

Grape Seed Adulteration • Cannabis Taxonomy • Tongkat Ali and Immune Function
Ashwagandha and Muscle Strength • Nobel Prize for Artemisinin

HERBALGRAM

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dear reader

On the cover this issue is another of our good friend Steven Foster's compelling photos — this time of saffron. Saffron is probably the most expensive spice on the market today, and it has been for centuries. The reason? Each plant contains only three yellow-gold stigmas per flower, and it is a laborious process to harvest these stigmas for any appreciable yield. (Reportedly, it takes 225,000 stigmas from 75,000 flowers to produce a single pound of saffron spice!) Previous *HerbalGram* issues have included Research Reviews of clinical trials on saffron, showing promising activity for depression, Alzheimer's disease, and several other conditions. Most of this research is conducted in Iran, where saffron grows and is a traditional spice and herbal medicine, and where a burgeoning saffron extract industry is now producing medicinal preparations of saffron stigmas *and* petals. Our Canadian herbal friends Linda Woolven and Ted Snider have compiled the available saffron clinical trials and provide a thought-provoking review. They previously published an overview of herbs for erectile dysfunction in issue 99.

As part of our ongoing series of extensive botanical profiles by ABC's Gayle Engels and Traditional Medicinals' Josef Brinckmann, we present stinging nettle, a time-honored herb with various health benefits. This profile covers both nettle leaf and root — an example of how two separate parts from the same plant can be used for totally different medicinal applications.

The world of medicinal cannabis continues to expand quickly, both in the US and in many other countries around the world. One of the questions that continues to surface about cannabis relates to its proper taxonomy: are *Cannabis sativa* and *C. indica* two separate, legitimate species? Botanical experts Robert Clarke and Mark Merlin, PhD, explore this question in this issue. They are co-authors of the highly informative and authoritative book *Cannabis: Evolution and Ethnobotany* (University of California Press, 2013). While some people in the cannabis industry may or may not find such taxonomic distinctions important, as a science-based organization, we at ABC consider such discussions not only relevant, but also interesting, and, yes, even fun!

As many *HerbalGram* readers are now aware, the 2015 Nobel Prize in Physiology or Medicine was awarded, in part, to the leader of a Chinese research team that discovered the highly effective antimalarial compound artemisinin, which is derived from the traditional Chinese herb sweet wormwood. Extensive study of the traditional Chinese medicine literature helped lead to the discovery of artemisinin, whose derivatives are reportedly the most potent and rapidly acting antimalarial drugs ever. This validation of the ethnobotanical approach to drug discovery is explored in great detail by *HerbalGram* Assistant Editor Connor Yearsley in his feature article.

In the quality control arena, we present news of the ABC-AHP-NCNPR Botanical Adulterants Program's Botanical Adulterants Bulletins, a new series of publications on adulterated herbs. Three Bulletins were published online in early May on bilberry fruit extract, grape seed extract, and skullcap herb. In these pages we have previously run extensive articles on bilberry and skullcap adulteration, but grape seed extract adulteration is a new subject for the Program. In this issue, we provide the full Bulletin on grape seed. This new series is designed to provide members of the herb and botanical industry, analytical laboratories, and other interested parties with authoritative reviews that confirm the adulteration of various botanical materials and extracts found in the US and global marketplace. The purpose of these reviews is to assist the industry in the proper analysis to authenticate the identities of botanical materials. Forthcoming Bulletins will cover arnica, black cohosh root and rhizome, ginkgo leaf extract, and numerous others. As a reminder, all documents on the Botanical Adulterants Program homepage of the ABC website are freely available to any ABC registered user. We appreciate further distribution of these important documents to stakeholders in the botanical community. In this way, we can be more certain that herbal preparations will be able to deliver the health benefits that people seek. HG

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Cannabis sativa
Photo ©2016 Steven Foster

44 **Cannabis Taxonomy: The ‘Indica’ vs. ‘Sativa’ Debate**

By Robert C. Clarke and Mark D. Merlin, PhD

When Carl Linnaeus dubbed hemp “*Cannabis sativa*” in 1753, he referred to the cultivated plant growing widely across the European continent. Since then, a complex discussion has arisen regarding the THC and CBD contents of different cannabis strains and their areas of origin, causing taxonomic confusion for scientists, cultivators, and many other stakeholders in the world’s growing medical cannabis and hemp industries. Botanical experts Robert C. Clarke and Mark D. Merlin, PhD, discuss the differences between *C. sativa* and *C. indica*, the intricacies surrounding their nomenclature, and the debate over these issues that continues in modern times.

50 **Artemisinin: A Nobel Prize-Winning Antimalarial from Traditional Chinese Medicine**

By Connor Yearsley

Chinese phytochemist Tu Youyou was awarded half of the 2015 Nobel Prize in Physiology or Medicine for her role in the discovery of the natural compound artemisinin, derived from the traditional Chinese herb *qinghao*, also known as sweet wormwood (*Artemisia annua*). Artemisinin-based combination therapies (ACTs), which combine an artemisinin derivative with another, longer-lasting antimalarial, are the most effective drugs ever discovered for combating malaria, one of the most devastating diseases in history. The Nobel Assembly’s recognition of Tu and artemisinin helps validate the ethnobotanical approach to drug discovery.

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By Ted Snider and Linda Woolven

Saffron has widespread use as a culinary spice in both ancient and modern times, but its history as a traditional Mediterranean medicine often is overlooked. New clinical research in Iran using preparations made from this useful flower shows promising results for both mental and physical conditions, paving the way for saffron’s possible future reputation as a safe and effective healing herb.

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Hibiscus spp., Malvaceae



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Saffron *Crocus sativus*.

Photo ©2016 Steve Foster

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Stinging Nettle

Urtica dioica, *U. urens*

Family: Urticaceae

INTRODUCTION

Urtica dioica, known as stinging nettle,^{1,2} greater nettle,² common nettle,³⁻⁵ giant nettle,³ European nettle,³ or simply “nettle,”^{1,5} and *U. urens* (burning nettle, lesser nettle, or dwarf nettle) are native to Europe and Eurasia and grow wild throughout temperate parts of the world.^{1,2} The family name Urticaceae, generic name *Urtica*, and species name *urens* are derived from the Latin verb *urere*, meaning “to burn,” a reference to the plant’s stinging hairs.^{1,2} The

species name *dioica* comes from the Greek for “two houses,” which refers to the male and female flowers that occur on separate plants (i.e., they are dioecious).^{1,2}

The materials of commerce may originate from either species or hybrids or mixtures of the two.⁶ *Urtica urens* is a low-growing, monoecious (each plant has both male and female reproductive organs) annual that typically is only 20-30 cm (7.9-11.8 in) in height, but can grow up to 80 cm (2.6 ft). *Urtica dioica* is a dioecious perennial that reaches up to 150 cm (4.9 ft) in height.⁶ There are significant differences in the contents of biologically active compounds between leaves of male and female *U. dioica* plants.⁷

While the American Herbal Products Association’s *Herbs of Commerce*, 2nd ed., narrowly defines stinging nettle as a subspecies (*U. dioica* subsp. *dioica*),⁸ the European Pharmacopoeia does not make such a distinction. Version 1.1 of The Plant List states that *U. dioica* subsp. *dioica* is a synonym of *U. dioica*.⁹ The taxonomy of *U. dioica* remains controversial, as demonstrated by the conflicting information in *Herbs of Commerce* and The Plant List. There is also some disagreement about the classification of *U. dioica* subsp. *gracilis* (California nettle). Many authors (likely incorrectly) state that *U. dioica* (or subspecies) is native to the Americas and eastern Asia. While older literature suggests that *U. dioica* is native throughout the entire Holarctic region (non-tropical parts of Europe, Asia, northern Africa, and North America), new taxonomic research calls this into question, suggesting that, for example, American species are distinct and should be removed from *U. dioica* and placed instead into *U. gracilis* as the “New World-sister” to *U. dioica*. In particular, it is proposed that *U. dioica* subsp. *gracilis* be changed to *U. gracilis* subsp. *gracilis*.¹⁰

The weedy, sprawling plants emerge in early spring from spreading rhizomatous roots, and bear opposite, toothed, variable leaves (ovate, elliptical, or lanceolate) and minute green, greenish-white, or pink flowers that form in clusters in the leaf axils.^{4,5} The stem and leaves are pubescent, and the stinging hairs (trichomes) can be distinguished from the other hairs by their shape and larger size.⁵ Each of the stinging hairs has at its base a secretory structure, a hollow, elongated tube like a syringe, and a bulbous tip that breaks off easily.⁴ The gland-like secretory structure supplies a combination of chemicals (see Modern Research section) responsible for the stinging, itching, or mild to severe burning sensation that can continue for minutes, or even hours, after contact with nettle.^{4,11} However, if the plant is dried and powdered, extracted, or cooked, no reaction takes place.¹¹

Stinging Nettle *Urtica dioica*
Photo ©2016 Steven Foster



Several plant parts are used medicinally, including the dried leaf, the dried herb (aerial parts collected in the flowering period), dried fruit (seed), and the dried root and rhizome. These are obtained primarily from wild-collection in eastern Europe, in particular Bulgaria, Hungary, Poland,¹² the Czech Republic,¹³ and Romania,¹⁴ and in southern Europe, especially Albania, Croatia,¹⁵ Bosnia and Herzegovina,¹⁶ Kosovo,¹⁷ Serbia,¹⁸ Slovenia,¹⁹ and Macedonia.²⁰ Wild-collection also takes place in western Asia, including Georgia²¹ and Turkey,²² and Central Asia, especially Kazakhstan.²³

Commercial cultivation takes place in Canada,²⁴ Mexico, and the United States,²³ in African countries, especially Egypt,²⁵ and in European countries, particularly the United Kingdom and Germany. Several named cultivars are protected in Germany, including “Urmed” (owned by Pharmaplant GmbH; Artern, Germany), and “Nesselgold” and “Wulfsdorf” (both owned by the University of Hamburg; Hamburg, Germany).⁶

This article does not address other *Urtica* species, such as *U. fissa*, for example, the dried leaves and roots of which are wild-collected in China, exported and traded under the English common name nettle²³ or the Chinese name *qian ma* (荨麻).

HISTORY AND CULTURAL SIGNIFICANCE

The use of nettle as a vegetable and folk remedy dates back to ancient times. It was mentioned by Hippocrates (ca. 460-370 BCE) and Theophrastus (ca. 371-287 BCE), by Dioscorides (40-90 CE) in *Materia Medica*, and by Pliny the Elder (23-79 CE) in *Naturalis Historia*.²⁶ The *Materia Medica* suggested nettle for gangrene, rheumatism, tumors, ulcers, and dog bites.

In the medieval period, nettles were recommended by German philosopher, natural historian, and abbess Hildegard von Bingen (1098-1179) in *Physica*; by the Swiss physician Paracelsus (1493-1541) in his writings on the doctrine of signatures; by English physician Andrew Borde (ca. 1490-1549) in *A Dyetary of Helth* (1542); and by German botanist and physician Hieronymus Bock (1498-1554) in *Kreütterbuch* (1546).²⁶

The English herbalist, physician, and botanist Nicholas Culpeper (1616-1654) said nettle was “an herb so well known, that you may find them by the feeling in the darkest night,” likely referring to its stinging hairs.²⁷ He recommended nettle to break up stones, stop bleeding, and increase urination, and for difficulty breathing, pleurisy, cough, and inflammation of the lungs. Culpeper also said that nettles provoke lust and help people hold their necks upright.²⁷

Along with dandelion (*Taraxacum officinale*, Asteraceae; profiled in *HerbalGram* issue 109), European elder (*Sambucus nigra*, Adoxaceae; profiled in *HerbalGram* issue 97), and the vari-

ous docks (*Rumex* spp., Polygonaceae), nettle featured prominently in British folk medicine.²⁸ It was used as a spring tonic “to cleanse blood” of the impurities that were believed to cause clouded eyes, boils, pimples, and various types of sores, and it was eaten to relieve anemia, as a counterirritant for rheumatic conditions, and for nose bleeds, colds, coughs, consumption (tuberculosis), dandruff, diarrhea, dropsy (edema), ear infections, epilepsy, headaches, and heart trouble. Nettle was also used for high blood pressure, insect stings, insomnia, jaundice, nervous conditions, paralyzed limbs, piles (hemorrhoids), ringworm, shingles (herpes zoster), stomach upset/indigestion, swelling (mumps) and swollen glands (goiter), worms, and, externally, for skin-cleansing.²⁸ Nettle beer was a popular remedy for rheumatism during the Middle Ages.²⁹ Additionally, the plant tops were used as a rennet substitute in making cheese, and the leaves were wrapped around fruits to help them ripen.²⁹

Although likely introduced species from Europe, American Indian tribes found uses for both *U. dioica* and *U. urens*.³⁰ They used the plants for food and for fiber to make bow strings, cords, ropes, cloth, fishnet, and baskets. Infusions and decoctions were used internally for ague (alternating periods of chills, fever, and sweating, as in malaria), bladder conditions, colds, dysentery, locomotor ataxia (the inability to control bodily movements), bleeding hemorrhoids, headache, hives and itching, paralyzed limbs, upset stomach and stomach pain, skin conditions, and the promotion of urination. They were also used during pregnancy

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and to support blood flow after childbirth. The Nitinaht tribe (Vancouver Island, British Columbia, Canada) chewed and swallowed young nettle shoots to prevent illness. Externally, steamed nettle leaves and roots were used in poultices and sweat baths for sore and/or swollen arthritic joints, colds, grippe (influenza), heat rash, and pneumonia. Nettles were rubbed on the body for aches, pains, and soreness, and the plant's juice was rubbed on the scalp to prevent hair loss and as a tonic for growing long, silky hair. More recently, some Native American tribes and others have used nettles to relieve arthritis and rheumatism through the practice of urtication, wherein the afflicted areas are whipped with nettle branches (flagellation). Curiously, this same method was used by married members of the Nitinaht tribe for "affection and faithfulness of spouses." Stems were put under splints to hasten healing of broken bones, and the plant fiber was used for headaches, inflammation, and was applied to the skin for various ailments. At least one tribe, the Makah of the Olympic Peninsula in Washington state, used the plant as a stimulant by rubbing it into the skin after bathing. They also rubbed whale hunters' bodies with the plant for strength.³⁰

Modern herbalists and other alternative health care providers use nettle for its astringent, tonic (i.e., nourishing, strengthening, and toning), hypotensive,³¹ anti-inflammatory,³² anti-hemorrhagic,^{33,34} diuretic,^{31,34,35} and hypoglycemic²⁹ actions. It is used to improve urine flow, decrease residual urine volume, and reduce urinary frequency and nocturia (excessive nighttime urination) in early-stage benign prostatic hyperplasia (BPH), to address inflammation in the lower urinary tract and treat renal stones,³⁶ to lower blood sugar levels, to alleviate myalgia (muscle pain), osteoarthritis,^{31,35} rheumatoid arthritis,^{31,34,35} allergic rhinitis (hay fever),^{32,34} childhood and psychogenic (especially nervous) eczema,^{31,33} and to detoxify the body.³¹ Midwives use nettles to address anemia in pregnant women, and, topically, for pruritic urticarial papules and plaques of pregnancy (PUPPP; a hives-like rash that sometimes occurs during pregnancy) in an *Aloe vera* (Xanthorrhoeaceae) gel, witch hazel (*Hamamelis* spp., Hamamelidaceae), or cream base.³²

From the 19th century until the end of World War II, *U. dioica* was cultivated in parts of Europe as a fiber crop alternative to cotton (*Gossypium* spp., Malvaceae). Due to cotton shortages during the World Wars, Germany switched to nettle fiber to make military uniforms. In the early 1940s, approximately 500 hectares (1,236 acres) of nettle were under cultivation in Austria and Germany, but this came to a halt when the nettle processing facilities were destroyed during World War II. In recent years, *U. dioica* cultivation has started up again in Germany.³⁷ (Interestingly, there is a German idiom — *sich in die Nesseln setzen* — which literally means "to sit down in nettles." In context, it means that someone got himself into trouble.)

* Per the US FDA Guidance Document: "Section 503A of the FD&C Act includes certain restrictions on the bulk drug substances that can be used in compounding and directs the FDA to develop a list of bulk drug substances that can be used in compounding under that section. FDA is developing this list of bulk drug substances (the 503A bulks list), and this guidance describes FDA's interim regulatory policy for licensed pharmacists in State-licensed pharmacies and Federal facilities, and for licensed physicians that compound human drug products using bulk drug substances while the list is being developed."⁵⁰

In 1986, the German Commission E approved the use of *Urticae Radix* (subterranean plant parts), prepared as an herbal tea infusion or in other galenical forms, as a nonprescription medicine taken orally to treat urination difficulties in BPH stages I and II.³⁸ Subsequently, in 1987, the Commission E approved the use of both *Urticae Folium* (leaf) and *Urticae Herba* (aerial plant parts), as an herbal tea or in other galenical forms, taken orally as irrigation therapy for inflammatory diseases of the lower urinary tract and for the prevention and treatment of kidney stones. For topical application, spirit of nettle (an alcoholic solution of distilled nettle; 50% alcohol by volume)¹ was approved as a supportive therapy for rheumatic ailments.³⁸ In the meantime, official national labeling standards monographs of European Union (EU) member states, such as those of the German Commission E, have been superseded by monographs of the European Medicines Agency (EMA).

There are English-language quality standards monographs established by the European Directorate for the Quality of Medicines (EDQM) for two articles, *Urticae Folium* PhEur and *Urticae Radix* PhEur,^{39,40} with corresponding labeling standards monographs established by the EMA.⁴¹⁻⁴³ The United States Pharmacopeia (USP) provides quality standards monographs for the dried roots and rhizomes of *U. dioica* L. subsp. *dioica* with *U. urens*, as well as for the dry extract of the roots and rhizomes.⁴⁴ Comprehensive monographs (quality and therapeutics) for *Urticae Radix* are available in the *WHO Monographs on Selected Medicinal Plants*,⁴⁵ the English and Russian editions of the *WHO Monographs on Medicinal Plants Commonly Used in the Newly Independent States* (NIS),⁴⁶ and the *American Herbal Pharmacopoeia and Therapeutic Compendium* (AHP).⁴⁷ There is also an AHP monograph for Stinging Nettle Herb.⁴⁸

CURRENT AUTHORIZED USES IN COSMETICS, FOODS, AND MEDICINES

In the US, plant parts or preparations of *U. dioica* and/or *U. urens* are not generally recognized as safe (GRAS) for use in food products, but are permitted as components of dietary supplement products. The US Food and Drug Administration (FDA) requires notification within 30 days of marketing (if a structure-function claim is made) and product manufacturing according to current Good Manufacturing Practices (cGMPs) for dietary supplements.⁴⁹ In October 2015, nettle (*U. dioica* subsp. *dioica*) leaf was nominated for use in pharmacy compounding and placed on the FDA's *503A List 1 – Bulk Drug Substances Under Evaluation*,⁵⁰ which means it is viewed as a bulk drug substance that may be eligible for inclusion on the 503A bulks* list, because sufficient supporting information was provided to the FDA for evaluation.⁵¹

In Canada, nettle is regulated as an active ingredient of licensed natural health products (NHPs), requiring pre-marketing authorization from the Natural and Non-prescription Health Products Directorate (NNHPD).⁵² The authorized uses for labeling of nettle NHPs vary somewhat depending on the plant part(s). Preparations of the aerial parts (as fluid extracts, tinctures, fresh juices, herbal tea decoctions or infusions) may be labeled with claims including “Traditionally used in Herbal Medicine as a diuretic,” and “Used in Herbal Medicine as supportive therapy to help relieve rheumatic complaints, as a nutritive tonic, and to help relieve seasonal [allergies].” Preparations of the root (dry or liquid extracts, herbal tea decoctions or infusions) may be marketed with the claim “Used in Herbal Medicine to help reduce difficulty in urination associated with the early stages of benign prostatic hyperplasia (BPH).”

In the EU, while it is possible to market nettle leaf-containing products as food products without health claims, various defined therapeutic preparations of nettle leaf, nettle herb, and nettle root are regulated as traditional herbal medicinal products (THMPs), requiring registration and pre-marketing authorization. The EU approves the following therapeutic indications for nettle herb (prepared as an expressed juice, fluid extract, herbal tea, tincture, or dry extract): (1) “THMP to increase the amount of urine to achieve flushing of the urinary tract as an adjuvant in minor urinary complaints”; (2) “THMP for relief of minor articular pain”; and (3) “THMP used in seborrheic (inflammatory) skin conditions.”⁴¹ Indications (1) and (2) are also permitted for preparations of nettle leaf.⁴² Preparations of nettle root (herbal teas or dry or liquid extracts) may be labeled with the claim “THMP for the relief of lower urinary tract symptoms related to benign prostatic hyperplasia after serious conditions have been excluded by a medical doctor.”⁴³ For marketing authorization, the applicant must specify the quality of the

nettle active ingredients according to pharmacopeial standards and assure consistent quality through implementation of the EMA’s Good Agriculture and Collection Practices (GACP) for starting materials of herbal origin.⁵³

For use in cosmetic products, the European Commission Health and Consumers Directorate lists *Urtica Dioica* Juice, *Urtica Dioica* Leaf Extract, *Urtica Dioica* Root Extract, and *Urtica Urens* Leaf Extract for skin-conditioning functions.⁵⁴ An extract of all aerial parts is authorized for antidandruff, astringent, hair-conditioning, skin-conditioning, soothing, and tonic functions.

