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Ashwagandha Profile

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Ashwagandha

Withania somnifera

Family: Solanaceae

INTRODUCTION

Ashwagandha is one of the most revered plants in traditional Ayurvedic medicine in India. It is an erect, greyish, subshrub with inconspicuous yellow or greenish flowers followed by small, spherical, orangish-red berries containing yellow, kidney-shaped seeds. It grows three-to-five feet tall, mainly on waste land, but is cultivated widely as the whole plant; most commonly the root and leaf are used medicinally.^{1,2}

The species is widely distributed in the northwestern Indian states of Gujarat, Madhya Pradesh, Maharashtra, Rajasthan, Uttar Pradesh, and the Punjab plains extending to the mountainous regions of Himachal Pradesh and Jammu.³ It also is cultivated in parts of Madhya Pradesh and Rajasthan.⁴ Northwest of India, its habitat extends into the Pakistani provinces of Sindh and Baluchistan, and on into Afghanistan. To the south-east of India, it occurs in Sri Lanka.⁵ In China, it is reported to grow in the western provinces of Gansu and Yunnan.⁶

HISTORY AND CULTURAL SIGNIFICANCE

The species name, *somnifera*, refers to ashwagandha's use as a sedative.¹ The common name comes from the Sanskrit *ashvagandha*,^{2,7} i.e., *ashwa* for horse, and *gandha* for smell, hence the common idea that the name means "smells like a horse." The Ayurvedic health practitioner Vaidya R. K. Mishra states that the translation can be taken literally, or that it could be interpreted to mean "horse essence" and that ashwagandha provides the strength, character, essence, or stamina of a horse.⁸

Ashwagandha is the Bengali name and variations are used in Nepalese (*aasogandha*) and Japanese (*aswangandha*).² Other common names include *asgandh* (Hindi), *amukkara* (Sinhalese), *asgandh valaiti* (Unani), *bahman* (Persian, Arabian), *ba-dzi-gandha* (Tibetan), *kutilad* (Pustu), *amurkkuralckizhangu* (Tamil), winter cherry (English), and *blærebæger* (Danish).^{2,9} It is sometimes errone-

ously called Ayurvedic or Indian ginseng, an incorrect appellation because it is not in the genus *Panax* or in the ginseng family, Araliaceae.¹⁰

Preparations of various plant parts have been credited with the following actions: abortifacient, adaptogenic, alterative, analgesic, antiarthritic, antiasthmatic, antibiotic, antidyspeptic, anti-inflammatory, antimitotic, antiproliferative, antitumor, aphrodisiac, astringent, bactericide, carminative, contraceptive, depurative, diuretic, emetic, febrifuge, fungicidal, hypnotic, immune-modulating, laxative, proteolytic, tonic, and nervine sedative.^{1,2,7,9,11} Additionally, it may have cytotoxic, chemopreventative, and radiosensitizing actions.⁹



Ashwagandha *Withania somnifera*. Photo ©2013 Steven Foster

Ashwagandha is one of the *rasayana* herbs in Ayurveda — one of the herbs that purportedly promotes youth and longevity and alleviates suffering.¹² It is thought to be especially rejuvenative for men; to strengthen bone marrow, muscle, and semen; and to imbue the user with intellectual facility, in addition to long life and youthful vitality.¹ However, it also is believed to be quite helpful to the elderly by providing energy and relieving pain, inflammation, and nervous debility.¹²

Ashwagandha has a wide variety of traditional uses, many of which have not been tested scientifically. Ethnobotanist James Duke, PhD, writes that ashwagandha (various plant parts) is a folk remedy for “adenopathy, anthrax, arthritis, asthma, bronchitis, cancer, candida, cold, cough, cystitis, debility, diarrhea, dropsy, dyspepsia, erysipelas, fever, furuncle, gynecopathy, hiccups, hypertension, inflammation, lumbago, marasmus, nausea, piles, proctitis, psoriasis, rheumatism, ringworm, scabies, senility, smallpox, sores, syphilis, tuberculosis, tumors, typhoid, uterosis, and wounds.”¹¹ Additional uses attributed to the plant, in general, are the treatment of alcoholism, anemia, colds, dropsy, fever, hypertension, insomnia, lumbago, ulcers, wasting in children, and removal of obstructions in any human body system.^{1,7,9,12}

Some of the documented uses of the root of ashwagandha include as a hypnotic for treating alcoholism (along with leaf); treatment for brain fog, colds and chills, childhood emaciation, emphysematous dysphonia (difficult speech caused by emphysema, with leaf), fever, glandular swelling, impotence or seminal debility; to increase breast milk; and to counteract loss of memory and muscular energy, nervous exhaustion, rheumatic fever, rheumatic swelling, senile and general debility, spermatorrhea, syphilis, and ulcers.^{2,7,11} In Tanzania, the root is used as a sexual stimulant and to promote uterine contractions.¹¹

The leaves are used to expel worms and are combined with warm castor oil (*Ricinis communis*, Euphorbiaceae) on carbuncles, inflammations, and swellings.^{2,7,11} The Masai use the leaf juice for conjunctivitis.¹¹ The fresh bruised berries are used on ringworm.^{2,11} The fruits or seeds are used to coagulate milk.^{2,7,11} The seeds also are used as a masticatory.¹¹ A bark infusion is used in Lesotho internally for asthma and externally for bedsores.¹¹ The tender shoots are eaten as a vegetable in India.¹¹

The dried root and the whole plant are used in the traditional medicine systems of Ayurveda, Siddha, Sowa-Rigpa (Amchi), and Unani, as well as in Indian folk medicine. The materials of commerce are obtained from both cultivated and wild-collected sources, mainly in India.¹³

Although ashwagandha is now cultivated on farms outside of its native habitat, and the unprocessed dried roots are being used as components of dietary supplement products and natural health products, in the Indian systems of medicine, the dried roots may be subjected to certain traditional fermentation, purification, or detoxification processes prior to therapeutic use.¹⁴

There are *W. somnifera* standards monographs published in the *Ayurvedic Pharmacopoeia of India* (Vol. I, 1989),¹⁵ *Siddha Pharmacopoeia of India* (Vol. I, 2008),¹⁶ *Unani Pharmacopoeia of India* (Vol. I, 2007),¹⁷ the World Health Orga-

nization (WHO) Monographs (Vol. 4, 2009),¹⁸ as well as in the currently valid editions of the *British Pharmacopoeia* (BP 2012),¹⁹ *Indian Pharmacopoeia* (IP 2010),²⁰ and *United States Pharmacopoeia* (USP 36).²¹

CURRENT AUTHORIZED USES IN COSMETICS, FOODS, AND MEDICINES

In countries where the Ayurvedic system of medicine is officially recognized and practiced (e.g., India, Bangladesh, Bhutan, Malaysia, Nepal, and Sri Lanka), the powdered dried root of ashwagandha is used, as a component of preparations, for treating inflammatory disorders, phthisis (any wasting or atrophic disease, weakness, diseases due to *vata dosha*), and male impotence.¹⁵

In countries where the Unani system of medicine is officially recognized and practiced (e.g., Bangladesh, India, Malaysia, Pakistan, and Sri Lanka), the dried mature root, referred to as “*asgand*,” is used as a component of medicinal formulations to treat leucorrhoea, spermatorrhea, decreased viscosity of semen, sexual debility, lumbago, and arthritis. Ashwagandha is often dispensed as a component of compound Unani medicines known as *majoon* or *halwa*. These preparations are made with prepared and powdered botanicals mixed with honey, resulting in a soft or semi-solid consistency like the popular confection halwa.¹⁷

In Siddha medicine — a Dravidian system of medicine originating in the southeastern Indian state of Tamil Nadu, now also practiced in the neighboring states of Karnataka, Kerala, and Andhra Pradesh, as well as in parts of Malaysia, Singapore, and Sri Lanka — the dried root (purified before use), referred to as *amukkara*, is used as a component of formulations indicated for treatment of conditions including oligospermia, lancinating pain, loss of body strength, anemia, convulsions/seizures/fits, disordered humor, eczema, edema/swelling, and tuberculosis.²²

In Canada, ashwagandha root is classified as an active ingredient of licensed natural health products (NHPs), requiring pre-marketing authorization from the Natural Health Products Directorate (NHPD) and manufacture in compliance with NHP Good Manufacturing Practices (GMPs). Authorized uses outlined in its NHPD compendial monograph include “traditionally used in Ayurveda as *rasayana* (rejuvenative tonic),” “traditionally used in Ayurveda to relieve general debility, especially during convalescence or old age,” “traditionally used in Ayurveda as a sleep aid,” “traditionally used in Ayurveda to balance aggravated *Vata* (nervine tonic, sedative),” and “traditionally used in Ayurveda for memory enhancement.”²³

In the United States, ashwagandha is not listed as Generally Recognized as Safe (GRAS) in the Code of Federal Regulations (CFR) for any uses in conventional food products, nor does it appear in FDA’s GRAS Notice Inventory database. Ashwagandha is permitted, however, for use as a dietary supplement component, requiring FDA notification within 30 days of marketing a product (if a “structure-function” claim is made) and product manufacturing according to dietary supplement GMPs. USP has developed dietary supplement quality standards monographs for “Ashwagandha Root,” “Powdered Ashwagandha Root,” and for “Powdered Ashwagandha Root Extract.” These USP

monographs are acceptable for use as dietary supplement component specifications and quality control testing to verify conformance to specification before use in a product.²¹

In the European Union (EU), ashwagandha is not subject to the Novel Food Regulation because it was on the market as a food or food ingredient and consumed to a significant degree before May 15, 1997. Other specific legislation, however, may restrict the placing of ashwagandha as a food or food ingredient on the market in some Member States.²⁴

For example, in 2008, the Government of India, Department of Ayurveda, Yoga & Naturopathy, Unani, Siddha and Homoeopathy (AYUSH) — as part of a global strategy for brand-building of Ayurvedic medicine — prioritized the promotion of ashwagandha preparations, in particular, for attaining marketing authorizations as medicinal products in several foreign markets including selected EU member states, as well as in Australia, Canada, and Commonwealth of Independent States (CIS) countries. The ashwagandha strategy was developed in collaboration with the International Trade Centre (ITC) of UNCTAD (Geneva, Switzerland).²⁵

By 2010, the BP developed a quality standards monograph for the dried mature root of *W. somnifera* specifically for use in Traditional Herbal Medicinal Products (THMPs), as defined under the EU Traditional Herbal Medicinal Products Directive (THMPD).¹⁹ The BP monograph was an important first step that provided applicants with a requisite quality control specification, thus paving the way for the use of ashwagandha as an active ingredient of THMPs that could be authorized by the Medicines and Healthcare products Regulatory Agency (MHRA) for marketing in the United Kingdom.

In July 2011, the Committee on Herbal Medicinal Products (HMPC) of the European Medicines Agency (EMA)

began the process of developing a labeling standards monograph (for use by applicants for the labeling of ashwagandha THMPs in the EU) by putting out a call for submission of scientific data that would be used in the assessment of *W. somnifera* radix as part of the establishment of Community herbal monographs and/or Community list entries.²⁶

Following their assessment, in October 2012, the EMA issued a draft public statement with the opinion that a Community herbal monograph on *W. somnifera* radix could not yet be established because the HMPC had not been able to find adequate evidence allowing them to develop a description of ashwagandha preparations, *i.e.*, insufficient extract specifications according to EU pharmaceutical quality requirements, despite the existence of data on uses within the EU of products containing *W. somnifera* radix. Additionally, the HMPC stated that they were unable to find evidence demonstrating the requirement of at least 30 years of medicinal use of ashwagandha preparations including at least 15 years in an EU member state.²⁷ As of the time of this publication, there are still no known ashwagandha-containing THMPs with marketing authorization granted in any EU member state.

Concerning its use in cosmetic products, the European Commission Health and Consumers Directorate lists several defined *W. somnifera* ingredients (root powder, root extract, leaf and root extract, and flower extract) for skin-conditioning function (maintains the skin in good condition). “*Withania somnifera* leaf extract,” however, is approved for several functions in cosmetic products, including as an antimicrobial (helps control the growth of microorganisms on the skin), antioxidant (inhibits reactions promoted by oxygen, thus avoiding oxidation and rancidity), bleaching (lightens the shade of hair or skin), emollient (softens and smoothes the skin), and humectant (holds and retains moisture).²⁸



Ashwagandha *Withania somnifera*. Photo ©2013 Steven Foster

MODERN RESEARCH

The main active chemical constituents in ashwagandha are steroid lactones (withaferin A, sitoindoside IX and X, [carbon-27 glycowithanolides], and acylsteryl glucosides [sitoindosides VII, VIII]); phytosterols; and alkaloids: tropane type (tropine and pseudotropine), plus isopelletierine, and anaferine.^{1,9}

An open-label, prospective, non-randomized, comparative clinical study published in 2013 addressed the potential use of ashwagandha root extract powder (Himalaya Drug Co.; New Delhi, India) for the mitigation of fatigue caused by chemotherapy and for improving quality of life in patients with breast cancer.²⁹ Patients undergoing chemotherapy for breast cancer were assigned alternately into the study group (n=50) or control group (n=50) and assessed for fatigue. The study group took 500 mg ashwagandha dry extract three times daily throughout six cycles of chemotherapy. The ashwagandha patients experienced less fatigue and better quality of life during chemotherapy than the control group.

In another 2013 clinical trial, three groups of infertile male patients were recruited from the infertility clinic at King George's Medical University, Lucknow, India; 60 with normal semen profile and infertility of unknown etiology, 60 with low sperm count and normal morphology, and 60 with normal sperm count and normal morphology but reduced sperm motility.³⁰ Controls were 50 age-matched men with normal semen profile who had initiated at least one pregnancy previously. Each patient in the study group took 5 g/day ashwagandha root powder (roots purchased from the Central Council for Research in Unani Medicine; New Delhi, India; dried in shade and ground to fine powder) orally in milk for three months. Semen samples were collected and centrifuged and the seminal plasma was assessed. Results showed that ashwagandha normalized markers in seminal plasma and may resolve infertility via action on metabolic, enzymatic, and hormonal pathways.

A 2010 prospective clinical study investigated the impact of ashwagandha on semen profile, oxidative biomarkers, and reproductive hormone levels in infertile men.³¹ The control group comprised normal healthy, fertile men (n=75) with normal semen profile who had initiated at least one pregnancy previously. The test groups comprised patients with infertility for more than one year (n=75; 25 with normal semen profile and infertility of unknown etiology, 25 with below-normal semen profile, and 25 with below-normal sperm motility). Patients with conditions known to influence oxidative stress were excluded from the study. For three months, the test group took 5 g/day ashwagandha root powder (Central Council for Research in Unani Medicine, New Delhi) orally with milk. Sperm concentration increased significantly in all three test groups after treatment. Sperm motility improved in all three groups but not significantly in the group with below-normal sperm motility. Semen volume increased significantly in all test groups except the group with below normal sperm motility. The ashwagandha also inhibited lipid peroxidation in the test groups, effectively reducing oxidative stress. Finally, the ashwagandha groups experienced increased serum testos-

terone and luteinizing hormone levels and reduced levels of follicle-stimulating hormone and prolactin — all indicators of semen quality.

A 2012 clinical study with a pilot arm and a therapeutic arm investigated the efficacy of ashwagandha as an adjunct therapy in treating tuberculosis.³² Recently diagnosed pulmonary tuberculosis patients who had yet to take any anti-tubercular drugs (ATD) were enlisted. In the pilot study, Phase 1 patients took either ATD or ATD plus ashwagandha (Stresscom, standardized to 4.5% withanolides, Dabur Research Foundation; New Delhi, India). In Phase 2, patients took either ATD, ATD plus ashwagandha, or ATD plus the Ayurvedic multi-herb-and-fruit formulation Chyawanprash (Dabur Research Foundation; New Delhi, India). The treatment groups in the therapeutic study were the same as those in Phase 2 of the pilot study. More improvement was seen in both herbal adjunct groups than in the ATD-only group, including reduced bacterial counts after 26 days in the ashwagandha group and 29 days in the Chyawanprash group.

A 2012 single-arm, uncontrolled, observational, dose-response study assessed the safety, tolerability, and activity of escalating doses of ashwagandha.³³ For 30 days, at 10-day intervals, 18 healthy participants took increasing doses of ashwagandha (8:1 pulverized ashwagandha root extract; source, preparation, and manufacturer not stated) starting with 250 mg in the morning and 500 mg in the evening (750 mg total/day) on days 1-10, 500 mg in the morning and 500 mg in the evening (1000 mg total/day) on days 11-20, and 500 mg in the morning and 750 mg in the evening (1250 mg total/day) on days 21-30. There were no significant changes in vital signs (blood pressure, pulse, body temperature, and respiration rate, taken at baseline and on days 11, 21, and 31), body weight, or blood markers during the study, nor were any significant changes in appetite, waste elimination habits, or sleep duration reported — although 33% of the subjects reported improved sleep quality. Muscle strength increased significantly and, although body weight and body mass index (BMI) did not change significantly, there was a trend toward increased lean body weight and decreased body fat percentage. Total cholesterol decreased significantly and decreasing trends were seen in fasting blood sugar, triglycerides, and LDL cholesterol.

A six-week clinical trial in 2012 evaluated the safety of an Ayurvedic formula used in the treatment of osteoarthritic knees.³⁴ The formula (preparation and manufacturer not stated) contained ashwagandha root powder, ginger (*Zingiber officinale*, Zingiberaceae), Indian tinospora or *guduchi* (*Tinospora cordifolia*, Menispermaceae), and tribulus (*Tribulus terrestris*, Zygophyllaceae). The formula showed no serious adverse events and none of the participants withdrew due to any drug-related toxicity.

A 2010 uncontrolled clinical study assessed the efficacy of ashwagandha and arjuna (*Terminalia arjuna*, Combretaceae) alone and in combination on physical performance and cardiorespiratory endurance in healthy young adults.³⁵ Of 40 subjects over the course of eight weeks, 10 received 500 mg/day standardized aqueous root extract of ashwagandha, 10 received 500 mg/day standardized aqueous bark extract of arjuna, and 10 received 500

mg/day both ashwagandha and arjuna extracts encapsulated together (all herbs provided by the Central Council for Research in Ayurveda and Siddha; Delhi, India). A control group of 10 participants received encapsulated flour. The ashwagandha group experienced increased velocity, power, and maximum oxygen consumption, while the arjuna group experienced increased maximum oxygen consumption and lowered resting systolic blood pressure. In combination, participants experienced improvement in all the parameters mentioned above. None of the groups experienced improved balance or diastolic blood pressure.

Two 2009 double-blind, pilot studies investigated ashwagandha and four other Ayurvedic herbs for their immune-enhancing effect.³⁶ Study 1 included 32 volunteers randomized to two treatment groups of 16 each who consumed three cups daily of Natural Care tea (ashwagandha [0.5%]; licorice [*Glycyrrhiza glabra*, Fabaceae, 0.5%]; ginger [1.5%]; holy basil [*Ocimum tenuiflorum*, Lamiaceae, 0.5%]; and cardamom [*Elettaria cardamomum*, Zingiberaceae, 1.5%]; Hindustan Unilever Research Center; Bangalore, India) or regular tea (*Camellia sinensis*, Theaceae) for two months. Natural killer (NK) cell activity was measured after one and two months of tea consumption. There were no significant changes in either group at the end of month one, but NK cell activity was significantly increased after two months in the NC tea drinkers but not in the regular tea group.

Study 2 was a larger, double-blind, crossover study in which 110 subjects (60 male, 40 female [sic]) were randomly assigned to two groups.³⁶ Each group consumed three cups of tea (Natural Care or regular tea) per day for two months. NK cell activity was measured before a 15-day washout period when no tea was drunk. The groups then switched to the other tea for another two months, after which NK cell activity was measured again. NK cell activity increased in both groups after two months, but the increase in the Natural Care tea drinking groups was approximately 4.2 times higher than before, while the NK cell activity in the regular tea group was about 2.9 times higher.

A randomized, controlled trial published in 2009 addressed the efficacy of ashwagandha for moderate-to-severe anxiety lasting more than six weeks per self-assessment.³⁷ Participants were randomized to receive naturopathic care with ashwagandha (n=41), a multi-vitamin, dietary counseling, and cognitive-behavioral therapy, or standardized psychotherapy intervention (n=40). The ashwagandha group took 300 mg, two per day, for six weeks of ashwagandha extract standardized to 1.5% withanolides from root obtained from Swiss Herbals (now Swiss Natural; Richmond Hill, ON, Canada). Outcomes were measured at four, eight, and 12 weeks, with the results suggesting that both treatments caused a significant reduction in anxiety, but the ashwagandha group also experienced significant improvement in quality of life, including reduction of stress, improved vitality, motivation, general health, and patient-specific

concerns. The authors stated that it is difficult to assess the precise effect of each of the component therapies and that future studies should focus on isolating the effects of component therapies and use a blinded independent assessment rather than a patient-reported assessment.

A small, uncontrolled study assessed the immunologic effects of ashwagandha.³⁸ Twice a day for 96 hours, five participants consumed 6 mL ashwagandha root liquid extract (grain ethanol and spring water extraction, Gaia Herbs; Brevard, NC) followed by 8 fl oz whole cow's milk. Blood samples were taken at 0, 24, and 96 hours, and analyzed for immune cell activation. A significant change in immune cell activation occurred across the sample indicating that further study is warranted to determine if ashwagandha might be helpful in the prevention and treatment of infectious disease, cancer, and other immune-related conditions.

Bone and Mills (2013) reported on four studies between 1980 and 2008 that investigated ashwagandha for its tonic activity, a concept often misunderstood in Western medicine. Tonics are restorative, supportive, sometimes adaptogenic (*i.e.*, helping the body to adapt to stressors) substances. In these studies, ashwagandha was found to significantly increase hemoglobin, red blood cell count, seated stature, and hair melanin content, as well as decrease serum cholesterol and erythrocyte sedimentation, improve men's sexual performance, and counter decrease in nail calcium. It also improved alertness and state of awareness, responsiveness,



Ashwagandha *Withania somnifera*. Photo ©2013 Steven Foster

sleep patterns, and physical capabilities of trainee mountaineers over a six-day trek with a 5,200 m (17,000 ft.) altitude gain; modestly improved muscle strength and muscle performance in healthy elderly men; and improved stress markers for chronically stressed patients.⁹

FUTURE OUTLOOK

Of the estimated 960 medicinal plant species that form the source of 1,289 botanical raw drugs in trade in India, *W. somnifera* is among the top 117 species whose annual domestic consumption exceeds 100 metric tons (MT). Ranking at #4 in terms of volume, Indian domestic consumption of ashwagandha is estimated at 4,575 MT, of which about 24% relates to production by large herbal manufacturing units and about 76% by small and very small companies. Annual trade volume was estimated at between 2,000 to 5,000 MT in 2008. Much of the commercial supply is now produced by cultivation in Madhya Pradesh, Rajasthan, and parts of peninsular India.³⁹

Although the Government of India's strategy to promote Ayurvedic medicine to the world, initially focusing on ashwagandha as an emblematic Indian medicinal product, has not yet manifested as hoped — in part due to the EU regulatory framework, which makes it exceedingly complex, expensive, and almost impossible for even the larger Indian Ayurvedic medicine manufacturing companies to achieve marketing authorization for any non-European herbal medicinal products — ashwagandha-based products are taking hold in non-EU markets. The EU's THMPD is viewed by Indian herbal medicine companies as a legislative market access barrier while entering the market in Commonwealth of Nations countries; in particular, entering Australia, Canada, Malaysia, and New Zealand has been less burdensome. Additionally, there are herbal companies situated in these countries interested in formulating new products that contain ashwagandha.

At the same time, some ashwagandha-containing Ayurvedic medicines are being labeled and marketed as food products, even in some EU member states. For example, the well-known Ayurvedic multi-herb tonic formulation Chyawanprash is available in the EU from several different Indian manufacturing companies. Some EU companies also are marketing products with food supplement labeling, for example Pukka Organic Ashwagandha vegetarian capsules (Pukka Herbs Ltd.; Bristol, England).

In the Australian market, at the time of this writing, there are 130 listed medicines that contain ashwagandha as an active ingredient.⁴⁰ In the Canadian market there are presently 325 licensed NHPs that contain ashwagandha as a medicinal ingredient.⁴¹ In the United States, ashwagandha dietary supplement products are marketed by many of the major herbal brands. HG

—Gayle Engels and Josef Brinckmann

REFERENCES

1. Williamson EM, Hooper M. *Major Herbs of Ayurveda*. Edinburgh: Churchill Livingstone; 2002.
2. Kapoor LD. *CRC Handbook of Ayurvedic Medicinal Plants*.

- Boca Raton, FL: CRC Press; 1990.
3. Indian Drug Manufacturers' Association. *Indian Herbal Pharmacopoeia*, Revised New Edition 2002. Mumbai, India: Indian Drug Manufacturer's Association. 2002;467-478.
4. Siddha Pharmacopoeia Committee. Amukkara (Root). In: *Siddha Pharmacopoeia of India*, Part I, Vol. I, First Edition. New Delhi, India: Govt. of India, Department of Ayurveda, Yoga & Naturopathy, Unani, Siddha and Homoeopathy (AYUSH). 2008;1-3.
5. Central Council for Research in Unani Medicine. Asgand. In: *Standardisation of Single Drugs of Unani Medicine*, Part III. New Delhi, India: Govt. of India, Central Council for Research in Unani Medicine. 1997;9-14.
6. Zhang ZY, Lu A, D'Arcy WG. Solanaceae. In: *Flora of China*. Beijing: Science Press, and St. Louis: Missouri Botanical Garden Press. 1994;17:312-313.
7. Nadharni KM. *Indian Materia Medica*, Vol. 1. Bombay: Popular Prakashan; 1976.
8. Ashwagandha – Learn about a great herb for stamina. Shaka Vansya Ayurveda website. Available at: www.vaidyamishra.com/products/Ashwagandha-%252d-Learn-About-a-Great-Herb-for-Stamina.html. Accessed July 7, 2013.
9. Bone K, Mills S. *Principles and Practice of Phytotherapy: Modern Herbal Medicine*. Edinburgh: Churchill Livingstone; 2013.
10. Awang DVC. What in the name of *Panax* are those other "ginsengs"? *HerbalGram*. 2003;57:30-35.
11. Duke J, ed. *Handbook of Medicinal Herbs*. Boca Raton, FL: CRC Press; 1985.
12. Puri HS. *Rasayana: Ayurvedic Herbs for Longevity and Rejuvenation*. London: Taylor and Francis; 2003.
13. Ved DK, Goraya GS. *Demand and Supply of Medicinal Plants in India*. Dehra Dun, India: Bishen Singh Mahendra Pal Singh. 2008.
14. Saeed A, Qureshi T, Shafi U. Revisiting the concept and application of the phenomenon of tadbir (detoxification). *Intl Chem Pharm Med J*. 2005;2(1):207-212.
15. Ayurvedic Pharmacopoeia Committee. Asvagandha. In: *The Ayurvedic Pharmacopoeia of India*, Part I, Volume I. New Delhi, India: Government of India, Ministry of Health and Family Welfare, Department of Ayurveda, Yoga & Naturopathy, Unani, Siddha and Homoeopathy (AYUSH). 1989.
16. Siddha Pharmacopoeia Committee. *Siddha Pharmacopoeia of India*, Part I, Vol. I, First Edition. New Delhi, India: Govt. of India, Department of Ayurveda, Yoga & Naturopathy, Unani, Siddha and Homoeopathy (AYUSH). 2008.
17. Unani Pharmacopoeia Committee. *The Unani Pharmacopoeia of India*, Part I, Volume I, New Delhi, India: Government of India, Ministry of Health and Family Welfare, Department of Ayurveda, Yoga & Naturopathy, Unani, Siddha and Homoeopathy (AYUSH). 2007;7-8.
18. World Health Organization. Radix Withaniae. In: *WHO Monographs on Selected Medicinal Plants*, Volume 4. Geneva, Switzerland: World Health Organization. 2009;373-391.
19. British Pharmacopoeia Commission. Withania Somnifera for use in THMP. In: *British Pharmacopoeia 2012*. London, UK: The Stationery Office on behalf of the Medicines and Healthcare products Regulatory Agency (MHRA). 2012.
20. Government of India Ministry of Health and Family Welfare. *Indian Pharmacopoeia 2010*. Ghaziabad, India: The Indian Pharmacopoeia Commission; 2010.
21. United States Pharmacopoeia Convention. Ashwagandha Root; Powdered Ashwagandha Root; and Powdered Ashwagandha Root Extract. In: *United States Pharmacopoeia*, 36th Revision (USP 36). Rockville, MD: United States Pharmacopoeial Convention. 2013;1336-1341.
22. Siddha Pharmacopoeia Committee. Appendix 5.2 Cutti

- (Purification) of crude drugs. In: *Siddha Pharmacopoeia of India*, Part I, Vol. I, First Edition. New Delhi, India: Govt. of India, Department of Ayurveda, Yoga & Naturopathy, Unani, Siddha and Homoeopathy (AYUSH). 2008;278-281.
23. Natural Health Products Directorate (NHPD). Monograph: Ashwagandha. Ottawa, Ontario: NHPD. April 18, 2007. Available at: <http://webprod.hc-sc.gc.ca/nhpbd-bdpsn/monoReq.do?id=35&lang=eng>. Accessed July 4, 2013.
 24. European Commission Health & Consumers Directorate. Novel Food Catalogue. Brussels, Belgium: European Commission. Available at: http://ec.europa.eu/food/food/biotechnology/novelfood/novel_food_catalogue_en.htm. Accessed July 4, 2013.
 25. Basant S. Support to sustainable export development of Indian Ayurveda products [Letter to Josef Brinckmann, ITC Consultant]. New Delhi, India: Govt. of India, Ministry of Health and Family Welfare, Department of AYUSH. July 16, 2008.
 26. Committee on Herbal Medicinal Products (HMPC). Call for scientific data for use in HMPC assessment work on *Withania somnifera* (L.) Dunal, radix. London, UK: European Medicines Agency (EMA). 15 July 2011. Available at: www.ema.europa.eu/docs/en_GB/document_library/Herbal_-_Call_for_data/2011/07/WC500109102.pdf. Accessed July 4, 2013.
 27. Committee on Herbal Medicinal Products (HMPC). Public statement on *Withania somnifera* (L.) Dunal, radix. London, UK: European Medicines Agency (EMA). 20 November 2012. Available at: www.ema.europa.eu/docs/en_GB/document_library/Public_statement/2012/12/WC500136129.pdf. Accessed July 4, 2013.
 28. European Commission Health & Consumers Directorate. Cosmetic Ingredients and Substances (CosIng®) Database. Brussels, Belgium: European Commission. Available at: <http://ec.europa.eu/consumers/cosmetics/cosing/>. Accessed July 4, 2013.
 29. Biswal BM, Sulaiman SA, Ismail HC, Zakaria H, Musa KI. Effect of *Withania somnifera* on the development of chemotherapy-induced fatigue and quality of life in breast cancer patients. *Integr Cancer Ther*. 2013;12(4):312-322.
 30. Gupta A, Mahdi AA, Shukla KK, et al. Efficacy of *Withania somnifera* on seminal plasma metabolites of infertile males: a proton NMR study at 800 MHz. *J Ethnopharmacol*. June 21, 2013 doi:pii: S0378-8741(13)00444-3. 10.1016/j.jep.2013.06.024. [Epub ahead of print].
 31. Ahmad MK, Abbas AM, Shukla KK, et al. *Withania somnifera* improves semen quality by regulating reproductive hormone levels and oxidative stress in seminal plasma of infertile males. *Fertility and Sterility*. August 2010;94(3):989-996.
 32. Raut AA, Rege NN, Tadv FM, et al. Exploratory study to evaluate tolerability, safety, and activity of ashwagandha (*Withania somnifera*) in healthy volunteers. *J Ayurveda Integr Med*. July 2012;3(3):111-114.
 33. Debnath PK, Chattopadhyay J, Mitra A, et al. Adjunct therapy of Ayurvedic medicine with antitubercular drugs on the therapeutic management of pulmonary tuberculosis. *J Ayurveda Integr Med*. July 2012;3(3):141-149.
 34. Chopra A, Narsimulu G, Patwardhan B, Saluja M, Sarmukaddam S, Tillu G. Evaluating higher doses of shunthi-guduchi formulations for safety in treatment of osteoarthritis knees: a government of India NMITLI arthritis project. *J Ayurvedic Integr Med*. January 2012;3(1):38-44.
 35. Sandhu JS, Shah B, Shenov S, Chauhan S, Lavekar GS, Padhi MM. Effects of *Withania somnifera* (ashwagandha) and *Terminalia arjuna* (arjuna) on physical performance and cardiorespiratory endurance in healthy young adults. *Int J Ayurveda Res*. July-September 2010;1(3):144-149.
 36. Bhat J, Damle A, Vaishnav PP, Albers R, Joshi M, Banerjee G. *In vivo* enhancement of natural killer cell activity through tea fortified with Ayurvedic herbs. *Phyto Res*. 2010;24:129-135.
 37. Cooley K, Szczurko O, Perri D, et al. Naturopathic care for anxiety: a randomized controlled trial ISRCTN78958974. *PLoS One*. August 31, 2009;4(8):e6628. Doi: 10.1371/journal.pone.0006628.
 38. Mikolaj J, Erlandsen A, Murison A, et al. *In vivo* effects of ashwagandha (*Withania somnifera*) extract on the activation of lymphocytes. *J Altern Complement Med*. 2009;15(4):423-430.
 39. Ved DK, Goraya GS. *Demand and Supply of Medicinal Plants in India*. Dehra Dun, India: Bishen Singh Mahendra Pal Singh. 2008.
 40. Australian Therapeutic Goods Administration (TGA). Australian Register of Therapeutic Goods (ARTG). Woden, Australia: TGA. Available at: www.ebs.tga.gov.au/. Accessed July 4, 2013.
 41. Natural Health Products Directorate (NHPD). *Withania somnifera*. In: Licensed Natural Health Products Database. Ottawa, Ontario: NHPD. Available at: <http://webprod3.hc-sc.gc.ca/lnhpbd-bdpsnh/start-debuter.do?lang=eng>. Accessed July 4, 2013.

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dear reader

Qualifying an Analytical Laboratory and Avoiding a “Dry Lab,” etc.

As part of our continuing coverage of supply-chain integrity with respect to the identity and authenticity of various botanical raw materials, extracts, and essential oils — particularly the deplorable practice of economi-

cally motivated adulteration — in this issue, we present an extensive article on the practice referred to as “dry-labbing” and the need for dietary supplement and other herbal product manufacturers to properly qualify contract analytical laboratories.

In the past few years, when I mentioned the term “dry lab” or “dry-labbing” to dietary supplement industry veterans, I was surprised when some did not recognize the term — until last year, that is, when, in March, the television news magazine *Dateline NBC* exposed this unethical and illegal practice to millions. At that time, many industry insiders were aware of the practice of at least one contract analytical lab that allegedly performed dry-lab analyses for various manufacturers of dietary supplements. Numerous industry media gave the *Dateline NBC* story prominence, and the term dry lab became part of the modern herb and dietary supplement industry parlance.

Even before last year’s exposé, we were considering an article on dry-labbing. Frank Jaksch, Jr., CEO of ChromaDex — a leading independent analytical lab — and I had been discussing this when ABC Advisory Board member Paula Brown, PhD, of the British Columbia Institute of Technology, offered to write an article on the subject for *HerbalGram*. She teamed up with ABC Advisory Board member Joe Betz, PhD, of the Office of Dietary Supplements at the US National Institutes of Health, who also is an expert on analytical methods for botanical materials, and Jaksch. The three have co-authored a seminal article that has been peer-reviewed extensively by experts at other leading contract laboratories with experience analyzing botanicals and other dietary ingredients. Anyone in the business of producing botanical products, both in the United States and elsewhere, is advised to read this article carefully.

Regarding our cover story, in their continuing series of Herb Profiles on page one, ABC’s Gayle Engels and Josef Brinckmann of Traditional Medicinals provide a comprehensive profile of the traditional Ayurvedic herb ashwagandha, one of the most revered medicinal plants in India, and one with a wide range of uses as an adaptogen and other applications. Ashwagandha extracts are increasing in popularity in the United States and elsewhere.

In the past decade, there has been concern about the relative safety of various kava preparations, some of which have been associated with liver toxicity. An Australian company has developed a water-based kava extract, which is consistent with traditional kava use, and has published several clinical trials on this kava extract — one trial showing safety for generalized anxiety disorder and another showing that therapeutic doses do not result in impaired driving, a theoretical concern raised by the German Commission E in 1990 due to kava’s well-known skeletal muscle-relaxing effect.

Elsewhere, our in-house cannabis writer Lindsay Stafford Mader has authored an article discussing concerns about the effects of cannabis in exacerbating schizophrenia. Also, Canadian herbalists Linda Woolven and Ted Snider provide a review of botanicals that have various levels of support from traditional use and modern clinical research for treating erectile dysfunction — a condition for which pharmaceutical companies ubiquitously advertise in the United States.

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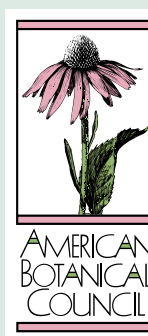
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Clinical Assistant Professor, Dept. of Medicine,
Arizona Center for Integrative Medicine,
University of Arizona, Tucson, AZ

Donald J. Brown, ND

Natural Products Research Consultants,
Seattle, WA

Paula N. Brown, PhD

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CEO and Managing Member, HeteroGeneity,
LLC, Washington, D.C.

