanzen und Jagdgifte* (Scientific Publishing Company, 1994), *African Traditional Medicine* (Medpharm Scientific Publishers, 2000), *Medicinal Plants of Southern Africa* by Van Wyk (Briza Publicaitons, 1997), *Plant Resources of Tropical Africa* (CTA Publishing, 2000), and the *African Herbal Pharmacopoeia* (Association for African Medicinal Plants Standards, 2010), to name just a few.

Twenty years later we are looking at a totally different picture. A Google Scholar search for "African medicinal plants" yielded just under 7,000 hits for the years 1900 to 1993, and just over 44,000 hits for the years 1994 to 2015. The search term "African herbal medicine" retrieved 3,600 results for the years 1900 to 1993 and just over 19,000 for the years 1994 to 2015. While this search strategy could be deemed overly simplistic, it does suggest a trend. The first edition of Iwu's *Handbook* is highly cited and scored about 1,000 hits alone.

Thus, it seems timely that CRC Press decided to publish a second edition of the *Handbook* in 2014. This second edition is not a mere reprint of an older classic; it has been thoroughly updated and expanded. The new edition adds around 30 plant profiles to the original 150, reflecting research trends as well as commercial relevance. The number of references cited increased from 873 to 1,150, including some as recent as 2013. An introductory chapter is followed by a table more than 100 pages long cataloging major African medicinal plants, followed by more in-depth pharmacognostical profiles and rounded off with chapters on African healing cultures, paradigms, healers, and methods of diagnosis and treatment of typical ailments, malaria, sexually transmitted diseases, gastrointestinal issues, and psychiatric disorders, as well as skin diseases and poisonings. Two indices, a subject index and one of species, genera, and plant families, along with detailed contents pages make navigation through the 506 pages quite easy. Sixteen pages of color plant images follow the catalog section, and more can be found throughout the detailed profiles.

Trying to assess completeness and accuracy of the information presented, I searched for entries on particular research interests. Alas, *Pelargonium sidoides* (Geraniaceae) — the primary component of a popular, clinically tested remedy for respiratory tract infections (Umckaloabo®; Dr. Willmar Schwabe GmbH & Co. KG; Karlsruhe, Germany) — is curiously and tragically absent from both the catalog and the profile section; *Harpagophytum procumbens* (Pedaliaceae), commonly known as devil's claw, receives an adequate but insufficiently referenced treatment. However, the coverage of *Sceletium tortuosum* (Aizoaceae) is adequate and up-to-date; the same is true for *Cyclopia* spp. (Fabaceae), or honeybush, except for citations. If this publication wants to raise the claim of being an academic textbook, all facts presented need to be referenced. The purpose of a profile of *Echinacea purpurea* (Compositae [sic!]) appears out of place as it is not an African medicinal plant; rather, the herb was merely introduced for cultivation. More thorough editing would have picked up on the numerous typos and misspellings of plant names and thus further increased the overall appeal. Nonetheless, this volume presents a valuable cross-section of the African medicinal flora and useful summaries of largely up-to-date knowledge.

All in all, this second edition is a worthy successor to the 1993 edition. Even with the numerous typos and misspellings, the *Handbook of African Medicinal Plants* deserves shelf-space in every textbook library, public or private, of those with an interest in African herbal medicine. HG

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Ernst Walter Stieb
1929-2015

Preeminent pharmacy historian Ernst Stieb, PhD, passed away on February 2, 2015, in Oakville, Ontario, Canada. Dr. Stieb's seminal text, *Drug Adulteration: Detection and Control in Nineteenth-Century Britain* (University of Wisconsin Press, 1966), explored the growth of pharmacognosy as a discipline and its relationship with drug adulteration, tracing the history of herb adulteration through more than two millennia, as well as the evolution of analytical techniques, social change, and legislative actions related thereto.

Dr. Stieb, a native of Windsor, Ontario, earned his bachelor's and master's degrees in pharmacy from the Ontario College of Pharmacists and the University of Toronto, respectively; he completed his doctorate in history of pharmacy from the University of Wisconsin in 1959. In time, his major field of study — the adulteration of drugs (including many plant drugs) — became his doctoral thesis, which formed the basis for *Drug Adulteration*. He wrote *Drug Adulteration* in collaboration with his mentor Glenn Sonnedecker, PhD, one of America's key leaders in the area of pharmacy history.