Stinging Nettle *Urtica dioica*
Photo ©2016 Steven Foster



MODERN RESEARCH

Chemicals produced in the stinging hairs of nettle include histamine, acetylcholine, serotonin, and formic acid.^{4,34,55} Other constituents found in nettle include leukotrienes, oxalic acid, tartaric acid,¹¹ flavonoids (glucosides and rutinoides of isorhamnetin, kaempferol, and quercetin), caffeoyl-esters (caffeoylmalic acid [*U. dioica* only], chlorogenic acid, and neochlorogenic acid), caffeic acid, scopoletin (cumarin), sitosterol (-3-*O*-glucoside), polysaccharides, fatty acids, vitamin C and other vitamins, minerals, protein, and dietary fiber.^{31,34,55,56}

Pharmacological studies of nettle extracts have shown the following effects in vitro and in vivo: analgesic,^{56,57} anesthetic, antianemic,⁵⁶ antibacterial,⁵⁸ anti-inflammatory, antilipidemic, antimicrobial,⁵⁶ antioxidant,⁵⁶⁻⁵⁸ anti-ulcer,⁵⁷ cardiovascular, central depressive, chemopreventive, diuretic, endocrine, gastrointestinal, hepatoprotective, platelet-aggregating, immunomodulatory, and vasoconstrictive.⁵⁶

Clinical studies and case reports of varying quality have investigated the use of nettle alone, or in combination with other herbs, to address symptoms of type 2 diabetes, urinary conditions related to prostate health, osteoarthritis, allergic rhinitis, excessive bleeding after dental surgery, and episiotomy repair.

Much of the recent research on the use of nettle in treating symptoms of type 2 diabetes has been conducted in Iran and Pakistan. There were 285 million cases of diabetes in the world in 2010, a number expected to increase to 439 million by 2030, and there is considerable interest in these countries as to how traditional medicinal plants can be used for treatment instead of, or in addition to, pharmaceutical drugs.

One randomized, double-blind, placebo-controlled (RDBPC) clinical study published in 2014 investigated the effect of nettle's aerial parts on glycemic control and insulin resistance in patients with type 2 diabetes.⁵⁹ Sixty patients were randomly assigned to take either 100 mg/kg per day of nettle extract (no additional information provided) or placebo after each of three main meals for eight weeks. Patients were asked to not make any changes to their current drug treatments, diet, or exercise routines during the study. After eight weeks, the nettle group experienced significantly increased insulin concentration, β -cell function, and insulin sensitivity, significantly decreased insulin resistance, and no differences in fasting blood sugar, compared to the placebo group.

In a RDBPC study published in 2012, nettle leaf extract was evaluated for its efficacy in treating type 2 diabetes in patients resistant to conventional oral anti-hyperglycemic drugs who required insulin shots.⁶⁰ Patients refusing insulin with glycosylated hemoglobin (HbA1c) levels above 200 mg/dL of blood ($N = 22$) took either placebo or 500 mg of encapsulated nettle leaf extract (70% ethanol, 30% water; solvent removed in a rotary evaporator; extract encapsulated with 12% toast powder excipient) three times per day for three months. Drug treatment, diet, and physical activ-

ity did not change during the study. Fasting blood glucose, two-hour postprandial (post-meal) glucose, and HbA1c levels were taken at the beginning and end of the study. After three months, patients in the nettle group experienced a significant lowering of HbA1c levels, and no significant effects on other blood parameter levels, compared with the placebo group. Also, the test group's fasting glucose and HbA1c levels decreased significantly between baseline and endpoint with no other significant blood parameter changes. The placebo group's blood parameters did not change significantly between baseline and endpoint. The authors conclude that nettle could be safe and effective in improving glycemic control in patients with type 2 diabetes.

In another RDBPC study published in 2012, 50 diabetic patients were randomized to take either 100 mg/kg of hydroalcoholic nettle extract (45% ethanol, 55% water; 2.7 g dry aerial parts; prepared by the Traditional Medicine Association of Iran-Eastern Azerbaijan and Giah Esanse Company; Gorgan, Iran) or placebo in three portions dissolved in water after each of three main meals every day for eight weeks.⁶¹ At the end of the study, the nettle group experienced a significant increase in total antioxidant capacity and superoxide dismutase (an antioxidant enzyme) compared to the placebo group. The authors note that hydroalcoholic nettle extract can improve antioxidant status and may help prevent cardiovascular disease.

A similar randomized, double-blind study published in 2011 examined a hydroalcoholic extract of nettle leaf on insulin sensitivity and inflammatory markers in patients with type 2 diabetes.⁶² Fifty patients were randomly assigned either 100 mg/kg of nettle extract (45% ethanol, 55% water; 2.7 g dry aerial parts; prepared by the Traditional Medicine Association of Iran-Eastern Azerbaijan and Giah Esanse Company; Gorgan, Iran) or placebo in three portions per day for eight weeks. At the end of the study, there was a significant decrease in interleukin 6 and high-sensitivity C-reactive protein in the nettle group, compared to the placebo group, suggesting that hydroalcoholic nettle extract may protect patients with type 2 diabetes from cardiovascular disease by decreasing certain inflammatory markers.

One large RDBPC crossover study published in 2005 investigated the effect of nettle therapy for relief of lower urinary tract symptoms (LUTS).⁶³ Patients with LUTS ($N = 620$) were randomized to take either a nettle root fluid extract made by fractional percolation and standardized to 100 mg of root extract per 1 mL (no further information provided) or placebo three times per day with meals. At the end of six months, patients were evaluated using the International Prostate Symptom Score (IPSS). In addition, maximum urinary flow rate (Qmax), post-void residual urine volume (PVR), serum prostate-specific antigen (PSA) levels, testosterone levels, and prostate size were measured. Further, at the end of the trial, both groups took the nettle preparation for up to 18 months. Of the 558 patients who completed the study, 232 of the 287 patients (81%) in the nettle group reported improved LUTS compared to 43 of

the 271 subjects (16%) in the placebo group. The IPSS and Qmax improved more with the nettle preparation than with placebo, and PVR decreased in the nettle group only. Neither group experienced changes in serum PSA levels or testosterone levels. Also, patients who took nettle extract for up to 18 additional months experienced even more improvement.

A 2004 RDBPC multicenter study examined Bazoton-uno[†] (459 mg of stinging nettle root dry extract [drug extract ratio 7.1-14.3:1, solvent 20% methanol] per film tablet; Abbott GmbH & Co.; Wiesbaden, Germany) for its efficacy in the long-term treatment of BPH.⁶⁴ Patients with BPH (N = 246) were enrolled in the study (which had a four-week placebo run-in phase followed by a 52-week therapy phase) and were randomized to take either Bazoton-uno or placebo once per day after breakfast. Clinical evaluations were performed at weeks four, 12, 24, 36, and 52. During the course of the study, the mean IPSS improved continuously in the test group compared to placebo. Qmax and median volume of residual urine showed a pronounced improvement in the test group compared to the placebo group, but the change was not statistically significant.

In 1985, in a nine-week, double-blind study on Bazoton (300 mg of stinging nettle root extract [drug extract ratio 5:1, solvent 20% methanol] per capsule; Kanoldt Arzneimittel GmbH; Hochstadt/Donau, Germany), 50 patients with BPH took one capsule of Bazoton or placebo in the morning and evening.⁶⁵ Patients were evaluated at three, six, and nine weeks. Regarding subjective symptoms, patients reported no changes in frequency of urination, alguria (painful urination), or night-time dribbling, but dysuria (difficult urination), with delayed onset and respectively diminished flow, improved markedly in the Bazoton group compared to placebo.

At least six studies have been conducted on Prostagutt forte ("PRO"; Dr. Willmar Schwabe Pharmaceuticals; Karlsruhe, Germany), a combination product containing 160 mg of saw palmetto (*Serenoa repens*, Arecaceae) extract (WS 1473, an ethanolic [90% by weight] extract containing a minimum of 70% fatty acids and esters) and 120 mg of nettle root dry extract. The study evaluated the product's ability to relieve symptoms of, and to delay surgery for, BPH. One study showed that PRO was equivalent in efficacy to, but had fewer adverse events than, finasteride.⁶⁶ A study published in 2012 showed that

PRO decreased white blood cell counts in prostatic secretion, decreased prostate volume, and relieved inflammation more rapidly than nonsteroidal anti-inflammatory drugs (NSAIDs).⁶⁷ In a study published in 2007, PRO reduced the IPSS, increased urinary flow, and decreased residual urine volume.⁶⁸ Another study reported that PRO was not inferior to tamsulosin in relieving LUTS.⁶⁹ One study reported that a year of PRO therapy was well-tolerated and effective compared to placebo.⁷⁰ Another study found that treatment with PRO was an effective method for avoiding or delaying surgery for BPH.⁷¹

There have been a number of studies on another combination product for prostate health, called ProstaMEV Plus (FarmaceuticaMEV; Siena, Italy), which contains 320 mg of saw palmetto, 0.4% nettle (plant part not specified), and 1600 gelatin digesting units (GDUs) of bromelain (an extract of enzymes found in pineapple; *Ananas comosus*, Bromeliaceae).⁷² In one study published in 2015, two groups treated with ProstaMEV Plus for two months experienced greater improvements in IPSS, urinary flow, and sex life than did the groups treated with only 320 mg of saw palmetto, irrespective of antibiotic use.⁷³ In another study, ProstaMEV (containing saw palmetto and nettle [plant part not specified], but not bromelain) improved the efficacy of the antibiotic prulifloxacin in bacterial prostatitis patients.⁷⁴



Stinging Nettle *Urtica dioica*. Photo ©2016 Steven Foster

[†] Bazoton products were initially marketed by Kanoldt Arzneimittel GmbH. Kanoldt was acquired in 2000 by Abbott GmbH & Co. In 2014, Abbott was acquired by Mylan Inc. The Bazoton products are now manufactured by Riemser Specialty Production GmbH (Laupheim, Germany), and marketed by Mylan Healthcare GmbH (Hannover, Germany).

Stinging Nettle *Urtica dioica*. Photo ©2016 Jerry Kirkhart



A RDBPC, parallel-arms clinical study published in 2009 examined the commercially prepared combination food supplement Phytalgic (Phythea Laboratories; Savignyle-Temple, France) — containing 150 mg of *U. dioica* dry extract (plant part not specified), 1,350 mg of fish oil, 45.8 mg of microencapsulated zinc sulfate, and 10 mg of vitamin E — for its efficacy in treating osteoarthritis (OA).⁷⁵ Patients (N = 81) with OA of the knee or hip regularly using NSAIDs and/or analgesics were randomized to take either three capsules per day for three months of Phytalgic or placebo. The primary outcome measure was the use of NSAIDs or analgesics (500 mg of acetaminophen-equivalent tablets/week). After three months, the mean use of NSAIDs and analgesics was significantly different in the test group compared to placebo. The test group also scored significantly better with regard to pain, stiffness, and function.

One randomized, double-blind study published in 1990 investigated the effects of a freeze-dried preparation of nettle, containing 300 mg of nettle leaf (Eclectic Institute; Sandy, Oregon), on symptoms of allergic rhinitis.⁷⁶ The 98 subjects who volunteered for the study were given either nettle capsules or placebo, and were instructed to take two capsules at the onset of allergy symptoms. Subjects recorded their responses to the medication, along with the

total number of doses taken over the course of the one-week study. (The author does not specify how or when the subjects were instructed to take additional doses.) Of the 69 subjects who completed the study, 16 in the test group (n = 31) rated nettle as less effective than conventional pharmaceutical hay fever medicines they had taken previously, and 15 rated it as equally or more effective than previous medicines. Thirty subjects in the placebo group (n = 38) rated it less effective than previous medicines, and eight rated it as equally or more effective. Sixteen subjects in the test group indicated that they would buy and use the medication in future, whereas only seven in the placebo group said they would.

FUTURE OUTLOOK

The International Union for Conservation of Nature (IUCN) European Red List of Medicinal Plants assigns both *U. dioica* and *U. urens* to the conservation category of Least Concern (LC), meaning that these species are not threatened.⁷⁷ Wild populations of nettle appear to be abundant in Europe and continue to serve as an important source of household income in rural areas throughout eastern and southern Europe.¹² Wild-collection enterprises are able to collect nettle herb (aerial parts) and nettle leaf in the summer months, and the subterranean parts (root and rhizome) in the fall. Families that collect nettle for income often collect other economically important wild medicinal plants that grow in the same areas, such as dandelion leaf and root, dog rose (*Rosa canina*, Rosaceae) hip, European elder flower and fruit, linden (*Tilia cordata* and *T. platyphyllos*, Tiliaceae) flower, and raspberry (*Rubus idaeus*, Rosaceae) leaf, among many others.¹²

Although trade data are not available through national databases, due to the absence of a species-specific tariff code for nettle, some countries keep records of quantities through export license declarations. For example, wild-collected nettle leaf (Folium Urticae) ranks as Bulgaria's fourth largest medicinal plant export by volume, with an average of 930,595 kg (more than 2 million lbs) exported annually. Nettle root (Radix Urticae) ranks eleventh, with an average annual export quantity of 432,780 kg (954,117 lbs). Bulgaria also exports a relatively small amount of nettle herb (Herba Urticae, aerial parts), at an average of 53,111 kg (117,090 lbs) annually.⁷⁸ Romania reportedly exports about 50,000 kg (110,231 lbs) of nettle herb annually.¹⁴ In addition, the single most important wild-collected medicinal plant from Poland, in terms of annual quantity harvested, is nettle leaf.⁷⁹ Another indicator of the widespread use of nettle is the relatively high number of nettle-containing herbal medicinal products with marketing authorizations in European and North American countries. For example, according to the drug information database of the German Federal Institute for Drugs and Medical Devices (BfArM), there are 1,540 medicinal products containing nettle leaf in Germany alone.⁸⁰ And, in Canada, at the time of this

writing (March 2016), the Licensed Natural Health Products Database (LNHPD) listed 650 licensed NHPs that contain *U. dioica* herb or root as an active ingredient, and 54 NHPs that contain *U. urens* herb or root as an active ingredient.⁸¹

There is evidence that nettle production is occurring increasingly through sustainable wild-collection methods and sustainable agriculture practices. Cultivated certified-organic nettle is presently coming to market from farms in Germany,⁸² the UK,⁸³ Egypt,²⁶ Canada, Mexico, and the US,²³ and many wild-collection operations have implemented the “organic wild-crop harvesting practice standard” for certified-organic wild-collected nettle, particularly in Albania, Bosnia and Herzegovina, Bulgaria, Hungary, Kazakhstan, Macedonia, and Poland. Several organic-wild nettle operations have also implemented the FairWild Standard, which includes criteria not only for ecological sustainability, but also for economic and social sustainability for the harvesters and their communities.¹² There is also cultivated nettle with fair trade certification coming from Egypt.²⁵ With the increasing uptake of credible sustainability standards that help protect the ecosystems where nettle and other medicinal plants are harvested, the tradition of wild-collection has a chance to continue, as local and rural people begin to rely on better income through organic and fair trade pricing structures. HG

—Gayle Engels and Josef Brinckmann

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American Botanical Council Launches ‘Herbal MediaWatch’ Online News Feed

New ABC educational service highlights timely, relevant medicinal plant-related headlines

The American Botanical Council (ABC) is pleased to announce a new feature on its website — Herbal MediaWatch, a continually updated compilation of headlines from media stories relevant to virtually all fields of herbal medicine represented in ABC’s diverse member base.

Herbal MediaWatch highlights articles from a range of sources, from leading national and international newspapers and magazines to industry publications, research websites, and blogs. The headlines featured in each Herbal MediaWatch post are organized by topic, including the following categories: Science & Research, Legal & Regulatory, Community & Industry, Cannabis Update, Dietary Supplements, Consumer & Popular, Quality Control & Adulteration, Trends & Technology, Environment & Conservation, Traditional Medicine, and more.



Herbal MediaWatch is free and available to the public, a benefit of ABC’s nonprofit educational mission. A link to each news update will be posted to ABC’s Facebook and Twitter feeds.

“It is ABC’s intention that Herbal MediaWatch helps individuals, both personally and professionally, keep up to date with the exploding amount of coverage the fascinating and important area of health and health-related practices is receiving in the media,” said Denise Meikel, ABC’s director of development.

ABC members, registered users of the extensive ABC website, and others can access ABC’s HerbalMediaWatch by liking ABC on Facebook and/or following ABC’s Twitter feed.

As with the Media Watch summaries featured in each monthly issue of ABC’s HerbalEgram and weekly issue of ABC’s Herbal News & Events, the links included in each Herbal MediaWatch update are live at the time of posting. However, some news organizations and websites remove articles and disable links at various times. Accordingly, ABC posts the links to the articles as an educational service, but cannot guarantee their longevity or the accuracy of the information in them. HG

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Leading International Natural Products Companies Participate in ABC's Adopt-an-Herb Program

Brassica Protection Products, HG&H Pharmaceuticals, and Nature's Way support ABC's HerbMedPro database, helping provide timely updates of scientific and clinical research

The American Botanical Council (ABC) gratefully acknowledges three international natural products companies for their participation in and support of ABC's Adopt-an-Herb Program: Brassica Protection Products LLC (Baltimore, Maryland), a leader in the research and development of nutritional ingredients derived from cruciferous vegetables; HG&H Pharmaceuticals (South Africa), producers of Zembrin, a standardized extract of the South African herb *Sceletium*; and Nature's Way (Lehi, Utah), a leading herb and dietary supplement brand and member of the Schwabe Group.

HerbMedPro is a comprehensive, interactive online database that provides access to important scientific and clinical research data on the uses and health effects of more than 250 herbs and medicinal plants. Each adopted herb is continuously researched for new scientific articles and pharmacological, toxicological, and clinical studies, ensuring that its HerbMedPro record stays current and robust. The result is an unparalleled resource for researchers, health professionals, industry, consumers, and all members of the herbal and dietary supplements community.

Through their respective adoptions, Brassica Protection Products, HG&H Pharmaceuticals, and Nature's Way are helping ABC keep its unique HerbMedPro database up to date with the latest scientific and clinical research on a total of seven medicinally important botanicals: broccoli (*Brassica oleracea*, Brassicaceae), scelletium (*Sceletium tortuosum*, Aizoaceae), black cohosh (*Actaea racemosa*, Ranunculaceae), ginkgo (*Ginkgo biloba*, Ginkgoaceae), hawthorn (*Crataegus* spp., Rosaceae), lavender (*Lavandula angustifolia*, Lamiaceae), and umckaloabo (*Pelargonium sidoides*, Geraniaceae).

Brassica Protection Products' Adoption Supports Significant HerbMedPro Updates for Broccoli

ABC recognizes the adoption of broccoli by Brassica Protection Products, a nutritional supplements company that focuses on the research and development of ingredients derived from cruciferous vegetables, especially broccoli.

Broccoli, a cultivar group in the same species as cabbage (*Brassica oleracea* var. *capitata*), cauliflower (*B. oleracea* var. *botrytis*), and Brussels sprouts (*B. oleracea* var. *gemmifera*), dates from the 6th century, but it was not introduced into the North American produce market until the 1920s. It is relatively high in vitamins A, B, and C, as well as calcium, carotene, iron, magnesium, potassium, and fiber. Broccoli is also a rich source of glucosinolates and isothiocyanates that have well-documented health benefits.

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Glucoraphanin, a phytonutrient found in broccoli, is the precursor to sulforaphane, a natural inducer of phase 2 detoxification enzymes, which support the body's detoxification pathways to help eliminate free radicals and help protect the body from environmental pollutants.

"For more than 15 years, Brassica has been dedicated to delivering consistently, high-quality sources of glucoraphanin from broccoli seeds through our truebroc ingredient brand," said Tony Talalay, CEO of Brassica Protection Products. "We are deeply committed to making the extensive health benefits broccoli can deliver to our bodies, including long-lasting antioxidant activity and protection against oxidative stress, easily accessible for consumers. We're excited to partner with the American Botanical Council to further educate academic and consumer communities about broccoli and its important phytonutrient glucoraphanin, which produces sulforaphane in the body."

Founded in 1997, Brassica Protection Products extracts its glucoraphanin from broccoli seeds and sells its truebroc glucoraphanin for use in supplements, functional foods, and beverages. Brassica also markets Brassica Tea and Coffee, gourmet tea and coffee containing truebroc glucoraphanin.

"ABC is pleased to partner with Brassica Protection Products to recognize the fast-growing science on broccoli and to curate decades of scientific and clinical research in HerbMedPro," said Mark Blumenthal, ABC's founder and executive director. "Broccoli is one of the most extensively studied food plants. This program will make broccoli research more easily available to health care professionals, researchers, consumers, and industry members who are hungry to learn about this crucifer's compelling health benefits."