David Hoffmann BSc, FNIMH

Medical herbalist, author, and research
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Sebastopol, CA

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Director of Science Communications and Investigator in the Laboratory of Microbiology and Genomics, Nature Research Center of the North Carolina Museum of Natural Sciences, Raleigh, NC

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Chair, Medicinal Plants Specialist Group, Species Survival Commission, International Union for the Conservation of Nature, Ottawa, Ontario, Canada

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Professor of Botany, University of Hawaii, Mānoa, HI

Joe-Ann McCoy, PhD

Director, Medicinal Germplasm Repository Bent Creek Institute / NCSU Asheville, NC

Dennis J. McKenna, PhD

Senior Scientist, British Columbia Institute of Technology, Burnaby, B.C., Canada

Mark Messina PhD, MS

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Private Practice in Forensic Medicine, and Policy Institute for Integrative Medicine, Bethesda, MD

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Senior Teaching Fellow, Peninsula Medical School, Exeter, England

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Ginkgo *Ginkgo biloba*. Photo ©2013 Steven Foster

34 Herbs and Erectile Dysfunction: A Review of Traditional Use and Modern Clinical Evidence

By Linda Woolven and Ted Snider

For millennia, plant-based remedies have been used to improve sexual performance. Today, erectile dysfunction (ED) affects more than half of all men between the ages of 40 and 70, and folkloric, pharmaceutical, and herbal remedies abound. Reports of unscrupulous manufacturers adulterating supplements with unlabeled prescription drugs have tarnished the reputation of some plant-based dietary supplement products marketed for assistance in ED. A growing body of scientific and clinical research provides promising rationale for the use of various herbal preparations to help alleviate this common condition, although more research is clearly warranted.

46 Cannabis and Schizophrenia

By Lindsay Stafford Mader

Although the popular media would lead one to believe that cannabis unequivocally can cause a person to develop schizophrenia, the actual link between this herb and the severe psychological disorder is much less certain and much more complex. Based on limited available evidence — which includes epidemiological studies, surveys, brain morphology analyses, and a few human studies — most experts agree that cannabis intake might have a negative impact on individuals who have schizophrenia or those who are at risk for developing it, perhaps due to alterations in their bodies' endocannabinoid systems. In healthy populations, however, little conclusive evidence suggests that cannabis causes schizophrenia. Meanwhile, preliminary research and a small human study on the non-psychoactive compound in cannabis, known as CBD, suggest a potentially important therapy for treating schizophrenia symptoms if positive results are replicated in future research.

52 How to Qualify an Analytical Laboratory for Analysis of Herbal Dietary Ingredients and Avoid Using a “Dry Lab”

A review of issues related to using a contract analytical laboratory by industry, academia, and regulatory agencies

By Paula M. Brown, PhD, Joseph M. Betz, PhD, and Frank L. Jaksch, Jr.

Although not a new phenomenon, the deceitful practice of dry-labbing received national attention in 2012 after a *Date-line NBC* story aired, exposing the way in which some contract laboratories fail to perform adequate analyses on manufacturer-supplied test samples, including herbal dietary ingredients. In some cases, dry labs conduct no analyses whatsoever, providing clients with fabricated data that matches the expected specifications. With decades of combined experience in botanical and natural products research, analytical and quality control services, and regulatory issues, the co-authors of this article present a detailed guide to finding and maintaining a relationship with reputable laboratories, including seven basic tips for interested parties seeking an analytical lab, and a list of red flags for spotting potential dry labs.

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Ashwagandha *Withania somnifera*.
Photo ©2013 Steven Foster

Contributors

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Francis Brinker, ND

Paula M. Brown, PhD

Shari Henson

Freddie Ann Hoffman, MD

Frank L. Jaksch, Jr.

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Contributing Editor

Josef Brinckmann
Contributing Editor

Lance Lawhon
Advertising Sales
512-832-1889
lance@herbalgram.org

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Noted Herb Expert Joins American Botanical Council as Chief Science Officer

Dr. Stefan Gafner Brings Years of Technical Expertise as Pharmacist and Natural Products Chemist to ABC's Educational Publications and Programs

The American Botanical Council (ABC) is pleased to welcome Stefan Gafner, PhD, to its staff as the organization's first-ever Chief Science Officer. For more than a decade, Dr. Gafner has served as a research scientist and director of analytical chemistry in the research and product development department of Tom's of Maine, a leading manufacturer of natural oral and personal care products. Among other products he researched and developed at Tom's, Dr. Gafner co-developed a breath-freshening licorice (*Glycyrrhiza glabra*, Fabaceae) extract that is a component of Tom's bestselling Wicked Fresh® toothpaste.

Dr. Gafner received his degree in pharmacy at the University of Bern School of Pharmacy in Bern, Switzerland. He earned his doctorate in pharmaceutical sciences — with a focus on phytochemistry (the chemistry of plants) — at the University of Lausanne in Switzerland, from the internationally respected phytochemist Professor Kurt Hostettmann. His doctoral thesis focused on the search for new antibacterial and antifungal compounds from African medicinal plants in three plant families (Asteraceae, Bignoniaceae, and Myricaceae). Dr. Gafner conducted his postdoctoral research at the University of Illinois – Chicago, in the College of Pharmacy's highly regarded Department of Medicinal Chemistry and Pharmacognosy (the study of medicines from plants and other natural sources).

Highlights of Dr. Gafner's impressive career include the discovery of dozens of new natural products, the development of more than 40 methods for the identification and authentication of herbal extracts, and the validation of methods for more than 20 over-the-counter drug ingredients for consumer products.



He has participated as an expert peer reviewer for many respected scientific journals including *Phytochemistry*, *Planta Medica*, *Journal of AOAC INTERNATIONAL*, *Journal of Agricultural and Food Chemistry*, and the *Journal of Natural Products*, and he co-chaired the organization of the American Society of Pharmacognosy's 48th annual meeting.

"ABC welcomes Dr. Stefan Gafner as our first Chief Science Officer," said ABC Founder and Executive Director Mark Blumenthal. "Stefan will provide significant energy and expertise in furthering ABC's nonprofit mission to educate the public about medicinal herbs and other beneficial plants."

Blumenthal also noted that Dr. Gafner's laboratory analytical experience will be especially helpful with respect to the

ABC Advertising Representative Profile: Lance Lawhon

For ten years, the American Botanical Council has depended on Lance Lawhon to sell all of its print and online ad space, bringing in much-appreciated revenue for the nonprofit organization while informing ABC members about relevant events and reputable products. Lawhon, who is a contract worker, lives in Austin, Texas, where ABC is located.

"I have always felt like I'm a part of the ABC family even though I don't come in to the office all the time. And it's been a very easy and friendly relationship. So there's a lot of familiarity and trust that's been built up between me and staff that have been there for a while. And I love ABC's mission. It's something I can really get behind. It's much easier to sell advertising for an organization that I actually really believe in."

Exuding kindness and lacking brashness, Lawhon is not a typical salesman and did not expect to be involved with advertising. He received his master's degree in English from Texas State University in San Marcos. He has

gone on to teach creative writing courses at Austin Community College, and finished his first novel, *The Second Apprentice*, about two years ago.

"For the longest time I was like, 'Oh, I'm going to write the great American novel,'" said Lawhon. But the process of publishing his work took longer than expected. In the meantime, he took a job at a company selling mailing lists, where he discovered that he actually enjoyed sales. When the company, which gained ABC as a client in 2003, laid off half of its sales force, ABC contracted Lawhon to work as its advertising sales representative.

"I decided, well, I'll keep doing this and I'll do it on my own," said Lawhon. "So ABC was one of my first clients. ABC has treated me very, very graciously. It's been a great relationship."

ABC Founder and Executive Director Mark Blumenthal did not always want the organization's quarterly peer-reviewed journal *HerbalGram* to feature ads. So when he decided it was time, Blumenthal required all



technical aspects of the ABC-AHP-NCNPR Botanical Adulterants Program — a nonprofit consortium managed by ABC that educates industry, researchers, and health professionals on how to identify adulterants in botanical materials, and helps to ensure proper identity and authenticity in herbal raw materials.

“It is a privilege to join the American Botanical Council as its first Chief Scientific Officer,” said Dr. Gafner.

“I remember hiking the Swiss Alps as a high school student with my camera and two friends taking pictures of every wildflower we could shoot,” he reminisced. “Fellow hikers would sometimes look at us as if we were from the moon, but on occasion, also stop and ask us about the plants we were looking at.”

“I never fathomed that this passion would lead to a career in pharmacognosy and allow me to join a pioneering organization like ABC,” added Dr. Gafner. “I am delighted to be part of a group with its primary goal to educate people on the benefits of medicinal plants, and look forward to the prospect of working closely with Mark Blumenthal, one of the most respected people in the medicinal plant community, and with an advisory board that lists many of the renowned scientists in the area of medicinal plant research.”

Dr. Gafner continued, “I’ve never seen so many new technologies applied to plant science — this is possibly the most interesting time to be involved in medicinal plant research and I’m just thrilled to be part of the team whose mission it is to make it more available to the public.”

“I was delighted to learn that Stefan Gafner will become the first Chief Science Officer of the American Botanical Council,” said noted author and herbalist Steven Foster, chair of ABC’s Board of Trustees. “Stefan is an energetic scientist who embodies the needs of the many facets of ABC stakeholders. He is a practical pharmacist and phytochemist who understands the commercial landscape of the world of herbs, and perhaps most

importantly, from my perspective, he is equally at home in nature as he is in the lab.

“Fifteen years ago,” Foster elaborated, “Stefan introduced me to the Alpine wild herbs of his native Switzerland, where he generously drove me to remote mountain villages to explore local herbs. Stefan brings a collaborative spirit, love of nature, and broad scientific experience to ABC.”

Dr. Gafner also received high praise from other professional colleagues.

“Stefan Gafner is a superb choice to serve as ABC’s first Chief Science Officer. He is an exceptionally skilled pharmacognosist and pharmacist, and comes to ABC with great experience in herbal supplements and personal care products from his service at Tom’s of Maine,” said ABC Advisory Board member John Cardellina II, PhD. “I think he brings a wonderful mix of energy, commitment, and understanding of the critical issues facing the herbal industry to ABC. He will be an immediate asset to ABC projects such as the ABC-AHP-NCNPR Botanical Adulterants Program.”

Cindy Angerhofer, PhD, executive director of botanical research at Aveda, said, “I have had the pleasure of working with Stefan for nearly 15 years in the natural products industry and academic community. His passion and extensive background as a Swiss pharmacist and PhD phytochemist seem ideal for this new role.”

“Stefan has been an excellent mentor and role model for the technical team at Tom’s, as well as a competent educator of customers, the trade, and scientific peers,” continued Dr. Angerhofer. “The creation of this new position at ABC is an exciting development for the organization, and I have great expectations for Stefan’s contributions as the Chief Science Officer.” HG

—Ash Lindstrom

advertising to be vetted for accuracy when necessary. A large part of Lawhon’s job consists of helping potential advertisers navigate this unique and complex advertising peer-review system.

When Lawhon pitches to a company, he makes sure to mention ABC’s ad peer-review requirement. If interested, the company will submit an ad, which Lawhon passes to Blumenthal, who gives it a quick review and either approves it or sends it on to ABC’s advertising claims review committee. There is often back-and-forth between the advertiser and ABC, which can consist of asking the advertiser to change part of the ad’s wording or to send supporting documentation so that ABC can ensure the claims are appropriate and accurate based on existing scientific evidence.

“That is a level of complexity that I don’t have with other clients. On the one hand, it’s good that ABC does it because there is a level of credibility that is unique and important. And I think a lot of our advertisers will understand that. But not all of them do.”

“Our advertising claims review process is an actual disincentive for some potential advertisers,” said Blumenthal. “And, it’s certainly challenging for anyone, like Lance, who is in the somewhat difficult position to try to market and

sell advertising in a publication like *HerbalGram*. Throughout the decade that he’s worked for us, Lance has always been a gentleman; he’s polite and respectful with our members, potential advertisers, the ABC staff, and he is particularly patient with the sometimes difficult ad claims review process — a process that would have probably sent many or, perhaps, even most other salespeople running for an easier and more lucrative opportunity. This speaks to Lance’s sense of values and his commitment to ABC’s core values.”

When he is not selling ads for ABC or his other clients — which include the California Psychological Association and the Texas Nursery and Landscape Association — Lawhon enjoys writing fiction, organic gardening, being involved with his church, and cooking. In fact, his Mayan cookies are a favorite among ABC staff members, who eagerly await their arrival at each year’s winter holiday cookie exchange. In a recent interview with *HerbalGram*, Lawhon divulged his secret ingredient:

“I put in cayenne pepper. That’s what gives it the kick.” HG

—Lindsay Stafford Mader

American Herbalists Guild Welcomes New Executive Director and Journal Editor

In February of 1989, 20 herbalists from around the country gathered at the home of Christopher Hobbs and Beth Baugh in the mountains of Santa Cruz, California, to discuss the creation of an association of herbalists bound together by their love and appreciation of the healing power of plants. Shortly thereafter, the American Herbalists Guild (AHG) was born. Roughly 25 years later, AHG boasts more than 2,000 members, has 15 chapters around the country, and publishes the biannual *Journal of the American Herbalists Guild* (JAHG).¹

AHG has a multifaceted approach to promoting the practice of herbal medicine in the United States and abroad. According to its website, AHG supports the development of high educational standards for professional practitioners; encourages collaboration and cooperation among other healthcare providers, professional associations, and regulatory agencies; fosters “high standards of ethics and integrity in the education and the practice of therapeutic herbalism;” and promotes “ecological health and increase[d] awareness of issues surrounding plant sustainability.”²

At a reception held in Asheville, North Carolina, in March 2013, friends and members of AHG welcomed two new leaders of the organization: Executive Director Mimi Hernandez, RH, and JAHG Editor Anne de Courtenay.

Mimi Hernandez

Hernandez’s exposure to the healing power of plants began at an early age by watching her Mexican and Colombian grandmothers in their gardens. “My Mexican ‘abuelita’ was a barrio healer in Mexico City,” she said (email, April 17, 2013). “From a young age I watched her grow and harvest herbs and make folk remedies and administer them all from a foundation of prayer and a spiritual perspective of plants and wellness. This lineage gave me a strong urge toward honoring the wisdom of jungle medicine and the treasure of plant diversity. It has also given me a cultural foundation of travel from a young age of exposure to real world medicine, which is often plant-based.”

Years later, Hernandez developed an academic interest in the sciences, specifically biochemistry, physiology, research, and human health in general. “Through the sciences, ecology and botany reconnected me with plants, and when I started to combine my love of plants with my love of physiology, herbal medicine emerged as a natural vocational interest which soon evolved into a full-fledged passion and life’s obsession,” she explained.



Initially, she felt her options for serious academic pursuit of herbal medicine were limited, so she engaged in self-study and found mentorship opportunities through the Indiana Amish communities. The skepticism and resistance she experienced from family members, professors, and peers only strengthened her resolve to study the beneficial medicine she witnessed firsthand from her grandmothers.

Eventually, she discovered the work of the famous ethnobotanist and author James Duke, PhD, an ABC Board of Trustees member, and quickly became what she called one of his “groupies.” “I deeply resonated with his approach upon which my own experiences seemed to shadow through a unique blend of academic sciences, South American shamanism, and American folk,” said Hernandez. “Our relationship has evolved beautifully from that of teacher-student to that of friends and colleagues. Now we work on projects together. It is my deepest honor to call Jim my colleague. In my wildest dreams I never imagined it would be so.”

Before coming to AHG, Hernandez served most recently as coordinator and director of the Appalachian Center for Ethnobotanical Studies (ACES) at Frostburg State University. According to its website, the mission of ACES is to study the medicinal and useful properties of plants, and to conserve plants, their ecosystems, and Appalachian culture “as it relates to wild plant harvesting and traditional use, and to promote the economic benefit to the region that may be derived from managed development of botanical resources.”³

Hernandez also worked previously with the Mountain Herbalists Series and the West Virginia Mountain Roots Series, both educational programs related to ACES that promote ethnobotanical awareness of Appalachian medicinal plant use, conservation, and knowledge.

Further, Hernandez was the founder and director of the One World Healing Arts Institute in Asheville, North Carolina, an herbalism organization with a student-run clinic that focuses on spreading the message of healing plants through a combination of science, tradition, and intuition.

“I found that my natural ability to speak from a place of traditional reverence, scientific understanding, and/or intuitive awareness gave me a sense of balance and gave my clients and students an ability to connect with this knowledge base despite which background they resonated with more,” said Hernandez. “Don’t get me wrong. I’d have the occasional law firm who would invite me to give staff work-

shops [and] who would request that I not mention ‘the intuitive,’ but I’ve also taught at grassroots events that would rather I skip ‘the science.’ It’s all in being able to relate and speak to different belief systems and this ultimately has enhanced my credibility amongst differing communities and has given me the opportunity to be a bridge builder between such communities.”

Anne de Courtenay

Chicago-native Anne de Courtenay holds a bachelor’s degree from the Medill School of Journalism at Northwestern University, and also is a graduate of the Chicago School of Healing Arts and Michael and Lesley Tierra’s East West School of Planetary Herbology. Like Hernandez, de Courtenay’s interest in healing plants began at an early age.

“Like most herbalists you meet, I’ve been fascinated with plants and folk remedies since childhood,” said de Courtenay (email, April 17, 2013). “My dad had two aunts who were herbalists, the sort who wildcrafted around the orchards where they lived.”

After completing her degree at Northwestern, she discovered she could continue an academic pursuit of herbalism, much to the chagrin of her parents, who were still aware of the student-loan debt that often accumulates when attending prestigious university programs.

“When I found out that you could receive education for and train to become an herbalist, I just *knew* that it was the path for me,” said de Courtenay. “I wasn’t looking for it — it synchronistically appeared. By that time I had earned my degree in journalism and had been out of university for a few years. The career shift irritated my parents at first.”

De Courtenay studied Western and Chinese herbal medicine practices with Althea Northage-Orr, who runs the Chicago Center for Psychophysical Healing, which specializes in clinical services including acupuncture, craniosacral therapy, energy healing, psychotherapy, and herbal and nutritional counseling, among other services.⁴

De Courtenay, who currently also practices herbal consultations and bodywork at her clinic, Imagine Health, in Chicago, found the combination of multiple healing modalities to be an especially appealing way to practice medicine.

“What appeals to me most about herbal medicine — aside from the fact that it works — is the idea that harmony and health can be created between two completely different



life forms on this planet, and that this concept underscores a responsibility we must have to protect and respect plant life,” she said. “The idea that this medicine is ancient and available to all who can go out and harvest, say, dandelions, is empowering to all who care to explore it.”

Besides her longtime teacher Northage-Orr, de Courtenay credits Michael Tierra as being part of her inspiration to pursue herbalism. “But through the AHG,” she added, “I have met many amazing herbalists from different traditions whose work propels me to grow and diversify.” As for her journalistic muses, de Courtenay mentioned famed naturalist and filmmaker David Attenborough. “For me, no one has ever topped him in terms of wedding passions of the natural world and communication, really expanding the minds and awareness of his readers and viewers,” she said.

De Courtenay hopes to combine her passions for journalism and natural healing in propelling the *Journal of the American Herbalists Guild* to become an increasingly vital component of the organization.

“I look forward to the *Journal* becoming a forum that reflects the membership of the American Herbalists Guild — that is, I’d like to feature voices of clinical experience from varying traditions across the great spectrum of what we call ‘herbalism’ these days,” she said. “From ancient traditions with centuries of empirical evidence to modern phytotherapy supported by clinical trials, I envision our publication enriching and sparking our members’ practices, and therefore transforming the lives of their clients and eventually, moving herbal medicine into a more accepted and understood form of healthcare.”

Aside from preparing for HerbDay 2013, and numerous conferences and symposia throughout the year, the American Herbalists Guild has announced its 24th annual national symposium, “Celebrating Abundance in Herbalism,” which will take place November 7-10, 2013, in Bend, Oregon. The event will feature more than 45 clinical herbalist speakers, a vendor marketplace, and more. For more information, visit www.americanherbalistsguild.com, or www.ahgsymposium.com. HG

—Tyler Smith

References

1. AHG Chapters. American Herbalists Guild website. Available at: <http://americanherbalistsguild.com/node/99>. Accessed April 25, 2013.
2. AHG History & Mission. American Herbalists Guild website. Available at: www.americanherbalistsguild.com/mission. Accessed April 29, 2013.
3. About ACES. Appalachian Center for Ethnobotanical Studies website. Available at: www.frostburg.edu/aces/about-aces/. Accessed April 25, 2013.
4. About us. Transformational Techniques website. Available at: www.transformationaltechniques.com/?page_id=10. Accessed April 25, 2013.

Traditional Roots Institute Established in Portland

Embracing the botanical origins of modern medicine and a resurgent interest in this rich history, the Portland-based National College of Natural Medicine (NCNM) recently established the Traditional Roots Institute. Launched in spring of 2013, Traditional Roots joins NCNM's several existing programs, including the Women in Balance Institute and the Ending Childhood Obesity and Food as Medicine Everyday projects. It aims to "raise awareness and forge a deeper understanding of the healing power of botanical medicine."¹

Because a large part of the natural products industry is driven by dietary supplements and nutraceuticals*, Traditional Roots founder Susan Hunter, who is the vice president of advancement at NCNM, said there was concern that the botanical roots of the natural health movement would be lost and that the general public would become increasingly disconnected from the healing process.

"Why I started this institute is that we didn't want to lose the central place where [medicine] is Mother Nature's bounty," Hunter explained (oral communication, June 11, 2013). "It is the earth; it is planet earth and the amazing plants and flowers that have been used for centuries. Medicine isn't always as complicated as some of the formulas being offered by the nutraceutical [companies]. Yes, some of them are amazing. But there are many others that have served the test of time, namely things that are very, very pure, such as garlic."

"The overarching goal is to bring the people's medicine — that is, herbal medicine — back to the people," said Orna Izakson, ND, RH (AHG), Traditional Roots director and lead physician (email, June 10, 2013). "We're doing that by educating individuals and educating healthcare providers. We want people to be empowered about what they can do for their own health and also to understand they have that power."

Traditional Roots will be dispersing botanical information for laypersons and healthcare practitioners through its website and a variety of events. In all of its educational outreach, the Institute focuses on acknowledging both science and the art of herbalism.

"Science is very much like close-up photography," said Dr. Izakson. "Think about images of individual snowflakes. They're interesting just from the perspective of being curious about the world, and it can give great insights into clinical applications. The same is true for ethnobotany and traditional herbalism. The ultimate goals are getting new people excited about working with herbal medicine and helping folks who already are excited [to] use herbs effectively and safely. We need all aspects of herbal wisdom — clinical, the scientific, the traditional, and the ethnobotanical — to achieve those goals."

Hunter had the idea to create an institute such as Traditional Roots for some time, but needed funding because taking NCNM student tuition was not an option, she said.



So she approached Oregon-based Herb Pharm, a manufacturer of quality botanical extracts, to sponsor the Institute's first two years of operation. In response, Herb Pharm donated \$70,000.

"They didn't bat an eye," said Hunter. "I was kind of flabbergasted because they're not that big of a company. But thank god for Herb

Pharm. Without them we wouldn't have gotten this far."

The core of Traditional Roots' educational efforts is its recently launched website, www.TraditionalRoots.org. Here the institute provides several resources, including general interest articles on topics like using weeds for medicine, *materia medica* articles that detail the medicinal properties of plants such as great mullein (*Verbascum thapsus*, Scrophulariaceae) and the various ways one could use the plant at home or in a healthcare setting, recipes for dishes such as an herbal "Change of Season" soup for immune strength, and articles with tips for people who frequently work with herbs.² In the near future, Traditional Roots hopes to offer online-event video streaming and video archives, free digital versions of classic botanical texts, and botanical photo essays because, as Dr. Izakson said, "beauty is its own medicine, and so many plant medicines are so incredible to look at."

"Our events are in Portland, but the Internet gives us international reach," said Dr. Izakson. "We want to help folks find educational opportunities both online and in person. My hope is TraditionalRoots.org will become the go-to website when folks are looking for any information about herbs or where to learn more. [The] word 'hub' is exactly what we want the website to be — not just for what we're doing, but as one of the central points for herbalism in general."

In addition to its website, Traditional Roots hosts lectures, in-depth community workshops, as well as monthly guided herb walks to educate the public and healthcare practitioners on herbal medicine. Its June 1st kick-off event, for example, was titled "Nature, Health + Ecology" and featured medicinal plant growing and usage classes, guest speakers, and more. Traditional Roots also is sponsoring a Summer Garden Social Series, which runs until September 2013 and features experts discussing an herbal topic of interest at NCNM's Min Zidell Healing Garden. And, in just under a year, on May 16-18, 2014, the Institute will host NCNM's first-annual national herbal medicine conference.

* Nutraceuticals are loosely defined as foods or products that provide both health and basic nutritional benefits. Sometimes "nutraceutical" is used as a market synonym for "dietary supplement."

"This year is all about creation," said Dr. Izakson. "We're brainstorming events, developing connections, building partnerships, trying new things, seeing what works and what people like, and getting our legs firmly under us."

In the future, Traditional Roots will help the college provide direct herbal education to medical professionals, such as physicians and nurses, by helping to develop and launch a postgraduate certificate in botanical medicine, which NCNM has received state approval to offer.

"The potential for interaction between herbal medicine and pharmaceuticals has grown as more and more Americans turn to [complementary and alternative medicine]," said Dr. Izakson. "Healthcare professionals have a real need for information about herbal medicine. We hope to begin to fill [the] gap. We're already making connections

to healthcare professionals of all stripes. We want them to understand the power of herbal medicines and know how to use them effectively and safely." HG

—Lindsay Stafford Mader

References

1. NCNM launches Traditional Roots Institute [press release]. Portland, Oregon: National College of Natural Medicine; May 21, 2013. *The Lund Report*. Available at: www.ncnm.edu/images/News/Lund_Report-05-21-13.pdf. Accessed June 3, 2013.
2. Resources. Traditional Roots Institute website. Available at: <http://traditionalroots.org/resources/>. Accessed June 3, 2013.

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The ABC-AHP-NCNPR Botanical Adulterants Program is a wide-scale, multi-year program designed to educate members of the herbal and dietary supplement industry about accidental and intentional adulteration.

For more details about the Program and the free-access publications produced to-date, please see the Program website at www.herbalgram.org/adulterants. For information on how your company can join, please contact Denise Meikel at denise@herbalgram.org.



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Killing of Endangered Animals Continues for Usage in Traditional Medicine and Bogus Remedies

Since *HerbalGram*'s 2010 exposé on the usage of endangered animals in cultural healing systems and the botanicals that can replace tiger bone wines and bear bile soups,¹ some nonprofit organizations and a few countries' governments have made progress toward realizing the end of this heinous situation. But the outlook for most involved species, unfortunately, remains bleak and uncertain, as apparent in the World Wildlife Fund's (WWF) December 2012 announcement that the illegal trade of wildlife has become the "fourth largest illegal global trade, after narcotics, counterfeiting, and human trafficking."²

Tigers

Tigers most often are killed for their bones, which are used in various remedies, and other tiger parts also are used medicinally, including the blood, penis, tail, and eyes.¹ Although tiger-based tonics, wine, and other products are used much less commonly now than they were throughout their long history in Traditional Chinese Medicine (TCM), the trade in illegal tiger parts continues and the challenges faced by these revered cat species remain serious.

"It's difficult to say with certainty whether the situation [for tigers] has improved or got worse, but one thing we can say with certainty is that the trade is certainly ongoing," said Richard Thomas, communications coordinator of TRAFFIC International (email, March 27, 2013).

Since the 2010 *HerbalGram* piece was published, the International Union for the Conservation of Nature (IUCN) has continued to classify tigers as endangered, as they have been since 1986.³ WWF recently announced that tiger populations are further decreasing, and poaching for tiger body parts — most often destined for China — is their primary threat.^{3,4} In March 2013, TRAFFIC issued an updated report on the illegal tiger trade, noting that at least 1,425 tiger carcasses and body parts were seized by officials during the last decade.⁵

"There are an estimated 3,200 tigers left in the wild today and in most places where tigers live, the population remains in jeopardy," said Barney Long, WWF's Asian species expert (email, January 24, 2013). "Destinations for tiger parts differ based on the product. For example, there is demand coming from Chinese Tibet for skins and pelts; demand from China and Vietnam for tiger bone, etc. In recent years, the largest factor contributing to the illegal trade of tiger parts is their status symbol value in China and Vietnam, which is driving their use in tonic wines and as exotic meats."

Although more than a dozen botanical alternatives to tiger remedies have been identified and encouraged in the past — including Chinese clematis (*Clematis chinensis*, Ranunculaceae) root and rhizome, pubescent angelica (*Angelica pubescens*, Apiaceae) root, dong quai (*A. sinensis*) root, and Sichuan lovage ('Chuanxiong'; *Ligusticum sinense*, Apiaceae) rhizome, among others¹ — most current efforts focus on enhancing law enforcement in countries of concern, as well as repopulating wild tiger populations.

Unfortunately, in February 2013, the nonprofit Environmental Investigation Agency released a report claiming that the Chinese government is quietly fueling domestic trade in tiger parts, and — despite the country's 1993 ban on tiger medicinal

products — the federal government has issued "secret" notices to traders that encouraged the production of wine made from the bones of tigers from Chinese tiger farms, which reportedly house 5,000 to 6,000 tigers as of early 2013.⁶

Bears

Bear bile contains high levels of the anti-inflammatory compound ursodeoxycholic acid (UDCA), and it has been used medicinally in TCM for many years.¹ Due to increased awareness of the cruel way in which bile is harvested from the gallbladders of live bears — that are often kept in inhumane conditions on overcrowded, filthy bear farms — its usage in TCM has decreased somewhat. However, bear bile is increasingly being sold for non-scientific and non-traditional uses in unregulated shops and markets, in addition to being given as an expensive gift to represent wealth or status.

"Bear bile, historically, has been used in limited amounts for specific diseases and illnesses, and nothing could be further from the truth of how it's exploited and sold today," said Jill Robinson, founder and CEO of Animals Asia, an animal welfare organization (oral communication, January 27, 2013). "In Vietnam, for example, we've been picking up bile that originated in China and is being sold as hangover cures. It's also being sold in wines and tonics and, despite the fact that every farmed and extracted bear has contaminated bile, it continues to be ingested by people who are persuaded by the farmers that it can cure a multitude of ills."

Still, the situation for bears, according to Robinson, is improving. In January 2013, Animals Asia won its fight against a pending eviction from the Vietnam Bear Rescue Centre in Tam Dao National Park, which is home to many bears that the organization saves from farms and the chain of illegal trade.

"Vietnam," said Robinson, "has seen some quite interesting developments in that the official government figure there has reduced the number of bears, from an estimated 4,000 on the farms to about 2,400. So the numbers are coming down on the farms and that gives us a lot of confidence in the work that we're doing."

But, Robinson also recognized that the number of farmed bears in China is increasing. "China is at the heart of this industry; there is no question about it," she said. The Chinese public, however, is learning more about the cruelties of the bear bile trade and also is speaking out against it more frequently. According to Robinson, "bear farming" was one of the top 10 most-discussed topics in China in 2012, and at one point was the second most-searched term on the Chinese Internet. And

more and more celebrities are endorsing the anti-bear-farming cause, she said, in addition to a new documentary film that went viral in China.

“What we’ve seen in China in the last year is unprecedented outrage across the country,” said Robinson. “I’ve never seen anything like this in 20 years of campaigning against bear farming. And it gives us a lot of confidence that we’re turning a corner.”

In May 2013, *The New York Times* reported that vehement protests in China recently resulted in the withdraw of a Shenzhen Stock Exchange application by Guizhentang Pharmaceutical, the country’s largest bear bile extract manufacturer.⁷

Animals Asia recently launched its “Healing Without Harm” campaign, which has successfully convinced about 140 TCM pharmacies to stop selling, stocking, and prescribing bear bile. In the next year, the organization will continue to focus on these efforts, and is expecting more pharmacies, including some large chain businesses, to join in taking the pledge. Furthermore, Professor Yibin Feng of the University of Hong Kong — who conducted research in 2009 on botanicals to replace bear bile — will soon disseminate informational documents on the medicinal efficacy of plants in the goldthread genus (*Coptis* spp., Ranunculaceae), an antibacterial, antiviral, anti-inflammatory, and anti-hypertensive herb that is a promising alternative to bear bile.

Rhinos

For thousands of years, the keratin-rich horn of the rhino has been a common TCM treatment for numerous conditions, including fever, convulsions, and hemorrhaging.¹ Although alternatives to rhino horn have been encouraged, poaching of rhinos has only escalated. The South African government announced that poachers killed a record 668 rhinos in 2012, 50 percent more than the 448 rhinos killed in 2011, and significantly more than the 13 rhinos killed in 2007.⁸ More than 500 rhinos already had been killed in the first seven months of 2013.⁹ Rhino poaching also has increased in other African countries, such as Kenya, as well as in some parts of India — where officials estimate one average-sized horn yields \$90,000 to \$100,000.¹⁰

“We can say with absolute certainty that the last three years have been getting progressively worse [for the rhino],” said Thomas of TRAFFIC.

“We’re dismayed, obviously; we’re very upset,” added Susie Ellis, executive director of the International Rhino Foundation (IRF). “Again, the root cause is essentially the same and the primary reason behind it seems to be that there is an emerging market in Vietnam, where rhino horn is purported to be a cancer cure. But it is also emerging as a high-value gift that people give one another. It’s not used decoratively; it’s just used

for medicinal purposes. It’s also being used as a hangover cure in Vietnam. These are new uses” (oral communication, January 23, 2013).

Ellis noted that the demand for rhino horn also is present in China, where she said the use of it is ongoing and not showing signs of decreasing. Ellis purported that the current Asian demand partly stems from the increasing Asian presence in Africa, where Chinese companies are being awarded construction and infrastructure contracts.

Perhaps a greater cause for the demand, Ellis continued, is the strong cultural belief in these remedies in Vietnam, China, and other Asian countries, where rhino horn is available for sale whole over-the-counter and ground-up in prepared remedies. Thomas of TRAFFIC added, “It’s important to stress that the horns are not in demand for traditional medicine — they are being sought for new uses; in Viet Nam ground horn is used as a body detoxifier — essentially a hangover cure, also given as a high value gift, and to some extent also used as a supposed (though medically unsupported) cancer cure. The traditional, centuries-old use of rhino horn is in a concoction used to treat high fever.”

The outlook for most involved species, unfortunately, remains bleak and uncertain, as apparent in WWF’s December 2012 announcement that the illegal trade of wildlife has become the “fourth largest illegal global trade, after narcotics, counterfeiting, and human trafficking.”

IRF and other groups are planning to implement an education campaign in Vietnam informing the public that these remedies are baseless and have no scientific support. Additional conservation and wildlife groups have been trying to quell poaching through the dispersion of a similar message. The theme of 2011’s World Rhino Day, for example, was “Rhino Horn is Not Medicine,” and at the Convention on International Trade in Endangered Species of Wild Flora and Fauna (CITES) meeting in early March 2013, Thomas said, “countries were instructed to develop strategies to reduce the demand for rhino horn. This would naturally include the promotion of alternatives to the use of horn as well as more frequently employed measures such as stronger penalties for those caught trafficking, etc.”

Ellis also noted the importance of educating the public that real animals are being killed.

“There’s not much wildlife left in Vietnam, for example, and I’m not sure that the end-user always knows that [the remedy] even comes from a live animal that was killed,” she said. “The majority of rhinos are killed with AK-47s. Some of the more sophisticated poachers are coming in and — obviously have the involvement of veterinarians — with helicopters and are darting the animals with drugs. But, by and large, they’re so interested in getting every single shred of horn that they hack down into the animal’s skull. They bleed to death; they die from trauma and shock. Occasionally they live, but only one or two actually survived more than a few days.”

Because it is very difficult to address the deep, cultural root of the problem, however, Ellis’s organization and others

largely focus on deterring and preventing poaching, as well as encouraging local authorities to punish those involved with poaching.

Future Outlook

Offering hope for the future of these beloved animal species is the increasing presence and awareness that illegal wildlife trafficking is obtaining among charity groups, the media, and public and government officials. Several wildlife groups are taking action to address the overall situation, such as TRAFFIC's distribution of educational wildlife crime kits to customs officials in Southeast Asian countries.¹¹ Robinson of Animals Asia emphasized the important role that the public has to play, especially by contacting relevant authorities, as well as the media in the United States and in China.

"Please, please to anyone reading [this] article that is remotely interested and wants to help," she said, "don't underestimate the power of your pen and how much you can help. Please, please, keep raising it."

Recent journal articles suggest interest in using DNA testing to detect the presence of endangered animal species in Chinese medicines. A February 2013 article published in *PLoS One*, for example, discussed the use of DNA barcoding to successfully identify endangered Saiga antelope and Sika deer particles in known animal-based products.¹² According to the Chinese authors, "... We believe that the identification (DNA barcoding) of threatened animals combined with seeking substitutions (bio-response) can yet be regarded as a valid strategy for establishing a balance between the protection of threatened animals and the development of traditional medicine."

A similar paper, published in *PLoS Genetics* in 2012, details DNA testing that revealed Asiatic black bear and other threatened animals in TCM samples, substances that "were rarely declared on the product packaging."¹³ High-throughput sequencing of DNA, the Australian authors wrote, could be a cost-effective and efficient way to screen TCM products, especially when genetic reference databases become better established.