After receiving his doctorate, Dr. Stieb taught history of pharmacy at the University of Wisconsin's School of Pharmacy. He also continued as secretary of the American Institute of the History of Pharmacy (AIHP) and contributing editor of the Institute's publication, *Pharmacy in History*, which he had held since 1957. He served the University and AIHP until 1967, after which he joined the pharmacy faculty at the University of Toronto, assuming the title "Historian of Pharmacy." At Toronto, Dr. Stieb taught, pursued his research, and served in several administrative positions, including assistant dean from 1975-1978, associate dean from 1978-1994, and interim dean from 1993-1994. These roles, according to the tribute posted by the University, "allowed Professor Stieb to shape the course of pharmacy education in Canada and influence generations of pharmacy students."[1]

The impact of *Drug Adulteration* was recognized in academic circles at the time of publishing, and its influence continues today. A review of the text in the journal *Medical History* called it "[A] pioneering achievement … [of] inestimable value, a value which is enhanced with a particularly comprehensive bibliography … which, like the text, can only occasionally be faulted or, in questions of interpretation, queried."[2] Steven Foster, a noted botanist, author, and botanical photographer who has used Dr. Stieb's work as a reference on many occasions, proclaims that it is "one of the most important historical works on medicinal plant adulteration" (email to M. Blumenthal, May 4, 2015).

The ever-looming specter of drug and food adulteration and the role of pharmacists in ensuring safe, effective medicines for their clients created a constantly evolving landscape to navigate. Dr. Stieb stayed active in the field throughout his career, preserving and passing down the history of his field for the betterment of his students and their livelihoods. His contributions to academia and the numerous organizations that he supported through membership and leadership stretch over decades. "From the time he entered the graduate program, Ernie held a teaching or research position," said John Bachynsky, PhD, professor emeritus for the pharmacy faculty at the University of Alberta.[3] "His advancement was based on his scholarly work, which included several books, many historical papers, consulting with a variety of historical and professional organizations and teaching the history of pharmacy."

Dr. Stieb played a proactive role in his field, assuming a remarkable number of leadership positions. He served on many different committees during his tenure at the University of Toronto, as well as on behalf of the Association of Faculties of Pharmacy of Canada (AFPC), co-editing the history of AFPC along with Bernard Riedel, PhD. According to Professor Riedel, Dr. Stieb "has been most active and most influential on the nature of the document which this has become. [He was] a true historian with appreciation for the scientific significance of proper documentation, and of the importance of accurate reporting of facts and details."[3]

Dr. Stieb was also an active member of the American Association of Colleges of Pharmacy, AFPC's American equivalent. He helped found the Canadian Academy of the History of Pharmacy in 1968; he also served as curator of the Niagara Apothecary Museum, on the Canadian Council on Continuing Education in Pharmacy, as a board member and committee member with the Canadian Foundation for Pharmacy, in administrative capacities for the Canadian Hospital Pharmacy Residency Board, and as a consultant and member of the editorial advisory board of the Canadian Pharmaceutical Association (now the Canadian Pharmacists Association).

Outside of his lifelong passion for history and teaching, Dr. Stieb enjoyed traveling, photography, reading, painting and music, and spending time with family, friends, and pets. He is survived by his wife of 60 years, Cathy; his sister, Helen; his children, Sue and Dave; and five grandchildren. A memorial celebrating Dr. Stieb's life was held on February 7, 2015, in Oakville, Ontario. HG

Acknowledgement: *The author would like to thank Dr. John Bachynsky for his detailed information about Dr. Stieb's lengthy career.*

—Hannah Bauman

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Lester A. Mitscher
1931-2015

Natural products chemist Lester Mitscher, PhD, passed away on May 8, 2015, at the age of 83 after a battle with cancer. Throughout his lengthy and lauded career, Dr. Mitscher's research and studies were devoted to naturally occurring antimicrobial and anticancer agents, including the untapped potential of herbal medicines. His work impacted scientists, researchers, students, and the natural products pharmaceutical industry. In particular, he focused on equipping and empowering laboratories in developing countries, holding training workshops at university chemistry departments.

While studying to earn his doctorate from Wayne State University in Detroit, Michigan, Dr. Mitscher had the opportunity to work under the late Carl Djerassi, PhD, on the structure of coffee (*Coffea* spp., Rubiaceae) oil diterpenes. Dr. Mitscher completed his PhD in 1958 and continued to pursue his interest in natural products chemistry, joining the staff of Lederle Laboratories in New York and eventually becoming a group leader in antibiotic discovery. He held the position until 1967, when he left New York to become an associate professor at the College of Pharmacy at Ohio State University. He gained full tenure before accepting a job in the department of medicinal chemistry at the University of Kansas School of Pharmacy in 1975. Though Dr. Mitscher would go on to pursue his interests in the industry and government sectors, he eventually returned to the University of Kansas in 1992. He remained a professor at the University until 2011, when he retired as a professor emeritus. He lent his name to the Lester A. Mitscher Faculty Fellowship in Medicinal Chemistry. During his tenure at Kansas, he also held academic appointments at the University of Missouri in Kansas City and the Victorian College of Pharmacy in Melbourne, Victoria, Australia.