More information about Brassica Protection Products can be found at www.brassica.com.



HG&H Pharmaceuticals Adopts Scelletium, a South African Herb with Mood-balancing Properties

HG&H Pharmaceuticals continues to support ABC's Adopt-an-Herb program through its adoption of the South African herb *Sceletium tortuosum*.

Scelletium is a perennial in the ice plant family (Aizoaceae). The indigenous San and Khoikhoi peoples were the first to

discover the plant's medicinal benefits, while Europeans later used it to make a psychotropic tincture (i.e., an extract used to affect mental processes). Also known by its local name *kanna*, sceletium has been used in traditional South African medicine to relieve thirst, hunger, and fatigue, to elevate mood, and as a sedative. Most recent scientific research and human clinical trials on sceletium have focused on the anxiety-reducing and mood-enhancing effects of Zembrin, the proprietary sceletium extract produced by HG&H.

Founded in 2006 by Nigel Gericke, MBBCh, and Deon Hofmeyr, HG&H Pharmaceuticals uses a rigorous evidence-based approach to scientifically and medically validate the safety, efficacy, and quality of Zembrin. HG&H was the first company to be granted an integrated export and bioprospecting permit from the South African government, and Zembrin is the only sceletium product on the market endorsed by the South African San Council because of a formal benefit-sharing agreement between the company and the tribe.

"ABC is deeply grateful to HG&H Pharmaceuticals and our good friend Dr. Nigel Gericke in South Africa for their support of ABC by ensuring that we are able to keep up with new research on this emerging herb," said Blumenthal. "The company is approaching the creation of a new phytomedicine from a traditional herb in an admirable manner, using sustainable sources of supply, creating benefit-sharing agreements with indigenous peoples, and subjecting their extract to human clinical trials to document safety and efficacy."

More information about HG&H Pharmaceuticals can be found at: www.zembrin.com.

Nature's Way Adopts Five Botanicals through the Adopt-an-Herb Program

Nature's Way, a premier supplement manufacturer and member of the Schwabe Group, has adopted five herbs in ABC's HerbMedPro database: black cohosh, ginkgo, hawthorn, lavender, and umckaloabo.

The botanicals supported by Nature's Way include some of the most popular phytomedicines on the market. Their uses are varied: black cohosh is popular for menopausal support in middle-aged and older women; hawthorn leaf and flower extract is recognized for its cardiotonic benefits; the South African herb umckaloabo root strengthens the immune system and supports recovery from colds and respiratory infections; lavender flower essential oil can be applied topically, inhaled through aromatherapy, or taken internally for relief from anxiety; and ginkgo leaf standardized extract is one of the



most well-known herbs on the market, famous for its cognitive-enhancing abilities.

"ABC is deeply grateful to Nature's Way for its long-standing and strong support for herb and phytomedicinal research," said Blumenthal. "Nature's Way and its parent company Dr. Willmar Schwabe Pharmaceuticals in Germany are recognized world leaders in medicinal plant research, being the first-ever company to receive ABC's prestigious Varro E. Tyler Commercial Investment in Phytomedicinal Research Award in 2007. Nature's Way's/Schwabe's research and education commitment help to benefit millions of people who look to phytomedicines for self-care and in health care."

Since its founding in 1968, Nature's Way has sought to balance traditional knowledge with scientific advancements. It was the first major supplement company in the United States to be certified as an organic processor and certified by TRU-ID, an independent authenticity testing program. The company also is certified by the Non-GMO Project and NSF International. In 2009, Nature's Way integrated with Dr. Willmar Schwabe Pharmaceuticals, a global leader in plant-based medicine.

More information about Nature's Way can be found at www.naturesway.com.

Support Continues to Grow for ABC's Adopt-an-Herb Program

Brassica Protection Products, HG&H Pharmaceuticals, and Nature's Way are three of the 39 companies that have supported ABC's educational efforts to collect, organize, and disseminate reliable, traditional, science-based, and clinical information on herbs, medicinal plants, and other botanical- and fungal-based ingredients through the Adopt-an-Herb program. To date, 45 herbs have been adopted, ensuring that their HerbMedPro records contain the latest scientific and clinical research data.

HerbMedPro is available to ABC members at the Academic level and higher. Its "sister" site, HerbMed, is free and available to the general public. In keeping with ABC's position as an independent research and education organization, herb adopters do not influence the scientific information that is compiled for their respective adopted herbs.

Individuals, companies, and organizations interested in the Adopt-an-Herb program can contact ABC Development Director Denise Meikel for

more information at (512) 926-4900, ext. 120, or by email at denise@herbalgram.org.

To learn more about each of these adopted herbs, visit ABC's HerbMedPro databases at www.herbalgram.org. HG

—ABC Staff



Black Cohosh
Actaea racemosa

Ginkgo
Ginkgo biloba

Hawthorn
Crataegus spp.

Umckaloabo
Pelargonium sidoides

Lavender
Lavandula angustifolia

ADOPT-AN-HERB

HerbMedPro™

P R O G R A M

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

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


















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

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

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



Herbal Adopters

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

Become an adopter today!

Visit us at www.herbalgram.org/adopt

Adopt-an-Herb is an exciting and mutually beneficial way to support ABC!

Contact Denise Meikel at 512-926-4900 x120 or by email at denise@herbalgram.org

Arnica *Arnica montana*
Photo ©2016 Steven Foster

Herbal Adopters

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

American Botanical Council Presents Annual Botanical Excellence Awards

The American Botanical Council (ABC) hosted its 11th annual Botanical Celebration and Awards ceremony on March 10, 2016, at the Hilton Anaheim in Anaheim, California, in conjunction with the Natural Products Expo West trade show. This popular event celebrated outstanding contributions to the herbal community with the presentation of its prestigious ABC Botanical Excellence Awards. The event also provided a unique venue to acknowledge the much-appreciated support of ABC's Sponsor Members.

The Celebration created an opportunity for approximately 350 guests to come together in support of ABC. Attendees included ABC Sponsor Members, members of the ABC Board of Trustees, Advisory Board, and Director's Circle, and many others. The evening, which was filled with intriguing conversations, vegetarian hors d'oeuvres, and a wide variety of cocktails, was capped off with a short ceremony during which the Excellence Awards were presented.

The Varro E. Tyler Commercial Investment in Phytomedicinal Research Award was presented by ABC Chief Science Officer Stefan Gafner, PhD, to MediHerb, an Integra Healthcare brand, of Warwick, Australia. Michelle Sackim, Brand Manager - Retail Brands (NZ), accepted the award on behalf of the phytomedicinal company.

Ed Smith, herbalist and co-founder of Herb Pharm, was presented with the second ABC Champion Award. ABC Founder and Executive Director Mark Blumenthal introduced Smith, who spoke passionately about herbs and their positive impact on the health and lives of millions of people.

The fourth annual Mark Blumenthal Herbal Community Builder Award was given to Michael Tierra, LAc, OMD, AHG, widely considered the primary founder of the American Herbalists Guild (AHG), a group of professional herbal practitioners. Tierra accepted the award and expressed his deep gratitude for being recognized by ABC for his decades of educational efforts in training thousands of herbalists.

For the first time, the James A. Duke Excellence in Botanical Literature Award was presented to a book focused on aromatherapy: *Clinical Aromatherapy: Essential Oils in Healthcare*, 3rd ed., by Jane Buckle, PhD, RN. Buckle's acceptance was delivered to the audience via video.

Finally, Gafner introduced the

11TH ANNUAL

AMERICAN BOTANICAL
Celebration

Norman R. Farnsworth Excellence in Botanical Research Award recipient, John Thor Arnason, PhD. Arnason, a professor of biology at the University of Ottawa in Ontario, Canada, has made significant contributions to the medicinal plant-related scientific literature, particularly in the field of ethnobotany. Arnason also appeared on video to accept his award.

Additional details about the ABC Awards and recipients:

Aromatherapy Book for Clinicians Receives Duke Award for Excellence in Botanical Literature

Clinical Aromatherapy: Essential Oils in Healthcare, 3rd ed., was written by Jane Buckle, PhD, RN, and published by Churchill Livingstone in 2015.

The ABC James A. Duke Excellence in Botanical Literature Award was created in 2006 to honor noted economic botanist and author James A. Duke, PhD. It is awarded annually to books that contribute significantly to the medicinal plant-related literature, and the fields of botany, taxonomy, ethnobotany, phytomedicine, and/or other disciplines. Along with his many other prestigious career achievements in economic botany and ethnobotany, and decades of work at the United States Department of Agriculture, Duke has authored more than 30 reference and consumer books. He is also a co-founding member of ABC's Board of Trustees, and currently serves as Director Emeritus.

Clinical Aromatherapy is the first completely peer-reviewed and evidence-based book on the clinical uses of essential oils. "The book is intended to give an overview of research into the clinical use of essential oils and how they are currently being used in various hospital departments," said Buckle. "It is intended for health professionals who might be interested in what clinical aromatherapy could add to



their practice and any aromatherapist who wants to know about modern research.”

“I am deeply grateful to the reviewers who gave their time and advice so generously and made the book what it is,” Buckle said. “My aim has always been to put the ‘clinical’ into clinical aromatherapy. It is the chemistry of an essential oil that gives it its therapeutic properties and may indicate the safest way to use it.”

Herbalist and aromatherapist Mindy Green reviewed *Clinical Aromatherapy* in *HerbalGram* issue 107. “[Buckle] provides an excellent overview of how essential oils can contribute to a healthier medical system, enhancing patient care and lowering medical costs at a critical time in this community,” Green wrote. “[T]his text examines issues within conventional and integrative medical practices with applications relevant to a variety of settings and circumstances. ... I highly recommend this book, both as a resource and a highly informative read; the compilation of bibliographic citations alone is significant.”

Blumenthal similarly praised the work. “Jane Buckle’s book elevates the use of essential oils to a high standard and provides a strong research basis for clinical applications,” he said.

Past recipients of ABC’s Duke Award include: *Ancient Pathways, Ancestral Knowledge* (McGill-Queens University Press, 2014); *Principles and Practice of Phytotherapy*, 2nd ed. (Churchill Livingstone, 2013); *Medicinal Plants and the Legacy of Richard E. Schultes* (Missouri Botanical Garden, 2012) in the reference/technical category and *Smoke Signals* (Scribner, 2012) in the consumer/popular category; *Healing Spices* (Sterling Publishing, 2011) in the consumer/popular category and the American Herbal Pharmacopoeia’s *Botanical Pharmacognosy* (CRC Press, 2011) in the reference/technical category; *Botanical Medicine for Women’s Health* (Churchill Livingstone, 2010); *An Oak Spring Herbaria* (Oak Spring Garden Library, 2009); and *Mabberley’s Plant-Book*, 3rd ed. (Cambridge University Press, 2008).

MediHerb Receives Tyler Award for Investment in Phytomedicinal Research

MediHerb, a division of Integria Healthcare, is a leading Australian natural products company that specializes in research-based botanical medicines designed by and for professional health care providers and clinicians.

“This is a great honor and a much-appreciated reward for our many years of research into the phytochemistry, quality, and therapeutic properties of medicinal plants,” said Kerry Bone, a professor and the co-founder of MediHerb and director of research and development.

The ABC Varro E. Tyler Commercial Investment in Phytomedicinal Research Award was

created to honor one of the most respected scientists in late-20th century herbal medicine and pharmacognosy (the study of medicines of natural origin). Professor Tyler was an early trustee of ABC, dean of the Purdue University College of Pharmacy and Pharmaceutical Sciences for 20 years, and vice president of academic affairs at Purdue. He was the senior author of six editions of the leading textbook in the field, as well as numerous other professional and popular books and articles in the academic literature. Tyler encouraged scientific and product integrity, and envisioned a rational phytomedicinal health care sector that valued the proper evaluation of products’ quality, safety, and efficacy.

“I am a firm believer that herbal therapy (or phytotherapy) should always be adding to its clinical evidence base, but in a way that respects and is compatible with its traditional principles,” Bone said. “Understanding complex modern diseases in their totality and applying subtle but effective, chemically complex interventions underpinned by that knowledge is, to me, the height of rationality. This has always guided our research approach.”

Integria Healthcare invests more than \$5 million in research and development each year, according to the company. Echinacea Premium and Kava Forte are two of



Integria’s Michelle A. Sackim, Brand Manager/ Retail Brands (NZ), and Neil Dalton, National Account Operations Manager (AU), display the ABC 2015 Tyler Research Award received by MediHerb. Photo ©2016 ABC



MediHerb's most popular clinically studied natural products.

"MediHerb and Integria Healthcare have supported around 25 human clinical trials of MediHerb products, 22 of which have been published in peer-reviewed journals," said Hans Wohlmuth, PhD, manager of research and development at Integria. "In addition to clinical trials, MediHerb has funded a large number of phytochemistry and in vitro studies on botanicals. Much of this work has focused on quality issues, an area in which MediHerb has always been a leader."

Both Bone and Wohlmuth are members of the ABC Advisory Board.

"ABC is pleased to recognize MediHerb for its strong commitment to conducting clinical research on its herbal products," Blumenthal said. "I consider MediHerb to be a prime example of Professor Tyler's wish that herb and phytomedicinal companies document the efficacy of their products through appropriate clinical trials."

Gafner added: "MediHerb is a company that has invested millions of dollars to back up the benefits of herbal medicine with sound science. This philosophy of testing products in human clinical studies as a basis for rational phytotherapy makes MediHerb a much-deserving awardee."

Previous recipients of the ABC Tyler Award include Soho

Flordis International (2014); Wakunaga Pharmaceutical Company, Ltd. (2013); Horphag Research (2012); Bioforce AG (2011); New Chapter, Inc. (2010); Bionorica AG (2009); Indena SpA (2008); and Dr. Willmar Schwabe Pharmaceuticals (2007).

John T. Arnason, Ethnobotanical Expert, Receives Farnsworth Award for Excellence in Botanical Research

John Thor Arnason, PhD, is a professor of biology at the University of Ottawa in Ontario, Canada, where his lab specializes in the phytochemistry and biological activity of plants.

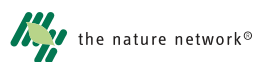
ABC presents this award each year to a person who has made significant contributions to research in the fields of ethnobotany and/or medicinal plant research.

Norman Farnsworth, PhD, who died in 2011 at 81, was one of the co-founding members of ABC's Board of Trustees, a research professor of pharmacognosy, and a senior university scholar in the College of Pharmacy at the University of Illinois at Chicago.

"I knew Norman Farnsworth very well," Arnason said. "I really admired his efforts to make traditional [herbal] medicine a recognized field of study in North America."

Arnason's career began in the late 1970s when he worked

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with Maya healers in Belize. He then did post-doctoral work in Vancouver with Neil Towers, PhD, a pioneer of botanical medicine. In 1980, Arnason started his own lab at the University of Ottawa. He and colleagues studied the ethnobotany of eastern Canada and the adjacent United States. They published an article, "Use of plants for food and medicine by Native Peoples of eastern Canada," which identified more than 400 medicinal plants with 2,000 uses.

In the 1990s, Blumenthal asked Arnason to be part of ABC's Ginseng Evaluation Project, which looked at the quality of ginseng (*Panax* spp., Araliaceae) root products available on the North American market. Also in the 1990s, Arnason and his colleagues revised details of the taxonomy, phytochemistry, and biological activity of the genus *Echinacea* (Asteraceae).

Now, Arnason is working with the northern Cree people, in collaboration with Pierre Haddad, PhD, to look for new treatments for diabetes, a serious health problem on native reserves in Canada and the US. "What we found is that some of the plants have completely novel compounds in them that are as active as standard diabetic drugs," Arnason said.

In addition, Arnason's team is working with Costa Rican botanists and Maya healers to find mental health treatments. This work involves plants in the little-studied Marcgraviaceae family. "The plants in this family are very good at reducing anxiety," Arnason said. He has also worked with traditional healers in Borneo, East Timor, and Togo.

"Thor exemplifies some of the best aspects of medicinal plant research," Blumenthal said. "He is an ethnobotanist, working with indigenous peoples who share their traditional plant wisdom, and he is also a laboratory scientist who explores the chemistry of these plants."

Gafner added: "I consider Thor to be one of the foremost North American researchers in ethnobotany. He has also contributed to our knowledge of many of the more widely used botanicals. But most of all, he is a very generous and humble person."

Past recipients of the Farnsworth award include: Harry Fong, PhD (2014); Gordon Cragg, PhD (2013); De-An Guo, PhD (2012); Djaja Soejarto, PhD (2011); A. Douglas Kinghorn, PhD (2010); Rudolf Bauer, PhD (2009); Ikhlas Khan, PhD (2008); Hildebert Wagner, PhD (2007); Edzard Ernst, MD, PhD (2006); and Joseph Betz, PhD (2005).

'Herbal' Ed Smith, Medical Herbalist and Herb Pharm Co-founder, Receives ABC Champion Award

Ed Smith, medical herbalist and co-founder of Herb Pharm, an herbal products manufacturing company in Williams, Oregon, received ABC's second Champion Award. In addition to Herb Pharm's unwavering support of ABC and its educa-

tional mission and programs, Smith recently made a generous personal donation.

The ABC Champion Award was created to recognize an individual or individuals who have been outstanding supporters of ABC, helping the organization promote and achieve its mission. The generosity of ABC's friends and members is vital to the nonprofit's continued success and growth.

"I have always appreciated Ed's strong personal and professional commitment to herb ingredient quality, and I consider him to be one of the best herbal medicine makers in North America," said Blumenthal. "Ed is a highly passionate advocate for the herbal agenda."

Smith's career spans more than four decades of learning and teaching about herbs and their benefits. During this time, he has given countless lectures, held herb classes, and traveled many miles. Smith has studied and sourced herbs in many regions of the world, including western Europe, northern and eastern Africa, Asia, the Indian subcontinent, Central and South America, the Caribbean, and the South Pacific Islands.

"The things I saw and experienced definitely sparked my passionate interest in herbs and seeded my life and work as an herbalist," said Smith.

Smith was a founding member of AHG, taught at the California School of Herbal Studies for more than a decade, and co-founded Herb Pharm in 1979. Smith has worked with some of the most highly respected herbalists and teachers in the community, including renowned herbalist John Christopher, with whom he co-founded the Foundation for Natural Living and the Pacific College of Naturopathic Medicine. He has also worked with Ann Wigmore, the founder of the Hippocrates Health Institute.

"I am very happy to be receiving the ABC Champion Award from the American Botanical Council," said Smith. "I'm honored by this recognition of my and Herb Pharm's support of ABC and its important work for herbal medi-

Ed Smith, co-founder of Herb Pharm, accepts the 2015 ABC Champion Award. Photo ©2016 ABC



cine consumers, the American herb industry, and the herbal academic and sciences community.”

“Ed Smith has been a close personal friend and professional colleague for almost 40 years, since we met at an Herb Trade Association herb symposium at the University of California at Santa Cruz in 1978,” Blumenthal said. “From the very beginning of ABC in 1988, he and his company Herb Pharm have always been at the forefront of companies that have advocated for ABC and its unique nonprofit educational mission to promote the responsible use of herbs and phytomedicines.”

ABC created the Champion award in 2015. The first recipient was Terry Lemerond, founder of Europharma, Inc. and Enzymatic Therapy.

Michael Tierra, Author, Clinician, and Herbal Advocate, Receives ABC Community Builder Award

The annual award, named for ABC Founder and Executive Director Mark Blumenthal, is given to an individual who has played a significant role in creating a sense of community among herbalists, researchers, members of the herb and natural products communities, and related groups, who work in the area of medicinal plants.

Tierra said he is “very honored” to receive the award. “Coming from *HerbalGram* and Mark Blumenthal, as a representative of the American Botanical Council, an organization that I’ve followed for many years with a lot of respect, it means a lot to me,” he said.

Tierra is an author, licensed acupuncturist, doctor of Oriental medicine, and an AHG professional member. He began studying herbs in 1968 while living in an interdependent community called Black Bear Ranch in northern California. He learned about various medicinal plants from the Karuk and Yurok Native Americans, and eventually began harvesting the plants and giving them back to the Native community, which, at that time, had forgotten much of its traditional herbal knowledge.

He then studied with herbalists John Christopher and Norma Myers, and, after moving to San Francisco, began teaching herbal medicine and treating patients. He also studied with Chinese herbalist Foon Lee Wong. After the California law that legalized the practice of acupuncture (and the use of herbal medicines in the practice) was passed in 1978, Tierra was among the first to be licensed.

He moved to Santa Cruz where he studied Ayurvedic medicine with Baba Hari Dass, and, in 1983, published *The Way of Herbs* (Lotus Press), based on his clinical experiences. In the book, which is still in print and has become a best-seller, he began advertising his correspondence course. This course eventually grew into the East West School of Planetary Herbology, which combines Ayurvedic, Western, and Chinese herbal medicine systems in a unique way. According to Tierra, at least 9,000 students have taken his course worldwide.

“My nature has always been such that any information I learn, I’m always eager to share with the world with a great deal of zeal and enthusiasm. And I’m always eager to empower other people who want to be herbalists,” Tierra said.