Still, the situation remains complex and is far from being solved, especially considering the large role played by unregulated shops and markets that sell remedies for uses with no scientific or traditional support. And the problem touches many animals in addition to the species covered in this article; pangolins (a small, scale-covered Asian mammal), the most commonly traded mammal — two species of which are endangered — are killed for their scales and blood;¹⁴ manta rays are killed for their gills that are bogusly purported to treat cancer, chickenpox, and suppressed immune systems.¹⁵ The list goes on and on.

Thomas said he thinks the key to seeing a significant improvement is to address possibly the most difficult aspect of the situation: reduce demand for the endangered wildlife products in the first place.

"Close that down," he said, "and you take away the reason to source and supply it. There needs to be a coordinated strategy, ranging from simple public awareness raising of the impacts the demand is causing; more information about what the actual rather than perceived medicinal benefits of the product; what

legal, cheaper, effective alternatives may exist, etc. Such activities should be focused in user groups/destination countries. Alongside there should be other measures, such as higher penalties, stronger monitoring, and enforcement to reduce or curtail the supply of the product. These should be applied across the entire trade chain — from source to end user." HG

—Lindsay Stafford Mader

References

1. Cavaliere C. Medicinal use of threatened animal species and the search for botanical alternatives. *HerbalGram*. 2010;86:34-49. Available at: <http://cms.herbalgram.org/herbalgram/issue86/article3527.html>.
2. Illegal wildlife trade threatens national security, says WWF report [press release]. New York, NY: World Wildlife Fund; December 12, 2012. Available at: http://wwf.panda.org/wwf_news/?207054/Illegal-wildlife-trade-threatens-national-security-says-WWF-report. Accessed January 18, 2013.
3. *Panthera tigris*. The IUCN Red List of Threatened Species. Version 2012.2. Available at: www.iucnredlist.org/details/15955/0. Accessed November 26, 2012.
4. Poaching still biggest threat to recovery of world's tiger populations. World Wildlife Fund website. November 23, 2012. Available at: http://wwf.panda.org/what_we_do/endangered_species/tigers/news_pubs/?206807/Poaching-still-biggest-threat-to-recovery-of-worlds-tiger-populations. Accessed January 18, 2013.
5. New study reveals scale of persistent illegal tiger trade [press release]. Bangkok, Thailand: TRAFFIC; March 7, 2013. Available at: www.traffic.org/home/2013/3/7/new-study-reveals-scale-of-persistent-illegal-tiger-trade.html. Accessed March 15, 2013.
6. Hidden in Plain Sight: China's Clandestine Tiger Trade. Environmental Investigation Agency. February 2013. Available at: www.eia-international.org/hidden-in-plain-sight-chinas-clandestine-tiger-trade. Accessed March 28, 2013.
7. Jacobs A. Folk remedy extracted from captive bears stirs furor in China. *New York Times*. May 21, 2013. Available at: www.nytimes.com/2013/05/22/world/asia/chinese-bear-bile-farming-draws-charges-of-cruelty.html?pagewanted=all&_r=0. Accessed July 31, 2013.
8. Rhino poaching toll reaches new high [press release]. Cape Town, South Africa: TRAFFIC; January 10, 2013. Available at: www.traffic.org/home/2013/1/10/rhino-poaching-toll-reaches-new-high.html. Accessed January 11, 2013.
9. South Africa rhino toll tops 500 in 2013 [press release]. Johannesburg, South Africa: TRAFFIC; July 26, 2013. Available at: www.traffic.org/home/2013/7/26/south-africa-rhino-toll-tops-500-in-2013.html. Accessed July 31, 2013.
10. Bhaumik S. Spike in rhinoceros deaths worries India. December 15, 2012. Available at: www.aljazeera.com/indepth/feature/2012/12/20121212122842576905.html. Accessed January 29, 2013.
11. Wildlife crime-fighting training package for ASEAN customs officers [press release]. Bangkok, Thailand: TRAFFIC; March 8, 2013. Available at: www.traffic.org/home/2013/3/8/wildlife-crime-fighting-training-package-for-asean-customers-o.html. Accessed March 15, 2013.
12. Yan D, Luo JY, Han YM, Peng C, Dong XP, Chen SL, Sun LG, Xiao XH. Forensic DNA barcoding and bio-response studies of animal horn products used in traditional medicine. *PLoS One*. 2013;8(2):e55854. doi: 10.1371/journal.pone.0055854. Epub 2013 Feb 8.
13. Coglan ML, Haile J, Houston J, Murray DC, White NE, Moolhuijzen P, Bellgard MI, Bunce M. Deep sequencing of plant and animal DNA contained within traditional Chinese medicines reveals legality issues and health safety concerns. *PLoS Genet*. 2012;8(4):e1002657. doi: 10.1371/journal.pgen.1002657. Epub 2012 Apr 12.
14. Hance J. Pity the pangolin: little-known mammal most common victim of the wildlife trade. Mongabay.com. February 11, 2013. Available at: <http://news.mongabay.com/2013/0211-hance-pity-pangolin.html>. Accessed March 28, 2013.
15. Hooper R. Glider of the sea threatened by 'traditional' medicine. *New Scientist*. March 25, 2013. Available at: www.newscientist.com/blogs/short-sharpscience/2013/03/manta-ray-mouth.html. Accessed March 28, 2013.

Zembrin® Sceletium Extract Shown Safe in Trial in Healthy Adults

Reviewed: Nell H, Siebert M, Chellan P, Gericke N. A randomized, double-blind, parallel-group, placebo-controlled trial of extract *Sceletium tortuosum* (Zembrin®) in healthy adults. *J Altern Complement Med.* February 2013; [epub ahead of print]. doi: 10.1089/acm.2012.0185.

Sceletium (*Sceletium tortuosum*, Aizoaceae) is a short-lived perennial plant that is indigenous to the Namaqualand and Karoo region of South Africa. The plant has a documented history of use as a medicinal herb in this region that dates back to the mid-1600s. In 1738, it was proclaimed “the greatest cheerer of the spirits, and the noblest restorative in the world.”¹ In *S. tortuosum*, there exists a wide intraspecies chemotypic variation that has resulted in an extremely broad range of clinical applications. According to the authors, preparations (dry herb used as a masticatory, and, less often, as a tea) made from *S. tortuosum* leaves, stems, and sometimes roots are used to relieve thirst, hunger, and fatigue, and for the plant’s restorative, mood-elevating, and sedative effects, including its therapeutic use for anxiety and depression. Intoxication and euphoria are also reported with its use, particularly with fermented material that includes roots.² In clinical case reports, anxiolytic and antidepressant activities have been observed with consumption of tablets and capsules of milled scelletium above-ground plant material.³

These authors conducted a randomized, double-blind, parallel-group, placebo-controlled trial to evaluate the safety and tolerability of two different doses of Zembrin® (extract manufactured by Gehrlicher GmbH; Eurasburg, Germany; capsules manufactured by Pharmaceutical Contractors [Pty] Ltd.; Isando, South Africa) — a proprietary standardized and characterized commercial dry extract of scelletium aerial parts — in healthy adults.

Zembrin is a 2:1 dry aqueous-ethanolic extract of the entire aboveground portions of a cultivated selection of naturally occurring *S. tortuosum*, with an alkaloid content of not less than 0.38% by weight and having a specific profile of the mesembrine alkaloids. Safe daily doses of raw, unprocessed *S. tortuosum* herb are reported to vary from 50 mg to 5,000 mg, a range that is due to both the chemotypic variability and the intended use. The authors selected low doses of 8 mg and 25 mg of Zembrin (equivalent to 16 mg and 50 mg, respectively, of crude *S. tortuosum* herb), considering the doses to be safe and to have potential for inclusion in functional food and dietary supplement products. The Zembrin used in this study was standardized to 0.4% w/w total for four alkaloids, including mesembrenol, mesembrenone, mesembrine, and mesembranol. Each gelatin capsule contained 0 mg, 8 mg, or 25 mg of the scelletium dry extract, as well as various excipients.

A preliminary screening visit was followed by a two-week placebo run-in period during which 37 subjects recorded their daily use of placebo medication to assess compliance. At the third visit, the subjects were randomly assigned to one of the following three treat-

ment groups for three months: 12 subjects were allocated to the 8 mg Zembrin group, 12 to the 25 mg Zembrin group, and 13 to the placebo group. All but one subject completed the trial. The 37 healthy men and nonpregnant women (no gender differentiation provided) were between 18 and 55 years of age, weighed >50 kg (>110.2 lb), and had a body mass index ranging from 18.5 to 29.9 kg/m².

Visits three, four, five, and six were scheduled monthly. At visits two, three, four, and five, the subjects were given a diary and asked to record the occurrence of adverse events (AEs), their daily use of the study product, and the intake of other medications. Safety assessments performed at the screening visit and at visits four, five, and six included vital signs; physical examination; hematology, biochemistry, and urine analysis; 12-lead electrocardiogram (ECG); and the recording of patient-reported adverse events AEs.

The authors report that the greatest incidence of AEs occurred in the placebo group, followed by the 25 mg and 8 mg Zembrin groups. Twenty-two of the 37 total assigned subjects (59%) experienced at least one AE. Four of the 12 subjects (33.3%) in the 8 mg group reported six AEs. Seven of the 12 subjects (58.3%) in the 25 mg group reported 14 AEs, and 11 of the 13 subjects (84.6%) in the placebo group reported 22 AEs.

Headache was the most common AE, with eight incidences reported by seven of the 37 subjects (18.9%). Of those, four occurred in four subjects in the placebo group, three in two subjects in the 25 mg Zembrin group, and one in one subject in the 8 mg Zembrin group. Other AEs included abdominal pain (five incidences in three of the 13 subjects in the placebo group), upper respiratory tract infection (four incidences in four of the 13 subjects who received placebo), and influenza (three incidences in three subjects; one from each group).

All but two AEs were mild or moderate and were considered unrelated to the study medication. The two severe AEs were reported in the placebo group. One subject reported abdominal pain, which was considered as possibly related

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to the study product. One subject who complained of headache, which was considered as probably related to the study product, withdrew from the trial.

The authors reported no marked, clinically relevant differences in the changes in vital signs among the three treatments, except for a difference in diastolic blood pressure (DBP) between the placebo and the 8 mg Zembrin groups. Among those in the 8 mg group, a mean increase in DBP of 1.92 mmHg occurred from the screening visit to visit six; the subjects in the placebo group experienced a mean decrease in DBP of 6.17 mmHg. This resulted in a mean difference of 8.08 mmHg (95% confidence interval: 1.51-14.65) between those two treatments ($P=0.02$). No such significant difference in DBP was seen between the 25 mg Zembrin group and the placebo group.

Other safety results showed no differences among the three treatments in ECG or physical examination findings during the three months, and no significant changes were observed in laboratory parameters or in body weight.

Five subjects offered unsolicited positive comments in their study diaries about changes in their mental/emotional health. These comments were from one subject (8.3%) in the 8 mg Zembrin group, three subjects (25%) in the 25 mg Zembrin group, and one subject (7.7%) in the placebo group, and included sleeping better at night, coping better with stressful situations, and feeling better in general.

According to the authors, the spectrum of reported scelerium uses suggests a dose response that is specific to the alkaloid content and profile. The lowest doses are ingested at the food side of the spectrum, higher doses at the botanical medicine side, and the highest doses at the intoxicating end of the spectrum. "In addition to dose-response for total alkaloid content, the alkaloid composition is likely to be a key factor that determines effects and adverse effects," wrote the authors.

The results of this trial show that both treatments of Zembrin at doses of 8 mg and 25 mg once daily for three months were well tolerated and safe.

One of the authors, Nigel Gericke, discloses that he is the director of medical and scientific affairs of HG&H Pharmaceuticals (Pty) Ltd in South Africa, the company that developed Zembrin. HG

—Shari Henson

References

1. Kolben P. Medley G, trans. *The Present State of the Cape of Good-Hope*. Vol. 1, 2nd ed. London, UK: Printed for W. Innys and R. Manby; 1738.
2. Gericke N, Viljoen AM. Scelerium — a review update. *J Ethnopharmacol*. 2008;119(3):653-663.
3. Gericke N. Clinical application of selected South African medicinal plants. *Australian Journal of Medical Herbalism*. 2001;13(1):3-7,9-11,13-15.

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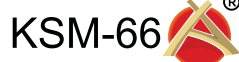
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Acute Dose of Bacopa Extract Improves Cognitive Performance

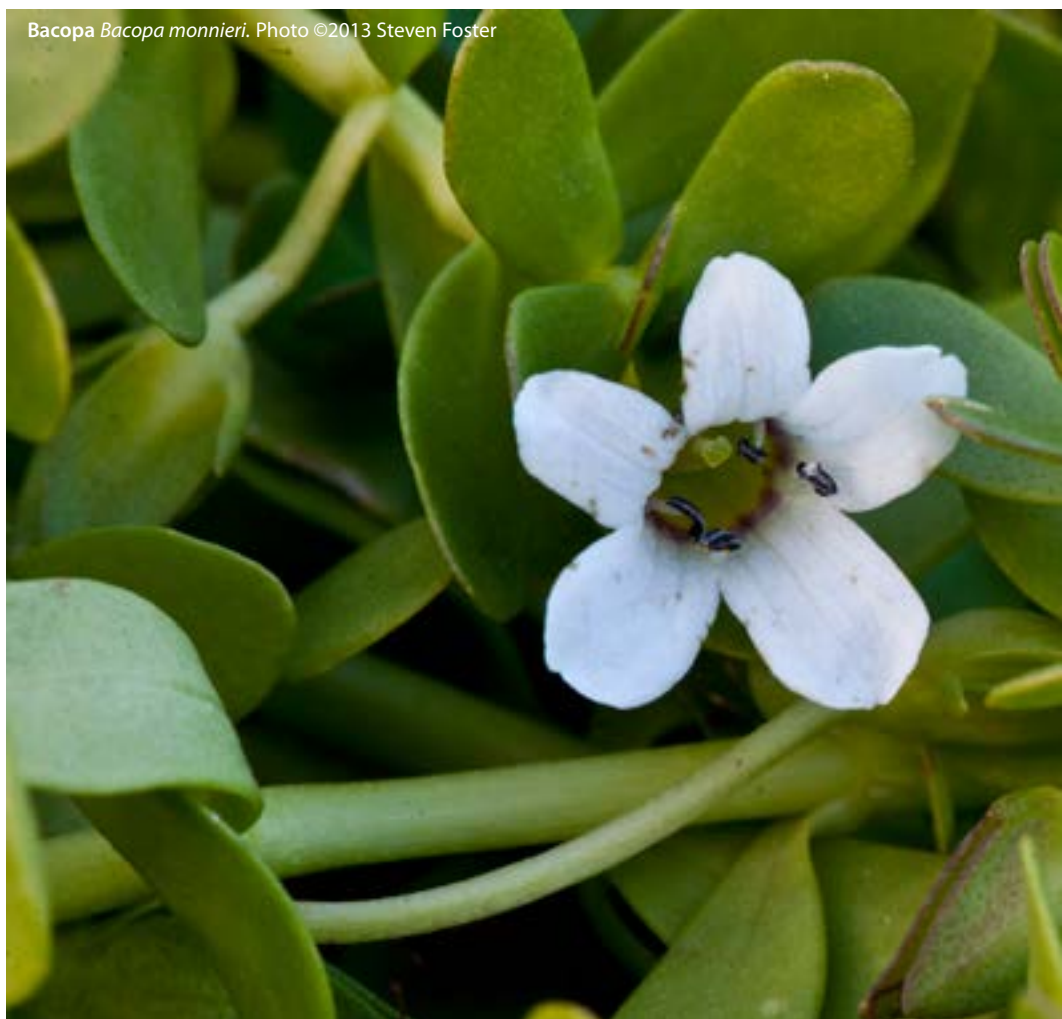
Reviewed: Downey LA, Kean J, Nemeh F, *et al.* An acute, double-blind, placebo-controlled crossover study of 320 mg and 640 mg doses of a special extract of *Bacopa monnieri* (CDRI 08) on sustained cognitive performance. *Phytother Res.* December 2012; [epub ahead of print]. doi: 10.1002/ptr.4864.

In Ayurvedic traditional medicine in India, Brahmi or bacopa (*Bacopa monnieri*, Scrophulariaceae) is a valued memory-enhancing, anti-amnesic, anxiolytic, sedative, and anti-epileptic treatment. Modern *in vitro* and *in vivo* studies have provided evidence suggesting several possible mechanisms for these effects. Over a dozen clinical trials have documented the positive effects of bacopa preparations (usually extracts) on learning, memory, information processing speed, and anxiety, as well as its antidepressant and cardio-

vascular effects. However, the majority of clinical trials have investigated the effects of chronic bacopa treatment; to date only one study has assessed its acute nootropic or cognitive-enhancing effects. The purpose of this double-blind, placebo-controlled, crossover clinical trial was to evaluate the effects of two dosage levels of special bacopa extract on mood, cardiovascular activity, and cognitive performance.

Healthy volunteers (n=24; aged 18-56 years, with a body mass index of 15.4-32.7 kg/m²) participated in

Bacopa monnieri. Photo ©2013 Steven Foster



this study conducted in Australia. Pre-screening exclusion criteria were as follows: smoking; any history of psychiatric disorders or neurological diseases; endocrine, gastrointestinal, or bleeding disorders; chronic illness and infection; pregnancy or lactation; and current use of medications or herbal supplements.

Subjects received a single acute dose of placebo (four 160 mg capsules of inert plant-based materials), 320 mg, and 640 mg of bacopa extract (KeenMind® [CDRI 08]; SFI Flordis; St. Leonards, NSW, Australia) in a three-arm crossover design. Each treatment was separated by a one-week washout period. The 50% ethanol bacopa extract was prepared from stems, leaves, and roots of a cultured variety of bacopa collected from West Bengal, India, and standardized to 55% total bacosides.

Each subject attended four assessment sessions — one practice visit and three study visits. On each study visit, tests were conducted prior to the acute dose (baseline) and then two hours after dosing. The tests included a cognitive demand battery (CDB) and assessments of blood pressure, arterial stiffness, and cerebral blood flow. The CDB was comprised of a subjective assessment of stress and mental fatigue on a visual analogue scale (VAS), serial threes and serial sevens subtraction tests (counting backward from a given number by threes or sevens), and the Bakan Rapid Visual Information Processing (BRVIP) task (identifying the consecutive series of odd or even numbers in a random series, evaluated for both accuracy and reaction time). Each CDB took 10 minutes and was conducted seven times per visit; one test before ingestion of the study medication and then six continuous tests starting two hours after ingestion.

Compared with placebo, 320 mg of this bacopa extract significantly improved performance of the serial threes subtraction test at the first ($P=0.05$) and fourth repetition ($P=0.02$). For all groups, there was a significant improvement over time on the serial threes test ($P<0.001$). There were no other significant findings for the serial threes test.

For the serial sevens subtraction test, the only significant change was an improved performance of the 640 mg dose of bacopa extract compared with the 320 mg dose at the first repetition ($P<0.05$). For all groups, there was a significant improvement over time on the serial sevens test ($P<0.001$).

There were no significant changes in the BRVIP task. The CDB significantly increased the subjective ratings of stress and fatigue ($P<0.01$); none of the treatments attenuated these effects. There were no significant changes in the cardiovascular assessments, and no adverse events occurred.

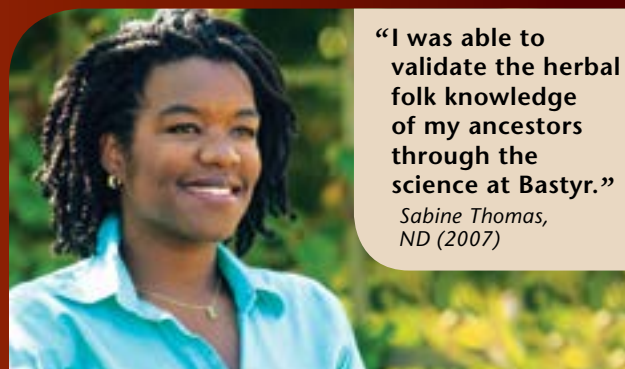
The authors hypothesize that greater cognitive enhancement could have occurred prior to the two-hour post-treatment assessment, which may explain why the improvements took place during the earliest repetitions. The authors conclude that the acute nootropic effect of this bacopa extract may be limited to early windows of activity (*i.e.*, < two hours post-dosing).

It cannot be ruled out that any statistical significance may be due to chance, since there were six post-dosing tests conducted, and few showed any alterations. Another point

to consider is that not all extracts are created equally, and other bacopa extracts may behave differently in this paradigm. HG

—Heather S. Oliff, PhD

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Saffron Extract Improves Retinal Function in Patients with Early Age-Related Macular Degeneration

Reviewed: Piccardi M, Marangoni D, Minnella AM, *et al.* A longitudinal follow-up study of saffron supplementation in early age-related macular degeneration: sustained benefits to central retinal function. *Evid Based Complement Alternat Med.* 2012;[epub ahead of print]. doi: 10.1155/2012/429124.

Common signs of early age-related macular degeneration (AMD) include large, soft drusen (subretinal pigment epithelial deposits that are co-characteristic of, but not uniquely associated with, AMD); hyper/hypopigmentation of the retinal pigment epithelium (RPE); and mild-to-moderate loss of central vision. In the late stages of the

disease, the RPE atrophies, severely impairing central vision — a major cause of irreversible vision loss in the elderly.

Several factors have been associated with the risk for photoreceptor degeneration/dysfunction in AMD patients. Some documented risk factors appear to be oxidative and/or proinflammatory in nature,¹⁻³ while corresponding protective factors are antioxidant and/or anti-inflammatory.⁴⁻⁶ In an earlier randomized clinical trial,⁷ the investigators reported that short-term (three month) saffron (*Crocus sativus*, Iridaceae) supplementation improved retinal flicker sensitivity in patients with AMD. In this clinical trial, the authors report on their longitudinal, open-label study that evaluated whether the observed functional benefits of saffron supplementation are reproducible over a longer follow-up duration.

Twenty-nine patients (mean age = 69.3 ± 7 years) with a diagnosis of bilateral early AMD were recruited over an eight-month period from outpatients of the eye, ear, nose, and throat department of the Università Cattolica del Sacro Cuore in Rome, Italy. Sixteen men and 13 women underwent standard general and ophthalmic examinations. Clinical diagnosis of early AMD was established by direct and indirect ophthalmoscopy, as well as retinal biomicroscopy, when any of the following lesions in the macular area of one or both eyes was identified: soft distinct or indistinct drusen, areas of hyperpigmentation associated with drusen, or areas of hypopigmentation of the RPE associated with drusen, without any visibility of choroidal vessels.

The patients had to have a best-corrected visual acuity of 0.5 or better in the studied eye, central fixation (to see clearly by using the center of the visual field), normal color vision, no signs of other reti-



Saffron *Crocus sativus*. Photo ©2013 Steven Foster

nal or optic nerve disease, and clear optical media (eyes that do not have cataracts, corneal scars, or other obstructions).

Patients underwent a clinical examination and a focal electroretinogram (fERG)-derived macular (18°) flicker sensitivity estimate at baseline and every three months over a 15-month period of treatment and follow-up. The treatment material was 20 mg of saffron daily (Zaffit™; Hortus Novus; L'Aquila, Italy).

The main outcome was fERG sensitivity derived from the estimated response amplitude thresholds. (fERGs measure the rapid change in the resting ocular potential caused by exposure to a flash of light and can provide information about the macular function.) Visual acuity was a secondary outcome. The authors reported an overall increase in fERG amplitude soon after the first three months of supplementation, followed by stabilization over the subsequent follow-up period. Mean fERG threshold decreased by 0.3 log units compared with baseline values ($P < 0.01$) and remained stable during the follow-up period.

At the third month of supplementation, mean visual acuity improved by two Snellen lines (chart commonly used by eye professionals to measure visual acuity) compared to baseline values ($P < 0.01$) and remained stable during the study period. All patients reported improved vision, particularly improved contrast and color perception, reading ability, and vision at low levels of luminous intensity. Periodic funduscopy examination did not show any significant change in drusen number or size, or in the extent of RPE abnormalities.

These results show that saffron supplementation may induce a long-term, stable improvement in retinal function, as measured by fERG responses. The changes in fERG threshold after supplementation were within-session consistent, reproducible, and durable over the 15-month follow-up period.

According to the authors, this study is limited by “its open-label nature, which may have affected mainly the subjective patients’ results, and the assumed stability of the main outcome measure, the fERG, without treatment.”

The improved macular function, the authors said, may result from the combined activity of saffron’s phytochemical compounds, especially the carotenoid derivatives crocin and crocetin, which possess antioxidant properties and may act through a protective mechanism similar to that seen with carotenoid supplementation. Results from an earlier study in rats⁸ showed that saffron may protect photoreceptors against retinal stress, maintaining both morphology and function, and probably downregulating programmed cell death.

The authors note that their results can be applied only to patients in the early or moderate stage of AMD. Whether saffron supplementation exerts a beneficial protective effect in patients with more advanced stages of the disease is unknown. Also unclear is how saffron’s efficacy compares with that of other available antioxidant supplements. According to the authors, “While further studies are needed to define the upper beneficial limit of saffron supplementa-

tion, the present approach seems to be promising for a long-term treatment of early retinal dysfunction associated with AMD.”

The saffron pills and additional support were provided by Hortus Novus. HG

—Shari Henson

References

1. Hageman GS, Anderson DH, Johnson LV, et al. A common haplotype in the complement regulatory gene factor H (HF1/CFH) predisposes individuals to age-related macular degeneration. *Proc Natl Acad Sci U S A*. 2005;102(20):7227-7232.
2. Hollyfield JG, Bonilha VL, Rayborn ME, et al. Oxidative damage-induced inflammation initiates age-related macular degeneration. *Nat Med*. 2008;14(2):194-198.
3. Rivera A, Fisher SA, Fritsche LG, et al. Hypothetical LOC387715 is a second major susceptibility gene for age-related macular degeneration, contributing independently of complement factor H to disease risk. *Hum Mol Genet*. 2005;14(21):3227-3236.
4. Age-Related Eye Disease Study Research Group. A randomized, placebo-controlled, clinical trial of high-dose supplementation with vitamins C and E, beta carotene, and zinc for age-related macular degeneration and vision loss: AREDS report no. 8. *Arch Ophthalmol*. 2001;119(10):1417-1436.
5. Weismann D, Hartvigsen K, Lauer N, et al. Complement factor H binds malondialdehyde epitopes and protects from oxidative stress. *Nature*. 2011;478(7367):76-81.
6. Wong WT, Kam W, Cunningham D, et al. Treatment of geographic atrophy by the topical administration of OT-551: results of a phase II clinical trial. *Invest Ophthalmol Vis Sci*. 2010;51(12):6131-6139.
7. Oppel-Sutter M. Saffron supplementation improves visual acuity symptoms of early age-related macular degeneration. *HerbClip*. November 15, 2010 (No. 101061-412). Austin, TX: American Botanical Council. Review of Influence of saffron supplementation on retinal flicker sensitivity in early age-related macular degeneration by Falsini B, Piccardi M, Minnella A, et al. *Invest Ophthalmol Vis Sci*. 2010;51(12):6118-6124.
8. Maccarone R, Di Marco S, Bisti S. Saffron supplement maintains morphology and function after exposure to damaging light in mammalian retina. *Invest Ophthalmol Vis Sci*. 2008;49(3):1254-1261.



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Medicinal Dose of Water-Based Kava Extract Does Not Impair Driving Ability

Reviewed: Sarris J, Laporte E, Scholey A, *et al.* Does a medicinal dose of kava impair driving? A randomized, placebo-controlled, double-blind study. *Traffic Inj Prev.* 2013;14(1):13-17.

It is well known that alcohol and certain pharmaceutical and recreational drugs can impair driving and increase the risk of accidents. Some medical researchers have expressed concerns that kava (*Piper methysticum*, Piperaceae) root and its preparations have the potential to cause inebriation similar to that caused by psychotropic substances such as alcohol and benzodiazepines (a class of pharmaceutical anti-anxiety drugs, which includes the well-known drug Valium[®]). Therefore, it is possible that kava may impair the motor skills and cognitive abilities required for safe driving. For this reason, the German Commission E, in its therapeutic monograph on kava published in 1990, included a precaution with respect to driving an automobile or operating heavy machinery while under the influence of kava.^{1*}

The purpose of this three-arm, randomized, placebo-controlled, double-blind, crossover trial was to evaluate the acute effects of kava on driving performance. This study was part of the Kava Anxiety-Lowering Medication (KALM) Project, conducted by the Brain and Psychological Sciences Research Centre at Swinburne University of Technology in Melbourne, Australia. Men and women (n=22; aged 16-65 years) with mild-to-moderate anxiety were recruited via advertising media distributed in Hawthorn, Victoria, Australia. Patients were excluded for the following criteria: current use of antidepressants, mood stabilizers, antipsychotics, opioids, analgesics, or cannabis; substance abuse or dependency disorder in the previous six months, including alcohol abuse/dependency; previous adverse reaction to kava or benzodiazepines; regular use of kava or benzodiazepines in the previous 12 months; more than one occasion of benzodiazepine or kava use each week over the past month; pregnancy, trying to conceive, or those who could be pregnant; regular smokers (more than one cigarette a week); and those with abnormal liver function.

Participants were subjected to a 10-minute practice session on a driv-

ing simulator. They then received either three kava tablets containing a combined total of 180 mg of kavalactones, 30 mg of oxazepam (a benzodiazepine), or placebo. All treatments looked identical. The kava tablets (MediHerb Kava, Integra Healthcare Pty Ltd; Warwick, Australia) were standardized to contain 60 mg of kavalactones per tablet. The kava preparation was manufactured using a water-extracted precipitate of the peeled rootstock from a Vanuatu noble cultivar. An independent assay using high-performance liquid chromatographic analysis revealed higher concentrations of the kavalactones dihydrokavain, kavain, and dihydromethysticin; moderate levels of methysticin and yangelin; and lower levels of desmethoxyyangonin. The alkaloid pipermethystine was not present.

Following treatment administration, the patients relaxed for 90 minutes until their blood serum had appropriate levels of kava constituent. They then began a 15-minute comput-

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Kava *Piper methysticum*. Photo ©2013 Steven Foster



*The German Commission E monograph notes under Duration of Administration: "Even when administered within its prescribed dosages, this herb may adversely affect motor reflexes and judgment for driving and/or operating heavy machinery."

Water-Based Kava Extract for Generalized Anxiety Disorder Shows No Adverse Effects in Liver Function

Reviewed: Sarris J, Stough C, Teschke R, Wahid ZT, Bousman CA, Murray G, Savage KM, Mouatt P, Ng C, and Schweitzer I. Kava for the treatment of generalized anxiety disorder RCT: analysis of adverse reactions, liver function, addiction, and sexual effects. *Phytother Res*. January 2013; [epub ahead of print]. doi: 10.1002/ptr.4916.

Empirical observations and clinical trial evidence suggest that preparations made from the root of kava (*Piper methysticum*, Piperaceae) are efficacious in the treatment of anxiety; however, cases of hepatotoxicity associated with kava use have led to its withdrawal or restricted use in many Western countries. Considering that kava has anxiolytic effects, questions arise as to whether kava is addictive, has adverse sexual side effects, or has withdrawal effects that might be similar to pharmaceutical anxiolytic drugs such as the benzodiazepines (drugs with an anti-anxiety effect). Uncertainty regarding the cause of the liver toxicity centers on poor-quality raw material, plant cultivars, and extraction solvents. Hence the purpose of this randomized, double-blind, placebo-controlled study was to evaluate adverse events (AEs), withdrawal/addiction effects, and liver function effects associated with kava use in patients with generalized anxiety disorder (GAD). Also, genetic polymorphism (when more than one different phenotype exists in the same species) of the liver enzyme cytochrome P450 2D6 (CYP2D6), which metabolizes compounds in kava, was evaluated to determine whether subjects who were poor or extensive metabolizers have different AEs using water-extracted kava from noble cultivars (that is, kava cultivars with higher levels of kavain and lower levels of dihydromethysticin).¹

Patients (n=58; aged 18-65 years) with DSM-IV (*Diagnostic and Statistical Manual of Mental Disorders*, 4th Edition) diagnosed with GAD were recruited from the Greater Melbourne area in Victoria, Australia, via mass media. Patients were excluded if they had any of the following conditions: major depressive disorder or elevated depressive symptomatology (greater than 17 on the Montgomery-Asberg Depression Rating Scale); a DSM-IV diagnosis of a psychotic or bipolar disorder; significant suicidal ideation in the previous six months; current use of antidepressants,

mood stabilizers, antipsychotics, opioid analgesics, or St. John's wort (*Hypericum perforatum*, Clusiaceae); diagnosed hepatobiliary disease/inflammation; substance abuse or dependency disorder in the previous six months; a previous adverse reaction to kava or benzodiazepines; kava or benzodiazepine use in the previous 12 months; or abnormal baseline liver function. The study began with a one-week run-in phase to identify placebo responders. Any subject who showed a 50% improvement on the Hamilton Anxiety Scale (HAM-A) score during this placebo phase was excluded from the study.

For six weeks, patients received placebo or an aqueous kava extract with the equivalent of 120 mg of kavalactones/day, which was titrated to 240 mg/day in patients showing no response at three weeks. The kava was formulated from pressed, dried, aqueous peeled rootstock of kava (Medi-Herb, Integria Healthcare; Eight Mile Plains, Queensland, Australia). The kava extract was independently analyzed at Southern Cross University at Lismore, Australia, and was determined to contain various kavalactones: dihydrokavain (15.5 mg, 26%), kavain (12.5 mg, 21%), dihydromethysticin (11 mg, 18%) methysticin (8.5 mg, 14%), yangonin (8 mg, 13%), and desmethoxyyangonin (5mg, 8%); the alkaloid pipermethystine, which has been implicated in some kava extracts associated with cases of liver dysfunction, was not detected.

At weeks two and seven, AEs were assessed via questionnaire, and blood was drawn for liver function tests and to determine polymorphisms.

No significant AEs were reported. One case of dermatitis and one case of minor stomach upset were associated with kava intake. Withdrawal was assessed by treating all patients with placebo for one week at study end. There was no signifi-

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erized driving simulator program, followed by a visual analog assessment. One week later, patients were crossed over to another treatment. This routine was repeated a total of three times, once for each treatment.

Oxazepam produced a significantly slower braking reaction time than placebo ($P=0.002$) and kava ($P=0.003$). Concentration lapses were significantly fewer with kava than with oxazepam ($P=0.033$). An equal number of participants in each treatment group crashed. Results were not modified by the covariates of driving experience, driving status, or treatment order. Oxazepam-treated patients reported that they were significantly less alert than when exposed to the other treatments. All patients were more fatigued after driving, irrespective of the treatment.

According to the authors, this is the first study to evaluate the acute effects of a medicinal dose of kava on driving performance and safety compared to a benzodiazepine. The authors concluded that at medicinal doses, kava does not alter driving in the same way as benzodiazepines. Apart from its small sample size, this study had several limitations. Blood levels of oxazepam peak at two-to-three hours, and the driving analysis occurred after 90 minutes; therefore, oxazepam may have produced a more

profound effect if evaluated later. The patients were not screened for medical conditions that could have altered driving vigilance, and the simulator did not exactly mimic real driving conditions. Also, the participants had mild-to-moderate anxiety, so the data may not be extrapolated to the general population.

This study gives important insight into the effects of a medicinal dose of kava on a population that would use it (*i.e.*, patients with anxiety). However, when people use kava for recreational purposes, they consume much higher doses. Similar to alcohol, as the dose of kava increases, the ability to safely operate a vehicle may diminish. This study should be replicated with a recreational dose of kava. HG

—Heather S. Oliff, PhD

Reference

1. Blumenthal M, Busse WR, Goldberg A, Gruenwald J, Hall T, *et al.* *The Complete German Commission E Monographs: Therapeutic Guide to Herbal Medicines*. Austin, Texas: American Botanical Council; Boston, MA: Integrative Medicine Communications, 1998.

Kava *Piper methysticum*. Photo ©2013 Steven Foster



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cant increase in AEs in either treatment group. Addiction was assessed by evaluating the number of patients who said that they wanted an increase in dose. Both treatment groups had the same number of patients who wanted to increase the dosage. There were no significant differences from baseline in liver function tests, and no patients developed clinical signs of hepatic abnormality. However, gamma-glutamyl transpeptidase (GGT) showed a trend toward elevation in kava-treated patients compared with those who took placebo at week seven ($P=0.08$). This finding may be due to an outlier; one patient (an extensive CYP2D6 metabolizer) had isolated increases in GGT and alanine aminotransferase (ALT) that both returned to baseline levels after the study. However, intermediate or extensive CYP2D6 metabolizer status had no significant impact on the type or frequency of AEs or abnormal liver function tests. Kava did not diminish sexual performance or enjoyment in men or women. However, there was a trend for kava-treated men to have more difficulty reaching orgasm ($P=0.067$). Kava-treated women had a significant increase in sex drive ($P=0.04$).

The authors conclude that water-extracted kava from noble cultivars has no deleterious effects on sexual function and pleasure, has no addictive qualities or withdrawal issues, and is safe for patients with GAD when taken for six weeks. The researchers also wrote that patients with GAD would require treatment for longer than six weeks, so a larger, longer-term study is needed to confirm the findings. Nonetheless, this study contributes to the growing body of evidence that water-soluble, standardized formulations of kava from noble cultivars are safe. The authors conclude that these data may assist in the reintroduction of kava in restricted markets. This study uses a medicinal dose of kava, and the results cannot be extrapolated to traditional recreational use with higher doses of kavalactones. HG

—Heather S. Oliff, PhD

Reference

1. Sarris J, Stough C, Bousman CA,

Wahid ZT, Murray G, Teschke R, Savage KM, Dowell A, Ng C, Schweitzer I. Kava in the treatment of generalized anxiety disorder: a double-blind, randomized, placebo-controlled study. *J Clin Psychopharmacol*. 2013;33(5):1-6.