In his work for the nonprofit International Organization for Chemical Sciences in Development (IOCD), Dr. Mitscher blended his research knowledge with a deep sense of philanthropy. "Les developed very simple antibacterial/anti-infective/antiviral assays which could be performed by chemists in typically poorly-equipped developing countries' labs," wrote Michael Tempesta, PhD, who worked closely with Dr. Mitscher at the IOCD (email, June 26, 2015). "[He] incorporated them into hands-on training workshops … in South America and Africa in the late 1980s and early 1990s." This approach allowed scientists to conduct bioassays on various natural materials for active ingredients in their own facilities, negating the need to send samples abroad. "The foresight and cleverness of Les was apparent in this effort to provide powerful tools to chemists in developing countries," added Dr. Tempesta. "Later, Les provided a complete electronic medicinal chemistry course via IOCD, which continues today and is quite popular." Dr. Mitscher always included a session on intellectual property rights, allowing the scientists a better understanding of the patent process for natural products and more control over their own work.

Dr. Mitscher was published widely in the field of medicinal plants, with more than 270 research publications and seven technical books on natural product drug discovery and properties. He was on the editorial board of 20 journals, including the *Journal of Medicinal Chemistry* and the *Journal of Natural Products*, which published a special issue in his honor in 2013. He also consulted widely among industry pharmaceutical firms and for the National Institutes of Health, serving as senior advisory council member of firms such as Abbott Laboratories, Searle Laboratories, and DuPont-Merck, and as a member of the executive committee of the IOCD.

Dr. Mitscher was an active member of the scientific advisory board of Nu Skin Pharmanex, a global producer of natural consumer products based in Utah, for nearly 20 years, according to Mark Bartlett, PhD, vice president of global research and development at Nu Skin. "His expertise and experience as a natural products chemist contributed greatly to our ability to assess new ideas and innovate them into new products, especially in the area of nutrition and phytochemicals," said Dr. Bartlett (email to M. Blumenthal, July 15, 2015). "Dr. Mitscher had a keen sense of humor and an infectious smile. He will certainly be missed by all of us at Nu Skin."

Dr. Mitscher held 15 US and international patents, and his research and writing received numerous awards and recognitions throughout the industry, including the Research Achievement Award in Natural Products Chemistry from the American Pharmaceutical Association (now the American Pharmacists Association) in 1980, the Ernest H. Volwiler Award for Research Achievement from the American Association of Colleges of Pharmacy in 1985, the Higuchi-Simons Award in Biomedical Sciences at the University of Kansas in 1986, the Bristol-Myers Squibb/Edward E. Smissman Award in Medicinal Chemistry from the American Chemical Society in 1989, the Division of Medicinal Chemistry Award from the American Chemical Society in 2000, and the Norman R. Farnsworth Research Achievement Award from the American Society of Pharmacognosy in 2007.

Dr. Mitscher is survived by his wife of 62 years, Betty; sons, Kurt and Mark; three grandchildren; and five great-grandchildren. He was preceded in death by his daughter, Katrina Chapman, and his brother, Ronald. Services honoring his life were held in Lawrence, Kansas, on May 15, 2015. "Les was a very dedicated scientist," concluded Dr. Tempesta, "with an excellent and dry sense of humor — a scientist's scientist, and he will be missed by many." 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, 33 Reserve Street, Annandale, NSW 2038, Australia.

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

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Marshmallow (*Althaea officinalis,* Malvaceae)

Lorinda Sorensen, ND, an assistant professor of clinical sciences at the National University of Health Sciences in Lombard, Illinois, is the winner of HerbalGram's Photo Finish contest for issue #107. (Nikon Coolpix L830 digital camera, 1/800 sec @ F/10 ISO 400 exposure)

Marshmallow grows, as the name implies, in damp areas and salt marshes. Native to Europe and western Asia, it has been naturalized in North America.[1] Due to the mucilaginous nature of its leaves and roots, marshmallow has been used as a traditional treatment for cough, inflammation, and sore throat in Greece and Egypt for over 2,000 years. The German Commission E approved both the leaves and roots for irritation or mild inflammation of the mouth and throat and dry cough.[2] Healers and druggists began using the sticky juice of the mallow root to make lozenges, both for its healing properties and sweet taste,[3] and by the 1800s, French pharmacists developed a confectionery known as *pâté de guimauve*, which was flavored with rose (*Rosa* spp., Rosaceae) water. The marshmallow in the recipe was eventually replaced with egg whites and then gelatin, transforming the *guimauve* into the modern marshmallow confection.[4] HG

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