In 1989, when herbs in North America were not being used in any organized way clinically or professionally, Tierra and other herbalists founded AHG, which gives memberships to professional herbalists based on peer-reviewed evaluations.

“Michael is considered the founding force of AHG, and for that very reason alone, he warranted consideration for our Community Builder award,” said Blumenthal. “He is one of North America’s most venerated herbalists, and his many writings, teachings, and activities have resulted in creating a growing community of professional herbal practitioners throughout the United States and beyond.”

About a year and a half ago, Tierra started the East West Free Herbal Clinic to provide free herbal treatments to underserved members of the community, including the homeless, mentally handicapped, and veterans. The clinic also trains young herbalists to treat patients, harvest herbs, and make herbal preparations. Tierra donates plant materials to the cause and has persuaded companies like Threshold Enterprises and Bio Essence Corporation to donate as well. “And that’s been quite a deep level of fulfillment in my life at this point,” he said.

Tierra is also an avid classical pianist, choral conductor, and composer. He recently commissioned a piece for solo piano on the theme of herbs and healing, which he premiered on March 20 in Santa Cruz.

Past recipients of ABC’s Mark Blumenthal Community Builder Award are Loren Israelsen (2014), president and founder of the United Natural Products Alliance, Herb Pharm co-founder Sara Katz (2013), and herbalist and author Rosemary Gladstar (2012). HG



Michael Tierra (right), shown with Mark Blumenthal, is the recipient of ABC's 2015 Community Builder Award.
Photo ©2016 ABC

—ABC Staff

University Pharmacy Research Centers Endorse Botanical Adulterants Program

The American Botanical Council (ABC) is pleased to announce the endorsement of the ABC-AHP-NCNPR Botanical Adulterants Program by two leading interdisciplinary pharmacy programs: the Center for Natural Products Technologies (CENAPT) at the University of Illinois at Chicago (UIC) School of Pharmacy and the Biodiversity and Medicines research cluster at the University College London (UCL) School of Pharmacy in the United Kingdom.

The Botanical Adulterants Program is a coalition of three nonprofit groups: ABC, the American Herbal Pharmacopoeia (AHP), and the University of Mississippi's National Center for Natural Products Research (NCNPR). More than 175 US and international parties have supported the Program, which educates and provides advice about the various challenges related to adulterated herbs, botanical extracts, and other botanical ingredients in commerce. These parties include nonprofit organizations, analytical laboratories, professional scientists, integrative health care practitioners, natural products industry members, and others.

The CENAPT is an interdisciplinary botanical pharmacognosy research program funded by the US National Institutes of Health's (NIH's) Office of Dietary Supplements (ODS) and National Center for Complementary and Integrative Health (NCCIH). According to its website, the center aims to "provide access to advanced technologies and resources that can help the [natural products] research communities in finding solutions, overcoming methodological obstacles, and connecting scientists ... with state-of-the-art methodologies."

CENAPT Director Guido Pauli, PhD, and Chun-Tao Che, PhD, the Norman R. Farnsworth Professor of Pharmacognosy at UIC, expressed their support for the Program in a letter to ABC Founder and Executive Director Mark Blumenthal. "We look forward to working with you and strengthening our existing collaborative relationship by providing expertise to the BAP program," they wrote. "Our CENAPT and the collaborating laboratories in our College are in a strong position to provide orthogonal [independent] information and innovative perspectives on the botanical adulteration topic."

The UCL School of Pharmacy's Biodiversity and Medicines cluster, also an interdisciplinary research program, focuses on the study of natural products and analytical method development. Among its primary goals, the group investigates the quality and safety of herbal medicines, historical uses of medicinal plants, disease mechanisms, and new anti-inflammatory, anti-cancer, and anti-infective compounds.

"Biodiversity and Medicines brings together experts in biological pharmacy, including medicinal biochemistry, molecular biology, microbiology, natural product research, metabolomics, pharmacognosy, ethnopharmacology, and biomimetic synthesis," wrote Michael Heinrich, PhD, professor of pharmacognosy and head of Biodiversity and Medicines. "I am happy



to let you know that the group has agreed to endorse the BAP."

"These two academic research groups are among the leading medicinal plant research centers in the world," said Blumenthal. "We are profoundly grateful for their recognition of the significance of our Program, and their willingness to collaborate with us."

ABC Chief Science Officer Stefan Gafner, PhD, added: "Much of what we know about herbal dietary supplement adulteration in the marketplace comes from laboratory investigations initiated by academia. Both UIC and UCL have established themselves as pioneers in the characterization of

botanical materials by applying cutting-edge analytical technologies to measure chemical profiles of herbal extracts, thus providing enhanced tools to detect adulteration. Therefore, we are very honored by their endorsement of and participation in our program."

In addition to their support of the Botanical Adulterants Program, Pauli, Che, and Heinrich are also members of the ABC Advisory Board.

The ABC-AHP-NCNPR Botanical Adulterants Program has published extensively peer-reviewed and referenced articles on the history of adulteration, adulteration of the

herbs black cohosh (*Actaea racemosa*, Ranunculaceae) and skullcap (*Scutellaria lateriflora*, Lamiaceae), and adulteration of bilberry (*Vaccinium myrtillus*, Ericaceae) fruit extract and so-called "grapefruit" (*Citrus × paradisi*, Rutaceae) seed extract." These open-access articles are available on the Program's webpage.

The Program also publishes a quarterly newsletter, the Botanical Adulterants Monitor, which highlights new scientific publications related to botanical authenticity and analysis to detect possible adulteration, recent regulatory actions, and Program news. Issue 6 of the Monitor was released in January 2016.

In November 2015, the Botanical Adulterants Program published its third Laboratory Guidance Document (LGD) on black cohosh. The purpose of this ongoing series is to help industry and third-party analytical laboratories determine the most effective analytical methods for detecting adulteration and authenticating botanical raw materials and extracts. The first two LGDs were on skullcap and bilberry extract, respectively.

Additional publications from the Program are scheduled for release in the coming weeks and months. HG

—ABC Staff



New Series of 'Botanical Adulterants Bulletins' to Help Raise Awareness of Current Herb Adulteration

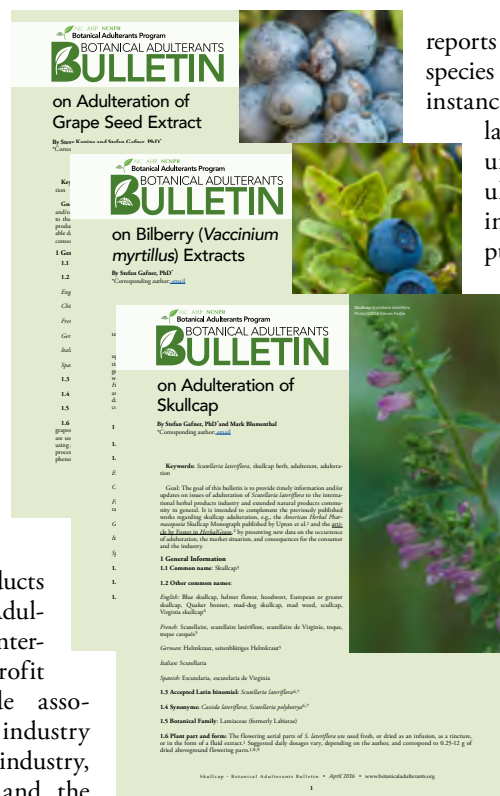
First Bulletins on grape seed extract, bilberry extract, and skullcap provide timely information and updates on adulteration issues to the international herb industry and natural products community

The ABC-AHP-NCNPR Botanical Adulterants Program announces a new series of reviews on adulteration of botanical ingredients. These documents, the Botanical Adulterants Bulletins (BABs), provide information about adulteration of plant materials that have not been covered by the Program (e.g., grape [*Vitis vinifera*, Vitaceae] seed extract), or that complement previously published reviews (e.g., bilberry [*Vaccinium myrtillus*, Ericaceae] fruit extract and skullcap [*Scutellaria lateriflora*, Lamiaceae] herb).

The goal of the Bulletins is to provide accounts of ongoing issues related to botanical identity and adulteration, thus allowing quality control personnel and lab technicians in the herbal medicine, botanical ingredient, and dietary supplement industries to be informed about adulteration problems that are apparently widespread and/or that may imply safety concerns.

The Bulletins begin with general information on the plant species, followed by data on cultivation, harvest, and market size. The main section covers known adulterants, frequency of adulteration (when known), possible therapeutic and/or safety issues with the adulterating species, and analytical approaches to detect the adulterant.

The American Botanical Council (ABC)-American Herbal Pharmacopoeia (AHP)-National Center for Natural Products Research (NCNPR) Botanical Adulterants Program (BAP) is an international consortium of nonprofit professional organizations, trade associations, analytical laboratories, industry members, and others that advises industry, researchers, health professionals, and the public about the various challenges related to adulterated botanical ingredients sold in commerce. To date, more than 175 US and international parties financially support or otherwise endorse the Program. "The Botanical Adulterants Bulletins represent a new phase of the Botanical Adulterants Program," said Mark Blumenthal, founder and executive director of ABC and director of the Program. "Compared to our extensive Laboratory Guidance Documents, the Bulletins are a more rapid means of confirm-



ing suspected and/or alleged adulteration and will become one of the key publications of the Program's educational activities."

Stefan Gafner, PhD, ABC chief science officer and BAP technical director, said: "The data included in the Botanical Adulterants Bulletins are predominantly from published reports on adulteration of a particular plant species or botanical extract. However, in some instances, industry companies and analytical laboratories have been forthcoming with unpublished information in their particular areas of expertise, adding valuable information to the knowledge already published in the peer-reviewed literature, thus making each Bulletin a more informative and relevant document."

In keeping with the Program's tradition of extensive peer-review of its publications, a total of 17 expert reviewers provided input on the first three Bulletins, with each Bulletin being reviewed by at least 13 experts.

"We are deeply grateful to the many experts from academia, government, and industry who donated their time and energy to provide peer-review services to help ensure the accuracy of these Bulletins," said Gafner. "With their invaluable assistance, these documents have a significantly high degree of credibility and authority."

The Botanical Adulterants Program plans to release additional Bulletins in the coming months. Currently in peer-review are the Bulletins on arnica (*Arnica montana*, Asteraceae) flower, black cohosh (*Actaea racemosa*, Ranunculaceae) root and rhizome, and goldenseal (*Hydrastis canadensis*, Ranunculaceae) root and rhizome. HG

—ABC Staff

on Adulteration of Grape Seed Extract

By Steve Kupina^a and Stefan Gafner, PhD^{b*}

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^b Technical Director, ABC-AHP-NCNPR Botanical Adulterants Program

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Keywords: *Vitis vinifera*, grape seed extract, adulterant, adulteration

Goal: The goal of this bulletin is to provide timely information and/or updates on issues of adulteration of grape seed extract (GSE**) to the international herbal products industry and extended natural products community in general. It is intended to present the available data on the occurrence of adulteration, the market situation, and consequences for the consumer and the industry.

1 General Information

1.1 Common name: Grape¹

1.2 Other common names:

English: European grape, wine grape¹

Chinese: Pu tao (葡萄)

French: Raisin

German: Traube, Weintraube

Italian: Uva

Spanish: Uva

1.3 Accepted Latin binomial: *Vitis vinifera*¹

1.4 Synonyms: *Cissus vinifera*^{2,3}

1.5 Botanical family: Vitaceae

1.6 Plant part and extract production method: The seeds of grapes, obtained as a by-product from the juice or wine industry, are used fresh or, more commonly, dried to produce a liquid extract using a solvent (e.g., water, or mixtures of water with ethanol or acetone). The liquid extract is filtered and may be subjected to further processing before it is typically spray-dried to obtain a dry extract containing high levels of naturally occurring grape seed phenolic compounds.



Grape *Vitis vinifera*
Photo ©2016 Steven Foster

1.7 General use(s): GSE is known as a dietary ingredient, and a number of commercial materials have received self-affirmed “generally recognized as safe” (GRAS) status as food additives. GSE contains phenolic compounds with antioxidant properties and is used in dietary supplements, nutritionally enhanced beverages, and functional foods. The most significant application for GSE is as an ingredient in dietary supplements (known as “food supplements” in some countries outside the United States).

2 Market

2.1 Importance in the trade: Due to the long history and widespread acceptance of grapes and wine, GSE has received acceptance almost globally as an ingredient for human consumption. It is one of the more widely used botanical extracts due to increasing scientific findings supporting its health benefits. However, it remains a specialty item relative to some global commodities. In the United States, GSE supplements have ranked among the top 20 best-selling dietary supplements in the Food, Drug, and Mass Market channel (excluding sales at Walmart) from 2008-2011 with sales between US \$1.4 million and \$2.8 million each year (see Table 1).⁴⁻⁸ Sales in the Mainstream Multi-Outlet channel (the new name for the Food, Drug, and Mass Market channel) were down to US \$1.1 million and \$0.9 million in 2013 and 2014, respectively, with GSE supplements ranking 67th in 2014. Sales in the Natural channel (excluding sales at Whole Foods Market, a major natural products retailer in the US) were US \$1.5 and \$1.3 million in 2013 and 2014, respectively, with GSE ranking 59th in 2014 (T. Smith [American Botanical Council] e-mail to S. Gafner, September 3, 2015).

2.2 Market dynamics: GSE was at the height of its popularity in the early 2000s, with global sales of US \$60 million in 2000.⁹ According to data from *Nutrition Business Journal*, sales in 2011 were approximately \$25 million.¹⁰

The largest US producer of GSE is Polyphenolics, a division of Constellation Brands. Other key players in the market in the United States and internationally include Indena, Naturex, and Nexira. A number of Chinese manufacturers (e.g., Skyherb and JF Natural) are also active in the US GSE market. The primary application for GSE in both Europe and the United States is dietary/food supplements.

2.3 Supply sources: GSE is supplied by all major grape-producing countries and regions; the main producers are the United States, Canada, Europe, South America, South Africa, and Australia.

2.4 Raw material forms: GSE is almost exclusively supplied to dietary supplement manufacturers in the form of a dry extract. The extract contains phenolic compound concentrations ranging from ca. 50-90% of the extract, and sometimes there is further characterization of the phenolic compounds. The main phenolic compounds are flavan-3-ol monomers and polymers and their gallic acid esters. The polymers are known as proanthocyanidins (PACs); the term *oligomeric proanthocyanidin* (OPC) is not well-defined, in the sense that the number of monomer units in an oligomer varies among authors, but most often it is limited to a maximum of 10 units. Grape seeds contain predominantly B-type PACs, which are flavan-3-ol polymers in which the units are linked by a single bond (see Figure 1).

The extract has a characteristically bitter and astringent taste. Various companies manufacture their own GSE from purchased grape seeds. Intentional adulteration of GSE can occur at the extraction facility in order to artificially increase the concentration of total phenols and to increase the volume by using other PAC-rich substances (see Section 3, below). Contract manufacturers for the dietary supplement and food industries purchase bulk dry GSE and produce dietary supplements and/or beverages.

Table 1: Sales data for grape seed extract dietary supplements in the United States from 2011-2014.

Channel	2011		2012		2013		2014	
	Rank	Sales [US\$]	Rank	Sales [US\$]	Rank	Sales [US\$]	Rank	Sales [US\$]
Natural ^a	n/a ^b	1,553,155	52	1,481,374	55	1,518,647	59	1,327,495
Mainstream Multi-Outlet ^{c,d}	17	1,261,907	37	3,468,122	64	1,075,951	67	900,560

^aAccording to SPINS (SPINS does not track sales from Whole Foods Market.)

^bNot available

^cAccording to SPINS/IRI (The Mainstream Multi-Outlet channel was formerly known as the Food, Drug, and Mass Market channel [FDM], exclusive of possible sales at Walmart, a major retailer in the US and beyond.)

^dData for 2012 are according to Symphony/IRI and include Walmart, club stores (Sam's, Costco), military and dollar stores. Source: T. Smith (American Botanical Council) e-mail to S. Gafner, September 2, 2015 and September 3, 2015, and reference 8.

3 Adulteration

3.1 Known adulterants: Peanut (*Arachis hypogaea*, Fabaceae) skin extract, pine (*Pinus* spp., Pinaceae) bark, green tea (*Camellia sinensis*, Theaceae) extract, and PAC-rich (e.g., propelargonidin-containing) extracts from non-grape seed sources.^{12,13}

Propelargonidins, a particular type of PAC, are found in the following plants and plant materials: raspberry (*Rubus idaeus* subsp. *idaeus* or *R. idaeus* subsp. *strigosus*, Rosaceae), strawberry (*Fragaria vesca* or *F. virginiana*, Rosaceae), common beans (*Phaseolus vulgaris*, Fabaceae), almond (*Prunus dulcis*, Rosaceae), cinnamon (*Cinnamomum verum*, Lauraceae), buckwheat (*Fagopyrum esculentum*, Polygonaceae), mountain ash (*Sorbus aucuparia*, Rosaceae) berries, hops (*Humulus lupulus*, Cannabaceae), and green tea.¹⁴⁻¹⁸ The fact that these species contain propelargonidins does not mean that they have been used as adulterants of GSE.

3.2 Information confirming adulteration: There are at least four reports (one publication and three conference presentations) on GSE adulteration to date. Villani et al. analyzed the PACs in authentic GSEs, pine bark, and peanut skin extracts, and in 21 commercial GSE products that were obtained from a variety of sources, including dietary supplement retailers, supermarkets, and online vendors.¹² In six of the commercial samples, GSE was considered to be substituted with peanut skin extract, and an additional three samples showed evidence of admixture of an ingredient containing A-type PACs, which is inconsistent with the chemical profile of GSE. Based on the evaluation of the high-performance liquid chromatography-liquid chromatography/mass spectrometry (HPLC-LC/MS) profile, the adulterant appeared to be peanut skin extract. Cases of adulteration of commercial GSEs with peanut skin extracts were also presented by Sudberg et al.¹⁹ The results were similar to those of the Villani study.¹² In addition, evidence for GSE adulteration was presented in lectures at two conferences. One lecture reported on the detection of PACs (e.g., propelargonidins) from non-grape seed sources in products labeled as GSE,¹³ while the other exposed a case of GSE spiking with gallic acid and epicatechin.²⁰

3.3 Accidental or intentional adulteration: The motivation behind purposeful adulteration in commercial products is financial gain (aka economically motivated adultera-

tion) and, in the case of GSE, to increase the concentration in PACs. Peanut skin extract, which is a high-volume byproduct of the peanut industry, is less expensive and typically available at a much greater volume than GSE. In the United States, a typical peanut mill may produce up to 17 tons of peanut skins per week, and the material sold for as little as US \$0.02/kg in 2009.²¹ For example, in China, in 2015, the price of peanut skin extract was US \$10-13/kg, pine bark extract was US \$20-22/kg, and GSE was US \$30-35/kg, although proprietary GSEs may be sold for up to US \$110/kg (X. Jin [overseas sales manager at the dietary supplement manufacturer Skyherb] e-mail to S. Gafner, August 31, 2015). Thus, a bulk distributor of GSE or another manufacturer along the value chain can take advantage of the chemical similarity between GSE and peanut skin extract since the spectrophotometric assays typically used in industry are not specific enough to discriminate between PACs from grape seed and PACs from other plant extracts. Due to reliance on non-specific proximate assays across the value chain, adulteration can go undetected by those downstream in the commodity chain (e.g., companies involved in distribution, packaging, wholesale, and retail sales).

3.4 Frequency of occurrence: There are limited data available on the extent of the adulteration from the available studies. Villani et al. analyzed 21 commercial GSE products that were obtained from online vendors and from dietary supplement retailers and supermarkets in the United States and concluded that nine products (43%) had evidence of adulteration with peanut skins.¹² In the study by Sudberg et al., out of the five commercial GSEs analyzed by high-performance thin layer chromatography (HPTLC; see Figure 2), four extracts (80%) showed bands that are characteristic of peanut skin extract.¹⁹ Using the same HPTLC approach, testing of 254 commercial GSE samples performed by Alkemist Labs, a contract analytical testing laboratory, between August 2014 and January 2016, found the presence of peanut skin extract in 67 samples (26%) (H. Johnson [laboratory director at Alkemist Labs] e-mail to S. Gafner, January 22, 2016). This suggests that GSE adulteration in the market is not uncommon.