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HERBS & ERECTILE DYSFUNCTION

A REVIEW OF TRADITIONAL USE AND
MODERN CLINICAL EVIDENCE

By Linda Woolven and Ted Snider

A photograph of a large, mature Ginkgo biloba tree. The tree's trunk is thick and textured, with several large branches extending upwards. The leaves are a bright yellow color, indicating autumn. The background is a clear blue sky.

Ginkgo Ginkgo biloba. Photo ©2013 Steven Foster



French Maritime Pine *Pinus pinaster*. Photo ©2013 Steven Foster

Since ancient times, cultures around the world have turned to herbs for help with erectile dysfunction (ED). The astonishing number of plants that have been believed to possess aphrodisiac and performance-enhancing powers suggests that people in every geographical location and throughout every era have sought herbal help for fertility and reproductive power. Ethnobotanist James A. Duke's database of herbs lists 239 herbs that reportedly have been used as folkloric aphrodisiacs and 122 that have been used for impotence (J. Duke, email, July 2, 2013). There is an ancient and intimate relationship between man and nature in the quest for enhanced sexual power.

Although some of the folkloric solutions seem truly outrageous, others have been vindicated by science. While doing field work in Tobago, the authors of this article came across a popular beverage tellingly titled "Hard Wine," which combined the equally aptly named horny goat weed (*Epimedium sagittatum*, Berberidaceae) with eleuthero (*Eleutherococcus senticosus*, Araliaceae) and a tree bark called *bois bandé* — all soaked in a red fruit wine.

The label and the hyped claims lent the product an air of illegitimacy. But horny goat weed does have a tradition of increasing virility and fertility. Known in China as *yin yang huo*, which translates literally as horny goat weed, the herb has been used for more than a thousand years for sexual conditions, including those of impotence and fertility.¹ In Traditional Chinese Medicine (TCM), horny goat weed is used to increase sexual energy in both men and women through its ability to "warm the kidneys." In TCM, low energy of the kidney is often involved in sexual problems. Some studies support horny goat weed's long history of traditional use. One study found that people on dialysis for kidney failure had improved sex drives when given horny goat weed, compared to people who did not get the herb.² Other studies have found that horny goat weed can restore low levels of testosterone.³

The most mysterious herb in Hard Wine, and the one that generated the most discussion on the streets of Tobago, is *bois bandé* (*Richeria grandis*, Phyllanthaceae). Though virtually no reliable scientific information on this herb has been found, the authors did locate one published interview with healers from Trinidad and Tobago in which *bois bandé* came up as a treatment for ED.⁴

Likewise, Dr. Duke encountered an herbal formula with a name to rival Hard Wine. *Rompe calzon* is a Latin American aphrodisiac that, like Hard Wine, is soaked in wine or rum. *Rompe calzon* means "bust your britches." There are only anecdotes for this herbal formula, however, as no studies exist. But it is intriguing that both *rompe calzon* and another Latin American formula Dr. Duke encountered called *siete raíces* ("seven roots") contain the Peruvian herb clavohuasca (*Tynanthus panurensis*, Bignoniaceae). Could there be something to these formulae as there has been for horny goat weed?

The biggest problem facing herbal formulae for erectile dysfunction today, though, is not incredibility. Science actually has vindicated a number of the traditional herbs. Instead, the most common concern is deception and adulteration. Ignoring or distrusting the science that suggests certain herbs really work and wanting to exploit lucrative opportunities, some marketers are adulterating products — which claim

There is an ancient and intimate relationship between man and nature in the quest for enhanced sexual power.

on the label to be natural — with unlabeled pharmaceutical ingredients. As some responsible parties in the industry prefer to phrase this situation, unscrupulous sellers are illegally marketing conventional pharmaceutical drugs masquerading as herbal dietary supplements.

The problem started occurring with increasing frequency a few years ago. In 2004, researchers found that approximately half of 40 botanical ED products analyzed contained the active ingredients of Viagra® (sildenafil), Cialis® (tadalafil), or Levitra® (vardenafil).⁵ In another study a year later, two out of seven natural ED products tested contained either sildenafil or tadalafil.⁶ Again, in 2006, sildenafil analogues (compounds with similar chemical structures) were found in herbal products marketed for ED.⁷

Though probably a more common concern when buying “herbal” ED products online than when buying them in a retail store, the problem is both serious and ongoing. In 2011, Health Canada warned, “An increasing problem with ‘herbal’ or ‘natural’ unauthorized products promoted for erectile dysfunction is that they contain analogues of

erectile dysfunction drugs.”⁸ A year later, Health Canada issued a warning to consumers not to buy four herbal products promoted for ED because they were found to contain either prescription or unlicensed medicines. In 2011, the US Department of Agriculture issued a warning that an analysis had identified a sildenafil analogue in an herbal ED product. And in 2012, the US Food and Drug Administration (FDA) cautioned consumers on buying dietary supplements for ED online. An FDA Internet survey found that six of 17 products contained sildenafil or substances similar to it, and then listed 29 products to avoid.⁹ The Medicines and Healthcare Products Regulatory Agency in the United Kingdom said in 2013 that it was “advising consumers not to buy ‘herbal’ remedies sold as a treatment for erectile dysfunction” because “evidence from around the world suggests that such products are often adulterated with random quantities of pharmaceutical substances.”¹⁰

Herbs Showing Efficacy for ED

Erectile dysfunction is the inability to attain or maintain an erection sufficient for satisfactory sexual function. Fifty-two percent of men between the ages of 40 and 70 are affected by ED.¹¹ The prevalence of ED is expected to increase over the next several years until it affects 322 million men worldwide by the year 2025.¹²

There are several possible causes for ED. These include depression, stress, anxiety, fatigue, diabetes, hypothyroidism, prostate disorders, low testosterone, high estrogen, atherosclerosis, cigarette smoking, and excessive alcohol consumption.¹³ In fact, some research suggests that in 20% of ED cases the cause is psychological.¹⁴ Several pharmaceutical drugs also can cause ED; blood pressure-lowering drugs are the most problematic,¹⁵ but antidepressants,^{16,17} the ulcer medication cimetidine,¹⁸ and the benign prostatic hyperplasia drugs finasteride^{19,20} and tamsulosin (Flomax®)²¹ are also common culprits.

Not all botanical manufacturers of ED products are unscrupulous. The market also contains legitimate herbal products that have had their botanical identity and raw materials authenticated, and many have at least one or two well-controlled clinical trials, or substantial history of traditional use, supporting the ED claim. That these legitimate products should be cast under a negative shadow and that people who could benefit from taking them are warned away is unfortunate because ED is a serious and increasingly common problem, the pharmaceutical solutions are not without side effects, and legitimate herbal products do offer viable options for treatment.

Ginkgo Extract

A very promising herb for treating ED is the standardized extract of ginkgo (*Ginkgo biloba*,



Ginkgo Ginkgo biloba. Photo ©2013 Steven Foster

Ginkgoaceae) leaf. One of the most valuable and versatile of all herbs, ginkgo is well known for its ability to increase circulation to the extremities, including the head, hands, and feet. So it is not entirely surprising that a condition often caused by lack of blood flow to the penis could also be helped by ginkgo extract.

At least two studies show the promise of ginkgo for reducing symptoms associated with ED. One study included 60 men suffering from ED caused by impaired penile arterial blood flow. For 12 to 18 months, men consumed a low dose of 60 mg per day of ginkgo extract (EGb 761®, W. Schwabe, Karlsruhe, Germany*; 50:1; 6% terpenes, 24% ginkgo flavonol glycosides). What is especially interesting about the study is that all of the men had failed to respond to injections of papaverine, a conventional pharmaceutical drug composed of the alkaloid derived from opium poppy (*Papaver somniferum*, Papaveraceae) that is used to improve blood flow in people with circulatory problems. It works by relaxing blood vessels and is employed for ED. However, its use had not benefited any of the men in this study, suggesting that they were difficult-to-treat cases. But after only six-to-eight weeks on ginkgo, improvement in penile arterial flow was evident. And after six months, 50% of the subjects had resolved their ED. In another 20% of the study participants, a subsequent attempt at papaverine ED treatment was then successful.²²

The second study was double-blinded and administered the more common higher dose of 240 mg ginkgo extract (EGb 761). In this nine-month study, 50 men with arterial ED were divided into two groups: those who had experienced some previous success with medication, and those who had not. All of the men who had experienced some response to conventional drugs regained spontaneous erections after six months on ginkgo. All of them had objective improvement in erectile function, including improved rigidity at both the tip and the base of the penis, as well as improvements in arterial flow rate. Perhaps even more impressively, of the 30 men who had experienced no success with medications, 19 of them responded to the ginkgo. All study participants showed improved objective response parameters.²³

Ginkgo extract likely works by improving blood flow to the erectile tissue by enhancing arterial and vascular blood flow. Ginkgo relaxes the corpus cavernosum vascular smooth muscles. The corpora cavernosa are the cylindrical blood sinuses that form the erectile tissue of the penis and expand

when filled with blood. Ginkgo's effect on the corpus cavernosum is thought to be a mechanism of action that contributes to improvement in ED. Ginkgo extract also has vasodilating action.

Asian Ginseng Root

The herb that is generating perhaps the most scientific support for ED is Asian ginseng (*Panax ginseng*, Araliaceae), which has been employed for sexual dysfunction in traditional Asian medicine for centuries. The first important study of ginseng and ED was published in 1995. This trial gave either 1,800 mg of Korean red ginseng extract (extract description not given), a pharmaceutical drug (trazodone), or a placebo to a total of 90 men with ED, with 30 men in each group.²⁴ Red ginseng is the same root as white ginseng, but, whereas white ginseng is simply the dried mature root, red ginseng is the fresh root that has been steamed for two-to-three hours before it is dried. The steaming leads to a change in the profile of the major ginsenosides, and thus a change in the root's (and the extract's) pharmacol-

Asian Ginseng *Panax ginseng*. Photo ©2013 Steven Foster



*Mention of the name of a company that manufactures and/or sells a particular product or ingredient in a product referred to in this article is not a promotion or endorsement of said ingredient, product, or company. Mention of such information is consistent with the general editorial policy of the American Botanical Council in reporting pharmacological and clinical research on botanical preparations where there is often variability in the chemistry of such ingredients or preparations from one brand to another.

ogy.²⁵ Red ginseng is held to be “warmer” and “more stimulating,” according to the energetics principles of Asian traditional medicine. In the aforementioned trial, the ginseng increased erectile function in significantly more men: 60% in the ginseng group versus only 30% in the placebo and trazodone groups ($P<0.05$). Ginseng brought about significant improvement in the rigidity and width of the erection, as well as in the ability to maintain an erection and in patient satisfaction ($P<0.05$). As a bonus, it also significantly improved libido. Though there were no complete remissions in this study, the partial improvements were significant.

Further, in a double-blind, placebo-controlled study, a total of 45 men with ED were given either 900 mg of powdered Korean red ginseng or a placebo three times a day for eight weeks. Sixty percent of the men on the ginseng had improved erections, according to the global efficacy questionnaire. Erection scores increased by 41.7% in the ginseng group compared to only 6% in the placebo group. The total five-part International Index of Erectile Function (IIEF) scores were significantly higher in the ginseng group than in the placebo group, with an improvement of 36.2% versus 10.4% ($P<0.01$). Penile rigidity was significantly better in the ginseng group. Penetration and maintenance of erection were significantly higher in the ginseng group than in the placebo group ($P<0.01$). And, again, ginseng improved sexual desire.²⁶

Another double-blind, placebo-controlled study gave either 1,000 mg of Korean red ginseng (presumably dried powdered root) or a placebo three times per day to 60 men with mild-to-moderate ED. After 12 weeks, IIEF scores had improved from 16.4 ± 2.9 to 21.0 ± 6.3 ($P<0.0001$). In the ginseng group 66.6% of the men had improved erections; there was no significant effect in the placebo group. The ginseng was significantly better for rigidity, penetration, and maintenance ($P<0.01$) as well.²⁷

In the first-ever systematic review of clinical research on Korean red ginseng and ED, researchers found seven randomized, controlled clinical studies that included a total of 363 men. In the six studies that compared ginseng to a placebo, the ginseng improved erectile function more than the placebo in each individual trial. Combining the studies into a meta-analysis, the researchers found that this was not due to a placebo effect, as the ginseng had a significant effect ($P<0.00001$). Ginseng is not only effective, but safe; adverse events were scarce and mild. Interestingly, the meta-analysis found that the red ginseng also produced significant improvement when the ED was from psychological causes ($P<0.001$).²⁸

Recent studies have postulated that Asian red ginseng may help ED by directly inducing relaxation of the smooth muscles of the corpus cavernosum via nitric oxide pathways.^{27,29} Ginseng's mechanism of action against ED is not yet fully understood.

Muira Puama

Another potentially valuable herb for ED is *muira puama* (*Ptychopetalum olacoides*, Olacaceae). This potential application is no surprise in Brazil, where the herb is known as “potency wood,” and has been used for many years. *Muira puama* seems to address both the physical and psychological problems associated with impotency. A study done by Jacques Waynberg, MD, PhD, of the Institute of Sexology in Paris, found that of 262 men suffering from ED or lack of sexual desire, 62% of those with loss of desire were helped by 1-to-1.5 grams of *muira puama* extract (not described in the study), and 51% of those with ED benefited from the herb.³⁰ *Muira puama*'s efficacy for ED seems to be due in part to its nerve-

Miura Puama *Ptychopetalum olacoides*, Photo ©2013 Steven Foster



The market also contains legitimate herbal products that have had their botanical identity and raw materials authenticated, and many have at least one or two well-controlled clinical trials, or substantial history of traditional use, supporting the ED claim.



stimulating properties. The mechanism of action of its aphrodisiac effect on sexual desire remains unknown.

Multi-Herb Combination

A recent double-blind, placebo-controlled study combined *muira puama*, Asian ginseng, and ginkgo with horny goat weed and five additional herbs.³¹ The nature of these preparations was not specified or described in the trial. Seventy-eight otherwise healthy men with mild-to-moderate ED, scoring 11-23 on the Erectile Function domain of the IIEF, were given a placebo or a proprietary herbal product known as VigRx Plus® (Leading Edge Herbals; Greeley, CO). The capsules contain 100 mg Asian ginseng, 100 mg ginkgo extract, 100 mg hawthorn (*Crataegus monogyna*, *C. laevigata*, Rosaceae) berry, 50 mg *muira puama*, 50 mg catuaba (*Erythroxylum catuaba*, Erythroxylaceae), 25 mg Chinese dodder (*Cuscuta chinensis*, Convolvulaceae) seed, 15 mg horny goat weed, 75 mg tribulus (*Tribulus terrestris*, Zygophyllaceae), 100 mg damiana (*Turnera diffusa*, Turneraceae), and 5 mg BioPerine® (a proprietary standardized extract of piperine from the fruit of black pepper [*Piper nigrum*, Piperaceae]; Sabinsa Corporation, East Windsor, New Jersey). The capsules were administered at a dose of two capsules twice per day, and the study lasted 12 weeks.

The men given the herbal combination had a statistically significant increase in erectile function compared to the placebo group ($P < 0.0001$). Scores on the Erectile Function domain of the IIEF increased by nine points (16.08 to 25.08) in the herb group compared to an increase of only 0.61 points (15.86 to 16.47) in the placebo group. Thirty-four percent of the herb group, compared to only 3% of the placebo group, attained erections that were always or almost always hard enough to achieve penetration. Equally importantly, as ED is the inability to attain or maintain an erection, the ability to penetrate and to maintain an erection after penetration improved by 59% and 63%, respectively, in the herb group, but by only 4% and 9% in the placebo group. Fourteen out of 39 men had scores greater than 25 by the end of the study, indicating no presence of ED, compared to only one of 36 in the placebo group. The men in the herb group also experienced significant improvement compared to placebo in all other categories of the IIEF, including sexual desire, orgasmic function, intercourse satisfaction, and overall satisfaction. The mean increase in the total IIEF score was 20.1 in the herb group compared to only 1.0 in the placebo group. The herbal treatment was rated as good or excellent by 95% of men, while the placebo was rated as poor by 67%.

On the Erectile Dysfunction Inventory of Treatment Satisfaction scale, the mean treatment satisfaction score was 82.31 in the herb group versus 36.78 in the placebo group. The difference in satisfaction was even greater for their partners: 82.75 in the herb group versus only 18.50 in the placebo group. Ninety percent of the men on the herbs wished to continue treatment compared to only 3% of the placebo group. The herbs were not only apparently effective but presumably safe; adverse effects were minor and similar in both groups.

Among the other herbs in the formula, though no clinical studies exist, the herb damiana has been prized as an aphrodisiac by Mexican cultures since antiquity. Damiana is thought to work by slightly irritating the urethra, which increases the

sensitivity of the penis.¹⁵ Hawthorn, especially the leaf and flower extract, exerts a blood pressure-lowering effect by dilating coronary vessels, acting as an ACE (angiotensin-converting enzyme) inhibitor and diuretic, and increasing heart function.³² Chinese dodder is used in TCM for impotence. Catuaba is a Brazilian herb that is a non-cocaine-containing relative of the coca plant (*E. coca*) used in the Amazon region as an aphrodisiac. Saw palmetto (*Serenoa repens*, Arecaceae) berry 9-12:1 ethanol extract (Prostasan[®]; A. Vogel Bioforce AG; Roggwil, Switzerland) has been shown in a pilot trial to improve sexual function by more than 30 percent in men whose ED is caused by benign prostatic hyperplasia.³³

Tribulus terrestris has been used in Ayurvedic medicine and in European folk medicine as an aphrodisiac and for the treatment of impotence. Several studies exist to support this traditional use.³⁴⁻³⁶ However, most of this research is non-blinded and of questionable quality. Much of it is research on animals that often has failed to be duplicated in human studies. For the most part, the published research is poorly designed with results that are not definitive. There is little in the way of well-controlled trials, making conclusions on tribulus difficult.^{37,38}

One recent double-blind study, however, is potentially promising because the comparison group received the drug Cialis (tadalafil).³⁹ The subjects in this study were 70 men over the age of 60 with reduced libido and with or without ED. They were given either Cialis or a supplement called Tradamixina[®] (Tradapharma, Lugano, Switzerland), consisting of 396 mg of tribulus (form not specified) combined with 150 mg of the brown algae arame (*Ecklonia bicyclis*, Lessoniaceae) and 144 mg of glucosamine (identified as D-glucosamine and N-Acetyl-D-glucosamine) twice per day for two months. Testosterone levels increased significantly in the tribulus combination group and non-significantly in the Cialis group. Nocturnal erections improved in the tribulus combination group, and total IIEF scores improved in the tribulus combination group but only non-significantly in the Cialis group. The specific erectile function area of the IIEF improved in both groups, but it improved more in the Cialis group; the Sexual Quality of Life score improved in both groups, but more so in the tribulus group. Libido improved in the tribulus group but not in the Cialis group. The authors concluded that Tradamixina is effective for mild-to-moderate ED in men with low testosterone and that it is free from the adverse side effects of Cialis.

A potential limitation of this study that somewhat interferes with drawing conclusions about tribulus is that it was combined with other supplements. Because some of the men in the study had ED and some did not, it would be interesting to determine if the tribulus improved symptoms in the specific subgroup of men with ED or whether the improvement was attributable to the observed improvement in libido.

[†]A peer reviewer of this article with expertise on maca has stated that there are up to 13 different phenotypes of maca — sometimes referred to as red, black, or yellow maca — each with various chemical profiles, and thus potentially varying biological activity. Such distinctions are seldom made in the pharmacological and clinical literature on maca, and thus, unless a specific phenotype is mentioned in the original research paper, such information is not included in this review article.

The primary active constituent in tribulus is believed to be protodioscin. Protodioscin is a steroidal saponin that is thought to convert to DHEA (dehydroepiandrosterone) and to increase testosterone, dihydrotestosterone, and luteinizing hormone.^{40,41} Protodioscin may also contribute to the relaxation of the corpus cavernosum.⁴² Many of these actions of tribulus await confirmation in human studies.

Maca, Pycnogenol[®], Rhodiola rosea, Eurycoma, Ashwagandha, Oats, and Yohimbe

Maca. Another South American herb that may help with ED is maca (*Lepidium meyenii*, Brassicaceae), an edible tuber that grows at high altitudes in the Peruvian Andes. In a double-blind study, 50 young men with mild ED were given either 1,200 mg of pulverized and dehydrated maca root or a placebo twice a day for 12 weeks.^{†43} IIEF scores improved significantly in both groups, but they improved significantly more in the maca group than in the placebo group (1.6+/-1.1 versus 0.5+/-0.6; P<0.001). Subjectively, though scores on the Satisfaction Profile (SAT-5) improved significantly in both groups, once again, the SAT-5 scores improved significantly more in the maca group (9+/-6 versus 6+/-5 in the placebo group; P<0.05). Further, only the maca produced significant improvement in the physical and social performance-related SAT-5 scores. Maca also has been shown to improve libido in healthy men.^{44,45}

Pycnogenol[®]. A botanical preparation that takes a promising approach to ED is the patented extract from French maritime pine bark (*Pinus pinaster*, Pinaceae), known commercially as Pycnogenol[®] (Horphag Research; Geneva, Switzerland). For an erection to occur, the blood vessels to the penis must dilate. Such dilation depends on nitric oxide (NO), which triggers the relaxation of the cavernous smooth muscle. Pycnogenol has been shown to enhance the production of NO.^{46,47} When researchers gave either 120 mg of Pycnogenol per day or a placebo to 21 men diagnosed with ED in a double-blind study, after three months, ED symptoms were significantly improved in the Pycnogenol group (P<0.05). The placebo had no effect. According to the IIEF-5 scoring, Pycnogenol decreased ED severity from moderate to mild.⁴⁸

Nitric oxide is dependent on the amino acid arginine, which may hold promise for helping ameliorate ED.⁴⁹ In a double-blind, placebo-controlled study, 50 men with ED were given either 5 g per day of L-arginine or a placebo for six weeks. Thirty-one percent of the men on arginine — but only 11.7% of the men on the placebo — reported significant improvement in sexual function. Objective variables remained unchanged. The men who responded to the arginine had lower levels of NO at the beginning of the study.⁵⁰

The combination of these two NO-enhancers has proven to be a promising approach to treating ED. In a study of 40 men, one month of arginine ingestion led to normal erections in only a non-significant 5% of the men. But when 40 mg of Pycnogenol twice a day was added in the second month, 80% of the subjects were restored to normal



erections. And when the dose was increased to 40 mg of Pycnogenol three times a day, the number of men who attained sexual ability increased to 92.5%. The researchers concluded that the combination of arginine and Pycnogenol causes significant improvement in ED without adverse effects.⁵¹

These promising results have been duplicated in at least two more rigorously designed, double-blind studies. In the first, 111 men with mild-to-moderate ED (IIEF score between 11 and 17) were given either a placebo or a combination product containing 40 mg of Pycnogenol and 1400 mg of arginine (Prelox®, Horphag Research; Geneva, Switzerland) twice per day. After three months, the Pycnogenol/arginine group's score on the IIEF had increased significantly from 15.2 to 25.2; the placebo group improved from 15.1 to only 19.1. And, after six months, the Pycnogenol/arginine group's score had continued to rise to 27.1, while the placebo group had started to drop slightly to a score of 19. The improvement in the Pycnogenol/arginine group was significant compared to the placebo ($P < 0.05$). Additionally, there was a significant improvement in orgasmic function, sexual desire, intercourse satisfaction, and overall satisfaction in the Pycnogenol/arginine group ($P < 0.05$) compared to the placebo group. Testosterone levels increased significantly from 15.9 to 18.9 nmol/L ($P < 0.05$), but barely at all in the placebo group.⁵²

In the second double-blind study, men with mild-to-moderate ED were given a supplement containing 60 mg Pycnogenol, 690 mg L-arginine, and 552 mg aspartic acid or a placebo each day for eight weeks. Total scores on the IIEF-5 improved in the supplement group. There was "marked improvement" in the hardness of erection and satisfaction with sexual intercourse items of the IIEF-5. There were no adverse reactions. The researchers concluded that Pycnogenol combined with L-arginine is safe and effective in mild-to-moderate ED.⁵³

***Rhodiola rosea* root.** *Rhodiola* (*Rhodiola rosea*, Crassulaceae) is a traditional herb of increasing popularity for its adaptogenic activities. It is known for its ability to help reduce symptoms of stress and fatigue, among other properties. With respect to ED, in one open clinical trial, 35 men who suffered from ED, premature ejaculation, or both, took 150–200 mg of rhodiola root extract for three months; 26 of them responded with substantially improved sexual function.⁵⁴

***Eurycoma longifolia*.** Another herb with a name that reflects its traditional use is longjack root, more commonly known by the Malaysian name *tongkat ali* (*Eurycoma longifolia*, Simaroubaceae). This herb is commonly found in Southeast Asia. In Malaysia, it is commonly employed as an adaptogen for general well-being and specifically as an aphrodisiac with claims of benefit for ED. In a recent double-blind, placebo-controlled clinical trial, researchers gave either 300 mg of freeze-dried standardized water root extract of *E. longifolia* (Physta®, Biotropics Malaysia Berhad, Shah Alam, Selangor, Malaysia) or a placebo to 109 men with no ED or only mild ED for 12 weeks.⁵⁵ Scores on the IIEF were a secondary endpoint. There was a significant improvement in erectile function in the *E. longifolia* group compared to the placebo ($P < 0.001$). There was an

8.7% increase in the ability to attain an erection and a 7.2% increase in penetration ability.

The important limitation of the study, however, is that its population consisted of healthy men with no or only mild ED; all subjects fell within the "no dysfunction range." This limitation leaves two possibilities: Either *E. longifolia* enhances erectile function in healthy men with unknown benefit for men suffering from ED, or the study shows that *E. longifolia* enhanced erectile function and may have shown even more positive results but, because the subjects were already healthy, there was limited possible benefit to be achieved by administering the herb. Future research will help clarify this matter.

***Ashwagandha* root.** When stress and anxiety are contributing factors, nervine herbs like ashwagandha (*Withania somnifera*, Solanaceae) and oats (*Avena sativa*, Poaceae) may be helpful. Ashwagandha is an adaptogenic root that may be useful for sexual problems related to nervous tension. It has long been used in India as a rejuvenating aphrodisiac. Ashwagandha contains withanolides, which act as hormone precursors that can convert into, and perhaps balance, human hormones.⁵⁶

***Oats*.** Oats are among the most effective tonic herbs for the nervous system, traditionally considered to support the nervous system while relaxing it, and have long been used as an aphrodisiac for boosting sexual vitality. Unpublished research at the San Francisco Institute for Advanced Study of Human Sexuality has found oat extract to be beneficial. A double-blind study found improved firmness of erection in men with no sexual dysfunction. A second study gave 300–600 mg oat extract to 30 men with ED. Nineteen of them experienced a partial or complete response, with erection ability returning to pre-impotence levels in all 19.⁵⁷ Though there is some evidence for oats as an herb for ED, the basis for the use of oats remains mostly folkloric.⁵⁸ However, several prominent herbalists and herbal researchers continue to endorse the use of oats as an appropriate nerve for stress and anxiety related to ED.^{59–61}

***Yohimbe*.** The African tree bark yohimbe (*Pausinystalia johimbe*, Rubiaceae) is a traditional aphrodisiac from which the alkaloid yohimbine, a recognized and previously employed pharmaceutical agent for impotence, is derived. Yohimbe is considered effective, but its myriad adverse effects, including blood pressure and heart rate-increasing properties, inhibit its utility.^{62,63}

Conclusion

Though many of the attempted folkloric solutions to ED seem improbably amusing, time and science have strongly suggested, and, in some cases, provided compelling evidence that there is some truth in the traditions. There is reasonable evidence supporting the notion that traditional herbs, such as horny goat weed, *muira puama*, and maca, may help improve symptoms of ED. And for some herbs — particularly Korean red ginseng, *Ginkgo biloba* extract, and the patented French Maritime pine bark extract known as Pycnogenol (especially when combined with L-arginine) — the scientific support is quite promising. Science seems to encourage the hope that for men suffering from ED, whether the condition is of physical or psychological origin,



there is a safe and effective natural, non-pharmaceutical path to improvement. HG

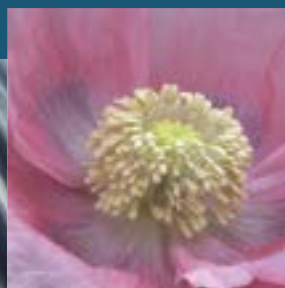
Linda Woolven is a master herbalist, certified acupuncturist, and solution-focused counselor with a practice in Toronto. She is the author of several books, including *Smart Woman's Guide to PMS and Pain-free Periods* (John Wiley & Sons, Ltd., 2008). Together, Woolven and **Ted Snider**, a natural health researcher and writer, are the authors of *Healthy Herbs: Your Everyday Guide to Medicinal Herbs and Their Use* (2006), *The Family Naturopathic Encyclopedia* (2011), and *Sex & Fertility: Natural Solutions* (2012), all published by Fitzhenry and Whiteside Limited. They also publish *The Natural Path newsletter*. Woolven and Snider can be reached at their blog at www.thenaturalpathnewsletter.com.

References

- Bensky D, Gamble A, Kaptchuk T. *Chinese Herbal Medicine Materia Medica*. Revised Edition, Seattle: Eastland Press, 1992.
- Liao HJ, Chen XM, Li WG. Effect of *Epimedium sagittatum* on quality of life and cellular immunity in patients of hemodialysis maintenance. *Zhongguo Zhong Xi Yi Jie He Za Zhi*. 1995;15:202-204.
- Low WY. Asian traditional medicine for erectile dysfunction. *J Men Health Gender*. 2007;4:245-250.
- Lans C. Ethnomedicines used in Trinidad and Tobago for reproductive problems. *J Ethnobiol Ethnomed*. 2007;3:doi:10.1186/1746-4269-3-13.
- Gratz SR, Flurer CL, Wolnik KA. Analysis of undeclared synthetic phosphodiesterase-5 inhibitors in dietary supplements and herbal matrices by LC-ESI-MS and LC-UV. *J Pharm Biomed Anal*. 2004;36:525-533.
- Fleshner N, Harvey M, Adomat H, et al. Evidence for contamination of herbal erectile dysfunction products with phosphodiesterase type 5 inhibitors. *J Urol*. 2005;174:636-641.
- Oh SS, Zou P, Low M-Y, et al. Detection of sildenafil analogues in herbal products for erectile dysfunction. *J Toxicol Environ Health A*. 2006;69:1951-1958.
- Adulteration of Natural Health Products. Health Canada website. Available at: www.hc-sc.gc.ca/hl-vs/iyh-vsv/med/nat-prod-adulter-eng.php. Accessed March 5, 2013.
- Hidden risks of erectile dysfunction "treatments" sold online. US Food and Drug Administration. Available at: www.fda.gov/ForConsumers/ConsumerUpdates/ucm048386.htm. Accessed March 5, 2013.
- Herbal sexual dysfunction products warnings and alerts. Medicines and Healthcare Products Regulatory Agency website. Available at: www.mhra.gov.uk/Safetyinformation/Generalsafetyinformationandadvice/Herbalmedicines/Herbalsafetyupdates/Herbalerecitesexualdysfunctionproductswarningsandalerts/index.htm. Accessed March 5, 2013.
- Laumann EO, Nocolosi A, Glasser DB, et al. Sexual problems among women and men aged 40-80 y: prevalence and correlates identified in the Global Study of Sexual Attitudes and Behaviors. *Int J Impot Res*. 2005;17:39-57.
- Ayta IA, Mckinlay JB, Krane RJ. The likely worldwide increase in erectile dysfunction between 1995 and 2025 and some possible policy consequences. *BJU*. 1999;84:50-60.
- Murray MT. *Male Sexual Vitality*. Rocklin, CA: Prima; 1994:12.
- Tharyan P, Gopalakrishnan G. Erectile dysfunction. *Clin Evid* 2006;15:1227-1251.
- Murray MT. *Male Sexual Vitality*. Rocklin, CA: Prima; 1994:17.
- Herman M, Goldbloom DS. Fluoxetine-induced sexual dysfunction. *J Clin Psychiatry*. 1990;42:25-27.
- Balon R, Yeragani VK, Pohl R, Ramesh C, et al. Sexual dysfunction during antidepressant treatment. *J Clin Psychiatry*. 1993;54:209-212.
- Murray MT. *Natural Alternatives to Over-the-Counter and Prescription Drugs*. New York NY: William Morrow; 1994:205.
- Carraro JC, Raynaud JP, Koch G, et al. Comparison of phytotherapy (Permixon®) with finasteride in the treatment of benign prostate hyperplasia: a randomized international study of 1,098 patients. *Prostate*. 1996;29:231-240.
- Wilt TJ, Ishani A, Stark G, et al. Saw palmetto extracts for treatment of benign prostatic hyperplasia: A systematic review. *JAMA*. 1998;280:1604-1609.
- Debruyne FG, Koch P, Boyle P, et al. Comparison of phytotherapeutic agent (Permixon®) with an alpha-blocker (Tamsulosin) in the treatment of benign prostatic hyperplasia: A 1-year randomized international study. *Eur Urol*. 2002;41:497-506.
- Sikora, R, Sohn M, Deutz FJ, et al. Ginkgo biloba extract in the therapy of erectile dysfunction. *J Urol*. 1989;141:188A.
- Sohn M, R. Sikora. Ginkgo biloba extract in the therapy of erectile dysfunction. *J Sex Educ Ther*. 1991;17:53-61.
- Choi HK, Seong DH, Rha KH. Clinical efficacy of Korean red ginseng for erectile dysfunction. *Int J Impot Res*. 1995;7:181-186.
- Blumenthal M (ed.). *The ABC Clinical Guide to Herbs*. Austin TX: American Botanical Council; 2003: 214.
- Hong B, Ji YH, Hong JH, et al. A double-blind crossover study evaluating the efficacy of Korean red ginseng in patients with erectile dysfunction: A preliminary report. *J Urol*. 2002;168:2070-2073.
- De Andrade E, de Mesquita AA, Claro Jde A, et al. Study of the efficacy of Korean Red Ginseng in the treatment of erectile dysfunction. *Asian J Androl*. 2007;9:241-244.
- Jang D-J, Lee MS, Shin B-C, et al. Red ginseng for treating erectile dysfunction: a systematic review. *Br J Clin Pharmacol*. 2008;66:444-450.
- Murphy LL, Lee TJ. Ginseng, sex behavior, and nitric oxide. *Ann N Y Acad Sci*. 2002;962:372-377.
- Waynberg J. Contributions to the clinical validation of the traditional use of *Ptychopetalum guyanna*. Presented at the First International Congress on Ethnopharmacology, Strasbourg, France, June 5-9, 1990.
- Shah GR, Chaudhari MV, Patankar SB, et al. Evaluation of a multi-herb supplement for erectile dysfunction: a randomized double-blind, placebo-controlled study. *BMC Complement Altern Med*. 2012;12:155.doi:10.1186/1472-6882-12-155.
- Pizzorno JE, Murray MT. *Textbook of Natural Medicine*, 4th ed. St. Louis, MO: Elsevier; 2013:695-696.
- Suter A, Saller R, Riedi E, et al. Improving BPH symptoms and sexual dysfunctions with a saw palmetto preparation? Results from a pilot trial. *Phytother Res*. 2013;27:218-226.
- Adimoelja A. Phytochemicals and the break-through of traditional herbs in the management of sexual dysfunctions. *Int J Androl*. 2000;23:82-84.
- Bardin CW, Swerdloff RS, Santen RJ. Androgens: risks and benefits. *J Clin Endocrinol Metab*. 1991;73:4-7.
- Protich M, Tsvetkov D, Nalbanski B, et al. Clinical trial of a tribestan preparation in infertile men. *Akush Ginekol*. 1983;22:326-329.
- Pizzorno JE, Murray MT. *Textbook of Natural Medicine*, 4th ed. St. Louis, MO: Elsevier; 2012:1529.
- Mackay D. Nutrients and Botanicals for Erectile Dysfunction: Examining the Evidence. *Alt Med Rev*. 2004;9:13.
- Iacono F, Prezioso D, Illiano E, et al. Sexual asthenia: Tradamixina versus Tadalafil 5 mg daily. *BMC Surgery*. 2012;12:S23.
- Gauthaman K, Ganesan AP. The hormonal effects of *Tribulus terrestris* and its role in the management of male erectile dysfunction—an evaluation using primates, rabbit and rat. *Phytomed*. 2008;15:44-54.
- Adimoelja A. Phytochemicals and the breakthrough of traditional herbs in the management of sexual dysfunctions. *Int J Androl*. 2000;23:S82-84.
- Do J, Choi S, Choi J, et al. Effects and mechanism of action of a *Tribulus terrestris* extract on penile erections. *Korean J Urol*. 2013;54:183-188.
- Zenico T, Cicero AFG, Valmorri L, et al. Subjective effects of *Lepidium meyenii* (maca) extract on well-being and sexual performance in patients with mild erectile dysfunction: a randomized, double-blind clinical trial. *Andrologia*. 2009;41:95-99.
- Gonzales GF, Cordova K, Vega K, et al. Effect of *Lepidium meyenii* (maca) on sexual desire and its absent relationships with serum testosterone levels in adult healthy men. *Andrologia*. 2002;34:367-372.