3.5 Possible safety/therapeutic issues: The adulteration of GSE with peanut skin extracts has the potential to be harmful to consumers and damaging to the dietary supplement industry. Peanuts are a common allergen worldwide. Because of this, the US Food Allergen Labeling and Consumer Protection Act requires that all packaged food products sold in the United States that contain peanuts as an ingredient must list the word “peanut” on the label. Any peanut-containing or peanut extract-containing product that is not labeled accordingly creates a situation in which the consumer is not only deceived by buying a product that is not what it is purported to be, but also, due to the allergenic potential of peanuts in

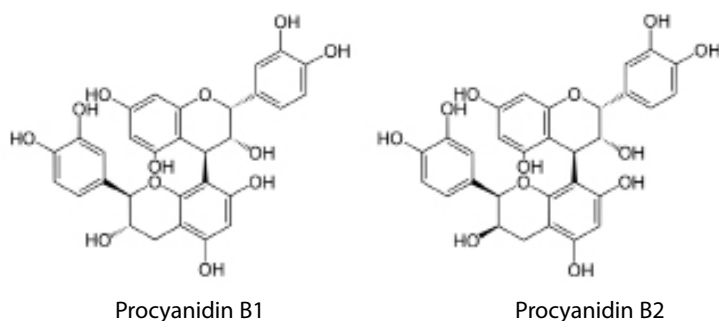


Figure 1: Chemical structures of the predominant proanthocyanidins in GSE¹⁹

general (even if the allergenicity of processed peanut skins is lower than that of peanuts themselves),^{22,23} is subjected to a potential safety risk. In the United States alone, the prevalence of people sensitive to peanuts or tree nuts was estimated to be 1.4% in 2008.²⁴ The self-determined prevalence of peanut allergies worldwide ranges from 0% in 18-month-old children in Iceland to 15% in a group of 15-17-year-olds in France.²⁵ Considering that peanut skin extract contains compounds similar to those in GSE, it is not known if efficacy is compromised.

Villani et al. also used HPLC with ultraviolet and mass spectrometric detection (HPLC-UV/MS) to obtain a chemical fingerprint of grape seed, peanut skin, and pine extracts.¹² While both analytical approaches were able to distinguish between grape seed and peanut skin extracts, GSE and pine bark extract were found to have a remarkably similar qualitative profile of PAC monomers and dimers. However, GSEs were generally found to contain larger amounts of PACs than pine bark extracts. The chromatograms were submitted to cluster analysis, and while GSEs were easily distinguished from peanut skin extracts, the lower-quality GSEs (i.e., those extracts containing lower concentrations of PACs) clustered with the pine bark extracts.¹² HPLC and HPLC-MS analyses were used by Kelm et al. to differentiate authentic and commercially obtained GSEs. Atypical peaks observed in HPLC profiles were further evaluated by HPLC-MS/MS, allowing the investigators to characterize structures that are uncharacteristic of the PACs found in grape seeds; therefore, this approach can be used to detect adulteration.¹³

For other methods, such as testing for peanut allergens, or genetic methods to detect peanut DNA, there are no published data available that have verified their fitness for the purpose of detecting GSE adulteration with peanut skin extracts.

3.7 Perspectives: Adulteration of GSE has been exposed only recently, but it seems to be widespread. According to GSE producers, many GSE products sold on the Chinese market are adulterated (X. Jin e-mail to S. Gafner, October 2, 2015). Demand for GSE is expected to increase as more health benefits are supported by human clinical studies, increasing the risk of adulteration and potentially eroding safety, efficacy, and consumer confidence if adulterants are used.

4 Conclusions

Adulteration of GSE in commercial products appears to be a significant problem. Villani et al. determined that out of the 21 commercial products tested, six samples contained no detectable quantities of GSE and were composed primarily of peanut skin extract as determined by comparison to authentic peanut skin.¹² Adulteration with peanut skin extract represents a safety concern due to the possibility of reactions to peanut allergens. In addition, peanut

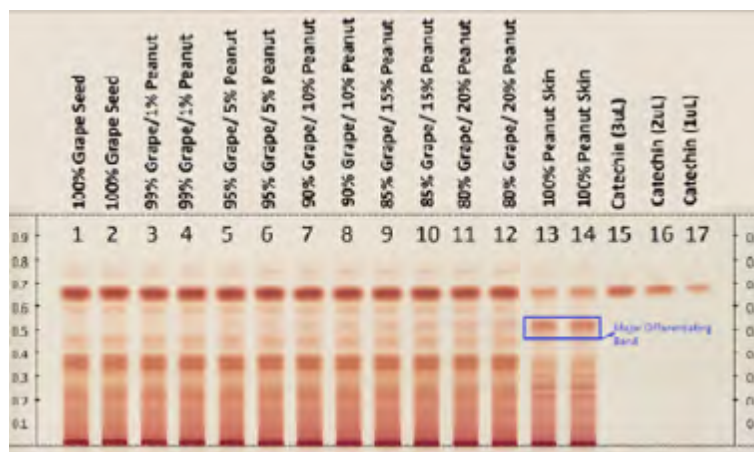


Figure 2: HPTLC analysis of authentic GSE (lanes 1-2), mixtures of GSE and peanut skin extract (lanes 3-12), authentic peanut skin extract (lanes 13-14), and the standard compound catechin (lanes 15-17). Concentrations for extracts were ca. 100 mg/mL, and 0.5 mg/mL for catechin. Image courtesy Alkemist Labs; Costa Mesa, CA.¹⁹

skins are much less expensive than GSE, and the sale of products adulterated with lower-cost material has a significant economic impact. Companies producing authentic GSE cannot compete with adulterated products and lose sales due to consumers making a price-oriented purchasing decision. More importantly, manufacturers that unknowingly buy adulterated products and perform analytical tests that are easily fooled are being defrauded, and they are also being put at risk of regulatory actions due to their GSE products being non-compliant with required current Good Manufacturing Practices (cGMPs).

One of the primary reasons that adulteration goes undetected is because many manufacturers rely on unspecific spectrophotometric methods for quality control of their materials. While spectrophotometric assays can provide reliable results for the contents in total phenolics, HPTLC, and HPLC-UV/MS are more appropriate for the purpose of accurate GSE identification.

****The acronym GSE should not be confused with acronym GFSE, referring to Grapefruit Seed Extract, which is an entirely different material. In some original publications on GFSE adulteration, the authors use “GSE” to refer to grapefruit seed extract.**

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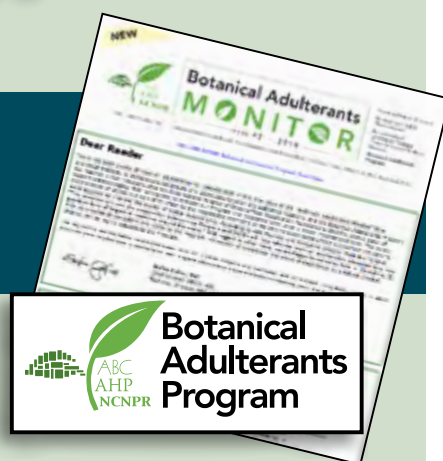
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For more details on joining the program, and access to the free publications produced to date, please see www.botanicaladulterants.org/ or contact Denise Meikel at denise@herbalgram.org.



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Interactive Map of Amazonian Travels of Noted Ethnobotanist Richard E. Schultes

By Mark Plotkin, PhD

Richard Evans Schultes, PhD, was the greatest Amazonian explorer of the 20th century. Boston-born and Harvard-educated, he set off for the Amazon in 1941 for a six-month expedition. He was so entranced by the plants and the peoples of this great rainforest that he essentially extended this expedition for more than a decade. Now, interested readers can follow his journeys in an interactive, informative story map.

Schultes (1915–2001) first learned of the concept of ethnobotany in an undergraduate course at Harvard University taught by the prominent orchidologist Oakes Ames. After Schultes wrote his term paper on the traditionally revered peyote cactus (*Lophophora williamsii*, Cactaceae), Ames sent Schultes to Oklahoma to experience the sacred cactus firsthand in a traditional Kiowa tribal ceremony. Later, Schultes returned to Harvard, and decided to pursue a PhD under Ames, focusing on the “magic mushrooms” of Oaxaca, Mexico. As a newly-minted PhD, he headed south to the northwest Amazon to study arrow poisons from the curare vines (e.g., *Chondrodendron tomentosum*, Menispermaceae), which, at the time, were being used as pre-surgical muscle relaxants in abdominal surgeries.

Cartographer Brian Hettler of the Amazon Conservation Team decided to recount Schultes’s travels and research in a compelling new story map.¹ With commentary and explanations supplied by this author, Hettler traces Schultes’s phenomenal journeys through the rainforest in search of healing plants. Using the capabilities of the story map format, Hettler has organized this information in a way that allows readers to click on a location and see photos of the location and/or the people that lived there. Perhaps even more impressive, readers can click on a list of plants collected by Schultes and see the actual herbarium specimen he collected in high resolution.



Hettler’s story map allows readers to follow the late ethnobotanist into some of the world’s most remote locales in search of exceedingly rare plants. It is hoped that this intriguing initiative will not only teach about the history and importance of the science of ethnobotany, but also will inspire others to use the story-map format to teach about botany in general, and medicinal herbs in particular, in new and compelling ways. HG

Mark J. Plotkin, PhD, is an ethnobotanist whose field research focuses on the plants and peoples of northern Amazonia. He currently serves as president of the Amazon Conservation Team, a nonprofit organization that conducts environmental and cultural sustainability activities in the Amazon basin (www.amazonteam.org). He is the author of several books and a member of the American Botanical Council Advisory Board.

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Previous *HerbalGram* Coverage of Richard E. Schultes, PhD

Book Review: *Medicinal Plants and the Legacy of Richard E. Schultes** by Bruce E. Ponman and Rainer W. Bussmann, eds.²
*Winner of the 2012 ABC James A. Duke Excellence in Botanical Literature Award

Photo Feature: *The Lost Amazon: The Photographic Journey of Richard Evans Schultes* by Wade Davis³

Book Review: *The Lost Amazon: The Photographic Journey of Richard Evans Schultes* by Wade Davis⁴

Book Excerpt: *One River: Explorations and Discoveries in the Amazon Rain Forest* by Wade Davis⁵

Lavender Aromatherapy Improves Sleep Quality in College Students

Reviewed: Lillehei AS, Halcón LL, Savik K, Reis R. Effect of inhaled lavender and sleep hygiene on self-reported sleep issues: a randomized controlled trial. *J Altern Complement Med.* 2015;21(7):430-438.

Sleep problems are associated with numerous health concerns, such as anxiety, depression, cardiovascular disease, hypertension, inflammation, obesity, impaired glucose tolerance, and diabetes. Essential oils with sedative or hypnotic properties, such as lavender (*Lavandula angustifolia*, Lamiaceae) flower oil, have been evaluated for their ability to relieve mild insomnia. The purpose of this randomized, double-blind, placebo-controlled study was to assess the effect of inhaled lavender essential oil on sleep quality and quantity in college students.

Students (N = 79, aged 18-36 years) with self-reported sleep issues (difficulty falling asleep, frequent awakenings during the night, or daytime sleepiness) were recruited from the University of Minnesota Twin Cities campus. Students were excluded if they were pregnant, worked a night shift, or used prescription sleep medication. All subjects received sleep hygiene information based on the following US National Institutes of Health (NIH) recommendations: (1) maintain a regular sleep schedule; (2) avoid fluid intake before bed, and food, caffeine, alcohol, and nicotine late in the day; (3) create a good sleeping environment (e.g., wear ear plugs and a sleep mask, and avoid screens and texting); (4) create a relaxing bedtime routine; (5) keep up with school work; and (6) exercise regularly.

For five consecutive nights, subjects applied a patch on their mid-upper chest at bedtime and removed it in the morning. Each 3-cm adhesive patch contained a 1-cm disc of absorbent material that was either unfilled or contained 55 µL (microliters) lavender oil (supplied by Wyndmere Naturals, Inc.; Minnetonka, Minnesota). Based on the gas chromatography-mass spectrometry analysis provided to the principal investigator, “the essential oil used was chemically consistent with the International Organization for Standardization (ISO) for *L. angustifolia*.” The patch (supplied by Bioesse Technologies, LLC; Minnetonka, Minnesota) had a skin-barrier backing to prevent skin absorption of the essential oil and was claimed to have a time-release function to last 6-8 hours.

Sleep quantity was measured via a sleep diary and a Fitbit One, which tracks sleep based on movement. Sleep quality was measured with the Pittsburgh Sleep Quality Index (PSQI) and the NIH Patient-Reported Outcomes Measurement Information System (PROMIS) sleep disturbance short form. Subjects also completed a sleep hygiene survey (SHS). Assessments were made at baseline, at day 5, and two weeks after the completion of treatment.

The majority of the subjects were white (67%) and female (69%); both treatment groups had similar demographics except for race. There were technical issues with the Fitbit One, resulting in unacceptable levels of miss-



Lavender *Lavandula angustifolia*

Photo ©2016 Steven Foster

ing data (only 14% of the data were recovered). The patches were reported to have fallen off during sleep in 37% of person nights ($n = 146$); however, the data analysis indicated that this was not a significant covariate.

Based on SHS scores, sleep hygiene was better during the five-day treatment phase compared to baseline and post-treatment in both groups. There were no significant differences in SHS scores between groups at any point. Based on the PSQI, both groups had poor sleep quality before the intervention, and there was no difference between groups at baseline.

Post-treatment sleep quantity did not significantly differ between groups. Both groups had significant decreases in awakenings ($P = 0.02$) and increases in being able to fall asleep easily ($P = 0.001$).

The PSQI and PROMIS assessments indicated that sleep quality was significantly better for the lavender group compared with the sleep hygiene-only group at day 5 ($P = 0.01$, PSQI and $P = 0.04$, PROMIS) and at follow-up ($P \leq 0.001$, PSQI and $P = 0.007$, PROMIS). In the sleep hygiene-only group, better sleep hygiene scores (per the SHS) were also associated with better sleep quality at day 5 ($P = 0.02$, PSQI and $P = 0.03$, PROMIS) and at follow-up ($P = 0.03$, PROMIS only), but the correlations were not as strong as those in the lavender group. The lavender group had a clinically significant improvement in sleep quality, while there was no clinically significant change in sleep quality in the sleep hygiene-only group. The lavender group had less daytime fatigue at day 5 and follow-up ($P = 0.02$ and $P =$

0.009, respectively) and was more likely to wake refreshed at day 5 ($P = 0.01$). The four adverse event reports (minor skin irritation, each lasting one night) were attributed to the patch adhesive.

The authors conclude that, in college students with self-reported sleep issues, lavender essential oil inhalation improved sleep quality, and the effect persisted for two weeks after lavender aromatherapy was suspended. "The persistent effect of lavender on sleep quality at two-week follow-up suggests a re-balancing or long-acting effect on the sleep cycle, although the exact mechanism of action is unknown," they write.

Limitations of the study include the lack of statistical power to evaluate potential differences due to race or ethnicity, the loss of objective Fitbit data regarding sleep quantity, the subjective nature of the self-reported data, the lack of standardized dosages due to the poor patch adherence, and the likely failure of subject blinding due to the lavender scent.

The authors conclude that this trial "supports the use of lavender and sleep hygiene as safe, accessible, and effective interventions for self-reported sleep issues in college students. Further research to study their effect on other populations and additional studies using a proper control and exploring the duration of intervention effects are needed." HG

—Heather S. Oliff, PhD

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Topical Black Cumin as Effective as NSAID Gel in Treating Cyclic Mastalgia

Reviewed: Huseini HF, Kianbakht S, Mirshamsi MH, Zarch AB. Effectiveness of topical *Nigella sativa* seed oil in the treatment of cyclic mastalgia: a randomized, triple-blind, active, and placebo-controlled clinical trial [published online November 19, 2015]. *Planta Med.* doi: 10.1055/s-0035-1558208.

Mastalgia, or breast pain, may interfere with quality of life and can occur as a non-cyclic phenomenon or as cyclic mastalgia, which occurs during the premenstrual phase of the cycle. Although there are a few standard treatments for severe mastalgia, including nonsteroidal anti-inflammatory drugs (NSAIDs), these common therapies can cause adverse side effects. Traditionally, black cumin (*Nigella sativa*, Ranunculaceae) seed and preparations thereof have been used both internally and externally as an analgesic, galactagogue, digestive stimulant, and antibacterial for a variety of ailments, including gastrointestinal problems, bacterial infections, dysmenorrhea, and hypertension. In Iranian traditional medicine, black cumin seed oil is used topically for mastalgia. This randomized, triple-blind, placebo-controlled trial compared the topical use of black cumin seed gel with diclofenac gel (an NSAID) and placebo.

The study included Iranian women (aged 25–45 years) with regular menstrual cycles who had cyclic mastalgia during at least three previous consecutive menstrual cycles, who experienced pain for at least seven days per month, and who had mastalgia severity scores greater than 4 on a visual analog scale (VAS; 0 = no pain to 10 = severe pain), requiring medical treatment. Those taking NSAIDs, hormones, or a hormone-based contraceptive, and those who had irregular menstrual cycles, cancer, a hysterectomy, or an oophorectomy (the surgical removal of ovaries) in the past were excluded. Patients who were pregnant, lactating, planning to become pregnant, or had severe health issues also were excluded.

Treatments consisted of cold-pressed black cumin seed oil gel (30% seed oil by weight; Barij Essence Pharmaceutical Company; Mashhad-e Ardahal, Iran), diclofenac gel (1% diclofenac by weight; Darou Pakhsh Pharmaceutical Company; Tehran, Iran), and placebo gel. The same gel base was used for all three treatments. Patients applied 2 g black cumin seed oil gel (equivalent to 600 mg of black cumin seed oil), 2 g diclofenac gel (equivalent to 20 mg of diclofenac), or 2 g placebo gel topically at the mastalgia site twice daily for two menstrual cycles.

The study's primary endpoint was pain improvement based on VAS scores during three baseline cycles and two treatment cycles at the late luteal phase (post-ovulation). Patients also reported any adverse side effects (the secondary endpoint). Returned treatment containers and patient self-reporting were used to measure compliance. Fatty acid concentrations, as well as fixed and volatile compounds in the black cumin seed oil, were measured using gas chromatography-mass spectrometry.

From a total of 181 patients screened, 159 were randomly assigned to black cumin seed oil gel, diclofenac gel, or placebo gel ($n = 53$ for each). In the black cumin seed oil and diclofenac groups, one and two patients, respectively, were lost to follow-

up for "personal reasons," leaving a total of 156 for the analysis. Patients reportedly "fully complied" with the study protocol.

No significant differences were noted in baseline pain scores between groups. Following the second treatment cycle, those in the black cumin seed oil group experienced a significant decrease in pain scores compared to baseline ($P < 0.001$). A significant decrease in pain scores was also seen in those using diclofenac ($P < 0.001$). A nonsignificant reduction in pain scores between baseline and endpoint was observed in the placebo group ($P > 0.05$).

The pain scores of those in the black cumin seed oil and diclofenac groups during both treatment cycles were significantly less than those of the placebo group ($P < 0.001$ for both comparisons). Additionally, no significant differences were noted between scores of the black cumin seed oil and diclofenac groups after either treatment cycle. Patients (98% of the black cumin seed oil group and 95% of the diclofenac group) reported more than 50% pain relief, with relief occurring 10–15 minutes following topical application. None of the patients reported any adverse side effects.

In the phytochemical analysis, the unsaturated fatty acids linoleic acid (58.24%), oleic acid (22.58%), and palmitoleic acid (0.28%) were prominent fixed compounds in the black cumin seed oil. The phytochemicals p -cymene (51.62%), thymoquinone (14.48%) and carvacrol (0.96%) were detected as volatile components.

In this study, both black cumin seed oil gel and diclofenac gel were effective in treating mastalgia compared with placebo. The data suggest that black cumin seed oil may be as effective as diclofenac, since no significant differences were noted between pain scores in treatment cycles of these groups. Since there were no adverse side effects reported during the treatment period, black cumin seed oil appears safe for use.

Thymoquinone and carvacrol have previously been shown to have analgesic effects, and may contribute to the pain-reducing effects seen with the topical application of black cumin seed oil gel. However, since these compounds were not directly tested, no conclusion can be drawn as to their bioactivity, and the pain modulation may be due to other undetected compounds. Further studies should investigate the potential mechanisms of action of black cumin seed oil.

The results of this trial suggest that topical black cumin may be a candidate for the list of evidence-based natural therapies for cyclic mastalgia, which includes chaste tree (*Vitex agnus-castus*, Lamiaceae) berry, evening primrose (*Oenothera biennis*, Onagraceae) seed oil, vitamin E, and molecular iodine. HG

—Amy C. Keller, PhD

Ashwagandha Improves Muscle Strength and Recovery in Men Performing Resistance Training

Reviewed: Wankhede S, Langade D, Joshi K, Sinha SR, Bhattacharyya S. Examining the effect of *Withania somnifera* supplementation on muscle strength and recovery: a randomized controlled trial [published online November 25, 2015]. *J Int Soc Sports Nutr*. doi: 10.1186/s12970-015-0104-9.

Traditional Ayurvedic medicinal plants are becoming increasingly popular as dietary supplement ingredients in the United States and elsewhere. Ashwagandha (*Withania somnifera*, Solanaceae) root, one of the most widely used Ayurvedic plants, is considered an adaptogenic herb (i.e., one that helps the body adapt to various types of stress). Although it has been shown to have a wide range of beneficial effects, ashwagandha has not been thoroughly studied for its potential performance-enhancing properties. The authors of this study hypothesized that ashwagandha supplementation would enhance the physiological adaptation of the body in response to the stress of resistance training. Hence, the purpose of this eight-week, randomized, double-blind, placebo-controlled study was to evaluate the effects of a proprietary, standardized ashwagandha extract on untrained men undergoing resistance training.