45. Gonzales G, Cordóva K, Vega K, et al. Effect of *Lepidium meyenii* (maca), a root with aphrodisiac and fertility-enhancing properties, on serum reproductive hormone levels in adult healthy men. *J Endocrinol*. 2003;176:163-168.
46. Fitzpatrick DF, Bing B, Rohdewald P. Endothelium-dependent vascular effects of Pycnogenol. *J Cardiovasc Pharmacol*. 1998;32:509-515.
47. Nishioka K, Hidaka T, Nakamura S, et al. Pycnogenol®, French Maritime pine bark extract, augments endothelium-dependent vasodilation in humans. *Hypertens Res*. 2007;30:775-780.
48. Durackova Z, Trebaticky B, Novotny V, et al. Lipid metabolism and erectile function improvement by Pycnogenol®, extract from the bark of *Pinus pinaster* in patients suffering from erectile dysfunction—a pilot study. *Nutr Res*. 2003;23:1189-1198.
49. Zorogniotti AW, Lizza EF. Effect of large doses of the nitric oxide precursor, L-arginine, on erectile dysfunction. *Int J Impot Res*. 1994;6:33-35.
50. Chen J, Wollman Y, Chernichovsky T, et al. Effect of oral administration of high-dose nitric oxide donor L-arginine in men with organic erectile dysfunction: results of a double-blind, randomized study. *BJU Int*. 1999;83:269-273.
51. Stanislavov R, Nikolova V. Treatment of erectile dysfunction with Pycnogenol and L-arginine. *J Sex Marital Ther*. 2003;29:207-213.
52. Ledda A, Belcaro G, Cesarone MR, et al. Investigation of a complex plant extract for mild to moderate erectile dysfunction in a randomized, double-blind, placebo-controlled, parallel-arm study. *BJU Int*. 2010;106:1030-1033.
53. Aoki, H Nagao J, Ueda T, et al. Clinical assessment of a supplement of Pycnogenol and L-arginine in Japanese patients with mild to moderate erectile dysfunction. *Phytother Res*. 2012;26:204-207.
54. Brown RP, Gerbarg PL, Ramazanov Z. *Rhodiola rosea*: A phytomedicinal overview. *HerbalGram*. 2002;56:40-52.
55. Ismail SB, Wan Mohammad WMZ, George A, Nik Hussain NH, et al. Randomized clinical trial on the use of PHYSTA freeze-dried water extract of *Eurycoma longifolia* for the improvement of quality of life and sexual well-being in men. *Evid Based Complement Altern Med*. doi:10.1155/2012/429268.
56. Anon. *Withania somnifera* Monograph. *Alt Med Rev*. 2004;9(2):211-14.
57. Aphrodisiacs improve sex lives of men and women: in studies at the Institute for Advanced Study of Human Sexuality. Smart Basics website. Available at: www.tasty-nuggets.com/gloss/news/1nat.sex.html. Accessed July 1, 2013.
58. Malviya N, Jain S, Gupta VB, et al. Recent studies on aphrodisiac herbs for the management of male sexual dysfunction—a review. *Acta Pol Pharm*. 2011;68:3-8.
59. Duke JA. *The Green Pharmacy*. New York, NY: St. Martins Press; 1998:234.
60. Gladstar R. *Herbal Remedies for Men's Health*. Pownal, VT: Storey Books; 1999:41.
61. Tierra M. *The Way of Herbs*. New York, NY: Pocket Books; 1998:172.
62. Murburg MM, Villacres EC, Ko GN, et al. Effects of yohimbine on human sympathetic nervous system function. *J Clin Endocrin Metabol*. 1991;73:861-865.
63. Tam SW, Worcel M, Wyllie M. Yohimbine: A clinical review. *Pharmacol Ther*. 2001;91:215-243.

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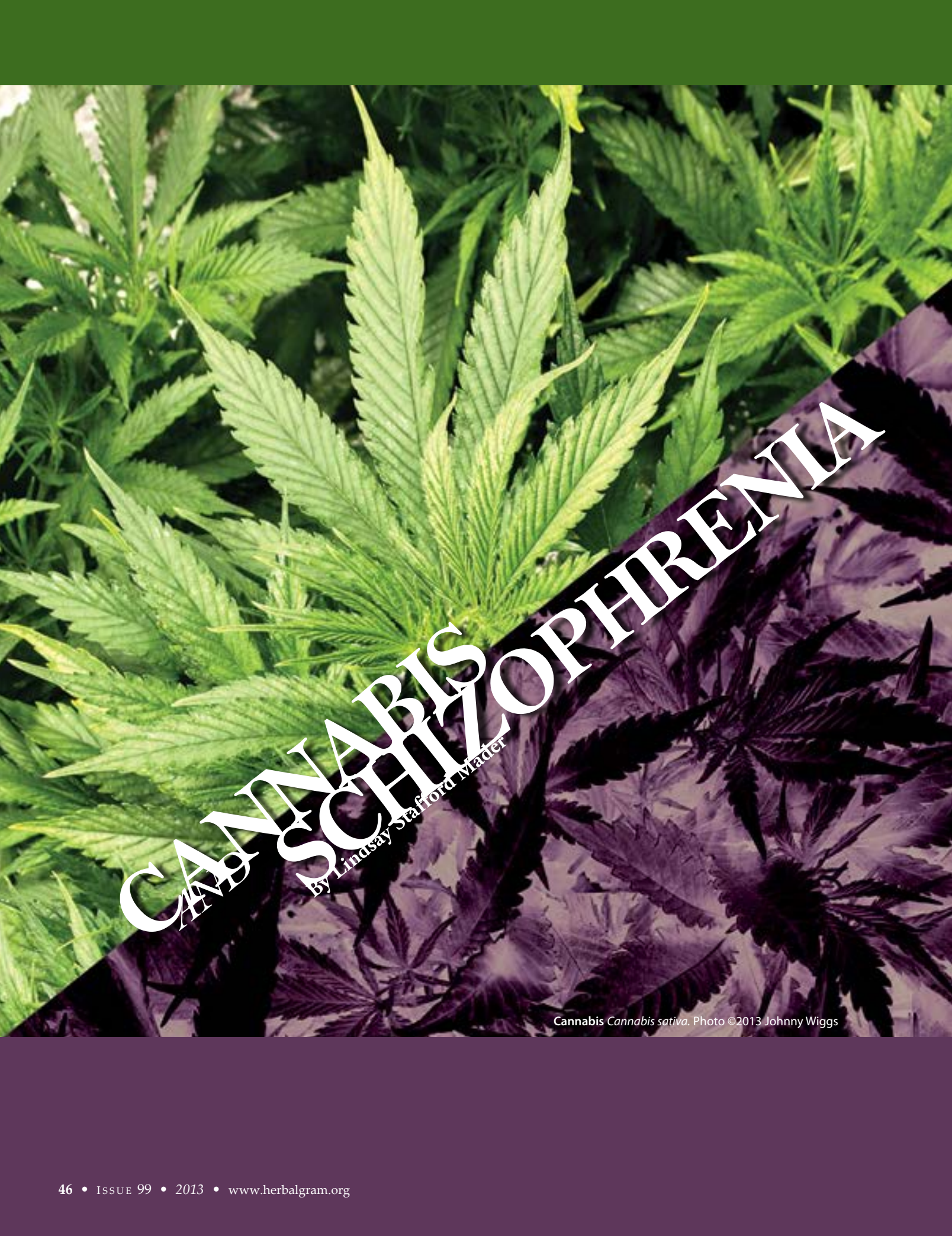


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CANNABIS SCHIZOPHRENIA

by Lindsay Stafford Mader

Cannabis Cannabis sativa. Photo ©2013 Johnny Wiggs

The proposition that cannabis causes schizophrenia has existed since at least the early days of the anti-marijuana movement in America, as illustrated in the 1936 film *Reefer Madness*, in which a character descends into psychosis after smoking a joint.¹ The cannabis-schizophrenia connection intensified during the “War on Drugs,” which produced propaganda linking the herb to schizophrenia, as well as cancer and brain damage.² Fast-forward more than seven decades since the film, and the academic and mainstream media continue to refer to cannabis’s ability to cause and increase the risk of developing this serious mental illness.^{3,4}

The link between cannabis (*Cannabis sativa*, Cannabaceae) and schizophrenia, however, is much more complex and much less certain. Cannabis and the brain have an interesting and unique relationship, part of which remains a mystery to researchers even today. After more than two decades of scientific analysis, researchers know that the human body contains receptors that bind with tetrahydrocannabinol (THC) and other cannabinoids from the cannabis plant, and also has neurotransmitters that activate these receptors in much the same way. The body’s receptors include the CB1 and CB2 receptors, and the endogenous cannabinoids, referred to as endocannabinoids, including anandamide and 2-AG.^{5,6}

Although this intricate endocannabinoid system of receptors and neurotransmitters — as well as the exact role played by the cannabis plant — is not yet fully understood, it clearly is involved in numerous physiological and pathological processes that are essential to human health. As Ester Fride and Ethan Russo, MD, wrote in the neuropsychiatry chapter of the 2005 book *Endocannabinoids: The Brain and Body’s Marijuana and Beyond* (CRC Press), “Endocannabinoids serve a modulatory function in many neurochemical and psychopharmacological processes, and deficiencies or excesses in any of these may produce manifestations of psychopathology.”⁵

Even more perplexing to scientists is the severe brain disorder called schizophrenia, which affects about 24 million people worldwide — approximately one percent of the population. According to the PsychCentral mental health web resource, “In spite of advances in the understanding of its causes, course, and treatment, schizophrenia continues to confound both health professionals and the public. It is easier for the average person to cope with the idea of cancer than it is to understand the odd behavior, hallucinations, or strange ideas of the person with schizophrenia.”⁷

Medical researchers believe that schizophrenia is tied to a genetic link as incidence among those with afflicted family members is increased by about nine percent.⁸ It is also thought that schizophrenia might be caused by the malfunction of a gene that creates important brain chemicals, as well as possible environmental triggers, and/

or an imbalance of the neurotransmitters dopamine and glutamate. Scans of schizophrenia patients’ brains have revealed that they have larger center-brain ventricles and less gray matter, and post-mortem brain analyses have shown differences in schizophrenics’ brain cell characteristics — perhaps occurring during abnormal fetal brain development. Schizophrenia presents itself through a variety of symptoms, including hallucinations, delusions, thought and movement disorders, monotonous voice, and motionless face when speaking (referred to as “positive” symptoms), as well as social withdrawal, inability to make decisions, lack of emotion and motivation, etc. (referred to as “negative” symptoms and “cognitive deficits”).

Research

While a fair amount of scientific research has examined the relationship between cannabis and schizophrenia, most of this consists of laboratory, animal, epidemiological, or post-mortem human studies. Recognizing the “tremendous

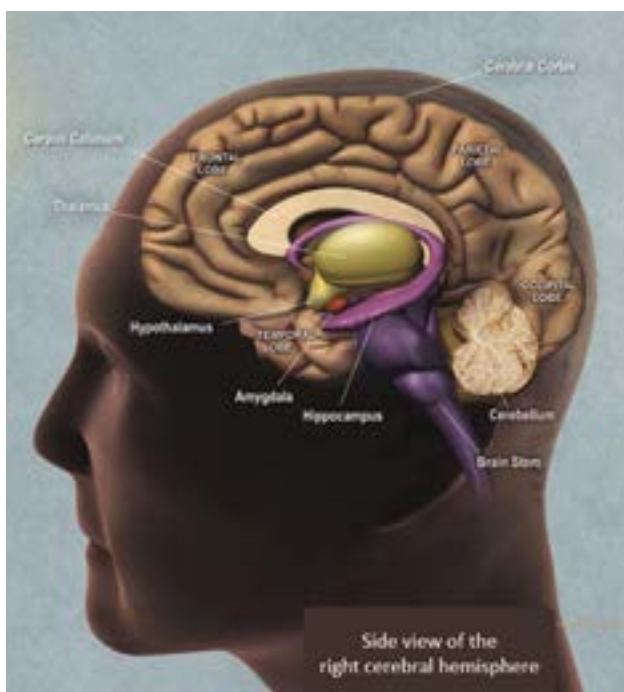


Image courtesy of National Institute on Aging



Cannabis *Cannabis sativa*. Photo ©2013 Johnny Wiggs

amount” of preclinical research on cannabis and schizophrenia, Martin Lee — author of the 2012 book *Smoke Signals: A Social History of Marijuana – Medical, Recreational, and Scientific* — noted the ethical implications of studying cannabis in humans.

“You’re not going to get experiments in the United States where the federal government will approve a researcher or a scientist giving marijuana to a schizophrenic, but you could do a survey of schizophrenics,” said Lee (oral communication, March 15, 2013).

Healthy Populations

Cannabis is well known to cause physiological and psychological side effects in almost all people who use it, particularly varieties that contain higher levels of THC. Thus, the concept that cannabis causes negative mental

experiences is not ridiculous; anecdotal reports of momentary post-cannabis psychosis and hallucinations have been shared for quite some time.²

While the psychological side effects of cannabis can be similar to the symptoms experienced by diagnosed schizophrenics — such as visual illusions, paranoia, mood alterations, and memory deficits⁹ — cannabis-produced symptoms typically disappear after three to five hours.¹⁰

Still, the allegation persists that cannabis can cause schizophrenia, a disease in which psychotic symptoms typically last throughout a patient’s life. When experts discuss this cannabis-schizophrenia relationship, they make sure to differentiate between cannabis’s impact on healthy populations and cannabis’s impact on diagnosed schizophrenic patients and individuals with risk factors for developing schizophrenia.⁹ This important detail is often not provided in media reports on the topic.

“I don’t think we should say cannabis induces schizophrenia, and so we should discourage people from using cannabis because they’ll become psychotics,” said Andrea Giuffrida, PhD, an associate professor of pharmacology at the University of Texas Health Science Center in San Antonio, who researches this topic (oral communication, March 25, 2013). “Maybe some of them have a higher risk, but not the entire population.”

Researchers and proponents of the argument that cannabis does *not* cause schizophrenia in the general population often cite epidemiological data that shows a significant increase

in cannabis usage during the last several decades while the rates of schizophrenia have remained largely static. As stated by the authors of a recent article titled, “Cannabis and Psychosis: What Causes What?,” “Most people who use cannabis do not develop schizophrenia, and many people diagnosed with schizophrenia have never used cannabis.”⁹

“As marijuana usage has increased in culture in the last 50 years, you haven’t seen that increase in schizophrenia,” said Lee. “If it was causing schizophrenia, you would probably see an increase, so the causal thing is just not there.”

But according to psychiatrists Patricia Gerbarg, MD, who has a clinical practice in New York City, and Richard Brown, MD, a professor at Columbia University, the lack of correlation could be explained in other ways. “For example,” they said, “improvements in prenatal nutrition and

healthcare are more likely to lower the incidence of schizophrenia.... Also, there may appear to be a lack of increase in schizophrenia because of a lack of increase in the diagnosis of schizophrenia, which could be due to the many changes in diagnostic categories since the 1970s. Many cases that would previously have been diagnosed as schizophrenia, would now be diagnosed as Asperger's or bipolar disorder" (email, March 16, 2013).

Some epidemiological surveys have shown that schizophrenic patients abuse cannabis more than any other illegal drug and also have cannabis usage rates higher than healthy population rates, which has been used as an argument that cannabis possibly causes or increases the chance of developing schizophrenia in otherwise healthy populations.¹¹ But according to Dr. Giuffrida, this is just a correlation, which, he points out, cannot establish causality. He additionally noted the hypothesis that schizophrenic patients might use cannabis more because they are attempting to self-medicate.

"Whether they smoke more because they are schizophrenic or they are schizophrenic because they smoke more cannabis, we don't know the direction of the connection," he explained.

Further, a Swedish survey published in 1987 of almost 50,000 male participants conducted over the course of 15 years found that those who self-reported heavy cannabis use were 50 times more likely to be diagnosed with schizophrenia.¹² But when these findings were reanalyzed and adjusted to account for other risk factors, the increased likelihood dropped to 6.7 times, and many of the participants who reported cannabis use also reported the use of other drugs that have the ability to precipitate psychosis.¹³

In examining the connection between cannabis and schizophrenia, researchers also study brain morphology. In a 2012 paper in the *European Archives of Psychiatry and Clinical Neuroscience*, a team of researchers from Germany and England analyzed 16 neuroimaging studies. The authors concluded that there is "no convincing evidence" that cannabis-related brain alterations happen before the onset of schizophrenia.¹¹ In fact, essentially none of the changes seen in the brains of schizophrenic patients using cannabis were observed in healthy individuals who used cannabis.

Some journals and other sources report that young people are especially vulnerable for developing cannabis-induced schizophrenia. A large-scale survey conducted in 2005 by Henquet *et al.* suggested that ingesting cannabis at a young age (14 to 24 years) was associated with an increased chance of developing psychotic symptoms,^{14,15} but this data did not analyze the risk of developing *full schizophrenia*, and those with predisposed risks for psychosis were more likely to develop psychotic symptoms. According to an expert peer reviewer of this article, while extra caution is always advised in adolescents, there is still no evidence that permanent, schizophrenia-related *de novo* damage is done to young, healthy individuals.

"The work of Henquet is very interesting,"

added Dr. Giuffrida, "but the assessment of cannabis use is based on an interview and consequently is not as precise as a study where cannabis is administered in a controlled fashion. I do believe we need more experiments before establishing a causal relation between cannabis exposure and schizophrenia development in the healthy population."

At-Risk and Diagnosed Populations

Most researchers agree that because schizophrenia likely is brought on by a variety of "component causes," one of which could include cannabis use, a healthy person with no risk factors is very unlikely to develop the disease from cannabis use alone.^{9,11,14} The situation is different, however, for individuals with predisposed risks.

Those at risk for developing schizophrenia include individuals with schizophrenic family members or those who exhibit symptoms of the prodromal stage (a precursor to a more full set of symptoms or disease), which typically consist of increased isolation and decreased motivation and appear a year before true schizophrenia symptoms.¹¹ Interestingly, recent research suggests that a mutation in the *AKT1* gene also might put an individual at increased risk for developing cannabis-associated schizophrenia.¹⁶ These at-risk groups are cautioned against using cannabis as epidemiological evidence and survey data show that they have worse psychotic-disorder outcomes when cannabis is a factor.¹⁵

The aforementioned 2012 brain morphology literature review by Malchow *et al.* found just three studies on high-risk individuals, in which an "additional effect of cannabis use on brain structure" was suggested.¹¹ These studies found that cannabis use was associated with a bilateral volume loss of the thalamus, a region of the brain that integrates and processes sensory and cognitive functions; increased thinning of the cortex, the largest region of the brain; and an increased volume of the brain's fluid-filled cavities known as ventricles. (The latter of these studies, however, analyzed cannabis *and* alcohol in high-risk subjects.)

The review authors conclude that there is "some weak evidence that cannabis abuse could affect brain structures in high-risk subjects, but replication of these findings is needed. The results of the identified neuroimaging studies are heterogeneous and inconclusive," for various reasons, including differing definitions of regional volume boundaries and differing volume extraction

Most researchers agree that because schizophrenia likely is brought on by a variety of "component causes," one of which could include cannabis use, a healthy person with no risk factors is very unlikely to develop the disease from cannabis use alone.

methods (when measuring content of the brain), as well as differing MRI techniques.¹¹

For patients who have been diagnosed with schizophrenia, the implications for using cannabis are somewhat better understood. Although few human clinical trials on cannabis and schizophrenics have been performed, epidemiological data and survey evidence indicate — and most experts agree — that ingesting cannabis can aggravate schizophrenia symptoms and/or increase their frequency.¹³ The few human studies found cannabis products (*i.e.*, hashish, THC) to exacerbate symptoms, although these were temporary effects. According to *Endocannabinoid's* neuropsychiatry chapter, “Taken together, most studies confirm the vulnerability hypothesis for cannabis use and schizophrenia. Thus, schizophrenia patients should probably not use cannabis because a psychotic episode can be induced in someone with a preexisting disorder and, indeed, increased hospitalization rates and symptom exacerbation have been demonstrated.”⁵

Malchow *et al.* noted that most brain imaging studies on cannabis and schizophrenia examined individuals with first-episode or recent-onset schizophrenia.¹¹ Some of this research suggested that schizophrenic patients who used cannabis had subtle brain abnormalities, increased ventricle volumes, thinning of various cortical regions, decreased gray and white matter volume, and “altered brain structure in particular regions ... with a high density of CB1 receptors.” The authors noted, however, that anti-psychotic medication has been strongly associated with reduced gray matter and that many of the studies included “comorbid patients consuming other substances than cannabis, for example, amphetamines, cocaine, and sometimes alcohol, making it difficult to focus on the effect of cannabis alone.”

“The results of these neuroimaging studies are again heterogeneous and remain inconclusive,” they wrote.

Researchers are beginning to understand that the connection between cannabis and schizophrenic individuals might lie in the human body’s mysterious and powerful endocannabinoid system. According to the authors of a 2008 article in *Expert Review of Neurotherapeutics*, “There are several lines of evidence suggesting that, at least in a subgroup of patients, alterations in the endocannabinoid system may contribute to the pathogenesis of schizophrenia.”¹⁵

Human studies have shown schizophrenics to have increased levels of anandamide and endocannabinoid-like molecules such as palmitylethanolamide, and these patients with higher levels of anandamide typically experience fewer psychotic symptoms.¹⁵ Additionally, frequent cannabis usage was found to decrease cerebral spinal fluid levels of anandamide, suggesting a possible explanation for why some schizophrenic patients sometimes have negative experiences after ingesting cannabis. Authors of additional studies have found a possible connection between lower levels of the endocannabinoid 2-AG and schizophrenia progression, as well as impaired endocannabinoid signaling associated with acute psychotic episodes.

“My preferred hypothesis is that frequent and intense cannabis smoking [reduces] an endogenous protective mechanism, mediated by anandamide, resulting in an increased risk for precipitation of psychosis,” said Daniele

Piomelli, PhD, PharmD, a professor of anatomy and neurobiology at the University of California at Irvine (email, March 22, 2013). “Please note that anandamide is not the only endocannabinoid present in the brain and that this theory does not rule out the possibility that other endocannabinoids (*e.g.*, 2-AG) might be pro-psychotic.”

In explaining why cannabis and endocannabinoids might not act in the same way, Dr. Giuffrida pointed to the different pharmacologic profiles of THC and anandamide. “For example, when you smoke cannabis and take in THC, you activate all the cannabinoid receptors in the brain. But when you elevate anandamide, the elevation does not happen all over the brain but happens in specific brain areas.”

Interestingly, the CB1 receptor is expressed in high levels in the prefrontal cortex — the region of the brain responsible for cognitive and emotional functions and thought to be the “primary dysfunctional area” in schizophrenia — as well as in other brain areas relevant to schizophrenia, such as the basal ganglia, hippocampus, and the anterior cingulate cortex.^{8,15} Some post-mortem studies have found schizophrenic patients’ brains to have even-further increased binding levels of the CB1 receptor.

“But again,” said Dr. Giuffrida, “whether this is a contributing factor to develop schizophrenia is unknown at this time.”

Dr. Giuffrida reiterated that cannabis can sometimes help certain schizophrenia symptoms, which might explain why some patients might self-medicate with the herb.

“We know that, in schizophrenic patients, cannabis intake can make positive symptoms worse. But, on the other side, there is some work showing that the cannabinoids have a beneficial effect on the negative symptoms of schizophrenia, so they make people interact more with each other. But what happens with marijuana, especially if you are a psychotic individual, the more you use cannabis, the worse your symptoms become over time. So it can be helpful in the beginning, but definitely not in the long run.”

Therapeutic Role of CBD

While THC, the compound in cannabis responsible for the euphoric “high,” is known to increase the severity of psychotic symptoms in schizophrenia patients, another cannabinoid in cannabis — the non-psychoactive cannabidiol (CBD) — has been shown to be therapeutic for schizophrenia symptoms.

Based on CBD’s known anti-anxiety activity, researchers conducted a small pilot study on CBD in 42 patients with paranoid schizophrenia in 2012. This Phase II, double-blind, four-week trial compared CBD treatment with the antipsychotic drug amisulpride and found that CBD improved symptoms as well as the pharmaceutical — and that it produced fewer negative side effects.¹⁷

“It’s a small study so we have to see if the data is replicated in larger groups of people,” said Dr. Giuffrida, noting that CBD “is definitely one of the most exciting areas in the cannabinoid field.” He explained that although CBD’s activity within the brain is not yet completely understood, this compound is pharmacologically different from THC in that it does not bind to the CB1 receptor in the brain, whereas THC does. Additionally, he said some animal and

human studies show that CBD boosts levels of the endocannabinoid anandamide, and elevated anandamide seems to have a beneficial effect on schizophrenia.

“These results suggest that the inhibition of anandamide activation may contribute to the anti-psychotic effect of cannabidiol,” said Dr. Giuffrida, “which possibly represents a completely new mechanism of treatment for schizophrenia.”

Conclusion

While CBD presents an exciting possibility as a novel schizophrenia treatment, additional research must be conducted to validate early studies. Likewise, more human research on cannabis's impact on schizophrenia would greatly broaden scientists' and medical professionals' understanding of this interesting and complex relationship. Based on the available evidence — which includes epidemiological studies, surveys, brain morphology analyses, and a few human studies — most experts accept that cannabis intake could have negative impact on individuals who have schizophrenia and that those vulnerable to developing schizophrenia can have psychotic episodes if they ingest high doses of cannabis.

“So there definitely is something there,” said Dr. Guiffida. “However, this is probably one of the components that may contribute to schizophrenia. It is not *the* cause of schizophrenia. And so I don't think we have yet enough evidence to say that cannabis causes schizophrenia, and this is particularly true for the healthy population.” HG

References

1. George A. Hirliman Productions. *Reefer Madness* [film]. Director, Louis Gasnier. 1936.
2. Lee M. *Smoke Signals: A Social History of Marijuana—Medical, Recreational, and Scientific*. New York, NY: Scribner; 2012.
3. Collingwood J. Cannabis may cause schizophrenia-like brain changes. PsychCentral. Available at: <http://psychcentral.com/lib/2012/cannabis-may-cause-schizophrenia-like-brain-changes/>. Accessed March 18, 2013.
4. Schwarz A. Drowned in a stream of prescriptions. *New York Times*. February 2, 2013. Available at: www.nytimes.com/2013/02/03/us/concerns-about-adhd-practices-and-amphetamine-addiction.html?pagewanted=all&_r=0. Accessed March 18, 2013.
5. Onaivi E, Sugiura T, Marzo V, eds. *Endocannabinoids: The Brain and Body's Marijuana and Beyond*. Boca Raton, FL: CRC Press; 2005.
6. Sulak D. Introduction to the endocannabinoid system. NORML website. Available at: <http://norml.org/library/item/introduction-to-the-endocannabinoid-system>. Accessed April 2, 2013.
7. Bengston M. Schizophrenia and psychosis. PsychCentral. Reviewed June 17, 2012. Available at: <http://psychcentral.com/disorders/schizophrenia/>. Accessed March 18, 2013.
8. What causes schizophrenia? National Institute of Mental Health website. Available at: www.nimh.nih.gov/health/publications/schizophrenia/what-causes-schizophrenia.shtml. Accessed March 18, 2013.
9. Castle DJ. Cannabis and psychosis: what causes what? *F1000 Med Rep*. 2013;5:1.
10. Cannabis/Marijuana (Δ^9 -Tetrahydrocannabinol, THC). Drugs and Human Performance Fact Sheets. National Highway Traffic Safety Administration website. Available at: www.nhtsa.gov/People/injury/research/job185drugs/cannabis.htm. Accessed April 2, 2013.
11. Malchow B, Hasan A, Fusar-Poli P, Schmitt A, Falkai P, Wobrock T. Cannabis abuse and brain morphology in schizophrenia: a review of the available evidence. *Eur Arch Psychiatry Clin Neurosci*. 2013;263(1):3-13.
12. Andreasson S, Allebeck P, Engstrom A, Rydberg U. Cannabis and schizophrenia: a longitudinal study of Swedish conscripts. *Lancet*. 1987;2(8574):1483-1486.
13. Sewell RA, Skosnik PD, Garcia-Sosa I, Ranganathan M, D'Souza DC. Behavioral, cognitive and psychophysiological effects of cannabinoids: relevance to psychosis and schizophrenia. *Revista Brasileira de Psiquiatria*. 2010;32:Suppl 1.
14. D'Souza D, Sewell RA, Ranganathan M. Cannabis and psychosis/schizophrenia: human studies. *Eur Arch Psychiatry Clin Neurosci*. 2009;259(7):413-431.
15. Müller-Vahl KR, Emrich HM. Cannabis and schizophrenia: towards a cannabinoid hypothesis of schizophrenia. *Expert Rev Neurother*. 2008 Jul;8(7):1037-1048.
16. Di Forti, Iyegbe C, Sallis H, et al. Confirmation that the AKT1 (rs2494732) genotype influences the risk of psychosis in cannabis users. *Biological Psychiatry*. 2010;72(10):811-816.
17. Leweke FM, Piomelli D, Pahlisch F, et al. Cannabidiol enhances anandamide signaling and alleviates psychotic symptoms of schizophrenia. *Transl Psychiatry*. 2012 Mar 20;2:e94.

Cannabis *Cannabis sativa*. Photo ©2013 Johnny Wiggs



How to Qualify an Analytical Laboratory for Analysis of Herbal Dietary Ingredients and Avoid Using a “Dry Lab”

A review of issues related to using a contract analytical laboratory by industry, academia, and regulatory agencies

By Paula M. Brown, PhD, Joseph M. Betz, PhD, and Frank L. Jaksch, Jr.

Romeo. “Your Plantain leaf is excellent for that.”

Benvolio. “For what, I pray thee?”

Romeo. “For your broken shin.”

— *Romeo and Juliet*, act I, scene II

Thus the lowly plantain (*Plantago* spp., Plantaginaceae) became a featured player in one of the most famous and beloved pieces of English literature. Being a man of his times (late 16th-early 17th century), William Shakespeare made numerous references to herbs in his work. In addition to the mention of plantain in *Loves Labors Lost* (act III, scene I), *Troilus and Cressida* (act III, scene XX), and *The Two Noble Kinsmen* (act I, scene II), there are references to roses (*Rosa* spp., Rosaceae) in *Romeo and Juliet*. And, in *Hamlet*, Ophelia presents to various characters rosemary (*Rosmarinus officinalis*, Lamiaceae), pansies (*Viola tricolor*, Viola-ceae), fennel (*Foeniculum vulgare*, Apiaceae), columbines (*Aquilegia vulgaris*, Ranunculaceae), rue (*Ruta graveolens*, Rutaceae), daisies (*Bellis perennis*, Asteraceae), and violets (*Viola odorata*, Violaceae). In fact, the Bard referred to so many plants in his works that “Shakespeare Gardens” dot the English-speaking world. A list of Shakespeare Gardens is provided by Wikipedia.¹ Shakespeare, of course, was not writing in an information vacuum. The plants to which he refers were all in common use at the time, and all can be found in more or less contemporary published herbals.

Nicholas Culpeper’s Herbal is both famous and fairly typical of Western herbal treatises. The entry for plantain begins with a simple physical description of the plant’s appearance and goes on to speak about where it might be found and for what it should be used. Not surprisingly his *The English Physician* was first published in 1652, *The Complete Herbal* in 1653, and no laboratory tests are mentioned.²

The structure of pharmacopeias* as they evolved was similar to that of the herbals, adding sections on standards of strength and purity to the descriptions of the properties, actions, uses, and dosages found in the earlier tomes. For instance, the first edition of the *United States Pharmacopeia*’s (1820)³ entry for plantain was quite brief, and Culpeper himself could have written the plant’s description.

The co-evolution of the herbal and the pharmacopeia seems to have been spurred by several historical trends. The first was the diligent application of the scientific method

and the attendant explosion of knowledge about the world. Author and photographer Steven Foster discussed the second trend in his *HerbalGram* article about historical adulteration.⁴ Meanwhile, as commerce grew and new processing methods for materials (medicines, as well as everything else) became available, incentives and opportunities to cheat also increased. Advances in science and technology provided the twin benefit of being able to better identify and test superior material *and* to detect cheats. The 1918 *United States Dispensary* (USD, 20th edition)⁵ entry for plantain provided descriptive information on the herb as well as a few newly identified organic chemicals. The Plantain Leaf monograph had been eliminated from the USD by the time the 25th edition was published in 1955,⁶ but Bisset and Wichtl’s *Herbal Drugs and Phytopharmaceuticals* (2001 edition)⁷ provided an authoritative treatise on plantain leaf that incorporated standards from the *Austrian Pharmacopoeia*, the *Pharmacopoeia Helvetica* (Switzerland), and the *German Pharmacopoeia*. In addition to the physical description of the plant (accompanied by color photographs), Bisset and Wichtl’s plantain monograph includes additional specifications and tests that require laboratory facilities.

For better or for worse, many of the simple, unprocessed, and easily identifiable herbs of a bygone era can be found in retail commerce only rarely and with some degree of difficulty. Many modern botanical products intended for health-related purposes are, for the most part, quite complicated, often requiring additional testing for authentication of identity and for the presence of accidental or intentional adulterants, including contaminants such as heavy metals, pesticides, noxious microbes, and mycotoxins.

As knowledge on the composition and properties of herbs has evolved, so too has the ability to evaluate those properties (e.g., marker compounds) using technology. The modern world also superimposes itself on commerce in the form of smelters, internal combustion engines, fecal coliforms, leaded gasoline, pesticides, prescription drugs, and other noxious substances that necessitate testing in addition to evaluating the inherent properties of the raw materi-

* Editor’s note: ABC prefers to use the spelling *pharmacopeia* without the second “o” in the diphthong, as is customarily the modern spelling, using the more archaic *pharmacopoeia* for those publications and/or organizations that still choose to use it, e.g., the American Herbal Pharmacopoeia, the European Pharmacopoeia, etc.

als and finished products. No evaluation of herbal quality would be complete without some means of assuring that these and other unintentional contaminants are absent.

In addition to an individual manufacturer's desire to create and sell only the highest quality products, there are significant regulatory requirements surrounding the sale of botanical goods. Whether they are called natural health products (Canada), therapeutic goods (Australia), dietary supplements (United States), or phytomedicines (Europe), there are regulatory requirements to set specifications and to test for conformity with those specifications. Thus, the laboratory enters the scene.

Role of Contract Analytical Labs

In the United States, at least, manufacturers are not required to have a laboratory as part of their dietary supplement operations. They are, however, required to have both raw material and finished product specifications, and to have a means to demonstrate that those specifications are met, *i.e.*, analytical tests. Many companies rely on independent commercial analytical laboratories to perform this required testing on a contractual basis — these are referred to as contract labs.

Contract analytical laboratories provide an extensive range of services and can be a cost-effective way to test the quality of raw materials and finished products. Whether to assist in guiding purchasing decisions, developing or verifying claim and labeling information, or performing routine quality control duties, the decision to identify and hire a laboratory partner generally begins with the identification of the company's needs.[†] From routine testing for compliance with current Good Manufacturing Practices (cGMPs) to testing in support of a company-sponsored clinical trial, it is imperative that the company clearly knows its requirements and compares those needs to a laboratory's capabilities.

Many laboratories offer an impressive suite of testing services, but every laboratory has different areas of expertise and competency. So rather than deciding whether or not “one-stop

shopping” is best suited for a particular manufacturer's needs, the company should independently evaluate each laboratory service. With dietary supplement testing, very little is really “routine,” and the quality of contracted work can vary significantly. Further, many laboratories that offer numerous contract testing services subcontract some of those tests to other laboratories, and it is important for manufacturers to know whether the laboratory work is being done in-house or sent out.

The complexity and variety of finished products, coupled with the freedom to change a formulation at will, result in a constant challenge for analytical laboratories. The majority of single-component dietary supplement products may be described as generic, but they are not necessarily identical, and any analytical method used on a given product should be valid for its intended use for that product.

Multi-component products are neither generic nor identical, so assuring suitability for intended use is even more important. The US dietary supplement cGMP regulations require that testing be performed using methods that are “scientifically valid.” Although the

rule fails to define the term, there is considerable agreement on its meaning within the scientific literature (see Betz *et al. Fitoterapia*. 2011;82:44-52⁸).

Questions of Accreditation

When evaluating contract laboratories, potential customers should seek documentation from the lab in the form of third-party accreditation of their operations to ensure the quality of the lab's measurements. Customers must ask not only if the lab has appropriate accreditation, but also if the accreditation's scope covers the contract analysis they wish to purchase. Unfortunately, there are no specific regulations that provide federal government oversight of the behavior of contract laboratories that service the supplement industry, so buyers of laboratory services must exercise considerable diligence and good judgment. In addition, regulators can hold accountable contract laboratories performing testing services that are part of

Contract analytical laboratories provide an extensive range of services and can be a cost-effective way to test the quality of raw materials and finished products.

Table 1. Acronyms Used in this Article

CRM	Certified reference material
HPLC	High-performance liquid chromatography
ISO	International Standards Organization
NIST	National Institute of Standards and Technology
OOS	Out of specification
QA	Quality Assurance
QC	Quality Control
RI	Refractive Index
SOP	Standard Operating Procedure

[†] This article is written primarily with respect to commercial companies that are purchasing botanical (and other) raw materials as ingredients for use in dietary supplements. However, the information in this article also can be relevant to the purchase of raw materials for use in herbal teas — often regulated as conventional foods in the United States, depending on how the teas are labeled, and thus not subject to the same level of stringency required by GMPs for dietary supplements. Also, many of these issues apply to the purchase of botanical materials for use in cosmetic products. Further, there are times when researchers of a clinical trial on an herbal dietary supplement will choose, or be required, to have the test material analyzed for identity and/or potential contaminants by a contract laboratory; in such cases, many of these issues and guidelines will apply.

a GMP-related process. A qualified contract laboratory should have a written standard operating procedure (SOP) that will define the GMP term “scientifically valid.” When selecting and qualifying a contract laboratory, customers should ask for a copy of this SOP, as it will provide a great deal of information on the laboratory’s position on the matter.

Selecting and qualifying a contract laboratory can be an important business decision for a manufacturer, one that should not be underestimated, as contract laboratories that perform analytical services can have an impact on meeting minimum GMP requirements. Experience has led to the identification of several easy-to-spot warning signs about laboratories-for-hire and several more signs that are not so easy to recognize. For instance, manufacturers should be wary of laboratories that claim to be certified by the US Food and Drug Administration (FDA). Contrary to some contract laboratory marketing materials and websites, there is no such thing as an “FDA-approved” or “FDA-certified” laboratory. A laboratory that makes such claims either does not understand the regulatory environment in which it operates or perhaps it may be actively deceiving potential clients. The FDA can inspect a laboratory, but the result of an inspection is not “certification” or “accreditation;” it is merely a clean inspection. All FDA inspections result in the generation of an inspection report, so if a laboratory that has been inspected is chosen by a company, that company should request the FDA inspection report, when available, to determine if the inspected laboratory’s operations are relevant to the analyses needed, whether or not significant deficiencies were found by FDA, and if such deficiencies have been corrected by the laboratory. Laboratories might be certified or accredited by the US Environmental Protection Agency under various state programs, but few, if any, of these programs are directly related to dietary supplement analytical endpoints. Complicating this picture even more, some laboratories advertise with the term “FDA-registered.” There is a “registration” process at the FDA for contract laboratories, but it is just that: a registration process that does not involve approval, certification, accreditation, or even inspection by FDA. Claims by laboratories that they are “FDA-registered” do not mean anything from a laboratory performance perspective.

Asking for certification or accreditation information provides pieces to a puzzle that helps customers decide if the lab meets their needs and expectations. As such, the answer is just one data point among many that can help the customer make a choice. There are different types of certifications, from the International Standards Organization (ISO) and others. Simply having an ISO certificate laying around the lab means little if it is the wrong ISO certificate.

Some ISO certifications are for business practices, others for general laboratory competence. The most rigorous ISO certification requires SOPs and extensive documentation for each laboratory method. And even with that, it is possible to get one of the higher-level accreditations and have some individual methods included within the scope of the accreditation and others (without SOPs, etc.) not within the scope. Customers must ask not only whether or not the lab has an accreditation, but also whether or not the contract analysis they wish to purchase is within the scope of that accreditation. The nature of the dietary supplement testing business, with the constant need to tweak methods for new matrices, makes it impractical for many contract labs to become accredited to the higher standard. The lower standard is reasonably generic, and a lab may decide it is too generic to mean anything. However, achieving the lower standard does demonstrate awareness by the lab that laboratory quality programs exist and a willingness to invest in having someone come in and have a look around. A customer who makes a purchasing decision based solely on presence/absence of an accreditation is asking someone else (the accreditor) to do his or her due diligence for them. Customers can and should ask the lab for as much information as is necessary to make them comfortable with the laboratory’s competence.

Good Laboratory Practices (GLPs) is a term with limited scope that applies to animal, drug, and environmental testing. GLPs are designed for studies in which a director is involved (*e.g.*, a clinical trial or animal study) and not for routine analysis. Laboratories that use GLPs as a selling point for routine testing services may either actively be prevaricating or possibly ignorant of the scope of such claims. That being said, if the careful documentation and controls required to maintain GLP-compliance are translated through to all the laboratory services, there could be a distinct advantage to contracting with a GLP-compliant laboratory. In sum, a lab can state that it performs studies according to GLPs in addition to routine analysis of dietary supplements.

There is one type of accreditation that may be of interest when considering whether or not to hire a contract laboratory. Documentary laboratory standards are produced and published by the ISO, and compliance with these standards is evaluated by third-party inspectors, not by ISO. There are several levels of ISO accreditation that range from low-end compliance with general quality management principles to highly detailed laboratory and method-specific programs, so manufacturers should determine the level of ISO accreditation claimed by the laboratory before entering into a contract. The main standard used by testing and calibration laboratories, ISO 17025, applies to overall laboratory operations as well as to individual methods of analysis conducted

No evaluation of herbal quality would be complete without some means of assuring that these and other unintentional contaminants are absent.

within the laboratory, so a dietary supplement manufacturing company must determine which methods are included in the accreditation. Analyses performed using a method that falls outside of the accreditation would not be considered ISO 17025 compliant.

Regulatory Context

According to the US dietary supplement cGMP regulations (21 CFR Part 111), manufacturers must identify every point in the manufacturing process that may require control and mandates that every step of the manufacturing, packaging, labeling, and holding process for dietary supplements must have specifications, and that all steps taken during manufacture be documented. GMPs are fundamentally about traceability in product manufacturing and rely heavily on documentation. In a laboratory, this translates to having SOPs for all operations, including laboratory test methods.

In choosing a laboratory, a company must ensure that the lab's operations, with respect to testing the company's raw materials and/or finished products, are in compliance with cGMPs. The FDA expects that laboratory work performed in the course of a product's manufacture, whether in-house or by a contracted laboratory, meets all the dietary supplement cGMP requirements. In some ways, the cGMPs appear vague and not particularly informative (*i.e.*, prescriptive) on this subject; that is because FDA has provided considerable latitude to companies in establishing their specifications and testing protocols. Evidence must be provided that the laboratory examination and testing methodologies are "appropriate for their intended use" (21 CFR 111.320(a)) and that methods used to determine whether or not specifications are met are "appropriate and scientifically valid" (21 CFR 111.75 (h)(1)).^{9,10}

Proof that these requirements are met requires data, collected by the laboratory, on each individual lot of each raw material or finished product. Because the cGMPs state that the burden is on the manufacturer to document that these requirements are met, a close working relationship with the contracted laboratory is highly recommended. According to an industry source,¹¹ in January 2012, FDA reaffirmed its intention to begin Section

111 GMP inspections of contract analytical laboratories. Contract laboratories are seen by FDA as an extension of the manufacturer and are thus within the scope of a Section 111 inspection. In general, contract labs have been at arms-length with FDA inspectors on the GMP front, having focused on paperwork rather than physical lab inspections

to verify lab performance. The consequences of a decision by FDA to inspect the labs themselves, whether in-house or contract, are potentially far-reaching for both laboratories and manufacturers. It is important to understand that there are not universal testing methods that work for a given marker in a wide range of different sample matrices. For example, a method developed and validated on a standardized botanical extract may not work properly for that same extract in a tablet that also contains 15 other ingredients. Therefore, a great deal of modification to any method is often needed to obtain valid data on a sample matrix that might vary from the original method. Some laboratories perform additional quality control (QC) measures, such as measuring replicates and spikes on a novel matrix to assure that they have some basis for defending the data, while others do not. These are the types of hidden value-added benefits that separate one lab from another, and usually will explain why one lab is charging a higher fee for what might appear to be the same service.

Choosing a Laboratory for Routine Analytical Testing of Dietary Ingredients and Finished Dietary Supplements

When choosing a contract lab, the first question should be this: Are the methods to be used by the contracted laboratory on a company's test articles compatible with its specifications? For example, if a vitamin manufacturer is seeking microbiological assay, an experienced food laboratory may not be of much use unless that laboratory can demonstrate experience with the company's product matrix, or at least related matrices (*e.g.*, how the products are actually formulated — what types of materials are included in

the production of the supplement, including tablet coatings, excipients, and other materials that can affect the ability to conduct an accurate analysis of targeted dietary ingredients and/or marker compounds). If the company has become comfortable with the concept of "off-the-shelf" testing on a one-off basis and shops for laboratories by price and/or turnaround time as the primary criteria for choosing a contract lab, the company may be in for a surprise when an FDA inspector stops by and wants to see the documentation related to work

conducted by the contracted laboratory.

The FDA will expect SOPs for testing and for making the determination that the tests are both scientifically valid and appropriate to the company's test articles. Inspectors also will expect the company's sampling plan, calibration, data, and justification for reference material selection, etc., to be

Contrary to some contract laboratory marketing materials and websites, there is no such thing as an "FDA-approved" or "FDA-certified" laboratory. A laboratory that makes such claims either does not understand the regulatory environment in which it operates or perhaps it may be actively deceiving potential clients.

Seven Basic Tips for Selecting a Contract Laboratory

A company (or any party wanting to use a contract lab to analyze dietary ingredients) should do the following:

1. Qualify the contract laboratories before sending samples and relying on the results they provide. Establish a Standard Operating Procedure for "Qualifying Independent Contract Testing Laboratories." Have a checklist of points to look for when performing due diligence on a laboratory before the lab is "qualified" for use.
2. Qualify more than one analytical laboratory. Not only is it doubtful that a company will be able to find one laboratory that can meet all of its needs, it is also better to use laboratories based upon their analytical expertise. In addition, having a back-up lab is a good idea in the event that the primary laboratory is unable to conduct work due to an emergency such as fire, flood, or instrumentation failure.
3. Sign a contract or agreement with the chosen third-party analytical laboratories that defines the relationship. If a company uses a third-party analytical laboratory, it should establish ground rules and expectations, which not only makes good business sense, but also is an important part of GMPs.
4. Visit, audit, and inspect contract laboratories. Contract laboratories performing analytical testing services for dietary supplement manufacturers are, in fact, a part of the GMP process, which makes them fully accountable for being GMP-compliant.
5. When sending samples to independent laboratories, a company should not provide the exact results it is expecting for the sample to be tested. The customer should provide the lab with information about the specifications for the sample, as it would make it very difficult for the lab to perform proper analytical testing without having some idea about the expected concentration range for the analyte (compound of interest). For example, if a company is testing a product that contains 75 mg of caffeine per capsule, the company would not want to tell the lab that it expects 75 mg per capsule. It would be more prudent to tell the lab that the company is expecting somewhere between 60 mg and 90 mg per capsule. By not providing the laboratory with the exact specification, it makes it very difficult for the lab to fabricate an expected value.
6. Some observers have suggested that manufacturers occasionally check on laboratory performance by sending "challenge samples" or "dummy samples," i.e., samples that provide intentionally misleading information about expected results. This practice can be wasteful and counterproductive if done as a "gotcha" exercise, as it flies in the face of recommendations that testing laboratories and manufacturers work collaboratively in a stable business relationship. However, challenge samples in the context of a long-term contract relationship could be beneficial. Such a program could be viewed by both parties as an ongoing process, if mutually agreeable.
7. Certified reference materials (CRMs), such as those produced by NIST, can be used as "check samples" to evaluate laboratory proficiency. By sending contract labs such proficiency samples, one can determine how accurate the labs' results are compared to the well-established values reported for the CRM. It is not unreasonable to expect a contract laboratory to participate in inter-laboratory comparisons and/or proficiency exercises. In fact, participation in such exercises is necessary to achieve ISO 17025 accreditation. Unfortunately, few such programs are currently available that focus on dietary supplement testing. Examples of such programs include the Dietary Supplement Quality Assurance Program run by NIST and sponsored by the NIH Office of Dietary Supplements¹⁷ or the Laboratory Proficiency Program administered by the British Columbia Institute of Technology.¹⁸

Note: If a company has qualified the contract laboratory it is using, details of the qualification process and outcomes should be provided. When testing under FDA

readily available. Each time a manufacturer begins a relationship with a new contract laboratory or changes one or more of its formulations, that manufacturer should require verification or validation of method performance on its materials and expect to pay for this additional information. Ultimately, jumping from laboratory to laboratory may be a false economy.

FDA always has had the authority to ask a company for evidence that its contract lab is in compliance with cGMPs. If the agency starts inspecting these labs and reviewing

their SOPs and records, a contracting dietary supplement manufacturer could have a problem if it has not done its homework by qualifying, auditing, and inspecting the laboratories it is using. Any company using contract laboratories should be sure that those laboratories are willing to support the company should it be inspected by FDA by providing the company and/or FDA with the supporting documentation or data requested. A situation in which a contract laboratory is unwilling to share supporting documentation or data that the lab deems "proprietary" should be viewed by

the customer company as a big red flag. One of the biggest potential hazards is not poor analytical method selection or even incomplete record keeping; it is outsourcing analytical laboratory work to a so-called “dry lab.” To be clear, the term “dry lab” is being applied in this context as described in Wikipedia[‡]: “...supplying fictional (yet plausible) results in lieu of performing an assigned experiment.”¹² The development of pharmacopeias over the past 500 years and the mere existence of advanced testing procedures are not evidence of compliance; there must be actual records, *i.e.*, documentation that demonstrates the samples were tested and the specifications were met.

Dry-labbing is a phenomenon that has been in existence for some time now, but had not really caught the attention of the supplement industry until a televised report by *Dateline NBC* (Season 20, Episode 29, March 18, 2012) exposed the practice to a wider audience. The dry lab story starts when the manufacturer sends a sample and a sample submission form to a contract laboratory. In most dry lab cases, the lab will request detailed information about the sample, including a range of expected results. Because legitimate labs may also request this information as a way to ensure that the methods employed will be valid for the sample type and to allow for accurate sample preparation, these questions alone should not be cause for suspicion. Nevertheless, when the dry lab receives the sample, it is not actually tested or an inexpensive generic analytical method is employed that yields no real useable data. The lab then generates a report that essentially affirms the expected result as provided by the customer.

While it has been suggested that challenging laboratories with “dummy samples” is a way to spot a dry lab, this is not the recommended approach for developing a relationship with a prospective contract lab (see sidebar “Seven Basic Tips for Selecting a Contract Laboratory” on page 56). Certainly, dummy samples could expose a dry lab, but companies can take less extreme actions to protect themselves. First, a company should take time and care in choosing the contract laboratory and never “lab shop” or buy services based solely on price. While spending an appreciable amount of money does not guarantee results, one can be fairly certain that if a lab is charging far less than most competitors, there is a reason. (More guidance on selecting a contract analytical lab can be accessed in the *Nutraceuticals World* archives for Dr. Brown’s Quality Focus column, titled “Outside Analytical Labs,” published in 2009.)¹³

It is recommended that site visits, paper audits, and even physical audits of a contract laboratory be conducted on a regular basis by the contracting company. The company should inquire about the lab’s experience in the type of testing being sent to them, including questions on participation in any industry initiatives, such as the Dietary Supple-

ment Quality Assurance Program managed by the National Institute of Standards and Technology (NIST). An audit should include the review of general and method-specific SOPs, staff education and training, method citations, date-stamped raw data, and analytical testing reports. Certificates of analysis for reference materials and purchase orders for reagents, chromatographic columns, and calibration standards should be reviewed. A contract lab should be able to walk their client through sample tracking procedures, including sample and equipment logs, laboratory notebooks, and the sample holding room. Instrument equipment logs also can be very telling: They should include details of instrument usage and maintenance. All of the information noted above, and more, is required for compliance with the GMP rule in the United States. If the laboratory refuses to show any of it, the manufacturer has no way to assure an FDA inspector that it is in compliance during a GMP inspection. Nonetheless, the manufacturer’s QC director should keep in mind that if the laboratory is testing multiple samples from different clients at the same time, the laboratory is responsible for protecting client confidentiality and, therefore, may rightfully show auditors only the records applicable to the testing being audited.

Certificates of Analysis and Analytical Test Reports

Company quality control personnel should pay close attention to the analytical test reports or certificates of analysis from contract laboratories, as warning signs are often found in such documents. Quality assurance personnel should be both qualified and prepared to evaluate carefully all available documentation. For example, unlabeled and undated chromatograms with no unique identifiers, such as the company’s product or material lot number and the date of analysis, can be recycled over and over again both for the contracting company’s samples and those of other clients of the laboratory. The manufacturer’s quality assurance team also can request to see chromatograms for their ingredients in different products that it manufactures. If the chromatograms look eerily similar, they might just be the same chromatogram. Photocopying an old chromatogram is obviously lower cost than buying and running a device that analyzes high-performance liquid chromatography (HPLC) and does not require technically trained operators. It is also important to keep in mind that chromatography raw data often results in a lot of questions and confusion; if the party reviewing the data is not familiar with the test or the protocol, the data alone can be meaningless. This can drive up the cost of testing because expert time is needed to explain data, yet many companies do not want to pay more for that level of service.

Telltale clues that a contract analytical laboratory is dry-labbing also can be found in the analytical test reports. The following is a list of red flags:

[‡] The use of Wikipedia to define “dry lab” is provided because this term is relatively new that it has not gotten into common parlance, except insofar as it is recently generated jargon within the herb, dietary supplement, and analytical laboratory communities in the United States (http://en.wikipedia.org/wiki/Dry_lab; accessed July 25, 2013).

- Analytical results reports that refer to modified official methods or modified USP (United States Pharmacopeia) methods but do not provide details on the modifications or data to support the validity and fitness for the purpose of the modified methods.
- Citations of methods from peer-reviewed scientific journals that are used to measure something “in urine” or “in serum,” but not in a dietary supplement matrix. This is especially true if the detector in the paper is a refractive index (RI) detector and the lab uses a UV detector. However, many old RI methods are now done using evaporative light scattering detectors (ELSD) or mass spectrometry detectors, so this alone is not proof of dry-labbing. Also related to this problem are references to very obscure journals for methods that are available in commonly utilized journals. This was observed in many dry lab situations in the past. Having to spend an enormous amount of time to find the citation often is a way to create ambiguity.
- Incompatibility between the equipment and/or detector employed by the contract lab when compared to that reported in the journal-cited method. For example, peaks generated by a chromatographic separation achieved using gradient HPLC will not be quantifiable if the HPLC column is coupled to an RI detector.
- The order of magnitude for the measurement being taken is different than that of the published test method — for example, using a method designed to test the purity of a 100% pure compound for measuring trace amounts of the compound in a complex matrix, or vice versa. Again, if data are *reported* in the analytical range expected in a matrix and the method is incapable of separating the analyte from matrix peaks or if the matrix findings are below the LOD/LOQ (the limit of detection and the limit of quantification) of the published method, then the report can be deemed fraudulent. In such a case (as with the “urine” or “serum” example), the burden of proof would be on the lab to prove that the method was capable of achieving the desired results. A simple citation on a certificate of analysis would not suffice. It should be noted that many of these clues also can serve as indicators that the lab is simply not using valid analytical methods even if it is actually performing the tests.
- Finally, additional warning signs also can include the lab’s refusal to produce copies of a lab notebook, its refusal to complete a lab audit questionnaire for the client, and its refusal to produce chromatograms or raw data for analysis (when appropriate).

The contract laboratory is essentially an extension of the manufacturer. Contract labs often must modify methods,

whether to adapt to new technology or to expand the scope and applicability of an existing method. This is not unusual, but when a method has been modified, the contracting company should insist it is privy to the details of the modification, the method re-validation or verification SOP, and the data that prove to the client company (and FDA) that the method remains scientifically valid and suitable for its intended use. That method suitability must extend to the company’s product type. Verbal or written assurances of such procedures are not sufficient; there must be adequate documentation. Anything else can put the client company at risk. The manufacturer should expect to pay for the extra services incurred in demonstrating method performance.

The contract laboratory is essentially an extension of the manufacturer.

The process of ensuring that a method is “fit for purpose,” or, in other words, is appropriate for its intended use, is generally demonstrable with some relatively simple experiments. The process of performing the experiments necessary to demonstrate that a method is scientifically valid is called a validation study, and both are fundamental requirements for method use in the dietary supplement cGMPs environment. There are internationally recognized definitions and guidelines for demonstrating method performance.^{14,15}

As more methods and reference materials become available, and as the dietary supplement industry becomes more accustomed to requesting that laboratories demonstrate that their methods are appropriate for their intended use, contract testing of dietary supplements will evolve. It should be remembered that sample matrices detailed in compendia protocols and tested using those protocols do not have to be validated in the laboratory again, but the lab does have to demonstrate proficiency in using the method. This can be done using spikes, calibrations, duplicates, etc.

If the ingredient supplier or finished-product manufacturer has a qualified in-house scientist, that person should review the analytical test reports. If not, the company should contract with a qualified expert to review the reports. If a method citation looks like unintelligible gibberish, there is a fair chance that some obfuscation is occurring. More information on what should be contained in an analytical test report or certificate of analysis can be found in the *Nutraceutical World* article, “Certificates of Analysis,” published in November 2008.¹⁶

A reliable and responsibly run contract lab should be willing to share information, and a contract laboratory must always provide copies of raw data upon request. A laboratory may choose to treat its in-house methods as intellectual property and may choose not to release copies of the methods, but methods must be made available for review during an inspection. If they are not made available for review, it is possible that they do not exist. All competent quality control managers should “think GMP” when considering their off-site operations, *i.e.*, outside contract laborato-

ries. Manufacturers should be wary of laboratories that are unwilling to allow an on-site visit or audit. Manufacturer QC personnel should be aware that inspections are disruptive and the schedule of the laboratory and availability of key staff should be considered. HG

Paula M. Brown, PhD, is a natural product chemist and the director of the British Columbia Institute of Technology's Natural Health and Food Products Research Group. She has been supporting the Canadian natural health products and the US dietary supplement industries for more than a decade through applied research activities including product development, establishment of quality standards, and regulatory compliance. She is actively involved with numerous nonprofit organizations, including AOAC International, and is a member of the ABC Advisory Board. She also has written the "Quality Focus" column for *Nutraceuticals World*, an industry trade publication.

Joseph M. Betz, PhD, received his doctorate in pharmacognosy from the Philadelphia College of Pharmacy and Science. He worked at the US Food and Drug Administration's Center for Food Safety and Applied Nutrition for 12 years, was vice-president of science and technical affairs at the American Herbal Products Association for two years, and has worked at the US National Institutes of Health since 2001. Dr. Betz is the recipient of the American Botanical Council's first Norman R. Farnsworth Award for Excellence in Botanical Research and the American Society of Pharmacognosy's Varro E. Tyler Prize for outstanding scientific contributions to the field of dietary supplements, with special emphasis on botanicals. He is a long-time member of the ABC Advisory Board.

Frank L. Jaksch, Jr., co-founded ChromaDex[®], Inc. in 1999 and serves as chief executive officer. Under his leadership, ChromaDex has focused on developing a comprehensive natural products chemistry business, expanded into international markets, and built a roster of Fortune 500 customers. ChromaDex is now a leading supplier of botanical reference standards and phytochemical products, analytical services, and novel ingredients to the dietary supplements, sports nutrition, food and beverage, cosmetic, and pharmaceutical markets. He is a member of ABC's Director's Circle.

References

1. Shakespeare garden. Available at: http://en.wikipedia.org/wiki/Shakespeare_garden. Accessed December 24, 2012.
2. Culpeper N. *The English Physician: Or the Astro-Physical Discourse of the Vulgar Herbs of This Nation*. London: Peter Cole; 1652.
3. Medical Societies and Colleges. *The Pharmacopoeia of the United States of America*. Boston, MA: Wells and Lilly; 1820.
4. Foster S. A brief history of adulteration of herbs, spices, and botanical drugs. *HerbalGram*. 2011;92:42-57.
5. Remington JP, Woods HC. *The Dispensatory of the United States of America*. 20th ed. Philadelphia: JB Lippincott & Co.; 1918.
6. Osol A, Farrar GE. *The Dispensatory of the United States of America*. 25th ed. Philadelphia: JB Lippincott & Co.; 1955.
7. Bisset NG, Wichtl M (eds). *Herbal Drugs and Phytopharmaceuticals — A Handbook for Practice on a Scientific Basis With Reference to German Commission E Monographs*. 2nd ed. CRC Press; 2001.
8. Betz JM, Brown PN, Roman MC. Accuracy, precision, and reliability of chemical measurements in natural products research. *Fitoterapia*. 2011;82:44-52.
9. Current Good Manufacturing Practice in Manufacturing, Packaging, Labeling, or Holding Operations for Dietary Supplements. US Code of Federal Regulations, Title 21, Volume 2, Section 111.320(a): What requirements apply to laboratory methods for testing and examination? Revised April 1, 2013. Available at: www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=111&showFR=1. Accessed July 21, 2013.
10. Current Good Manufacturing Practice in Manufacturing, Packaging, Labeling, or Holding Operations for Dietary Supplements. Requirement to Establish a Production and Process Control System. US Code of Federal Regulations, Title 21, Volume 2, Subpart E; Section 111.75 (h)(1). Available at: www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=111.75. Accessed July 21, 2013.
11. Czap A. Editorial — Atlas Shrugged (Kind of). *Altern Med Rev*. 2012;17:1-4. Available at: www.altmedrev.com/publications/17/1/1.pdf.
12. Dry Lab. http://en.wikipedia.org/wiki/Dry_lab. Accessed July 21, 2013. Accessed June 25, 2013.
13. Brown PN, Dentali S. Quality focus: outside analytical labs. *Nutraceuticals World*. January 2009;12(1):32-34. Available at: www.nutraceuticalsworld.com/issues/2009-01/view_columns/quality-focus-outside-analytical-labs/. Accessed January 16, 2013.
14. Horwitz W. Protocol for the design, conduct and interpretation of method-performance studies (technical report). *Pure & Applied Chem*. 1995;67:331-343.
15. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH Harmonised Tripartate Guideline — Validation of Analytical Procedures: Text and Methodology, vol. Q2, (R1). Available at: www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q2_R1/Step4/Q2_R1__Guideline.pdf. Accessed February 28, 2013.
16. Brown PN. Certificates of analysis. *Nutraceuticals World*. November 2008; 11(10):32-33. Available at: www.nutraceuticalsworld.com/issues/2008-11/view_columns/quality-focus-certificates-of-analysis/. Accessed January 16, 2013.
17. Dietary Supplement Analysis Quality Assurance Program. Available at: www.nist.gov/mml/csd/organic/dsqap.cfm. Accessed January 15, 2013.
18. British Columbia Institute of Technology. Available at: www.bcit.ca/appliedresearch/nrg. Accessed January 15, 2013.

Herb Supplement Sales Increase 5.5% in 2012

Herbal Supplement Sales Rise for 9th Consecutive Year; Turmeric Sales Jump 40% in Natural Channel

By Ashley Lindstrom¹, Carla Ooyen², Mary Ellen Lynch³, and Mark Blumenthal¹

¹ American Botanical Council, Austin, Texas, USA

² *Nutrition Business Journal*, New Hope Natural Media, Boulder, Colorado, USA

³ SPINS, Schaumburg, Illinois, USA

Total sales of herbal and botanical dietary supplements in the United States increased an estimated total of 5.5% in 2012, according to aggregated market statistics calculated by *Nutrition Business Journal* (Table 1). This total sales growth is greater than the 5% increase in total sales determined for 2011,¹ marking the 9th year in a row in which herb sales increased over the previous year (Table 2). These sales data do not include sales of herbal teas or herbs sold in natural cosmetic products.

As has been the case in previous years, total herb supplement sales growth in the different market channels varied, according to statistics provided by market research firms, from a respectable 2.2% over the previous year in the mainstream market (food, drug, and mass market retail stores, FDM) to a stronger 6.1% increase in the natural channel (natural and health food stores) (Table 1).

Unlike previous years when this annual report has been published in *HerbalGram*, the market research firms contributing econometric information have gained access to more robust sales data than were available last year; as a result, sales estimates from 2011 have been updated in several instances from those previously reported.

Mainstream Retail Channel – Food, Drug, and Mass Market (FDM)

In the FDM channel for 2012, a sales total of \$594,815,900 was calculated by the Chicago-based research firm SymphonyIRI — which would appear to be an increase from 2011's reported sales figure of \$379,286,600 (Table 3). However, SymphonyIRI's channel coverage expanded in 2012 to "Total US Multi-Outlet," which includes the previously measured supermarkets, drugstores, and mass market retailers, but now also covers military commissaries and select club and dollar retail discount chains. As a result of this more comprehen-

Table 1. Total Herbal Dietary Supplement Sales in Millions (USD) by Channel for 2011 & 2012

Channel Sales	2011	2012	% Increase
Mass Market*	966	987	2.2%
Natural & Health Food†	1,757	1,864	6.1%
Direct Sales‡	2,578	2,742	6.3%
Total	5,302	5,593	5.5%

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

* Mass market includes food/grocery, drug, mass merchandise, club and convenience stores, including Wal-Mart, Costco, etc.

† Natural & health food includes supplement and specialty retail outlets, including Whole Foods, GNC, sports nutrition stores, etc.

‡ Direct Sales include Mail Order (including catalogs), direct mail and direct response TV and radio; practitioners representing conventional and alternative practitioners selling to their patients, including ethnic herbals and herb shops; Multilevel (MLM) or network marketing representing firms like Advocare, Herbalife, Morinda Bioactives, Nature's Sunshine, Pharmanex/NuSkin, Nutrilite (Amway/Quixtar), Shaklee, USANA, etc.

Table 2. Total Estimated Herbal Dietary Supplement Sales in All Channels, 2000–2012

Year	Total Sales (Millions USD)	% Increase/Decrease
2000	4,230	2.9%
2001	4,356	3.0%
2002	4,238	-2.7%
2003	4,146	-2.2%
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	5,301	5.0%
2012	5,592	5.5%

Nutrition Business Journal's (NBJ) primary research includes NBJ surveys of supplement manufacturers, distributors, MLM firms, mail order, Internet and raw material/ingredient supply companies, as well as numerous interviews with major retailers (Wal-Mart, Costco, etc.), manufacturers, suppliers, and industry experts. Secondary sources include SymphonyIRI, SPINS, ACNielsen, *Natural Foods Merchandiser*, Insight, The Hartman Group, company data, and other published material.

Table 3. The 40 Top-Selling Herbal Dietary Supplements in the Food, Drug, and Mass Market Channel in the United States for 2012 (per SymphonyIRI)*

	<u>Herb</u>	<u>Latin Name</u>	<u>US Dollar Sales</u>	<u>% Change 2011</u>
1.	Cranberry	<i>Vaccinium macrocarpon</i>	\$65,483,940	-5.88%
2.	Garlic	<i>Allium sativum</i>	\$34,950,540	11.78%
3.	Saw palmetto	<i>Serenoa repens</i>	\$31,775,810	-3.00%
4.	Soy	<i>Glycine max</i>	\$28,017,310	-24.43%
5.	Ginkgo	<i>Ginkgo biloba</i>	\$25,853,420	-1.09%
6.	Milk thistle	<i>Silybum marianum</i>	\$21,143,560	7.25%
7.	Black cohosh root	<i>Actaea racemosa</i> †	\$16,925,990	-21.33%
8.	Echinacea‡	<i>Echinacea</i> spp.	\$15,898,880	-6.08%
9.	St. John's wort	<i>Hypericum perforatum</i>	\$12,193,790	-3.39%
10.	Ginseng§	<i>Panax ginseng</i>	\$11,136,960	-8.73%
11.	Valerian root	<i>Valeriana officinalis</i>	\$10,111,770	7.21%
12.	Green tea	<i>Camellia sinensis</i>	\$8,213,667	-5.93%
13.	Evening primrose	<i>Oenothera biennis</i>	\$7,288,381	-1.37%
14.	Bilberry	<i>Vaccinium myrtillus</i>	\$3,755,257	-11.04%
15.	Horny goat weed	<i>Epimedium</i> spp.	\$3,054,005	-0.87%
16.	Ginger	<i>Zingiber officinale</i>	\$3,049,945	5.33%
17.	Grape seed	<i>Vitis vinifera</i>	\$2,806,618	-14.28%
18.	Aloe vera	<i>Aloe vera</i>	\$2,512,607	18.76%
19.	Cascara sagrada	<i>Frangula purshiana</i>	\$1,772,893	3.55%
20.	Hawthorn	<i>Crataegus</i> spp.	\$1,431,057	11.18%
21.	Horse chestnut seed	<i>Aesculus hippocastanum</i>	\$1,345,819	2.76%
22.	Cayenne	<i>Capsicum annuum</i>	\$1,040,716	-5.88%
23.	Elderberry	<i>Sambucus nigra</i>	\$955,776	13.94%
24.	Olive leaf	<i>Olea europaea</i>	\$952,325	17.50%
25.	Spirulina	<i>Arthrospira</i> spp.	\$506,504	30.60%
26.	Alfalfa	<i>Medicago sativa</i>	\$416,858	100.14%
27.	Kava kava	<i>Piper methysticum</i>	\$387,801	6.74%
28.	Yohimbe	<i>Pausinystalia johimbe</i>	\$357,729	-19.75%
29.	Kelp	<i>Laminaria digitata</i>	\$285,491	-14.52%
30.	Damiana leaf	<i>Turnera diffusa</i>	\$225,691	6.10%
31.	Dandelion	<i>Taraxacum</i> spp.	\$225,691	6.10%
32.	Dong quai root	<i>Angelica sinensis</i>	\$205,622	101.16%
33.	Red clover	<i>Trifolium pratense</i>	\$200,478	-29.33%
34.	Pycnogenol®	<i>Pinus pinaster</i>	\$154,287	2.11%
35.	Feverfew leaf	<i>Tanacetum parthenium</i>	\$136,150	31.76%
36.	Barley	<i>Hordeum vulgare</i>	\$88,484	-10.46%
37.	Maca	<i>Lepidium meyenii</i>	\$70,259	22.84%
38.	Licorice root	<i>Glycyrrhiza</i> spp.	\$59,446	15.48%
39.	Gotu kola	<i>Centella asiatica</i>	\$54,752	20.02%
40.	Eyebright herb	<i>Euphrasia</i> spp.	\$52,826	-13.30%
Total Herb Sales (including multi-herb and those not shown) 			\$594,815,900	-1.06%

* Source: Symphony IRI Group, a Chicago-based market research firm. FDM market sales data for herbal supplements, 52 weeks ending December 23, 2012.

† Synonym: *Cimicifuga racemosa*

‡ Echinacea collectively refers to supplements made from roots and/or aerial parts of plants from three species in the genus *Echinacea*, including: *E. angustifolia*, *E. pallida*, and *E. purpurea*.

§ It is not clear from the SymphonyIRI data whether this figure also includes the sales of American ginseng root products (made from *Panax quinquefolius*), the sales of which are not as high as sales of supplements made from Asian ginseng (*P. ginseng*).

|| IRI's channel coverage expanded to Total US Multi-Outlet, which includes supermarkets, drugstores, mass market retailers, military commissaries, and select club and dollar retail chains.

Table 4. The 20 Top-Selling Herbal Dietary Supplements in the Natural and Health Foods Channel in the United States in 2012 (per SPINS)*

Herb†	Latin Name	US Dollar Sales	% Change 2011
1. Flax seed and/or oil	<i>Linum usitatissimum</i>	\$18,428,450	4.7%
2. Wheat or barley grass	<i>Triticum aestivum</i> or <i>Hordeum vulgare</i>	\$17,712,193	19.4%
3. Turmeric	<i>Curcuma longa</i>	\$16,873,153	39.8%
4. Aloe vera	<i>Aloe vera</i>	\$13,667,825	17.7%
5. Spirulina/blue green algae	<i>Arthrospira</i> spp.	\$9,178,398	18.5%
6. Milk thistle	<i>Silybum marianum</i>	\$8,552,702	2.5%
7. Elderberry	<i>Sambucus nigra</i>	\$6,170,991	5.1%
8. Saw palmetto	<i>Serenoa repens</i>	\$6,115,161	6.0%
9. Echinacea‡	<i>Echinacea</i> spp.	\$5,857,794	6.7%
10. Cranberry	<i>Vaccinium macrocarpon</i>	\$5,078,657	9.1%
11. Valerian	<i>Valeriana officinalis</i>	\$5,012,616	10.5%
12. Maca	<i>Lepidium meyenii</i>	\$4,806,878	40.0%
13. Garlic	<i>Allium sativum</i>	\$4,768,064	1.8%
14. Chlorophyll/chlorella§	NA/ <i>Chlorella vulgaris</i>	\$4,685,460	10.4%
15. Chia seed and/or oil	<i>Salvia hispanica</i> & other <i>Salvia</i> spp.	\$4,532,562	123.1%
16. Red yeast rice	<i>Monascus purpureus</i>	\$4,477,054	10.1%
17. Stevia	<i>Stevia rebaudiana</i>	\$4,474,406	11.2%
18. Echinacea-goldenseal combo	<i>Echinacea</i> spp.- <i>Hydrastis canadensis</i>	\$4,400,290	8.1%
19. Oregano	<i>Origanum vulgare</i>	\$4,361,248	9.4%
20. Ginkgo	<i>Ginkgo biloba</i>	\$4,153,010	7.4%
Subtotal Top-20 Herbs		\$153,306,912	
Subtotal All Other Herbs		\$142,177,463	
Total Herb Sales		\$295,484,348	14.7%

* Source: SPINSscan Natural, 52 weeks ending December 22, 2012. Does not include Whole Foods Market.

† Herb coded as primary ingredient.

‡ 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*.