Healthy men (N = 57, aged 18-50 years) with little experience in resistance training were recruited at a gym in Kolkata, India. Subjects were excluded if they were taking any medication or steroids to enhance physical performance, had lost more than 5 kg (11 lbs) in the previous three months, had a history of drug abuse, smoked more than 10 cigarettes per day, consumed more than 14 grams of alcohol (one “standard” drink) per day, were hypersensitive to ashwagandha, had orthopedic injury or surgery within the previous six months, had participated in other clinical studies during the previous three months, or had any other condition that the investigators deemed problematic. Subjects were instructed not to take anti-inflammatory agents, drink alcohol, or smoke tobacco during the study. No mention was made of screening for intake of known strength-, body composition-, or testosterone-modifying dietary ingredients, such as creatine monohydrate, beta-alanine, or fenugreek (*Trigonella foenum-graecum*, Fabaceae) seed extract.

Subjects were asked to take either a starch placebo or 300 mg ashwagandha root extract capsule (KSM-66; Ixoreal BioMed; Los Angeles, California) twice daily for eight weeks. The extract was produced using a water-based, “green chemistry” process, and was standardized to contain 5% total withanolides. The authors did not mention if the

extract’s chemoprofile was confirmed by a third-party laboratory. During the eight-week study period, subjects participated in a structured resistance training program based on the publications of the National Strength and Conditioning Association (NSCA). Subjects trained three times per week, exercising major muscle groups in both the upper and lower body. During the initial two-week acclimatization phase, each exercise set consisted of 15 repetitions at a lower load to allow the subject’s body and neurological system to adjust to the training. The subsequent six weeks of training consisted of varying numbers of higher-load repetitions.

The primary endpoints were upper-body and lower-body muscle strength. The secondary endpoints were muscle size (measured via tape measure and calipers), muscle “recovery” (defined as reduction of creatine kinase [CK] activity in the blood; CK is leaked from muscle cells after they have been damaged), serum testosterone, and body fat percentage (measured via bioelectric impedance; the machine used was not described). Muscle size was measured at the flexed mid upper arm, chest, and upper thigh. CK activity was measured between 24 and 48 hours after training. Subjects were assessed the first two days after the start of training, and two days after the end of the eight-week training period.

As expected, the resistance training resulted in improvements in all of the measured parameters in both groups. However, the ashwagandha group had a significantly greater increase in upper-body strength ($P = 0.001$) and lower-body strength ($P = 0.04$) compared with placebo. The ashwagandha group also had significantly lower blood CK activity ($P = 0.03$), yet subjective muscle soreness was not described. Compared with placebo, the ashwagandha group had a significantly greater increase in the muscle size of the arm ($P = 0.01$) and chest ($P < 0.001$), but there was no significant difference in the size of the upper thigh. Compared to the placebo group, the ashwagandha group had a significantly greater increase in serum testosterone ($P = 0.004$) and a significantly greater decrease in body fat percentage ($P = 0.03$). Total body mass (body weight) and fat-free mass changes were not reported. Ashwagandha was well-tolerated, and there were no serious adverse effects.



Ashwagandha *Withania somnifera*
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The authors conclude that “ashwagandha supplementation is associated with significant increases in muscle mass and strength and ... that ashwagandha supplementation may be useful in conjunction with a resistance training program.” They acknowledge that the trial was limited by the inclusion of only untrained young subjects, the small sample size, and the relatively short study duration.

A peer reviewer of this Research Review noted that additional weaknesses of the study include: (1) the absence of assessments performed halfway through the study; (2) the lack of reporting of other body composition changes (e.g., fat-free [lean] mass, total body mass, total body water); (3) the lack of independent authentication and phytochemical profiling of the test material; (4) failure to disclose the funding source(s) of the study; (5) a lack of dietary intake data collected over the course of the study, particularly for carbohydrates and protein; (6) lack of serum cortisol measurements (pre-clinical and clinical trial data suggest that ashwagandha can reduce cortisol, which has been shown to correlate with post-exercise CK activity); (7) equating blood CK activity alone as an indicator of “recovery,” coupled with the absence of any functional measures of subjective, athlete-relevant recovery (e.g., muscle strength, soreness, and/or range of motion); and (8) the lack of detailed reporting of the participants’ ages.

The authors of this study do not appear to have any prior research publications that assess muscular performance, post-exercise “recovery,” or body composition in humans, at least insofar as a PubMed search has revealed. Notably, researchers using a powdered *whole root* ashwagandha extract have reported similar effects on blood testosterone in normal males not engaged in resistance training. Overall, this study lacked sufficient design rigor, methodological detail, and peer review. The authors recommend that further studies evaluate the potential benefits of ashwagandha over longer periods of time and for different populations, including females, older adults, and individuals accustomed to resistance training. HG

—Heather S. Oliff, PhD

Tongkat Ali Improves Cell-mediated Immune Function in Healthy Adults

Reviewed: George A, Suzuki N, Abas AB, et al. **Immunomodulation in middle-aged humans via the ingestion of Physta® standardized root water extract of *Eurycoma longifolia* Jack — a randomized, double-blind, placebo-controlled, parallel study [published online January 27, 2016]. *Phytother Res*. doi: 10.1002/ptr.5571.**

Editor’s note: Two authors (A. George and A.B. Abas) are employed by Biotropics Malaysia Berhad, a sponsor of the study.

Tongkat ali (*Eurycoma longifolia*, Simaroubaceae) is a plant native to Southeast Asia. The roots have been used historically as a tonic, energy enhancer, and aphrodisiac. In Malaysia, it is sometimes inappropriately called “Malaysian ginseng” due to its tonic properties known in local folk medicine, but it is not related to “true ginseng” (i.e., Asian ginseng [*Panax ginseng*, Araliaceae]). In vitro studies indicate that the root extract has cancer suppression and antioxidant effects, suggesting that it may enhance immune function. Hence, the purpose of this randomized, double-blind, placebo-controlled, parallel-design study was to evaluate the ability of a proprietary water extract of tongkat ali root to enhance immune function in healthy, middle-aged adults.

Healthy subjects (N = 83, aged 40-59 years) participated in this study conducted in Tokyo, Japan. Excluded subjects had a history of heart failure, heart attack, atrial fibrillation, cardiac arrhythmia, hepatic disorder, renal disorder, cerebrovascular disorder, rheumatism, dyslipidemia, hypertension, or other chronic disease; used conventional pharmaceutical medicines, herbal medicines, or dietary supplements within 30 days of providing informed consent; had any allergies; were pregnant, lactating, or had plans to become pregnant during the study; had pollinosis (hay fever); or were currently tobacco (*Nicotiana tabacum*, Solanaceae) smokers.

Subjects were randomly assigned to receive either a rice (*Oryza* spp., Poaceae)-powder placebo or 200 mg tongkat ali standardized water-soluble root extract (Physta, known as LJ100 in the United States; supplied by Biotropics Malaysia Berhad; Shah Alam, Selangor, Malaysia) each day for four weeks. Each Physta hard gelatin capsule contained 30 mg fatty acid sucrose esters and 200 mg extract standardized to contain 0.8-1.5% eurycomanone, > 40% glycosaponin, > 30% polysaccharide, and > 22% protein.

At baseline and study end, subjects had blood drawn for the immune evaluation. The following primary endpoints were measured: number of neutrophils, lymphocytes, total T cells, CD4⁺ T cells, CD8⁺ T cells, CD8⁺CD28⁺



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T cells, naïve T cells, memory T cells, B cells, and natural killer cells; ratios of CD4⁺/CD8⁺ T cells and naïve/memory T cells; T cell proliferative activity, T cell proliferative index (TCPI), immunological age, T lymphocyte age, and immunological grade.

The researchers also used Scoring of Immunological Vigor (SIV) as a primary endpoint. SIV is a patented evaluation method designed to assess “immunity with eight immune parameters [that] are easily affected by aging, stress and illness. SIV is the sum of eight immunological functional scores with three-point grades.” The total scores correlate to five immunological zones: sufficiently high, safety, observation, warning, and critical.

Secondary endpoints were change in mood as evaluated by the Profile of Mood States (POMS, Japanese brief version) and laboratory safety parameters. Subjects were instructed to maintain their regular dietary and exercise habits.

At baseline, there were no significant differences between the groups in terms of gender ratio, age, SIV, immunological age, immunological grade, and T lymphocyte age. Eighty-three subjects completed the trial, but two subjects were excluded from the final analyses due to a cold and low compliance, respectively. All 81 subjects included in the analysis took 90% or more of the capsules.

At week 4, there were significant differences in SIV and immunological grades between the two groups ($P < 0.05$ for both). SIV and immunological grade increased significantly in the tongkat ali group compared to baseline ($P < 0.01$ for both), but they did not change in the placebo group. Immunological age decreased significantly by 3.7 years in the tongkat ali group compared to baseline ($P < 0.05$), but it did not significantly decrease in the placebo group ($P < 0.1$).

Between-group comparisons showed significant increases in lymphocytes ($P < 0.05$), total T cells ($P < 0.05$), CD4⁺ T cells ($P < 0.01$), and naïve T cells ($P < 0.05$) in the tongkat ali group. However, there were no significant between-group differences in naïve/memory T cells or TCPI. The authors suggest that the lack of significant change in these two parameters may be due to the homeostatic balance in the body, short study duration, or small sample size.

Immunological grade improved from “warning” to “observation zone” in the tongkat ali group and was maintained at “warning” in the placebo group. There were no significant differences in immunological age or T lymphocyte age between groups. The POMS score did not differ between groups, although the improvement in the anxiety/tension domain approached significance ($P < 0.054$) in the tongkat ali group.

There were no significant changes from baseline in blood and biochemical analyses, urinalysis, somatometry (measurements of the dimensions of the body), or blood pressure. All adverse events (AEs) were considered mild and unrelated to treatment. There was no significant difference in the incidences of AEs between groups, and there were no clinically meaningful changes in safety parameters.

Immune system efficiency declines with age; specifically, there is a reduction in the number of naïve T cells. Tongkat ali increased the number of lymphocytes, total T cells, and naïve T cells, and reduced immunological age of the subjects in this study. Based on the data, the authors conclude that the tongkat ali formulation improved cell-mediated immunity in this population.

Acknowledged limitations were that only cell-mediated immunity was evaluated, the study population included only middle-aged subjects, and the relatively small sample size and short study duration. This study had excellent reporting; all of the Consolidated Standards of Reporting Trials (CONSORT) of herbal interventions criteria were fulfilled.

Overall, the authors conclude that immunity was improved in healthy, middle-aged men and women with comparatively lower levels of immunity (i.e., baseline immunological grades of “warning”) who took 200 mg per day of a tongkat ali product for four weeks. Recommendations for future research include longer-duration trials, and the inclusion of participants in other age groups, those with allergies, and those who have altered immune systems. The study was funded by a grant from the Ministry of Agriculture and Agro-Based Industry Malaysia. HG

—Heather S. Oliff, PhD



Tongkat Ali *Eurycoma longifolia*
Photo ©2016 Mokkie

CANNABIS TAXONOMY:

By Robert C. Clarke and
Mark D. Merlin, PhD

Marijuana and hemp (*Cannabis*) and the closely related hop genus (*Humulus*) are the only widely known genera included in the small, but economically valuable, Cannabaceae family. Swedish botanist Carl Linnaeus, the “father of modern taxonomy,” first published the scientific name *Cannabis sativa* in his seminal *Species Plantarum* of 1753. The Latin name *Cannabis* derives from Greek (*kannabis*) and may have been originally derived from Scythian. The term *sativa* simply means “cultivated” and describes the common hemp plant that was widely grown across Europe in Linnaeus’ time. We, the authors, consider *C. sativa* to be native to western Eurasia and especially Europe, where, for millennia, the plant has been grown for its strong fibers and nutritious seeds, and from where it was introduced to the New World multiple times during early European colonization. *Cannabis sativa* plants also produce very small amounts of the compound delta-9-tetrahydrocannabinol (THC), the medically valuable and primary psychoactive cannabinoid found only in *Cannabis*. Since *C. sativa* evolved within the geographical limits of western Eurasia, it represents only a small portion of the genetic diversity seen in the genus *Cannabis* worldwide.¹

In 1785, European naturalist Jean-Baptiste Lamarck described and named a second species, *Cannabis indica*, meaning “*Cannabis* from India,” after the origin of the first samples of this highly psychoactive plant that

THE ‘SATIVA’ VS. ‘INDICA’ DEBATE



Ripe female marijuana flowers
are covered with glandular
trichomes or resin glands.¹

Photo ©2016 Todd McCormick

reached Europe. *Cannabis indica* has the genetic potential to produce relatively large amounts of THC. The species is used for marijuana and hashish production, but in many regions of eastern Asia it also has a long history of cultivation for fiber and seed. Humans make cloth out of *C. indica* fibers and eat the seeds, but this native eastern Eurasian species is more commonly used today as a drug plant with widespread social and medicinal importance reaching well beyond its original geographical range.¹

While Karl Hillig, PhD, was a doctoral student at Indiana University, he used morphological and chemical characteristics to investigate the diversity of the *Cannabis* genus and proposed taxonomic groupings (subspecies) that support the original two-species concept.²⁻⁵ Hillig recognized European cultivated *Cannabis* as a separate species (*C. sativa*). Because this species typically has narrow leaflets and is primarily used for hemp fiber and seed production, we refer to it as narrow leaflet hemp (NLH). European *C. sativa* NLH populations are much less genetically diverse than those found in many other regions.

Hillig assigned the remainder of the world's cultivated varieties to *C. indica* and divided them into three subspecies. One of these subspecies, *C. indica* subsp. *indica*, includes varieties that span the Indian subcontinent from Southeast Asia to western India and into Africa. These traditional drug varieties produce abundant amounts of THC with little if any cannabidiol (CBD). CBD is the second most common cannabinoid, and is non-psychoactive, but it has been shown to be medicinally effective for a variety of indications. By the 19th century, high-THC *C. indica* subsp. *indica* reached the Caribbean region and

steadily spread throughout Central and South America. Since the 1960s, most of the drug *Cannabis* that reached North America and Europe was *C. indica* subsp. *indica*. Marijuana users commonly call domestically grown plants of these varieties “sativas” because their leaflets are relatively narrow, and therefore exhibit a superficial resemblance to those of European NLH plants. However, in our construct, this is a misnomer as *C. sativa* plants produce little if any THC. Based on Hillig’s research, we now refer to members of *C. indica* subsp. *indica* as narrow leaflet drug (NLD) varieties. Although they have relatively narrow leaflets like NLH (*C. sativa*) plants, the NLD plants can produce an abundance of THC and are most commonly used for their psychoactive effects. Based on taxonomic tradition, these plants are properly called “indicas” rather than “sativas.”

A second *C. indica* subspecies originated in Afghanistan where crops were traditionally grown to manufacture sieved hashish, a mechanically concentrated *Cannabis* drug. From 1974, when descriptions and photos of Afghan *Cannabis* were published by Harvard professor Richard E. Schultes, PhD, it became readily apparent that it represented a type of drug *Cannabis* previously unknown outside of Eurasia, belonging neither to Linnaeus’ *C. sativa* nor Lamarck’s *C. indica*.⁶ Its shorter, more robust stature, and broad, dark green leaves easily distinguish it from the taller, lighter green, and more laxly branched NLD varieties. Because of its limited geographic range and restricted usage, the Afghan genome is less diverse than the NLD genome. By the late 1970s, seeds of Afghan hashish varieties reached Europe and North America and were rapidly disseminated among marijuana growers. At this time, all *Cannabis* vari-



Cannabis sativa
Photo ©2016 Steven Foster

eties were commonly considered to be members of a single species, *C. sativa*, and the familiar NLD marijuana varieties were called “sativas” to differentiate them from the newly introduced and quite different looking Afghan varieties commonly called “indicas.” Hillig named them *C. indica* subsp. *afghanica*, which we now refer to as broad leaflet drug (BLD) varieties to differentiate them from NLD varieties. On average, populations of BLD plants contain approximately equal amounts of THC and CBD. Although BLD varieties are also considered by us to be members of *C. indica*, it is more correct to distinguish them from subspecies *indica* from India by calling them subspecies *afghanica*, or simply “Afghans.”

Hillig’s third grouping within *C. indica* is subspecies *chinensis*, which comprises the traditional East Asian fiber and seed varieties and associated feral populations. We refer to this group as broad leaflet hemp (BLH). Like other subspecies of *C. indica*, varieties of *C. indica* subsp. *chinensis* possess the genetic potential to produce psychoactive THC, but East Asian cultural traditions, such as Confucianism, have long encouraged the selection of these varieties for their economically valuable fiber and seed, rather than their psychoactive potential. As a result, total cannabinoid production is lower than in subspecies *indica* and *afghanica*.

Evolutionary theory predicts that, at some point in time,

there must have been a putative ancestor of the two modern species, *C. sativa* and *C. indica*. This ancient ancestor is often referred to as *C. ruderalis*, which may have originated somewhere in Central Asia. However, by now it is probably extinct, and seemingly ancestral populations are more likely descendants of feral plants that escaped from cultivation long ago. Evolutionary hypotheses based on plant distribution studies, paleoclimate modeling, archaeological evidence, and the historical record propose that *C. sativa* NLH most likely originated in a temperate region of western Eurasia, possibly in the foothills of the Caucasus Mountains, from a putative hemp ancestor with diminished biosynthetic potential to produce THC. *Cannabis indica* likely originated in the Hengduan Mountains, in present-day southwestern China, from a putative drug ancestor that had evolved an enhanced ability to produce THC. Early *C. indica* populations diversified as they were introduced by humans to different geographical regions where they may have further evolved into the three subspecies, all of which produce THC.¹

Cultivated plant varieties are called cultivars, and when cultivars are grown and maintained by local farmers over generations, we refer to them as landrace cultivars, or landraces. Landraces evolve in a balance between natural selective pressures exerted by the local environment favoring

survival, and human selections favoring a cultivar’s ability to both thrive under cultivation and produce particular culturally preferred products. Early humans spread *Cannabis* into many new regions as they moved, and at each new camp or settlement they selected seed from superior plants that were suited to their own uses and processing methods. By sowing seeds from the most favorable individuals, traditional farmers developed and maintained the landraces upon which present-day hybrid hemp and drug cultivars were founded.

Hemp cultivars were derived from crosses between different European NLH landraces and East Asian BLH

Scientific name and Primary traits	Genome group	Origin and Diffusion →	Common uses
Landrace Genomes			
<i>C. sativa</i> ssp. <i>sativa</i> Rarely psychoactive Low resin CBD=THC (1:1)	NLH narrow-leaflet hemp	Europe → New World	Fiber and seed THC ≤0.3%
<i>C. indica</i> ssp. <i>chinensis</i> Mildly psychoactive Moderate resin CBD=THC (1:1)	BLH broad-leaflet hemp	East Asia → Europe → New World	Fiber and seed THC ≤0.5%
Indica – Wrongly called “sativa”			
<i>C. indica</i> ssp. <i>indica</i> Very psychoactive Moderate resin CBD<THC (1:20)	NLD narrow-leaflet drug	South Asia → Middle East → Africa → Europe → New World	Drug fiber and seed THC ≤20%
Afghan – Wrongly called “indica”			
<i>C. indica</i> ssp. <i>afghanica</i> Moderately psychoactive High resin CBD=THC (1:1)	BLD broad-leaflet drug	Afghanistan → Europe → New World	Drug THC ≤10%
Hybrid Genomes			
Hemp Cultivars CBD>THC ≈3:1	NLH/BLH narrow-leaflet hemp x broad-leaflet hemp	Europe → New World	Fiber and seed THC <0.5%
Sinsemilla Cultivars Variable psychoactivity Copious resin	NLD/BLD narrow-leaflet drug x broad-leaflet drug	New World → Europe → Worldwide	Drug THC <0.1% to >20.0% CBD <0.1% to >20.0%
THC cultivars: CBD<THC; 1:5 to 1:>20; THC >20.0%; Low CBD <1.0%			
CBD cultivars: CBD≥THC; 1:1 to >20:1; THC <5.0%; High CBD ≥4.0%			

Table 1. Twenty-first century *Cannabis* taxonomy

Cannabis is presently subdivided into two species, *C. sativa* and *C. indica*. *Cannabis indica* is further divided into three subspecies, *C. indica* subsp. *chinensis*, *C. indica* subsp. *indica*, and *C. indica* subsp. *afghanica*. *Cannabis sativa* and *C. indica* subsp. *chinensis* are hemp cultivars most commonly grown for fiber and seed. Cultivars of *C. indica* subsp. *indica* and *C. indica* subsp. *afghanica* are most commonly grown for their drug content, and most modern *sinsemilla* drug *Cannabis* cultivars are hybrids of *C. indica* subsp. *indica* and *C. indica* subsp. *afghanica* landraces.