§ Coding for this category includes chlorophyll or chlorella single or combination product.

sive coverage, SymphonyIRI determined that mainstream herb sales actually *decreased* by 1.06% in 2012. In general, however, the FDM channel represents continued mainstream acceptance and success of numerous popular herbs, including bilberry fruit extract, black cohosh root, garlic, ginger root, ginkgo leaf extract, Asian ginseng root (with some American ginseng sales possibly mixed into the statistics as merely “ginseng”), milk thistle fruit extract, saw palmetto berry, St. John’s wort herb extract, and others.*

According to SymphonyIRI (Table 3), few herbs among its top 20 experienced significant increases in growth, with one exception being garlic, which “overtook” both soy and saw palmetto for the first time since 2008, with an 11.78% increase over 2011 sales levels, making it the second highest-selling FDM herb in 2012. Other top-20 herbs that exhibited increases include milk thistle (+7.25%), valerian

root (+7.21%), aloe vera (+18.76%), and hawthorn (probably leaf with flower extract plus berry preparations; +11.18%). Last year’s Herb Market Report included, for the first time ever, sales data on top-selling herbs up to 40 (rather than just the top 20) in the FDM channel per SymphonyIRI. Herbs showing strong increases in the top 21-40 rankings in this year’s report include spirulina (+30.60%), feverfew (+31.76%), alfalfa (+100.14%), dong quai root (+101.16%), and maca (+22.84%).

Sales increases were not uniform across the board, with some herbs experiencing significant declines in the FDM market, according to the SymphonyIRI statistics. These include black cohosh (-21.33%), grape seed (-14.28%), yohimbe (-19.75%), and red clover (-29.33%).

Compared to the SymphonyIRI data, SPINS provides a slightly different ranking of total supplement sales in

*Interestingly, of these eight specific top popular herbs in FDM, five of them have been identified by the ABC-AHP-NCNPR Botanical Adulterants Program as being subject to intentional — *i.e.*, economically motivated — adulteration.

the mainstream channel — which it is now referring to as “AOC” (or “all other channels,” *i.e.*, other than the traditional rankings by SPINS of the natural channel, including FDM [including Wal-Mart], in addition to dollar stores, military stores, and club stores [excluding Costco]) due to its own expanded coverage — with sales actually increasing by 3.6% to \$860,384,627 (per listings in Table 5e, available in the online version of this article: <http://cms.herbalgram.org/herbalgram/issue99/hg99-mktrpt.html>).

Illustrating the complexity of any analysis of this segment, the *Nutrition Business Journal's* (NBJ) analysis for the total sales of herbal dietary supplements in the total mainstream/FDM channel (including estimated sales in buyers' clubs and convenience stores, including Wal-Mart, Sam's Club, Costco, etc.) shows that herbal dietary supplement sales grew somewhere between the figures reported by SymphonyIRI or SPINS, at an NBJ-calculated increase of 2.2%.

As was noted in last year's publication of this annual report, many of the most popular herbs sold in the FDM market are either conventional foods and/or common spices. These include barley, bilberry, cranberry, cayenne pepper, garlic, ginger, green tea, kelp, and soy. Other “edible” or food-oriented herbs include elderberry, grape seed, kelp, maca root, and spirulina.

Natural Channel

Some of the trends contributing to growth in the natural channel were the increase in shots (small, drinkable products containing liquid botanical extracts and other dietary ingredients used for enhanced energy and other applications) as a delivery system for dietary supplements as well as whole foods supplements. Despite some bad press in 2011 that linked it to contamination with *E. coli*, fenugreek sales rose, indicating continued consumer interest in herbs to aid

lactation and male libido. The so-called “Dr. Oz Effect” (the phenomenon of increased popularity of herbal dietary supplements featured on the television show of Mehmet Oz, MD) was observed throughout all channels, particularly illustrated by the increased sales of green coffee extract in the natural channel. Saffron sales are on the rise, perhaps indicating that hoodia has a successor in the weight-loss herbal supplement sector.

In the natural channel, total calculated sales for herbal supplements in 2012, according to SPINS, were \$295,484,348, representing a whopping 14.7% growth over 2011 sales (Table 4) — which were impressive at a 9% increase over 2010 sales.

The rising popularity of whole foods supplements and “food as medicine” — particularly for energy, stress reduction, and reproductive conditions — may account for a significant amount of the increased sales in this channel. Some herbal supplements are being packaged in a fashion that allows consumers to customize the product for themselves in homemade foods or beverages, such as smoothies. Typically, the natural channel is characterized by what some market experts refer to as “core shoppers” — those with a relatively strong commitment to a natural lifestyle, natural foods, and natural-health modalities (compared to the “peripheral shoppers” who have less of a personal commitment to natural foods, natural-health philosophy, and who purchase the majority of their dietary supplements in the FDM channel).

Key herbal supplements show evidence of significant growth in the natural channel; sales of the increasingly popular turmeric root (and its extract concentrated to curcumin levels) grew 39.8%, while various types of greens also showed remarkable growth, including: wheat and/or barley grass (+19.4%), spirulina blue-green algae (+18.5%) (SPINS codes spirulina single supplements and blue-green

**Table 6. Herb Sales by Category in All Channels:
Singles (Monopreparations) vs. Combinations**

2010

	<u>US Dollar Sales (millions)</u>	<u>% Growth</u>
Total Single Herb	3,334	1.8%
Total Combination Herbs	1,715	-2.6%
Total Herbs	5, 049	0.2%

2011

	<u>US Dollar Sales (millions)</u>	<u>% Growth</u>
Total Single Herb	3,473	4.2%
Total Combination Herbs	1,829	6.6%
Total Herbs	5,305	5.0%

2012

	<u>US Dollar Sales (millions)</u>	<u>% Growth</u>
Total Single Herb	3,567	2.7%
Total Combination Herbs	2,026	10.8%
Total Herbs	5,593	5.5%

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Solvents Used in the Manufacture of Botanical Extracts, Food Flavors, and Natural Food Ingredients: An Educational Guide for Ingredient Extractors; Manufacturers of Conventional Foods, Dietary Supplements, Botanical Drugs, Natural Cosmetics, and Other Natural Products; and Analytical Laboratories

by Jay Pierotti PhD and Mark Blumenthal

- Profiles of 22 Solvents Used or Found in Foods, Food Flavorings, Botanical Extracts, Dietary Supplements, etc.
- Review of US & International Regulatory Issues
- Solvent Properties
- Residue Level Limits
- Overview of Extraction Methods
- Review of Product, Processing, and Analytical Considerations

Solvent Profiles Include:

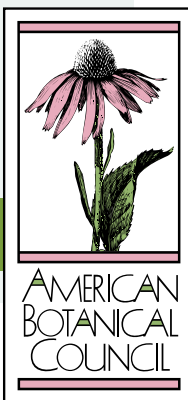
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algae single supplements in the same category; combinations of the two may also be represented), aloe vera (+17.7%), and chia seed/oil (a vegetable source of short-chain omega-3 fatty acids; +123.1%). Also showing significant sales in 2012 in the natural channel is maca, with a strong 40.0% increase from 2011.

Sales compiled by SPINS for the natural channel do not include herb supplement sales in Whole Foods Markets, the largest chain of natural food groceries in the United States. NBJ has estimated 6.1% growth for herb supplement sales in the total natural channel in 2012, with its estimates attempting to include sales at those natural retailers (e.g., Whole Foods) not included by SPINS. Some estimates suggest that sales of herbal dietary supplements in Whole Foods might constitute as much as 50% of the entire natural channel's sales, but such estimates are not confirmed. If these estimates are valid, sales for the *total* natural channel would be about 100% higher than those reported by SPINS in Table 4.

Direct Sales

Sales of herbal dietary supplements in the direct sales channel include multi-level marketing companies (aka network marketing companies, e.g., Advocare, Herbalife, Morinda Bioactives, Nature's Sunshine, Amway's Nutrilite, Pharmanex/NuSkin, Shaklee, USANA, and others), mail order and Internet sales companies (e.g., iHerb, Indiana Botanic Gardens, Swanson's, *et al.*), and healthcare practitioners. As shown in Table 1, further attesting to the overall robustness of the herbal supplement market in the past year, this segment experienced healthy growth of an estimated 6.3% at \$2,742,000, up from sales of \$2,578,000 in 2011 and \$2,469,000 in 2010.

As shown in Table 6, estimates for sales of single herbal dietary supplements in all channels of trade increased by 2.7% in 2012 over 2011, according to NBJ. This compares to a larger growth rate of 4.2% in 2011 over 2010. Sales of combination formulations (usually marketed for a specific function or benefit, e.g., maintaining normal cholesterol levels, normal blood sugar levels, urinary tract or prostate health, etc.) increased significantly by 10.8% in 2012 compared to 2011, continuing the upward trend noted in last year's report. HG

Reference

1. Blumenthal M, Lindstrom A, Ooyen C, Lynch ME. Herb supplement sales increase 4.5% in 2011. *HerbalGram*. 2012; 95:60-64.

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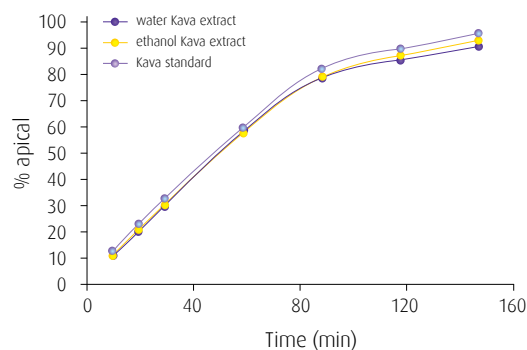
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- MediHerb invested in analytical research on the *in vitro* bioavailability of water versus ethanol extracts of Kava published in a peer-reviewed scientific journal, so health care professionals could have peace of mind in prescribing the new water based extract¹
- MediHerb has provided Kava tablets for several positive clinical trials and continues to work with researchers to better understand the therapeutic activity of Kava^{2-6*}

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**These statements have not been evaluated by the Food & Drug Administration. This product is not intended to diagnose, treat, cure or prevent any disease.*

1. A. Matthias et al. *J Clin Pharm Ther* 2007; **32**: 233-239 | 2. Sarris J, Stough C, Bousman CA et al. *J Clin Psychopharmacol* In Press | 3. Sarris J, Kavanagh DJ, Byrne G et al. *Psychopharmacology* 2009; **205**(3): 399-407 | 4. Sarris J, Adams J, Kavanagh DJ. *Aust J Med Herb* 2010; **22**(1): 12-16 | 5. Sarris J, Stough C, Teschke R et al. *Phytother Res* In Press | 6. Sarris J, Laporte E, Scholey A et al. *Traffic Inj Prev* 2013; **14**(1): 13-17

Botanical New Drug Applications – The Final Frontier

By Freddie Ann Hoffman, MD and Steven R. Kishter, MD, DDS

Marketing botanical ingredients as foods and dietary ingredients in the United States is commonplace. Getting them approved as prescription drugs is a somewhat new frontier, and so far only two botanicals have achieved this goal. On October 31, 2006, the US Food and Drug Administration (FDA) approved the first botanical drug, Veregen® (sinecatechins; ointment, 15%; Medigene, Planegg/Martinsried, Germany), a proprietary extract of green tea (*Camellia sinensis* Kuntze, Theaceae)* for treating genital and perianal warts.¹ FDA approved the second botanical New Drug Application (NDA) on December 31, 2012, for Fulyzaq™ (crofelemer; 125 mg tablet; Salix Pharmaceuticals; Raleigh, North Carolina), the first oral prescription botanical drug for the novel indication of HIV-associated diarrhea. Fulyzaq is a proprietary extract of the blood-red latex of the South American croton tree (*Croton lechleri* Müll Arg, Euphorbiaceae).^{2,3}

Defining “Botanical Drug”

FDA defines a “botanical” as a finished product containing ingredients and/or constituents of vegetable matter. This classification includes whole plants or plant parts — including plant materials such as juices, gums, fatty oils, scent oils, etc. — and also includes algae or macroscopic fungi and similar products. Excluded are fermentation products, isolated and purified ingredients, or homeopathic ingredients, all of which already have well-described drug regulatory pathways in the United States.⁴

Because both Fulyzaq and Veregen are intended to diagnose, treat, prevent, mitigate, or cure an abnormal condition, they are considered “drugs.” In particular, they are “new” drugs, i.e., drugs marketed in the United States after 1938 that prior to approval were “not generally recognized as safe and effective under the conditions prescribed, recommended, or suggested in the labeling.”⁵ As new drugs, the sponsors were required to submit NDAs for FDA pre-market approval. Each product underwent extensive product and clinical development to meet the drug requirements and to document safety and efficacy for its intended use(s). Unlike foods, dietary supplements, or cosmetic products, which are restricted from making disease claims, these botanical drugs can make disease claims that are supported by their approved NDAs. Both products are available only by prescription.

Initial Steps: Investigational New Drug (IND) Application

Botanical drug development begins long before FDA’s review process. A botanical must undergo identification and taxonomic classification. Raw material sourcing as well as collection, manufacturing, and formulation practices must be described adequately. Details of any prior and current human use also are important to obtain, as such information can significantly impact the regulatory requirements.⁴

After these critical steps, filing an Investigational New Drug (IND) application with FDA is the first part of the formal drug regulatory process that culminates with FDA’s decision on the NDA. An IND exempts the “investigational new drug” from federal requirements that it must be *safe* and *effective*, allowing for research and development activities to take place within US borders.⁶

Following an initial submission, FDA has 30 calendar days to review the IND. For early (Phase 1) clinical development, FDA focuses on the drug’s safety, which is based on its chemistry, toxicity profile, and use history. Novel chemicals submitted under IND require extensive nonclinical toxicology work, even for Phase 1. A botanical drug with a well-documented history of human use can often circumvent much of the toxicology requirements, at least initially, although some safety testing is generally required.⁴

Ultimate Step: New Drug Application (NDA)

Because new drugs must undergo FDA pre-market approval, NDA submission is the ultimate step in the development process.⁷ The NDA is a collation of data and analyses collected under the IND, a summary of which will become the drug package insert to support drug labeling and promotion. Requesting a “pre-NDA” meeting with FDA helps drug sponsors ascertain whether FDA agrees with their marketing proposals. FDA expects to meet with the NDA sponsor to discuss the content and format of the application prior to its submission, as well as any unresolved issues raised during the IND, and any further requirements for potential approval. This may include completion of nonclinical testing, pivotal trials analyses, and submission of key clinical study databases for FDA’s own review and analysis. The sponsor also will need to submit the status of any unexpired patents for the drug.⁸ FDA even has final say over the drug’s brand and scientific (“generic”) names.⁹

**HerbalGram* does not customarily refer to herbs by binomial and authority, but by the Latin binomial and family name listed in the American Herbal Products Association’s *Herbs Of Commerce*, 2nd edition. In this instance, the authors preferred to note the authority in the scientific name because for a drug, FDA insists on both the Latin binomial and authority.

†The term *pivotal study* refers to an adequate and well-controlled clinical trial designed to evaluate the specific dose, route, schedule, formulation, and specific clinical indication that will become the subject of the NDA. In particular, the drug product used for a pivotal study should meet FDA requirements for commercial manufacturing (Good Manufacturing Practices or GMPs).

The most important step of the process and, for botanicals, the most difficult step to satisfy, is FDA's review and acceptance of the chemistry, manufacturing, and controls (CMC). At the initial development stages (Phase 1 and early Phase 2), CMC requirements are relaxed. For example, FDA often allows the current nondrug formulation to be used in early phase studies. To support the NDA, however, later-stage (*i.e.*, Phase 2b and pivotal[†]) clinical studies must be conducted using finished drug product that conforms to pharmaceutical requirements (Good Manufacturing Practices). FDA also will want to review and negotiate the sponsor's plans for commercialization, including manufacturing scale-up, packaging, and lot-release protocols to be utilized in the commercial production of the drug following approval. Finally, the sponsor must be prepared for FDA to conduct a pre-approval inspection of the manufacturing facilities.

NDA Approval Requirements

FDA can approve the NDA when the drug meets the legal requirements discussed herein. Federal law requires that a new drug be safe and effective for its intended use, as demonstrated by *substantial evidence*, defined as "evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved." Additionally, data from the substantial evidence demonstration must show that the "drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling..."⁵ Control over the drug's lot-to-lot variation also must be adequately addressed.⁷

Botanical drug approval is a very different process from acceptance of the same ingredient as a non-drug. For example, foods and dietary supplements are allowed to be marketed if they are food ingredients or ingredients that are "generally recognized as safe" (GRAS), or contain ingredients with "a history of use or other evidence of safety" that "will reasonably be expected to be safe..."⁵ In contrast, a drug must demonstrate that its benefits outweigh its risks to the population for which its use is intended.

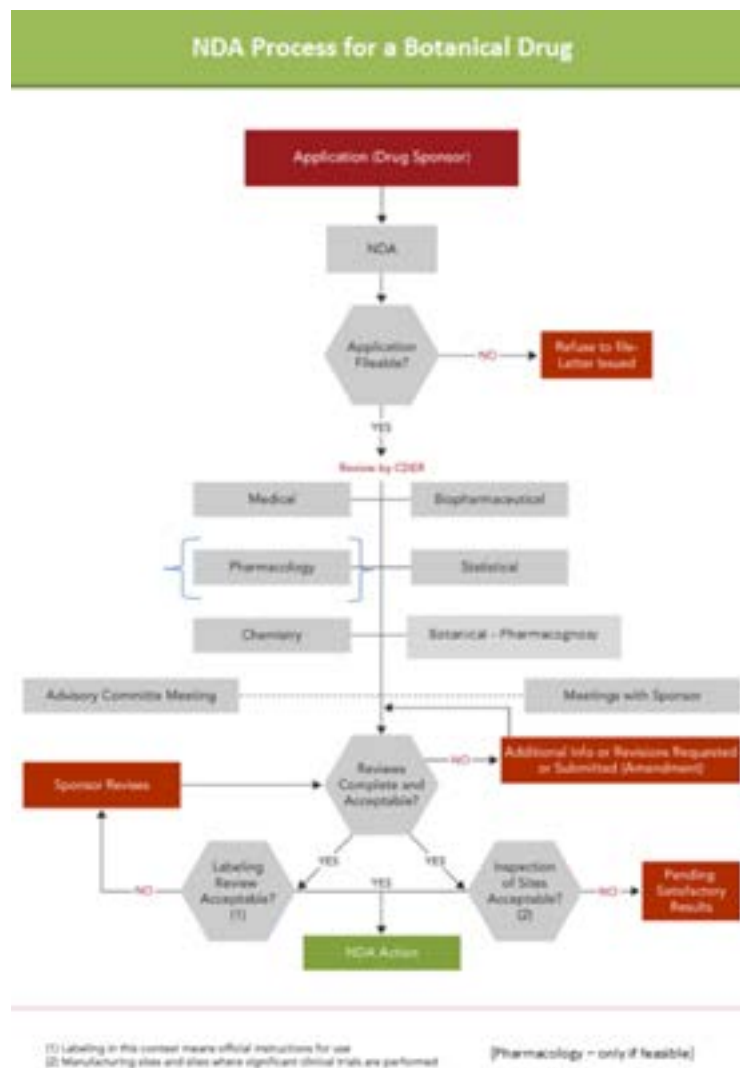
NDA Review Timeline and the "Prescription Drug User Fee Act" (PDUFA)

FDA's timelines for NDA reviews are guided by the current Prescription Drug User Fee Act (PDUFA). Originally enacted in 1992 by the US Congress to reduce lengthy NDA review times, PDUFA authorizes FDA to collect fees from sponsors whose applications require

Agency review. PDUFA fees support the Agency's review processes by allowing the hiring of experts and other activities. No fees are required if the NDA sponsor and/or product fits one or more of the following scenarios: first-time filer, product for a rare disease or condition under an Orphan Product Designation, product deemed necessary to protect the US public health, product for which user fees will pose a significant barrier to innovation due to limited resources or other circumstances, or a sponsor that is a small business (<500 employees) that does not yet have an approved drug on the US market.¹⁰

Upon receipt of an NDA, FDA has 60 days to review and accept it for filing. Incomplete or poorly organized applications can result in a "failure to file" notice. FDA's review "clock" does not start until the Agency allows the NDA to be filed (referred to as the "acceptance to file" notification; see Figure 1). Once the NDA is filed, the

Figure 1.



Adapted from: NDA Review Process (www.fda.gov/cder/handbook/)

Agency sets a goal (PDUFA) date — the date by which FDA should act on the application (see Table 1 on page 68).

FDA can modify the review timeline. It can hold the clock while waiting for a response to its request for information. Or, the timeline can be condensed when FDA assigns “Priority Review” to NDAs for drugs intended to treat a serious and life-threatening condition lacking satisfactory treatments. FDA also can utilize an “Accelerated Approval” process to decide on a drug prior to receiving all safety or efficacy data needed for approval. Although a drug can be marketed following Accelerated Approval, its sponsor will be required to collect and to submit additional efficacy and safety data at a later time for FDA to determine if the drug should remain on the market. If these data do not continue to support the drug’s safety or efficacy, FDA can revoke the approval.¹¹

On July 9, 2012, President Obama signed into law the fifth reauthorization of the Prescription Drug User Fee Act. Known as “PDUFA V,” the new law took effect on October 1, 2012. It includes the following timeframes used by FDA to project a calendar day (called the “PDUFA date”) — a goal, but *not a deadline* — by which it plans to return a decision, following the Agency’s review of the various types of marketing applications.

Botanical Drug Approvals

More than 500 pre-IND meetings and IND applications have been submitted to FDA for botanical drugs; two botanical drug NDAs have been submitted to FDA and both were approved. While it appears that many sponsors have accomplished the IND step, only two have reached the final NDA step. Why are there only two FDA-approved NDAs? Based on these authors’ experience, the following represent three of the most common reasons that could explain why more botanical drug NDAs have not been submitted to FDA for review:

- **Failure to show efficacy:** Failure to show clinically relevant and statistically significant efficacy is the single most common reason why most drugs — not just botanical drugs — fail to reach the NDA step. Although many sponsors “believe” that their product “works,” the stringent criteria for US drug approval consist of documented safety and efficacy from one or more multicenter “adequate and well-controlled” clinical studies. For pivotal studies (those efficacy studies that will be used to support

the NDA), it is very important that target populations be well-circumscribed by the protocol eligibility criteria, with appropriate and FDA agreed-upon outcome measures, proper controls (*e.g.*, placebo or active treatment), and be well-monitored and accurately analyzed.

- **Unrealistic Expectations:** Inexperienced drug sponsors often have unrealistic expectations when it comes to planning and executing a drug development program. This may be due, in part, to FDA’s relatively relaxed requirements during initial stages of IND development, which may give sponsors a false sense of security that the requirements for botanicals are less rigorous than those for non-botanical drugs. It also may be due to the fact that regulatory requirements for botanicals are not internationally harmonized, as they are for other drug categories, which creates confusion, because US requirements differ from those of other countries. Also, many botanical drug sponsors have never developed a drug for the US market, or come from different industries or regulatory environments. Some sponsors are unwilling to accept — or simply deny — that the United States requires submission of “raw” data (chemistry, nonclinical safety testing, clinical study databases, etc.) to

Table 1. FDA Review Timelines (under PDUFA V) for review of New Drug Applications (NDAs) and Biologic Licensing Applications (BLAs)

Submission Type	Approximate Timeframe (from receipt date to PDUFA date)	
	Standard Review Assignment	Priority Review Assignment
New Molecular Entity (NME) NDA and Original BLA	60-day filing period plus 10-month review = ~ 12 months	60-day filing period plus 6-month review = ~ 8 months
Non-NME NDA	10 months	6 months
Class 1 Resubmissions*	2 months	2 months
Class 2 Resubmissions*	6 months	6 months
Original NDA/BLA Efficacy Supplements	10 months	6 months
Class 1 Resubmitted Efficacy Supplements*	2 months	2 months
Class 2 Resubmitted Efficacy Supplements*	6 months	6 months
Manufacturing Supplements		
Prior Approval	4 months	
All others	6 months	

* Resubmissions of an NDA or BLA are classified by the information provided by the Sponsor to an FDA Action letter. These are further defined in *FDA Guidance for Industry — Classifying Resubmissions in Response to Action Letters* — April 1998. [Editor’s note: A delay in the PDUFA “goal” timeline can arise from any of the scientific or regulatory areas that are required for review (chemistry, nonclinical, clinical data, name selection, facility audits, negotiations on the package insert, etc.), as discussed above. (www.fda.gov/Drugs/ResourcesForYou/Consumers/ucm289601.htm)]

support drug filings, rather than data summaries or “expert” opinion, as is commonplace in other countries.

- **Insufficient Funding:** Lack of or insufficient funding to complete the development process is not an uncommon problem for many botanical drugs under IND. This may be due to the economic climate, lack of acceptance by the investment community, lack of patent status (although the product may enjoy other forms of intellectual property that may be superior to patents), or insufficient planning. Again, many botanical drug sponsors, particularly those whose products are in other market channels (*e.g.*, dietary supplements) or foreign markets, underestimate the level of documentation and data that FDA requires to assess that a drug does what it claims to do in its labeling.

Conclusion

For many botanical drugs, the path to NDA approval has the potential to be shorter and less costly than for “standard” new chemical entities. However, until the botanical community comes to grips with the realities of the legal requirements for drug approval in the United States, there will continue to be few sponsors that are able to traverse this final frontier. HG

References

1. FDA approves special green tea extract as a new topical drug for genital warts [press release]. Austin, TX: American Botanical Council; November 9, 2006. Available at: <http://cms.herbalgram.org/press/gthpv.html>. Accessed April 30, 2013.
2. FDA approves first anti-diarrheal drug for HIV/AIDS patients [press release]. Silver Spring, MD: US Food and Drug Administration; December 31, 2012. Available at: www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm333701.htm. Accessed April 30, 2013.
3. FDA approves crofelemer as first-ever oral botanical drug [press release]. Austin, TX: American Botanical Council; January 2, 2013. Available at: http://cms.herbalgram.org/press/2013/FDA_Approves_Crofelemer.html. Accessed April 30, 2013.
4. Guidance for Industry on Botanical Drugs Products. US Department of Health and Human Services. US Food and Drug Administration, Center for Drug Evaluation and Research. June 2004. Available at: www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070491.pdf. Accessed April 30, 2013.
5. Federal Food, Drug and Cosmetic Act and its Amendments, 21 USC Chapter 9 §§ 301–399f.
6. Investigational New Drug application. US Food and Drug Administration website. Available at: www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/default.htm. Accessed April 30, 2013.
7. New Drug Application. US Food and Drug Administration website. Available at: www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/NewDrugApplicationNDA/default.htm. Accessed April 30, 2013.
8. Applications For FDA Approval To Market A New Drug. Title 21 CFR §314.50.
9. Guidance for Industry: Contents of a Complete Submission for the Evaluation of Proprietary Names. US Department of Health and Human Services. Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER). February 2010. Available at: www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075068.pdf. Accessed April 30, 2013.
10. Prescription Drug User Fee Act (PDUFA). US Food and Drug Administration website. Available at: www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/default.htm. Accessed April 30, 2013.
11. FDA Commissioner removes breast cancer indication from Avastin label [news release]. Silver Spring, MD: US Food and Drug Administration; November 18, 2011. Available at: www.fda.gov/NewsEvents/Newsroom/ucm279485.htm. Accessed April 30, 2013.

We're taking a (super)critical look at extract quality



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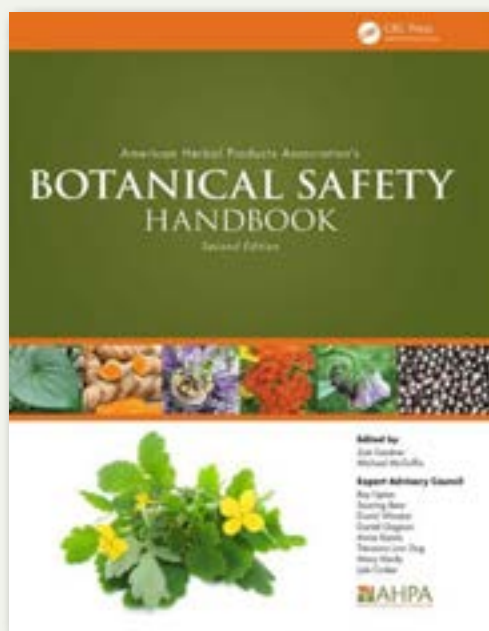


American Herbal Products Association's Botanical Safety Handbook, 2nd edition, edited by Zoë Gardner and Michael McGuffin. Boca Raton, FL: CRC Press, Taylor & Francis Group; 2013. Hardcover, 1042 pages. ISBN: 978-1-4665-1694-6. \$119.95.

Having often referred to the first edition of this book since its publication in 1997, I have long anticipated examining an upgraded second edition. I was pleased to find that the revised content included input from a highly qualified expert advisory council consisting of Roy Upton, Soaring Bear, PhD, David Winston, RH (AHG), Daniel Gagnon, Aviva Jill Romm, MD, Tieraona Low Dog, MD, Mary Hardy, MD, and Lyle Craker, PhD. The vastly expanded content provides safety information on more than 550 species of herbs and includes new herbs, many from the Ayurvedic tradition. (A few Western herbs deserving of inclusion have been overlooked, such as *Rhodiola rosea*, Crassulaceae] and olive [*Olea europaea*, Oleaceae].) This advanced edition relies extensively on primary literature sources and includes research on potential interactions with drugs and selected dietary supplements. Consequently, based on weight alone, it seems to have outgrown its designation as a "handbook."

This edition is again centered on classifying herbs by assigning each to a Safety Class; some first edition assignments have been changed after further research and reassessments. Class 1 includes herbs that can be safely consumed when appropriately used. Class 2 herbs are for those with certain restrictions, such as for external use, not to be used in pregnancy or when nursing, or other specific restrictions. A standard dose is provided for those herbs which carry a warning on excessive dosage. Class 3 herbs are only to be used under the supervision of a qualified expert, so a standard dose has not been specified for these most potent herbs such as Sichuan aconite (*Aconitum carmichaelii*, Ranunculaceae) or belladonna (*Atropa belladonna*, Solanaceae), though one is given for *Stillingia sylvatica*, Euphorbiaceae). The literature-referenced content has been greatly enlarged to supply a quick summary and an expanded review of the literature in support of these classifications, which are intended to provide evidence-based and easy-to-interpret information to healthcare practitioners, herbal supplement manufacturers, and retailers.

Each herb is also designated an Interaction Class in this edition. For Class A herbs, no clinically relevant interaction should be expected due to a lack of pertinent evidence. Class B includes those for which clinically relevant interactions are plausible, based on human or animal studies,



multiple case reports, and/or *in vitro* studies demonstrating biologically plausible mechanisms. Class C herbs have known clinically relevant interactions as evidenced by human pharmacological studies and/or case reports with probable causality.

One book cannot cover everything in detail. Certain considerations have been intentionally excluded from the assessment of herb safety, including excessive consumption and those toxicity concerns based solely on isolated constituents or from intravenous or intraperitoneal injections. The safety assessments do not include either Chinese or Ayurvedic traditional contraindications unless they can be interpreted in a biomedical context. Individual sensitivities

such as gastrointestinal, idiosyncratic, and allergic reactions (outside of the Asteraceae family), and contact dermatitis generally are not included.

Other items not covered include certain types of herbs and products including little-used plants of known toxicity (a number of these herbs in the first edition have been eliminated), homeopathic preparations, essential oils (except peppermint [*Mentha x piperita*, Lamiaceae] and European pennyroyal [*M. pulegium*]), products with chemical (even inherent phytochemical) additives, or those that have been compromised by contamination or adulteration. Isolated components whose presence impacts the safety of an herb are typically identified in a Notice. Nonetheless, in certain cases, such as artemisinin in sweet wormwood (*Artemisia annua*, Asteraceae), or hydroquinone derived from the arbutin in uva-ursi (*Arctostaphylos uva-ursi*, Ericaceae), pharmacological and toxicological studies on an isolate have been incorporated to help describe the potential effect of the herb. It is also beyond the scope of this text to consistently distinguish between the relative safeties of different preparations from the same plant.

The Appendices form a valuable feature in this edition, as they did in the first. Aristolochic acid and the herbs containing it have been eliminated as banned substances from Appendix 1, Herbal Constituent Profiles, and from the main text, respectively. However, several other original entries were removed without explanation from the second edition, including cardiac glycosides, lectins, and oxalates. As a result, some valuable information is missing, such as a useful overview of cardiac glycosides found in the Class 3 herbs *Apocynum* spp. (Apocynaceae), lily-of-the-valley (*Convallaria majalis*, Liliaceae), and *Digitalis* spp. (Scrophulariaceae). None of these three herb entries provide as much appropriate detail, and all seem inadequate in regard to potential interactions which for Class B *Conval-*

laria and Class C *Digitalis* are described simply as “the same as those for digoxin and other digitalis glycosides.” In Appendix 2, Herbal Action Profiles — though Diuretics has been added — GI Irritants and Monoamine Oxidase Interaction categories have been removed. The Nervous System Stimulants category is now included in Appendix 1 as Caffeine, following the elimination of banned *Ephedra* species from the text.

The new Appendix 3, Herbal Interaction Profiles, provides a simple but instructive two-page summary on pharmacokinetic interactions with drugs co-authored by a leading researcher and authority on the subject, Bill Gurley, PhD. While this excellent overview sets the stage, the main actors are missing. Aside from sections on mucilages and piperine, the absence of summary lists categorizing the mechanisms of herbs from the text with a Class B and Class C designation is perplexing. This would have been a useful and valuable addition to this appendix. Similarly, the exceptional discussion by Dr. Romm, in the new Appendix 4, Botanicals in Pregnancy and Lactation, could have been enhanced somewhat for several properties covered (teratogens and mutagens, phytoestrogens, nervous system stimulants or depressants) with simple summary listings identifying those herbs that have these properties and identified in the text as contraindicated in pregnancy (as was done with Abortifacients and Emmenagogues/Uterine Stimulants in Appendix 2). Appendix 5 (formerly Appendix 3) provides lists of

all herbs in Safety Classes 2a, 2b, 2c, and 3 and Interaction Classes B and C.

As an expert consensus on currently available data, these herb evaluations constitute a very valuable resource for anyone with an interest in understanding the safe use of therapeutic botanicals. Though other experts may take issue with certain assessments or particular conclusions, the referenced information supplied provides a sound framework to support the evaluations and rationales. There remains a need for updating scientific content as data expands, *e.g.*, as from a 2010 study that found a 21.6% increased frequency for both threatened miscarriages and preterm labors in pregnant women when chamomile (*Matricaria recutita*, syn. *M. chamomilla*, Asteraceae) was used regularly.¹ While the content for Class 3 herbs and some appendices could be fleshed-out, overall this book fills an essential niche by intelligently addressing specific practical issues in the broad context of botanical safety concerns. I certainly will be referring to it regularly. HG

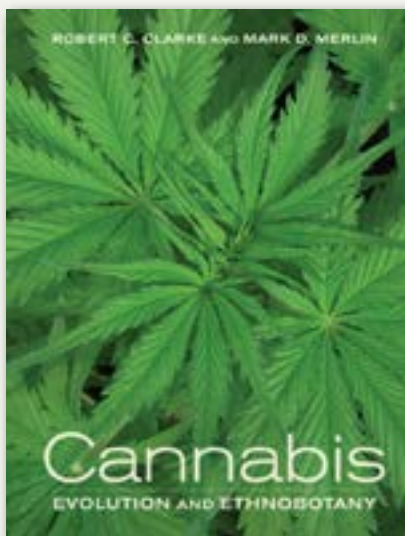
—Francis Brinker, ND
Author and editor
Tucson, AZ

Reference

1. Cuzzolin L, Francini-Pesenti F, Verlato G, et al. Use of herbal products among 392 Italian pregnant women: focus on pregnancy outcome. *Pharmacoepidemiol Drug Safety*. 2010;19:1151-1158.

Cannabis: Evolution and Ethnobotany by Robert C. Clarke and Mark D. Merlin. Berkeley, CA: University of California Press; 2013. Hardcover; 452 pages. ISBN-13: 978-0520270480. \$95.00.

The authors of this impressive book are well known to avid followers of cannabis (Cannabaceae) literature. Rob Clarke penned the popular books *Marijuana Botany* (Ronin Publishing, Inc., 1981) and *Hashish!* (Red Eye Press, 1998). He also was one of the principals of HortaPharm, the company in Amsterdam responsible for many key advances in selective breeding of novel cannabis chemovars in the 1990s. In the interim, he has extensively traveled the Eurasian continent to document ethnobotanical uses of cannabis as medicine, food, and fiber. Mark Merlin is a professor of botany at the University of Hawaii at Manoa, who wrote *Man and Marijuana: Some Aspects of Their Ancient Relationship* (Fairleigh Dickinson University Press, 1972), and who is an expert on ancient psychoactive plants as well as the botany of Oceania, as attested by his co-authorship of the excellent *Kava: The Pacific Elixir* (Healing Arts Press, 1997).



This eminently qualified pair has engaged in an ambitious project to summarize and analyze the voluminous literature from disparate sources on cannabis, and bring to the reader a better understanding of its origins and uses, as well as its relationship with man, its chief exploiter and manipulator. The title accurately conveys the focus of the book. Beyond any controversy, this plant is of great economic, ecological, social, and medical importance. Thus, the subject matter is timely and important. The book is unique in both its profound depth and wide scope.

It begins with a dedication to Richard Evans Schultes, PhD, the eminent Harvard University professor and 20th century Father of Ethnobotany, citing his ideals of ecology and human kinship with plants coupled with a cultural sensitivity to the various peoples under study, and an appreciation for their diverse spirituality and cosmology. This book is aptly written in the same spirit.

Although the book necessarily reviews a wealth of previous sources, it successfully bridges the gaps and suggests new and different ways to integrate the material through well-considered theories and approaches. Through care-

ful documentation of the world's writings on cannabis, the plant's archeology, and its countless names in dozens of cultures, the authors are able to synthesize the material through critical analysis. The interested scholar would need to read hundreds of articles and book chapters, many distinctly rare and inaccessible, to attempt to reproduce the material included. The authors' collective experience in the subject makes them uniquely qualified to interpret the material in a coherent and palatable form. The result is an eminently viable tome that is compelling in its exhaustive treatment of the material, as well as its accuracy. Its length may prove challenging to the casual reader, but will prove essential to the dedicated student of the subject who will find those very qualities attractive and rewarding. It is a worthy successor to, and a notable expansion on, Rubin's *Cannabis and Culture* (De Gruyter Mouton, 1975). It will definitely serve well as a reference work; in fact, it is difficult to imagine an equal resource on the subject matter.

The text is extremely well written, and is supplemented by excellent graphic matter, including tables, chronologies, full-color maps, and photography documenting cannabis morphology, the plant as grown *in situ*, and its use by man, whether as an artisanal raw material, ritual object, or foodstuff.

It is unusual to examine a book of this depth that is not an edited multi-author work. The advantage is a high level of consistency and coherence of the narrative. Inasmuch as I was privileged to see this book in its embryonic stages before acceptance by the University of California Press, I am able to emphasize this point: While a previous version of the manuscript suffered from some redundancy and challenges in its organization, those problems have been gratifyingly resolved. The remaining repetitions and other issues are few. Certain terms are defined in an ongoing fashion, and while this may be helpful to those of us who forget their meaning along the way, an alternative approach would have been to consider addition of a glossary of terms, particularly for the less familiar botanical jargon. While the sections on medical usage are comparatively weaker than the others, this is wholly acceptable given the title, scope, and intended focus of the book. This tome will be a perfect complement to upcoming titles focusing on medicinal usage of cannabis, such as Roger Pertwee's edited work, *Handbook of Cannabis* from Oxford University Press, and the cannabis monograph from the American Herbal Pharmacopoeia.

Other controversies will be evident in the book, as the subject of cannabis is never too far from debate. One notable area of contention will be the authors' viewpoints on cannabis taxonomy, a dialogue that has been ongoing since Linnaeus and Lamarck faced off on the matter in the 18th century. While many geneticists and taxonomists, such as Ernest Small, have championed the concept of a single cannabis species, citing the ability of all strains to interbreed, this criterion is curious to many of us. If sufficient as a sole factor, then one would have to accept that all the hundreds of neotropical Gesneriaceae (Afri-

can violet family) plants are of one species, as virtually all hybridizations produce fertile seed. Rather, Clarke and Merlin have adopted the view of their mentor, Professor Schultes, in the assignation of multiple species or forms of cannabis. They have concentrated on different origins for morphological variants of cannabis named Putative Ancestor, Narrow-Leaf Hemp, Narrow-Leaf Drug, Broad-Leaf Hemp, and Broad-Leaf Drug, based on chemotaxonomy recently advanced by Karl Hillig¹⁻⁴ and summarized by this author.⁵ The species debate will continue in all likelihood, since a true consensus on such matters is always an evanescent goal in the discipline of botany. In the interim, the authors' formulation presents a practical alternative to classify *Cannabis* according to geographical origins, chemical contents, morphology, and purpose of use. It remains of paramount importance to avoid the pitfall of assuming chemical attributes or psychotropic effects based merely on plant shape or size inherent in the current "sativa" and "indica" monikers popular on the street.

Numerous additional questions remain. How much have humans affected the evolution of cannabis? Do we need to consider the inverse? Does feral cannabis yet exist in the wild? These and countless other issues are weighed and considered in the text. What will certainly be evident to any reader will be the astounding versatility of this plant, which has been characterized as not only a phytochemical factory with a breathtaking breadth of therapeutic potential, but additionally, a foodstuff in its seed composed of high-quality protein and essential fatty acids, a fiber to clothe and insulate, a bait for fish, and a potential organic herbicide and antibiotic. These uses are examined country by country, and culture by culture.

Ritual and psychoactive use of cannabis is appropriately examined throughout the book, from ancient times onward. While cannabis' usage as a psychotropic or recreational agent garners most of the headlines, the book devotes well-deserved attention to hemp and its husbandry, examining its use as fiber for clothing and paper. Culinary applications are not forgotten either, as we learn of a triple-use plant from Nepal that is utilized medicinally, for clothing, and whose seed provides a tasty chortney/chutney, the recipe for which was previously published.⁶

Readers will be fascinated by discussions of how cannabis became a key component of Japanese Shinto rites, but is now distinctly rare in that country due to the insertion of the *Taima Torishimari Ho*, or Hemp Control Act, into the Japanese constitution after World War II. The threats to this herb have not merely been political, as it also has been the object of research on its eradication via *Fusarium oxysporum* fungi. Additional topics of interest include the following: hypotheses of cannabis evolution based on patterns of glaciation vs. human peregrinations, the history of hemp and fishing, hemp and hanging, and its usage in the belts worn by sumo wrestling champions. In short, this is a book that guarantees the reader will become a top contender in any cannabis trivia contest.

Cannabis: Evolution and Ethnobotany will appeal to students, scholars, and open-minded policymakers. As a potential undergraduate university textbook, an enlightened instructor and indulgent faculty with abundant backbone would be necessary. It also would be a useful addition to curricula in botany, phytochemistry, pharmacognosy, genetics, medical history, etc. To the graduate student or post-doctoral fellow in these disciplines, it should be required reading. In short, this is a superlative work on a most complex and fascinating botanical subject. HG

—Ethan Russo, MD
Senior Medical Advisor
GW Pharmaceuticals Group
Wiltshire, UK

References

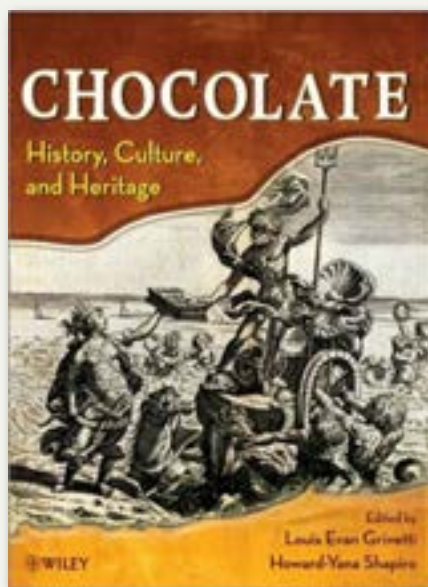
1. Hillig KW. Genetic evidence for speciation in *Cannabis* (Cannabaceae). *Genetic Resources and Crop Evolution*. 2005;52:161-80.
2. Hillig KW. A chemotaxonomic analysis of terpenoid variation in *Cannabis*. *Biochemical Systematics and Ecology*. 2004;32:875-91.
3. Hillig KW. A combined analysis of agronomic traits and allozyme allele frequencies for 69 *Cannabis* accessions. *Journal of Industrial Hemp*. 2005;10(1):17-30.
4. Hillig KW, Mahlberg PG. A chemotaxonomic analysis of cannabinoid variation in *Cannabis* (Cannabaceae). *American Journal of Botany*. 2004;91(6):966-75.
5. Russo EB. History of *Cannabis* and its preparations in saga, science and sobriquet. *Chemistry & Biodiversity*. 2007;4(8):2624-48.
6. Clarke RC. Traditional *Cannabis* cultivation in Darchula District, Nepal- seed, resin and textiles. *Journal of Industrial Hemp*. 2007;12(2):19-42.

Chocolate: History, Culture, and Heritage edited by Louis Evan Grivetti and Howard-Yana Shapiro. Hoboken, NJ: John Wiley & Sons; 2009. Hardcover; 975 pages. ISBN: 978-0-470-12165-8. \$103.95.

Such is the power of chocolate (*Theobroma cacao*, Sterculiaceae) to elicit our passions and emotions that, as it traveled through time and our human story, it left a profound and indelible imprint on many cultures and religions. *Chocolate: History, Culture, and Heritage* is an extensive work that documents chocolate's multiple roles throughout history by exploring source material in a methodical and detailed fashion.

This edition was compiled over a decade (1998–2009) by the Chocolate History Group of the University of California – Davis, and supported by Mars, Incorporated, a global manufacturer of confections, including chocolate. The group gathered together original texts from pre-Columbian America, early America, and Europe, exploring the development of chocolate in culinary and medicinal traditions. Much of the research was done with archive and library research, as well as fieldwork in Cuba, the Dominican Republic, and other important cacao-producing Central American countries. It also documents cacao's journey in the United States, where a significant amount of the world's chocolate is manufactured and consumed.

At 975 pages, it is a comprehensive compilation of facts gathered from pre-historic Mayan pottery and codices, handwritten Hispanic-era documents and letters, and translations from Spanish into French and Portu-



guese that chart cacao's trade routes. Port records and account ledgers were perused and examples of Chinese menus, advertising billboards, local advertisements, and early accounts of manufacturing techniques that describe its global reach and how it was utilized. The chapters on *chocolatières* and other chocolate accoutrements describe chocolate's adoption into French aristocratic circles during the reign of Louis XIV, assuring its prestige as a luxury and highly desirable beverage. Later, diaries and military records examined the use of chocolate and its specialized vessels during the American Civil War.

For this extensive work, many specialists and scholars dedicated their expertise to the project; paleographers helped to properly interpret nuances of early texts in a variety of languages. One-hundred-and-fifteen professionals — experts in agronomy, anthropology, archeology, biochemistry, dietetics, economy, genetics and plant breeding, statistics, nutrition, and many more — lent their skills and time to produce reliable information on the social, religious, culinary, and medicinal history of chocolate.

The Chocolate History Group chose early on “not to produce an integrated global history of chocolate,” which would have required an even more monumental effort to produce several thousand pages. The group believed that the information would have been out of date before it could be published as the story of chocolate is ever unfolding. Rather, the group chose a thematic approach to reveal “the sustained importance of chocolate through the millennia.”

For culinary historians and food scientists interested in the culinary and medicinal aspects of chocolate, the book includes recipes divided into four categories by chronology and geography: pre-Columbian era, early New Spain, 18th and 19th century New Spain/Mexico and Europe, and 18th century North America. Of interest is how the consumption of chocolate evolved from eating the raw beans in their cottony pulp to roasting or toasting the beans and making a drink that was used by healers to treat infections, severe cough and phlegm, and to reduce fevers and bloody dysentery. The chapters on chocolate recipes describe how cacao beans developed as a drink with the Spaniards who introduced one of the first instruments to froth the beverage — a stirring rod called a *molinillo* — which is still in use today. Spices were added over the centuries to enhance the flavor of the beverage and original texts translated into English from original French and Spanish manuscripts describe chocolate's journey as the beverage gained popularity throughout Europe in the 16th through the 18th centuries, and in North America during the 19th century. As noted in many recipes, while the flavor of the drink improved as more ingredients were added, chocolate never lost its medicinal cachet. The Swedish naturalist Carl von Linné, who is responsible for giving the cacao tree its Latin binomial, *Theobroma cacao* (*Theobroma* means “food of the gods” in Greek), reportedly said that the brew cured him of his hemorrhoids. In effect, the chapter concludes that it is difficult to separate the health and pleasurable aspects of chocolate. Chocolate has always had a dual purpose as food and medicine.

Early American cookbooks from the 18th and 19th centuries continued to emphasize the medicinal benefits of chocolate in what sociologists call their “cultural context,” as various immigrant groups imposed their customs, which reflected medicinal, culinary, sexual, and moral influences.

Chocolate-making has greatly changed since pre-Columbian times and never in its history has it been available to so many people and in so many forms as it

is presently. The evolution of chocolate manufacturing is reported in great detail, with illustrations of the tools, roasters, butter presses, and mills used to mechanize and refine the making of the chocolate as we know it today.

Nutritionists and dieticians, holistic and alternative care practitioners will find interest in the chapter on “Twenty-First Century Attitudes and Behaviors Regarding the Medicinal Use of Chocolate.” While food as medicine fell out of favor in the first half of the 20th century, there is a movement in the 21st century toward “functional foods.” Cacao's flavonols and other polyphenols are investigated, as are chocolate's “health promoting benefits,” particularly its cardiovascular functions. The results of a study conducted to discover American consumers' knowledge, attitudes, and behaviors toward chocolate as a health-promoting food may be of particular interest. The study's methods, analyses, and results are fully described as well as the present governmental views, definition, guidelines, and recommendations on “functional foods.” The chapter also delves into the adulterants and extenders found today in mass-produced chocolates.

Each chapter concludes with an acknowledgement of the individuals involved in the research on that section, with useful endnotes and several pages of references that may be utilized to pursue additional research.

Fifty-six chapters and 11 appendices, including 64 pages of illustrations, in this hefty five-and-a-half pound tome bring together a treasure trove of information on chocolate that should appeal to food historians, chocolate connoisseurs, artisans, writers, and researchers. As a reference guide, it is a masterful work, with new and previously unpublished information that will provide an unrivaled anthology of chocolate to study for years to come. HG

—Christine Raaphorst Roesch, MPC
Park City, UT

Functional Foods, Nutraceuticals, and Degenerative Disease Prevention edited by Gopinadhan Paliyath, Marica Bakovic, and Kalidas Shetty. Chichester, UK: Wiley Blackwell; 2011. Hardcover, 424 pages. ISBN: 978-0-8138-2453-6. \$199.95.

This book is a compilation of 15 chapters contributed by a number of scientists, mainly from Canada and the United States. It describes various so-called “functional foods” and nutraceuticals and their mechanisms of action in promoting health and reducing disease risk. The authors discuss in detail the biochemistry, molecular biology, and nutritional genomics along with relevant signal transduction and gene expression of the disease-preventive process, of a wide range of foods, herbal products, and spices. Each chapter is complemented with a current bibliography that

allows the reader to consult original sources of information in the book. Although regulation of functional foods and nutraceuticals has been mentioned, this is rather cursory in nature. What follows are detailed reviews of each chapter.

The first chapter, “Functional Foods, Nutraceuticals, and Disease Prevention: A Window to the Future of Health Promotion,” is written by two of the editors, Gopinadhan Paliyath, PhD, and Kalidas Shetty, PhD. While disease *prevention* might be an overly optimistic view, disease risk *reduction* is achievable. The contents describe the effects of lifestyle changes on health and socioeconomic burdens of chronic degenerative diseases. The authors also take the traditional route of recommending fruits and vegetables for promoting health.

Chapter 2, “Functional Foods and Nutraceuticals,” writ-

ten by Chung-Ja C. Jackson, PhD, and Dr. Paliyath, defines the terms and provides examples of functional foods that comprises a long list of plant-based materials, herbals, cereals, seeds, spices, herbal products, and certain fruits and vegetables as well as fish oils, wine, and dairy-based products. The bioactives responsible for health-promoting aspects of functional foods and their effects on specific conditions such as cardiovascular decline, cancer, type 2 diabetes, obesity, and Alzheimer's disease are also covered, and this section extends the discussion to the selected food categories noted above.

Chapter 3 focuses on nutritional genomics with respect to the "Fundamental Role of Diet in Chronic Disease Prevention and Control," and is written by Amy J. Tucker, PhD, Branden Deschambalt, and Marica Bakovic. It discusses nutrigenetics as well as complexities of research in this area for chronic diseases, with some emphasis on cardiovascular ailments and cancers, as well as the effects of phytochemicals — including phytoestrogens and polyphenols — and selected vitamins, carbohydrates, and lipids. The unique role of phytochemicals in nutritional genomics as therapeutic agents is emphasized.

Chapter 4, "Nutraceuticals and Antioxidant Function," is authored by Denise Young, Rong Tsao, PhD, and Yoshinori Mine, PhD. They discuss oxidative stress and the role of endogenous and exogenous reactive oxygen species. Defense against the deleterious effects of such events is covered in relation to antioxidative defense systems. Both endogenous antioxidant enzymes and exogenous dietary antioxidants such as polyphenols, amides, and carotenoids — and their mechanisms of action — are included. Assays related to antioxidant evolution, health benefits of antioxidants, and challenges experienced in the evaluation of antioxidants to demonstrate efficacy are thoroughly discussed. The section is well-referenced.

Chapter 5, "Composition and Chemistry of Functional Foods and Nutraceuticals: Influence on Bioaccessibility and Bioavailability," by Jissy K. Jacob and Dr. Paliyath, again covers polyphenols as antioxidants, but this time in relation to their bioaccessibility and bioavailability. This is an important topic that focuses on the amount/proportion of potentially absorbable forms of bioactives from the gastrointestinal tract and the amounts actually absorbed into the body, the latter being influenced considerably by the food matrix. Thus, the performance of micro- and ultrastructural analyses are vital; the role of dietary polyphenols with specific reference to juices and their role in health promotion is also covered.

The sixth chapter, "Cruciferous Vegetables – Derived

Isothiocyanates and Cancer Prevention," is written by Ravi P. Sahu, PhD, and Sanjay K. Srivastava, PhD. Glucosinolates or thioglucosides are broken down into isothiocyanates and related compounds upon the action of enzymes, and these broken-down products play an important role in the inhibition of different types of cancer. Specifically, this chapter covers cancers of the pancreas, prostate, brain, lung, breast, colon, liver, and bladder, plus ovaries, head and neck, skin, as well as multiple myeloma.

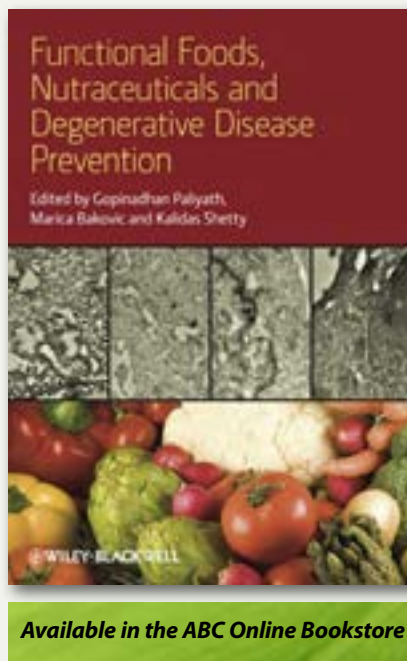
The seventh chapter is written by Rajeev Bhat, PhD,

and covers "The Disease-Prevention Potential of Some Popular and Underutilized Seeds." In particular, the authors discuss certain oilseeds such as those of black cumin (*Nigella sativa*, Ranunculaceae), sunflower (*Helianthus annuus*, Asteraceae), groundnut (*Apios americana*, Fabaceae), sesame (*Sesamum indicum*, Pedaliaceae), rapeseed (*Brassica napus*, Brassicaceae), safflower (*Carthamus tinctorius*, Asteraceae), and flax (*Linum usitatissimum*, Linaceae) along with spice seeds such as those of coriander (*Coriandrum sativum*, Apiaceae), caraway (*Carum carvi*, Apiaceae), black pepper (*Piper nigrum*, Piperaceae), cumin (*Cuminum cuminum*, Apiaceae), fenugreek (*Trigonella foenum-graecum*, Fabaceae), and legumes including soybeans (*Glycine max*, Fabaceae), tamarind (*Tamarindus indica*, Fabaceae), perilla (*Perilla frutescens*, Lamiaceae), chive (*Allium schoenoprasum*, Liliaceae), grape (*Vitis vinifera*, Vitaceae), pumpkin (*Cucur-*

bita maxima, Cucurbitaceae), and horse chestnut (*Aesculus hippocastanum*, Hippocastanaceae), among others. The chapter emphasizes the importance of identifying and characterizing various bioactives present in these source materials and provides a wealth of references.

In Chapter 8 covers the "Effects of Carotenoids and Retinoids on Immune-Mediated Chronic Inflammation in Inflammatory Bowel Disease," (IBD) and was written by Hua Zhang, Ming Fan, PhD, and Dr. Paliyath. The role of carotenoids in the downregulation of IBD is discussed with specific reference to their role in oxidation stress amelioration. Thus, intervention strategies using carotenoids and retinoids are recommended for reducing the symptoms of IBD and other inflammatory diseases.

The ninth chapter, "Ruminant Trans Fat as Potential Nutraceutical Components to Prevent Cancer and Cardiovascular Disease," is authored by Ye Wang, PhD, Catherine J. Field, PhD, and Spencer D. Proctor, PhD. Conjugated linoleic acid is present in milkfat and is made commercially for vegetable oils. Its role in modulating carcinogenesis has been thoroughly examined and its effect in reducing the incidences of coronary heart disease also has been covered



and is expected that they provide excellent opportunities that benefit the health of the population.

Chapter 10, “Nanotechnology for Cerebral Delivery of Nutraceuticals for the Treatment of Neurodegenerative Diseases” — by Jasjeet Kaur Sahni, PhD, Sihem Doggui, PhD, Lé Dao, PhD, and Charles Remassamy, PhD — makes an important contribution related to the delivery of bioactive compounds, paying special attention to catechins and curcumin, as well as the red wine compound resveratrol, in controlling oxidative damage. The conclusion section refers to antioxidants as micronutrients, which may be the wrong word choice, but regardless, the role of nanotechnology in better delivery of bioactives is well represented.

Chapter 11, “Cancer Prevention by Polyphenols: Influence on Signal Transduction and Gene Expression,” is written by Fatima Hakimuddin and Dr. Paliyath. This chapter discusses the genetic and biochemical mechanisms of carcinogenesis and emphasizes signaling pathways in breast cancer and methods for its prevention and therapy with emphasis on the use of phytochemicals. Polyphenols have again been discussed, as are the role of grapes, resveratrol, and flavonoids in modulating signaling pathways. Identification of flavonoid-mediated molecular targets and estrogen metabolism and signaling as affected by polyphenols is thoroughly discussed as are bioavailability issues.

Chapter 12, “Potato-Herb Synergies as Food Designs for Hypoglycemic and Hypertension Management,” authored by Saleem Fahad, Ali Hussein Eid, and Dr. Shetty, addresses type 2 diabetes and hypertension and their association with cardiovascular complications, either directly or indirectly. This diet uses phenolic-enriched potato (*Solanum tuberosum*, Solanaceae) to address concerns with respect to the above health issues and to help in the management of micro- and macrovascular complications, hence reducing the incidence of cardiovascular diseases associated with type 2 diabetes.

Chapter 13 discusses “Fermentation-Based Processing of Food Botanicals for Mobilizing of Phenolic Phytochemicals for Type 2 Diabetes Management,” and is authored by Chandrakant Ankolekar and Dr. Shetty. The chapter dates the origin of fermentation to 7,000 BCE in China and 5,400 BCE in modern-day Iran. Prevention of food decomposition

through acid/alcohol fermentation also is described, and effects on enrichment or release of micro- and macronutrients, aroma, and bioactives are discussed, too. In this chapter, fermentation of fruit juices such as those of apple (*Malus* spp., Rosaceae), pear (*Pyrus* spp., Rosaceae), and cherry (*Prunus* spp., Rosaceae) are presented and the enhanced benefits associated with the release of bound phytochemicals are explained to be a main factor in this regard.

Chapter 14, “Postharvest Strategies to Enhance Bioactive Ingredients for Type 2 Diabetes Management and Heart Health,” is authored by Dipayan Sarkar and Dr. Shetty. The work again discusses similar material, as well as the influence and role of polyphenols in glucose metabolism and cardiovascular disease. It also describes postharvest strategies for enhancing the content of bioactive phytochemicals in fruits and vegetables. Processing, biotechnological, and other strategies are covered. Although these latter chapters are targeted differently, they would have served better if they were integrated in a more meaningful manner.

The final chapter, Chapter 15, “Enhancing Functional Food Ingredients in Fruits and Vegetables,” is authored by Shaila Wadud and Dr. Paliyath. The ingredients of interest include minerals such as iron and zinc, antioxidants such as carotenoids — particularly lycopene and β -carotene — as well as phenolic compounds such as vitamin E, flavonoids and amino acids in proteins, and fatty acid composition of seed oils. Effects of processing on these bioactives are discussed.

In summary, the book provides some highly useful information, but the organization of the book could have been better managed. The book is useful as a reference and beneficial to senior undergraduate and graduate students. Scientists in the field of nutrition and food science also may find it of interest, as well as members of related industries. HG

—Fereidoon Shahidi, PhD, FACS
University Research Professor
Memorial University
St. John's, NL, Canada

Herbs and Healers from the Ancient Mediterranean through the Medieval West: Essays in Honor of John M. Riddle edited by Anne Van Arsdall and Timothy Graham. Farnham, England: Ashgate; 2012. Hardcover, 377 pages. ISBN: 978-1-4094-0038-7. \$124.96.

John Riddle, PhD, a professor in the department of history at North Carolina State University, is the author of three books on the relationship between plants and sexuality in human history,¹⁻³ a relatively uncharted area of investigation. In these books, Dr. Riddle claims that plant-based contraception was widespread in pre-modern times, and that this knowledge — systematically removed from medicinal treatises and herbal books because of

political and/or religious reasons — still lingers in folk medicine. This view was dismissed as basically unproven by many historians, and, because the ancients had very vague ideas on the biology of human reproduction, it will remain controversial due to the difficult interpretation of existing texts. Nevertheless, the combination of history, medicine, and pharmacy that characterizes Dr. Riddle's previous works makes them compelling and enjoyable, and they stand as an important contribution to the study of ancient medical treatises. Dr. Riddle has tried to read the ancient medical literature through the glass of contemporary medicine and pharmacy, and this book honors his work with a series of 11 essays on plant medicine in the

ancient and medieval Mediterranean area. Only one of them is directly related to Dr. Riddle's trilogy on plants and human sexuality, with the others addressing either general methodological issues or some specific topics related to various aspects of his scholarly productions.

For many readers, the most interesting essay will be the one dedicated to a critical analysis of the claim that the antidepressant activity of St. John's wort (*Hypericum perforatum*, Clusiaceae) was documented in the pre-modern medical literature, where depression was referred to as *melancholia*. In this essay, "Saint John's Wort ... in the Age of Paracelsus and the Great Herbals," Karen Reeds, PhD, convincingly explains why in Greco-Roman Galenic medicine no association was ever made between this plant and melancholia. As the archetypal malady was believed to be caused by an excess of black bile, melancholia was associated with a "cold and dry" temperament that required a "hot and moist" drug, like black hellebore (*Helleborus niger*, Ranunculaceae) and not a "hot and dry" agent like St. John's wort. Also, the folk use of the plant was essentially apotropaic (used to ward off devils, ghosts, or other evil spirits), requiring only the presence of the plant, with no need to consume it. The claim that the 15th century iconoclastic physician Paracelsus introduced the use of the plant as an antidepressant is debunked next, identifying in the first clear association between mental diseases and St. John's wort in the early-1700s work of the Italian physician Angelo. The take-home message of this essay is that, if one plant works clinically, there is no need to have fictional history or pompous testimonials to support its use.

The opening chapter by John Scarborough, PhD, outlines the medical scene of Alexandria at the time of Cleopatra. The town was then at the forefront of art and science, and Cleopatra had a keen interest in poisons, cruelly experimenting — according to her Roman detractors — on prisoners and criminals. Although it is not known exactly how she committed suicide, the costly composition of her *aphroditarion*, an eye-drop preparation aimed at producing a copious flow of tears and, allegedly enhancing sexual attractiveness, is puzzling. The next chapter by Alain Touwaide, PhD, who also wrote the introduction to the book, addresses one confusing issue of the old medical literature — the practice of substituting one herb for another with alleged similar properties (*quid pro quo*). In the modern pharmaceutical lingo, the issue at stake here is the "bioequivalency" of plants. The author provides a list of the most common substitutes for various plants, identifying a series of reasons for the frequency

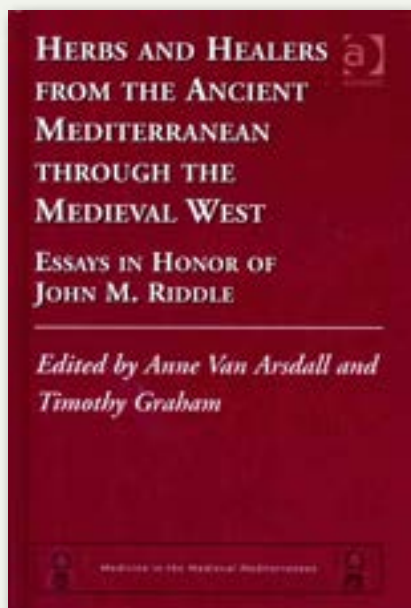
of the practice. Cost, rarity, or toxicity can underlie this practice, and also urbanization and loss of contact with the natural environment and its resources. The population density of ancient Rome or Alexandria was such that only limited natural resources existed within the urban area, and access to many plants was difficult.

A thorny issue in the study of medieval medical treatises is the lack of a Mediterranean medicinal *lingua franca*, with Latin, Greek, and Arabic coexisting for

many centuries. Florence Eliza Glaze, PhD, investigates this issue by analyzing a series of medical treatises from the Salerno medical school in southern Italy, the first "European" medical school. At the beginning of the new millennium, the Latin world was lagging behind the Arabic and the Greek ones. Many important Roman medical treatises had gone missing, and dependence on Greek and Arabic medicine was substantial. Translation of the medical literature, even from the more familiar Greek language, was not a simple task, and Glaze analyzes a series of glosses existing in various medical treatises from medieval southern Italy, in particular from Gariopontus's *Passionarius*, a medical bestseller of medieval Italy. Two chapters revolve around Constantine the African, a Tunisian physician of

the 11th century who converted to Christianity and translated the books of the great masters of Arabic medicine into Latin. These translations and Constantine's own books remained popular throughout Europe until the 17th century, and he is credited with bringing rationality to medieval medicine. Curiously, the work by Constantine fostered a series of herbal poems, presumably as mnemonic repositories of pharmacological knowledge. Fifty of them are listed. Science poetry is still alive today, a remarkable example being a three-page article in iambic pentameter that Burnett and Kearley published in the *Journal of Organic Chemistry* in 1971, to describe the reaction of dihalobenzenes with potassium amide.⁴

The contribution by Maria Amalia D'Aronco focuses on the identification of a problematic plant name (*elehtre*) that appears in medieval Anglo-Saxon medical literature. Using Dr. Riddle's approach to combine lexicographic and pharmacological information, D'Aronco claims that *elehtre* was not lupin (*Lupinus* spp., Fabaceae), but squinting cucumber (*Ecballium elaterium*, Cucurbitaceae). The following chapter by Linda Ehrtam Voigts is an analysis of late medieval English texts satirizing the use of herbs by so-called "quack doctors" and would-be healers. The best known example of this literature is found in the *Canterbury Tales* by Geoffrey Chaucer, in which expensive spices like grains-of-paradise (*Aframomum meleg-*



ueta, Zingiberaceae) and zedoary (*Curcuma zedoaria*, Zingiberaceae) are mentioned.

The essay by Gundolf Keil, MD, PhD, printed in German but with a long summary in English, is an analysis of a Silesian late medieval medical treaty to treat battlefield wounds and abscesses, while John K. Crellin, PhD, discusses how therapeutic uncertainties can affect the interpretation of medical texts, using the efficacy of emmenagogues and abortifacients as an example. The final chapter by Helen Klug, PhD, and Roman Weinberger describe an Internet tool, the Medieval Plant Survey, which aims to compile all currently available information on medieval plants. The project evolved from a blog and also stores medieval cooking recipes and 1,300 different ingredients, including 350 plants or plant products.

This book will be appreciated especially by scholars and academics, unlike Riddle's trilogy that can be read with pleasure by a larger share of readers. The many notes, the sections in Latin, and the chapter in German will probably deter many readers. Nonetheless, it represents a clear

demonstration of how valuable historical information can be, especially when critically evaluated, for a greater knowledge of medicinal plants. HG

—Giovanni Appendino, PhD
Department of Pharmaceutical Sciences
Università del Piemonte Orientale
Novara, Italy

References

1. Riddle JM. *Contraception and Abortion from the Ancient World to the Renaissance*. Cambridge, MA: Harvard University Press; 1992.
2. Riddle JM. *Eve's Herbs: A History of Contraception and Abortion in the West*. Cambridge, MA: Harvard University Press; 1997.
3. Riddle JM. *Godesses, Elixirs, and Witches: Plants and Sexuality throughout Human History*. New York, NY: Palgrave Macmillan; 2010.
4. Burnett JF, Kearley Jr. FJ. Comparative mobility of halo-gens in reactions of dihalobenzenes with potassium amide in ammonia. *J Org Chem*. 1971;36:184-186.

New Book Profiles

Smoke Signals: A Social History of Marijuana – Medical, Recreational, and Scientific by Martin A. Lee. New York, NY: Scribner; 2012. Hardcover; 528 pages. ISBN: 978-1-4391-0260-2. \$35.00.

In *Smoke Signals*, Martin A. Lee — author of the best-selling book, *Acid Dreams* — presents a chronological review of the history of the “devil’s weed,” commonly known as marijuana. This contentious drug has a long and complicated history. As Lee writes in the book’s prologue, “Ancient peoples during the Neolithic period found uses for virtually every part of the plant, which has been cultivated by humans since the dawn of agriculture more than 10,000 years ago. The stems and stalk provided fiber for cordage and cloth; the seeds, a key source of essential fatty acids and protein, were eaten as food; and the roots, leaves and flowers were utilized in medicinal and ritual preparations.” Today, according to Lee, approximately 15 million US citizens regularly use the drug, making it the most widely consumed illicit substance in the United States. The book’s nine chapters are broken down into wittily named sections such as “Flower Power,” “Reefer Sadness,” “Hip-Hop Hemp,” and “Senior Stoners.” *Smoke Signals* is the recipient of the 2012 ABC James A. Duke Excellence in Botanical Literature Award in the consumer/popular category.

Rhythms of Recovery: Trauma, Nature, and the Body by Leslie E. Korn. New York, NY: Routledge; 2013. Softcover; 336 pages. ISBN: 978-0-415-80750-0. \$39.95.

Leslie Korn, PhD, who has more than 35 years of private practice and community mental health experience, explores complementary and alternative medicine options for restoring patients’ physical and mental wellbeing after having experienced traumatic events. The book focuses on Eastern and Western healing traditions that are “culturally sensitive, multidisciplinary, and grounded in research.” *Rhythms of Recovery* is broken into eight chapters, among them “Paradigms of Disease and Diagnosis,” “Integrative Assessment,” “Nutrition,” “Botanical Medicine,” and “Spirit Molecules.” The botanical chapter includes detailed subsections on adaptogens, nervines, stimulants, anti-inflammatory agents, as well as information on herb-nutrient-drug interactions. Finally, the “Spirit Molecules” chapter contains data on the increasingly popular therapeutic use of consciousness-altering drugs, including cannabis (*Cannabis sativa*, Cannabaceae), ayahuasca (*Banisteriopsis caapi*, Malpighiaceae), and psychoactive mushrooms.

High Performance Liquid Chromatography Fingerprinting Technology of the Commonly-Used Traditional Chinese Medicine Herbs by Baochang Cai, Seng Poon Ong, and Xunhong Liu. Singapore: World Scientific Publish-

ing Co. Pte. Ltd.; 2012. Hardcover; 384 pages. ISBN: 978-981-4291-09-5. \$118.00.

In this highly technical and China-centric text, the authors present a detailed introduction to high-performance liquid chromatography (HPLC), a preferred method of chemical analysis and identification. “The HPLC fingerprinting technique has played a major role in quality assessment, standardizing cultivation, new product research and other areas in Chinese medicine, thus kick-starting the broadening applications in many experimental works,” wrote one author in the book’s preface. The first 50 pages of the book are dedicated to explanations of the various types of fingerprinting technologies and a step-by-step walkthrough of conducting an analysis. The rest of the book covers specific herbs used in traditional Chinese medicine. Each chapter includes an introduction to the herb, information about its chemical composition, experimental materials needed for fingerprinting, preparation methods, and a discussion of the resulting data. Herbs covered include *renshen* (*Panax ginseng*, Araliaceae), *shanzhuyu* (*Cornus officinalis*, Cornaceae), and *maidong* (*Ophiopogon japonicus*, Liliaceae).

Publications

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

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

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

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Pulsatilla (*Pulsatilla vulgaris*, Ranunculaceae)

Photo ©2013 Swanie Simon. An herbalist and holistic animal practitioner in Münchweiler, Germany, Simon is the first winner of the *HerbalGram* Page 80 photo contest.

Pulsatilla, which previously was known by the botanical name of *Anemone pulsatilla*, also is referred to by other common names including windflower and European pasqueflower. Although little human research on pulsatilla exists, this herb has a rich history of traditional medicinal use. Small internal doses of pulsatilla were used by the Eclectic physicians of the late 1800s and early 1900s in the United States, as well as some current American herbalists, to treat numerous conditions — particularly those of the female reproductive system, such as uterine disorders, menstrual pain, and lack of menstruation. The Eclectics also used it to relieve pain and congestion from middle-ear infections, and for many other health complaints, such as nervousness, insomnia, skin disorders, and wounds. It also was employed to improve emotional health by the Eclectics and early homeopathic practitioners, and is still available over-the-counter as a homeopathic medicine. Because pulsatilla contains ranunculin, it can be toxic and thus has been recommended for usage in only small doses.

Adapted from *Anemone pulsatilla*, prepared by M. Moore, Southwest School of Botanical Medicine Medicinal Plant Folio (www.swsbm.com/FOLIOS/PulsFol.pdf).

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