Cannabis sativa
Photo ©2016 Steven Foster

landraces. Traditional Asian, African, and New World drug landraces were, until relatively recently, all pure NLD types. Before the introduction of BLD landraces from Afghanistan in the late 1970s, hybrids between imported NLD landraces formed the core genome of domestically produced drug *Cannabis* in both North America and Europe. It is through crossing NLD and BLD landraces from such geographically isolated populations that modern hybrid *sinsemilla* (Spanish for “seedless”) cultivars were created.¹

Unfortunately, we cannot return today to a region previously known for its fine *Cannabis* and expect to find the same landraces that were growing there decades before. *Cannabis* is open-pollinated, with male and female flowers borne on separate plants, and, therefore, two plants are usually required to produce a seed. Random combinations of alleles (forms of a gene) and accompanying variation are to be expected. *Cannabis* landrace varieties are best maintained by repeated natural and human selection in situ — nature selecting for survival and humans selecting for beneficial traits.

Without persistent human selection and maintenance, these landrace varieties will tend to drift back to their atavistic, naturally selected survival mode.

market demand, and the quality of commercially available drug *Cannabis* began to decline. In addition, travelers returned to the supplying nations and introduced seeds of “improved” Western *sinsemilla* varieties that interbred with the local landraces and thus contaminated the local genomes. Landraces can no longer be replaced; they can only be preserved. The few remaining pure landrace varieties

Humans spread *Cannabis* worldwide for a variety of uses. The putative ancestor (PA) of all *Cannabis* originated somewhere in Central Asia. Our evolutionary hypothesis proposes that as *Cannabis* spread into new geographical regions and cultural contexts, it evolved into four major gene pools and taxonomic groups: *C. sativa* narrow leaflet hemp (NLH), *C. indica* subsp. *chinensis* broad leaflet hemp (BLH), *C. indica* subsp. *indica* narrow leaflet drug (NLD), and *C. indica* subsp. *afghanica* broad leaflet drug (BLD) landraces. These four groups also include feral escapes from cultivation and “wild” populations.¹

ies in existence now, some kept alive for decades as seeds and cuttings, are the keys to future developments in drug *Cannabis* breeding and evolution. It will be a continuing shame to lose the best results of hundreds of years of selection by local farmers. After all, our role should be as caretakers preserving the legacy of traditional farmers for the future benefit of all.

Cannabis research is a work in progress, and not all researchers agree on a single taxonomy.⁷ DNA sequencing is currently being used to characterize the diversity of many plant and animal groups, including *Cannabis*. While our knowledge grows and the evolutionary history of *Cannabis* is revealed, changes in taxonomic nomenclature will continue to reflect our deepening understanding of this medically valuable, yet controversial, plant. More broadly, whether we discover that *Cannabis* plants belong to one or more

species, we can be sure that humans have long known, used, dispersed, cultivated, and artificially selected these plants to perpetuate a truly wide range of diversity. HG

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Modern *sinsemilla* crops are vegetatively reproduced in glass houses to ensure uniformity and quality.¹

Photo ©2016 Todd McCormick





Artemisia annua, from which the antimalarial compound artemisinin is derived. Photo ©2016 Steven Foster

ARTEMISININ:

A Nobel Prize-Winning Antimalarial from Traditional Chinese Medicine

By Connor Yearsley

Half of the 2015 Nobel Prize in Physiology or Medicine was awarded to Chinese phytochemist Tu Youyou for her role in the discovery of the natural compound artemisinin, which is produced by the traditional Chinese medicinal herb *qinghao* (*Artemisia annua*, Asteraceae), also known as sweet wormwood. Artemisinin derivatives are commonly used in the treatment of malaria, one of the world's oldest and deadliest diseases.¹⁻³

The other half of the Prize was awarded to Japanese microbiologist Satoshi Ōmura, PhD, and Irish-American biologist and parasitologist William C. Campbell, PhD, for their discovery of avermectin, a natural anthelmintic compound (i.e., one that expels worms and other parasites from the body). Avermectin is produced by the bacterium *Streptomyces avermitilis*, and its derivatives have dramatically reduced the incidences of parasite-induced diseases, such as river blindness and lymphatic filariasis.³

Both halves of the Prize are a triumph for the field of pharmacognosy (the study of medicines derived from plants and other natural sources) and, according to many, Tu's half is also a win for China. Tu, who was born in 1930 in

Ningbo, a port city in Zhejiang province on the eastern coast of China, is the first citizen of the People's Republic of China (PRC) to be awarded a Nobel Prize in the sciences. (Five Chinese-born scientists have won the Nobel Prize in Physics, but none were citizens of the PRC.¹) Some people in China view the win as confirmation of the strength of Chinese science and medicine, while some traditionalists view it as a reminder that Chinese medicine is ignoring its heritage by using methods similar to those used by Western pharmaceutical companies.⁴

In truth, the discovery of artemisinin, which also involved ethnobotany, the study of people's historical uses of plants, may be a prime example of traditional Chinese medicine

(TCM) and Western practices complementing each other.

The discovery of artemisinin is considered one of the most important advancements in the treatment of malaria since the isolation of quinine in 1820. Quinine is a natural compound found in the bark of South American trees in the genus *Cinchona* (e.g., *C. officinalis*, Rubiaceae). These trees are native to the rainforests of the Andes Mountains, and extracts of their bark had been used to treat fevers caused by malaria at least as far back as 1632.^{2,5-7}

Artemisinin derivatives are the most effective of all current antimalarial drugs.⁸ In April 2001, the World Health Organization (WHO), which directs and coordinates international health within the United Nations (UN) system, first recommended the use of artemisinin-based combination therapies (ACTs), which combine an artemisinin derivative with another, longer-lasting antimalarial drug.⁹ Since then, ACTs have saved millions of lives.¹⁰

History of Artemisinin

The discovery of artemisinin can be traced back to 1967, during the tumult of the Chinese Cultural Revolution, when many Western-trained Chinese scientists were being persecuted by the Communist Party. At the same time, the Vietnam War was escalating, and many North Vietnamese soldiers were falling victim to malaria that had developed resistance to chloroquine (a synthetic analog of quinine) and other drugs.^{1,11} Communist North Vietnam, an ally to China, asked for China's help to find a new treatment for malaria, which was also afflicting many people in southern China, as well as thousands of American soldiers who were fighting against North Vietnam. (The US Department of Defense undertook its own drug hunt, which eventually produced mefloquine, another synthetic analog of quinine.)^{1,2,11}

In response to North Vietnamese President Ho Chi Minh's appeal, Chinese Premier Zhou Enlai and Chairman Mao Zedong set up a secret military project called Project 523 (because of its starting date, May 23, 1967) to find a solution. Progress was slow at first, despite the fact that the initiative reportedly involved the efforts of about 500 scientists working at about 60 laboratories and institutes in China.^{1,12} Though the project was kept covert, and some details of its history remain foggy even now, information flowed freely at joint meetings among the different research groups involved. Three new malaria treatments were produced by 1969.

Until the late 1960s, according to one source, the antimalarial remedy of choice in China,

perhaps by default, was *changshan*. The term "changshan" generally refers to the root of *Dichroa febrifuga* (Hydrangeaceae), rather than to the complex mixture that traditionally contained the root as a central component. Changshan was mentioned in the *Canon of the Divine Husbandman's Materia Medica*, which was written circa 200 CE, as a treatment for fevers. However, changshan has an intense emetic effect, which is compounded when the active alkaloids are used in isolation from the rest of the plant, and when the plant itself is used without the offsetting effects of the other ingredients traditionally used in the mixture (e.g., ginger [*Zingiber officinale*, Zingiberaceae], licorice [*Glycyrrhiza glabra*, Fabaceae], and betel nut [*Areca catechu*, Arecaceae]). This effect led to the eventual disuse of drugs derived from the root, and perhaps further necessitated the finding of a new, more palatable treatment option.¹³

Tu, who graduated from the Beijing Medical University School of Pharmacy in 1955 (she has no postgraduate degree or research experience abroad, neither of which was possible during the Cultural Revolution), did not become involved with Project 523 until January 21, 1969 when she was sent to Hainan Island off the southern coast of mainland China. Tu, 38 at the time, was working at the Academy of Traditional Chinese Medicine in Beijing when she was given the daunting task of searching nature for a new malaria treatment.

"The work was the top priority so I was certainly willing to sacrifice my personal life," Tu told *New Scientist* in 2011. While on the island, Tu observed firsthand the toll malaria

Tu Youyou (right) and her tutor, Lou Zhicen (left), in 1951. Photo courtesy of WenxueCity.

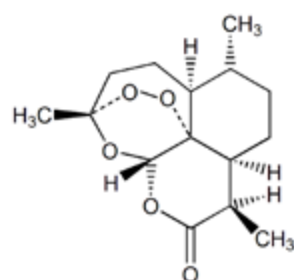
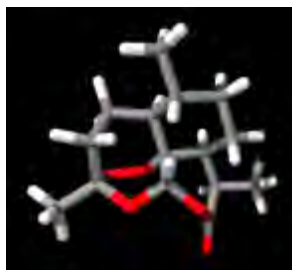


was taking on the population, and this was the beginning of a decade of work.^{1,10} “I saw a lot of children who were in the latest stages of malaria,” she said. “Those kids died very quickly.”

Tu also visited TCM practitioners across China and compiled a notebook: “A Collection of Single Practical Prescriptions for Anti-Malaria.”¹ Back in Beijing, Tu and her team investigated more than 2,000 traditional Chinese herbal preparations.¹⁰ According to a 2011 written account by Tu, her team “identified 640 hits that had possible antimalarial activities. More than 380 extracts obtained from [about] 200 Chinese herbs were evaluated against a mouse model of malaria. However, progress was not smooth, and no significant results emerged easily.”²⁹

According to the same account, the turning point came when an extract of *A. annua*, or *qinghao*, initially “showed a promising degree of inhibition against parasite growth.” But this observation was not reproducible in subsequent experiments. Tu and her team scoured the TCM literature looking for a possible explanation and found one in physician Ge Hong’s medical text *A Handbook of Prescriptions for Emergencies*, which was written circa 340 CE (some sources say the text is called *Emergency Prescriptions Kept Up One’s*

Three-dimensional structure of artemisinin. The 15 carbon atoms are represented by the gray joints, the 22 hydrogen atoms are represented in white, and the five oxygen atoms are represented in red.



Two-dimensional structure of artemisinin. The oxygen-oxygen bond of the endoperoxide bridge that is believed to be largely responsible for the compound’s biological activity is designated O—O.

Sleeve).^{29,30} One passage in the text described a method of preparing *qinghao* to be used for the treatment of “intermittent fevers,” one of the most telltale symptoms of malaria. The passage reads: “qinghao, one bunch, take two sheng of water [about two liters] for soaking it, wring it out, take the juice, ingest it in its entirety.”³⁰

Interestingly, the text *52 Prescriptions* contains the earliest known mention of *qinghao* being used as a treatment, but in this case for hemorrhoids. The text was compiled sometime between 1065 and 771 BCE, but it was sealed in a tomb in 168 BCE and was not discovered until 1973 (shortly after artemisinin was discovered), during the excavation of the Mawangdui archeological site in Changsha, Hunan, China.^{8,31} The earliest known mention of *qinghao* being used to treat a disease resembling malaria is contained in Zhang Ji’s text *On Cold Damage*, which dates to about the second century CE. The text recommends treating “fevers with sweating and jaundice” with a mixture containing boiled *qinghao*.⁸

Ge’s instructions to take a juice wrung out of the entire fresh plant (rather than an herbal tea prepared by pouring hot water onto dried plant material) probably resulted in an emulsion of water, flavonoids, and aromatic oils, with higher quantities of artemisinin than some other methods recorded in the Chinese

In-Depth: Malaria

Malaria, sometimes called the scourge of the tropics, has probably existed for hundreds of thousands of years, likely predating modern humans.^{2,14} It is thought that the first vertebrate hosts of the disease were reptiles.

In 400 BCE, long before the term “malaria” was coined, Hippocrates wrote about the disease in his treatise *On Airs, Waters, and Places*.¹⁵ And long before that, a Chinese medical text, *The Canon of Medicine*, from 2700 BCE, described several characteristic symptoms of malaria.¹⁶ It was not until 1880 that French army surgeon Charles Louis Alphonse Laveran discovered the parasites that cause the disease in the blood of a patient. For his discovery, Laveran was awarded the Nobel Prize in Physiology or Medicine in 1907.

The term “malaria” is derived from the Italian *mal’aria*, a contracted form of *mala aria*, meaning “bad air,” because the disease was once thought to be caused by the foul, vaporous air of marshy areas. The term is thought to have first been used by Italian historian Leonardo Bruni (circa 1370-1444).¹⁵

According to the WHO’s *World Malaria Report 2015*, there were 95 countries and territories with ongoing malaria transmission in 2015. This includes almost all of Africa, almost all of the Middle East, almost all of Central and South America, and most of Asia and Southeast Asia.¹⁷ Malaria was eliminated from the United States in the early 1950s.¹⁸

In 2015, there were about 214 million cases of malaria, an 18% decline from 2000 when there were about 262 million cases. About 88% of the cases in 2015 occurred in the WHO African region. In 2015, there were about 438,000 deaths

from malaria (an average of 1,200 deaths per day), a 48% decline from 2000 when there were about 839,000 deaths. About 90% of the deaths in 2015 occurred in the WHO African region. In 2015 about 306,000 deaths (70% of the total) were in children under five years old. About 95% of these deaths occurred in the WHO African region.¹⁷

Malaria in humans is caused by five protozoan species in the genus *Plasmodium*: *P. falciparum*, *P. vivax*, *P. malariae*, *P. ovale*, and *P. knowlesi* (though it has been shown that *P. knowlesi* is not spread from human to human like the other four species, but occurs when a mosquito becomes infected after biting an infected monkey and then infects a human [zoonotic transmission]).¹⁷ These primitive, unicellular protozoa are eukaryotic, meaning that unlike bacteria, which are prokaryotic, they contain membrane-bound organelles (e.g., a nucleus). And unlike viruses, which consist of genetic material encapsulated in protein and are smaller than single cells, these ancient, animal-like protozoa are considered living.^{19,20}

The life cycle of malaria parasites is fairly complex, and can be divided into two main phases: the asexual cycle in humans and the sexual cycle in female mosquitoes of the genus *Anopheles*. There are about 400 species in this genus, but only 30 are significant to the transmission of malaria.^{17, 21-24} When an infected female, acting as a “vector,” bites a human, it injects saliva to prevent the blood from clotting. From the mosquito’s saliva, the parasites (called sporozoites at this stage) move into the bloodstream, and, within about 30 or 40 minutes, make their way to the liver, part of the body’s blood filter system, where they invade liver cells (hepatocytes).

literature.³⁰ These instructions also gave Tu the idea that the heating involved with their original extraction method was probably destroying the primary active components of the plant.^{29,30} “Indeed, we obtained much better activity after switching to a lower temperature procedure,” Tu wrote.²⁹ This method was similar to the method Ge described, but involved diethyl ether as the solvent.³⁰ Organic solvents (i.e., solvents that contain carbon), such as diethyl ether, generally are better-suited for extracting hydrophobic compounds (i.e., compounds that are not soluble in water), such as artemisinin. Diethyl ether, however, is highly flammable.³²

Tu wrote that they separated the extract into its acidic and neutral portions, and that, on October 4, 1971, they obtained a nontoxic, neutral (pH of 7) extract that proved to be 100% effective when administered orally to mice that had malaria caused by parasites of the species *Plasmodium berghei* and monkeys with malaria caused by *P. cynomolgi*.

“During the Cultural Revolution, there were no practical ways to perform clinical trials of new drugs. So, in order to help patients with malaria, my colleagues and I bravely volunteered to be the first people to take the extract,” Tu wrote. After personally confirming the safety of the extract, Tu went back to Hainan Island with her team to test its efficacy in patients infected with both *P. vivax* and *P. falciparum*. “These clinical trials produced encouraging results: patients treated with the extract experienced rapid disappearance of symptoms — namely fever and number of parasites in the blood — whereas patients receiving chloroquine did not,” she wrote.²⁹

“We had just cured drug-resistant malaria,” Tu told *New Scientist*. “We were very excited.”¹

In 1972, Tu and her team identified a colorless, crystalline substance as the active component of the extract, and named it *qinghaosu* (artemisinin).²⁹ Artemisinin, whose structure was determined in 1975, is most abundant in the leaves of *A. annua*, but the



Artemisia annua. Photo ©2016 Steven Foster

Over the next 6 to 15 days, the parasites undergo asexual multiplication, copying their DNA over and over again. A single parasite can multiply thousands of times in a single hepatocyte. The specific molecular mechanisms that facilitate sporozoite selection and infection of hepatocytes are not fully understood, but the parasites avoid being overcome by white blood cells (leukocytes) and mature into schizonts in this environment. The schizonts then rupture and release daughter cells called merozoites, which are modified to infect red blood cells (erythrocytes). In *P. vivax* and *P. ovale*, a dormant liver stage (hypnozoites) can remain in the liver and cause relapse weeks, or even years, later, when they enter the bloodstream.

After infecting the erythrocytes, the parasites become young trophozoites (this is called the ring stage because of the parasite’s morphology at this point). This is the stage during which the parasite is absorbing nutrients from the host. As the parasite gets larger, the ring shape disappears, and the parasite is then known as a trophozoite. The trophozoites then undergo another round of asexual multiplication and develop into schizonts. The infected erythrocytes then burst and release the merozoites, which can then infect new erythrocytes and restart the process, or, inexplicably, develop into gametocytes (a dormant sexual stage).

When a female *Anopheles* mosquito takes a blood meal from an infected person, it becomes infected. Ingested parasites other than the gametocytes are digested in the stomach of the mosquito, but the gametocytes mature into male and female gametes. Male gametes fertilize female gametes, forming zygotes, which develop into actively moving ooki-

netes that migrate to the outer lining of the mosquito’s stomach, where they form cysts. Each cyst produces thousands of sporozoites that then infest the mosquito’s salivary glands, thus starting the life cycle over again.

Plasmodium falciparum is the species responsible for the majority of malaria deaths.¹⁷ It typically has a shorter incubation period (the time before the first symptoms present), can multiply rapidly in the blood, and causes severe malaria at least partially by a property not shared by the other four species that cause the disease in humans: sequestration, in which infected erythrocytes stick to the endothelial cells of blood vessels, causing obstruction of the microcirculation and the dysfunction of organs, typically the brain in cerebral malaria.²⁵⁻²⁷ *Plasmodium vivax*, however, is more widespread geographically than *P. falciparum* because it can develop in the mosquito host at lower temperatures and higher altitudes.¹⁷

It is important to note that blood stage parasites are responsible for the symptoms of malaria.²³ Symptoms of uncomplicated malaria include fever, chills, general malaise, sweats, headaches, nausea and vomiting, body aches, increased respiratory rate, weakness, enlarged spleen, enlarged liver, and mild jaundice. Symptoms of severe malaria include cerebral malaria (which can cause impaired consciousness, seizures, coma, etc.), severe anemia, hemoglobinuria (hemoglobin in the urine), acute respiratory distress syndrome (ARDS), low blood pressure, acute kidney failure, excessive acidity in the blood and tissue fluids, and hypoglycemia (low blood glucose).²⁸

compound has also been found in other species of *Artemisia*: *A. apiacea* and *A. lancea*, and in small quantities in *A. sieberi* and *A. scoparia*.^{30,33} In fact, in polymath Shen Gua's *Dream Pool Essays*, written in 1086 CE, it is suggested that *A. apiacea*, not *A. annua*, was the species the Chinese literature intended when referring to *qinghao*. A passage in the text reads: "In the depth of autumn, when the other hao are yellow, this one [*A. apiacea*] alone is blue-green; its smell is quite aromatic. I guess [this is] the one the ancients used, they considered this one the preferred one." For this reason, it has been suggested that the name *qinghao* ("blue-green hao") should be reserved for *A. apiacea* and that *huang-hauhao* ("yellow blossom hao") should be reserved for *A. annua*.³⁴ (Other species in the genus *Artemisia* have historically been used to treat malaria, including but not limited to *A. absinthium* and *A. abrotanum* in Europe, *A. afra* in Africa, and *A. argyi* in China.³⁵)

In 1973, artemisinin was altered to produce the semisynthetic derivative dihydroartemisinin (DHA), from which other important and widely used derivatives are produced, such as artesunate and artemether. "During evaluation of the artemisinin compounds, we found that dihydroartemisinin was more stable and ten times more effective than artemisinin," Tu wrote. "More importantly, there was much less disease recurrence during treatment with this derivative."²⁹ Furthermore, unlike artemisinin, DHA is water soluble.³⁰

Solubility is an important property of drugs, and one that often poses challenges to drug formulators. Drugs that

are hydrophobic have a low dissolution rate in the aqueous gastrointestinal fluids when administered orally, resulting in reduced bioavailability (the proportion of the administered amount of a drug that is available at the site of physiological activity).³⁶ On the other hand, drugs that are extremely hydrophilic also are poorly absorbed because they are unable to cross lipid-rich cell membranes.³⁷

In the 1980s, several thousand patients in China were successfully treated with artemisinin and its derivatives, and news of their efficacy attracted worldwide attention.^{29,38} However, the WHO would not recommend the use of ACTs until April 2001, almost 30 years after artemisinin was identified. This hampered the efforts of aid agencies, which could not buy drugs that were not approved by the WHO. Even after the WHO's recommendation, the drugs would not become widely available until 2006, according to *The New York Times*.^{2,9}

There were several reasons for this delay. China's isolationism certainly played a role. In addition, under communism, patent law was nonexistent in China, and the country took out no Western patents. This meant that anyone could use artemisinin, which prevented pharmaceutical companies from being able to exclusively produce and market the drug. There was also some general skepticism about artemisinin, as there is with most new drugs. Whatever the reasons, hundreds of thousands of African children were dying each year as artemisinin idled, causing some to call the delay "genocidal."²

The case of artemisinin exemplifies how complex legal, economic, and political landscapes can impede drugs from coming to market. It may also signal the need to minimize these barriers to entry to allow people to receive the care they need.

Lasker-Debakey Award and Nobel Prize

In 2011, the prestigious Lasker-Debakey Clinical Medical Research Award was given to Tu by the Lasker Foundation, which celebrates "the contributions of scientists, clinicians, and public servants who have made major advances in the understanding, diagnosis, treatment, cure, or prevention of human disease."^{2,39} The Foundation named Tu "the discoverer of artemisinin," which caused controversy in the scientific community. Some said it was unfair to credit the discovery to one individual, and named others they thought were equally deserving, but Tu is widely credited with having had a major hand in almost all of the events that led to the discovery.

Table 1: Malaria and Artemisinin Timeline

2700 BCE	A Chinese medical text described several characteristic symptoms of malaria. ¹⁶
400 BCE	Hippocrates wrote about malaria in his treatise <i>On Airs, Waters, and Places</i> . ¹⁵
340 CE	Chinese physician Ge Hong described a method for preparing <i>qinghao</i> (<i>Artemisia annua</i>) to be used for the treatment of "intermittent fevers," one of the main symptoms of malaria. ³⁰
1820	Quinine was isolated from the bark of trees in the genus <i>Cinchona</i> . ⁵
1880	French army surgeon Charles Louis Alphonse Laveran discovered <i>Plasmodium</i> parasites in the blood of a patient. ¹⁶
1930	Tu Youyou was born in Ningbo, China. ¹
1967	Project 523 was launched with the objective of finding a new malaria treatment. ¹
1971	Tu and her team obtained an extract of <i>qinghao</i> that proved to be 100% effective in mice with malaria. ²⁹
1972	Artemisinin was identified as the primary active component of the <i>qinghao</i> extract. ²⁹
1973	Artemisinin was altered to produce the more potent, water-soluble derivative dihydroartemisinin (DHA). ²⁹
1975	Artemisinin's structure was determined. ²⁹
2001	The World Health Organization (WHO) recommended the use of artemisinin-based combination therapies (ACTs). ⁹
2015	Tu was awarded part of the Nobel Prize in Physiology or Medicine. ¹

This controversy resurfaced in October 2015 when it was announced she would be awarded part of the Nobel Prize in Physiology or Medicine. Tu, who, because of the non-existent patent laws in China at the time, has never financially benefitted from the commercial use of artemisinin, said in a 2007 interview, “I do not want fame. In our day, no essay was published under the author’s byline.”^{10,40} In fact, Tu was one of four anonymous authors of the original 1977 paper on artemisinin.²

Shortly before accepting the Nobel Prize in December 2015 in Stockholm, Sweden, Tu, 84 at the time, responded to the controversy in an interview with *The New York Times*: “Everyone is entitled to his opinion. We all believed in collectivism. All I wanted was to do good work at my job. Of course, I’d be nothing without my team. Foreign countries, like the United States, care a lot about which individual should claim credit. Foreigners read historical records and picked me. Chinese awards are always given to teams, but foreign awards are different. This honor belongs to me, my team, and the entire nation,” she said.⁴⁰

In a different *New York Times* article, Tu is quoted as saying, “Artemisinin is a gift for the world people from the traditional Chinese medicine.”⁴¹

Chemistry of Artemisinin and Its Derivatives

Artemisinin belongs to a class of compounds known as sesquiterpene lactones, which contain 15 carbon atoms (three isoprene units with five carbon atoms each) and a lactone ring.

“Sesquiterpene lactones come in different types of classes, with the class also defining the stereochemistry of the molecules [i.e., the relative spatial arrangement of atoms within the molecules],” said Eloy Rodriguez, PhD, the James A. Perkins Endowed Professor of Environmental Toxicology and Medical Ethnopharmacognosy at Cornell University and member of ABC’s Advisory Board (oral communication, February 24, 2016). Rodriguez is an expert on this class of compounds, and has identified 30 or 40 novel structures with his colleagues and students. “Stereochemistry is very important in biological activity. ... The degree of oxygenation, or the degree of oxygens in the molecule, is [also] very important in determining biological activity,” he said. He also said that these compounds rarely contain nitrogen or chlorine and that they tend not to affect the central nervous system.

“[Sesquiterpene lactones have] been around for hundreds of millions of years,” Rodriguez said. “And what makes the sunflower [Asteraceae] family so unique is the fact that it makes this incredible array of sesquiterpene lactones.”

With more than 5,000 structures identified to date, sesquiterpene lactones are probably the largest class of secondary metabolites found in plants. These compounds display a wide range of biological activities, including antitumor, anti-inflammatory, analgesic, antiulcer, antibacterial, antiviral, antifungal, insect deterrent, and, of course, antiparasitic.³³

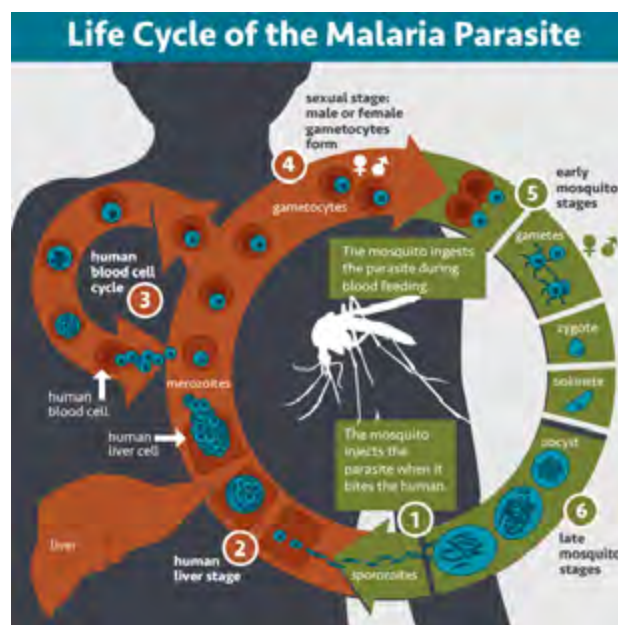
“These molecules evolved primarily as a defense, as insecticide, as repellent, against herbivores, things that like to eat plants, or like to infect plants, such as bacteria, fungi. So, these molecules, not only did they evolve, effectively,

to knock out enzymes in insects and other predators, it’s not surprising that [some] also have the same effect against *Plasmodium*, because, as far as the molecule is concerned, *Plasmodium* is just one big caterpillar inside of your body. It kills it the way it would kill a caterpillar,” Rodriguez said.

According to one source, artemisinin and its derivatives are the most potent and rapidly acting antimalarial drugs ever discovered.³⁵ They are highly active against and most commonly used for infections of *P. falciparum*, the deadliest species in humans, but some sources suggest they work as well, if not better, against *P. vivax*, the most geographically widespread species.^{42,43} These drugs, however, do not affect all stages of the parasite’s life cycle equally. They are inactive against the pre-liver stage (sporozoites) and liver stages. (Since symptoms do not manifest until the blood stages, diagnosis at this point is seemingly impossible anyway). In fact, they are inactive against all extra-erythrocytic forms, which also includes merozoites. Late-stage ring parasites and trophozoites are generally more vulnerable to artemisinin and its derivatives than are schizonts or small rings.^{43,44}

The inhibitory effects of artemisinin and its derivatives against trophozoites prevent the progression of the disease and reduce the formation of gametocytes, the dormant sexual forms of the parasite.⁴⁵ This is important because eliminating gametocytes in the human host prevents the parasite’s life cycle from restarting in the mosquito host, in the event that a female mosquito in the genus *Anopheles* were to take a blood meal from the infected human. Stage specificity is an important consideration with antimalarial drugs, especially for patients with severe malaria. Since severe malaria is usually fatal within 48 hours after symptoms present (i.e., the time it takes *P. falciparum*, *P. vivax*, and *P. ovale* to complete one asexual multiplication cycle within an infected erythrocyte), it is mainly the parasites present at the time the patient presents for medical care that will determine whether the patient lives or not.⁴⁶

Artemisinin and its derivatives are safe and well-tolerated.



Malaria parasite life cycle. National Institute of Allergy and Infectious Diseases (NIAID).

Some reported adverse effects include mild gastrointestinal disturbances, dizziness, tinnitus (ringing in the ears), and bradycardia (slow heart rate).⁴² The greatest concern regarding these drugs is the neurotoxicity that has been reported in some animal studies.⁴⁵

It should be noted that artemisinin itself is not used as a component in any of the five current WHO-recommended ACTs. This is primarily because of its poor solubility in both water and oil, and because of its poor bioavailability. DHA, artesunate, and artemether are all more potent and have greater oral bioavailability (> 60%) than artemisinin.^{33,42} Furthermore, since artesunate is more water soluble than other artemisinin derivatives, it can be administered effectively intravenously. It can also be given orally, rectally, or intramuscularly. Since artemether is lipid soluble, it can be administered effectively intramuscularly or orally. Non-oral (i.e., parenteral) administration is often necessary for patients with severe malaria, because they are often unconscious or too ill to swallow.³⁵

DHA is two- to threefold more active than artemether. Artemether, however, is metabolized back to DHA in varying amounts in vivo, depending on the route of administration used. The same is true for artesunate, which is preferred over artemether in the treatment of severe malaria. This is partly because after intramuscular injection, artemether is often absorbed more slowly and erratically than artesunate, which is absorbed quickly and reliably.⁴⁷

Artemisinin and its derivatives also have potent anticancer effects. They have been shown to target a wide variety of cancer cells (including leukemia, breast, colon, prostate, pancreas, ovarian, hepatic, renal, melanoma, osteosarcoma, central nervous system, and lung cancer cells), with almost no negative effects on healthy cells. In addition, DHA is active against other parasites, including *Trichomonas vaginalis* and *Giardia lamblia*, as well as against species of the genera *Schistosoma*, *Toxoplasma*, and *Leishmania*.³³

Artemisinin-based Combination Therapies

ACTs combine DHA, artemether, or artesunate with another antimalarial drug that lasts longer and has a different mode of action. The artemisinin component rapidly

clears the blood of the vast majority of parasites, while the partner drug eliminates the remaining parasites. ACTs are generally administered over a three-day treatment period.⁴⁷

The three-day course covers two of the parasite's 48-hour intra-erythrocytic asexual cycles.⁴⁷ The artemisinin component alone reduces parasite numbers by about 10,000-fold in each cycle (compared to 100- to 1,000-fold for other antimalarial drugs³⁵), ensuring that only a tiny fraction of the parasites (< 0.0001% of those present at the peak of the infection, according to one source⁴²) remain for the slowly eliminated partner drug to clear. This reduces the potential for parasites to develop resistance to the partner drug, and the partner drug reciprocally reduces the potential for parasites to develop resistance to the artemisinin component.

ACTs are recommended by the WHO as first-line treatment for uncomplicated *P. falciparum* malaria.⁴⁸ By April 2006, 60 countries had adopted ACTs into their national treatment policies, primarily as first-line treatment, and by the end of 2013, 79 countries had adopted them as first-line treatment policy.⁹ The WHO recommends treating *P. vivax* infections with chloroquine in areas where chloroquine is still effective. In areas with chloroquine-resistant *P. vivax*, ACTs should be used (except for pregnant women in their first trimester, who should be treated with quinine).^{47,48} In addition, adults and children with uncomplicated malaria caused by *P. malariae*, *P. ovale*, or *P. knowlesi* should be treated with either chloroquine (where effective) or an ACT.

For severe malaria, the WHO recommends treating adults and children with intravenous or intramuscular artesunate (or artemether, in preference to quinine, if parenteral artesunate is unavailable) for at least 24 hours. Once the patient is well enough to tolerate oral medication, treatment should be completed with an ACT for three days.⁴⁷

According to the third edition of the WHO's *Guidelines for the Treatment of Malaria*, all five recommended ACTs have been shown to result in cure rates of >95% in the absence of resistance.⁴⁷ ACTs have also been reported to reduce malaria mortality by 20-30% overall.³ Additionally, for uncomplicated *P. falciparum* malaria, ACTs have been estimated to reduce mortality in children aged one to 23 months by 99% (of the total who received an ACT), and

Table 2. Artemisinin Derivatives

	Dihydroartemisinin (DHA) ^{29,30,42,47}	Artesunate ^{35,47}	Artemether ^{35,47}
Solubility	Water soluble	Water soluble	Lipid soluble
Routes of Administration	Oral, rectal	Intravenous, oral, rectal, intramuscular	Oral, intramuscular
Other Properties	Significantly more potent than artemisinin, with greater oral bioavailability	Converted back to DHA in varying amounts in vivo, usually more quickly and more completely than artemether; preferred over artemether in the treatment of severe malaria	Also converted back to DHA in varying amounts in vivo
Parent Compound	Artemisinin	DHA	DHA
Other Antimalarials Combined With	Piperaquine	Amodiaquine, mefloquine, sulfadoxine-pyrimethamine	Lumefantrine

in children aged 24-59 months by 97%, according to the WHO's *World Malaria Report 2015*. Furthermore, in sub-Saharan Africa, parasite prevalence among children aged two to 10 years is estimated to have decreased from 33% in 2000 to 16% in 2015, and ACTs are estimated to have been responsible for 14% of that reduction.¹⁷

Though the primary purpose of ACTs is to avert severe disease and death, prompt treatment can also reduce the incidence of uncomplicated cases. It is estimated that ACTs averted 139.23 million cases of malaria in sub-Saharan Africa between 2001 and 2015. It is also estimated that, in sub-Saharan Africa, ACTs saved the public sector about \$156 million in health care costs between 2001 and 2014, based on the number of cases that are estimated to have been averted during that time period and the estimated number of those cases that would have sought care in the public sector.

From 2005 to 2014, the number of ACT treatment courses procured from manufacturers increased from 11 million to 337 million (almost a 3,000% increase). The WHO African region accounted for almost 98% of manufacturer deliveries of ACTs in 2014. Furthermore, in 2014, 223 million ACTs were delivered by manufacturers to the public sector and 169 million

ACTs (about 50% of those procured) were distributed by national malaria control programs (NMCPs; i.e., domestic funding mechanisms) through public sector facilities. International sources (including aid organizations like the Global Fund to Fight AIDS, Tuberculosis and Malaria; The United States President's Malaria Initiative; The World Bank; and UNICEF) spent \$403 million on ACTs in 2014.

There are at least three main reasons artemisinin derivatives are combined with partner drugs. First, though they are the most effective of all antimalarials, they are the most rapidly eliminated, with half-lives (i.e., the time it takes for half of the administered amount of a drug to be eliminated from the bloodstream) on the order of one hour.⁴² "You don't need a long life for it to work," Rodriguez said. According to him, predators trying to consume the sweet

wormwood plant would have almost immediately been met head-on by artemisinin. "I don't think [the plant is] going to put that much energy into making a molecule that's going to be as solid as a rock," he said. That being said, it is estimated that for a three-day combination treatment course, the half-life of at least one component should exceed 24 hours. Piperaquine, for example, which is combined with DHA, has an estimated half-life of two to three weeks.⁴²

Second, artemisinin derivatives, when used as monotherapy (i.e., without a partner drug), have relatively high recrudescence (i.e., relapse) rates of about 10%, and they need to be administered over about seven days for radical cure.⁸

Third, combination therapies prevent the development of resistance. "It's kind of difficult to develop resistance to multiple weapons, compared to one," Rodriguez said. "That's always been my argument why, in the long run, plant-derived mixtures work. The plant mixture might not be 100% effective, like a pure compound, but it will be more difficult for bacteria or parasites to develop resistance over a short period of time to a mixture."

For this reason, the WHO vehemently discourages the use of artemisinin monotherapies. In January 2006, the WHO issued a press

release urging pharmaceutical companies to stop marketing and selling monotherapies. The press release cautioned that once-popular antimalarials, including chloroquine and sulfadoxine-pyrimethamine, became widely ineffective due to the development of resistance.⁴⁹

"Our biggest concern right now is to treat patients with safe and effective medication and to avoid the emergence of drug resistance. If we lose ACTs, we'll no longer have a cure for malaria, and it will probably be at least ten years before a new one can be discovered," Arata Kochi, PhD, the former director of the WHO's malaria department, is quoted as saying in the press release. (That was 10 years ago, and nothing more effective than ACTs has become available.)

By 2015, artemisinin-resistant *P. falciparum* had been identified in Cambodia, Laos, Myanmar, Thailand, and



Artemisia annua. Photo ©2016 Steven Foster

Vietnam.¹⁷ According to Rodriguez, that's not too surprising. "Some of them [the parasites] probably already were resistant to it, but as more and more of the resistant strains take over the population, then you have resistance," he said. "[*Plasmodium*] is in a battle, and it wants to live too. It doesn't want to die, so resistance is going to be around forever." Encouragingly, as of November 2015, of the 78 national health authorities that need ACTs, 49 have taken regulatory measures to withdraw the marketing authorization of oral monotherapies and 22 have never registered them, leaving just seven that still allow the marketing of these therapies.⁵⁰

The five current WHO-recommended ACTs are artemether/lumefantrine, artesunate/amodiaquine, artesunate/mefloquine, DHA/piperaquine, and artesunate/sulfadoxine-pyrimethamine.⁴⁷ Artemether/lumefantrine, known as Coartem (Novartis; Basel, Switzerland), was the first ACT and the one that finally got the ball rolling in terms of making these drugs broadly available.²

Factors to be taken into consideration when choosing the appropriate ACT include local data on the efficacy of the ACT, local data on drug resistance, the adverse effects of the partner drug, availability, and cost.⁴⁷

Sustainability

As with other medicines derived from natural sources, there are challenges related to the sustainable supply of artemisinin. First, *A. annua* generally yields low quantities (between 0.01% and 0.80%) of the compound.⁵¹ Plants yielding higher quantities are chosen for cultivation, but large amounts of dried plant material still are required for relatively small amounts of artemisinin.

Long lead times also contribute to the challenge. *Artemisia annua* takes about eight months to reach full growth, at which point leaves are harvested and sent to extraction facilities that usually rely on large numbers of small farmers for their supply. In the past, China and Vietnam have accounted for about 80% of the harvest volume of *A. annua*, while East Africa has accounted for about 20%. After extraction, artemisinin is sent to specialized manufacturers (sometimes the manufacturer of the finished product) to be converted into its derivatives, and then the finished drug product is produced. The entire process, from the planting of the seed to the finished product, takes about 14 months.⁵²

The supply of artemisinin has been erratic over the years. During shortages, prices skyrocket, which causes more farmers to grow *A. annua*, and then the supply increases greatly, depressing prices and causing another shortage.⁵³ Consequently, artemisinin prices have fluctuated drastically, but there has been an overall downward trend over time. Prices ranged from \$800-\$1,100 per kilogram (\$363-\$499 per pound) in 2005, and from \$270-\$350 per kilogram (\$122-\$159 per pound) in 2013.⁵⁴

From 2013 to 2014, the total number of ACT treatment courses procured from manufacturers actually decreased from 392 million to 337 million.^{17,55} This is partially because of increased efforts to diagnose malaria before administering ACTs. In the past, patients with fevers were often treated with ACTs without being diagnosed with malaria. Many of them did not actually have the disease.⁵³

In fact, in sub-Saharan Africa, the number of diagnostic tests provided is now greater than the number of ACTs distributed. This was not previously the case. Despite the decrease in demand for ACTs from 2013 to 2014, between 68 and 80 million (74-87%) of the 92 million children with malaria in sub-Saharan Africa did not receive an ACT in 2014, so there is a need to increase availability of the drugs.¹⁷

Artemisia annua is not the only viable source of artemisinin. In 2004, the Bill and Melinda Gates Foundation helped fund the development of a semisynthetic process of producing the compound. The Foundation's goal was to stabilize the supply of artemisinin and lower the cost of each ACT treatment from \$2.40 to "well under a dollar."⁵³ The method that was eventually developed involves genetically modified yeast, which first converts glucose into artemisinic acid, a precursor to artemisinin. Then, a process using light converts the acid into artemisinin. French pharmaceutical company Sanofi has the capacity to produce between 50 and 60 tons of semisynthetic artemisinin per year using this method. That's enough to produce 125 million treatments.⁵⁴ In addition, this method drastically reduces the lead time to just a few days.⁵²

However, partially because of a plentiful supply and low prices of *A. annua*, Sanofi reportedly produced no artemisinin using this method in 2015, and plans to sell its manufacturing facility.⁵³ Despite this, the potential to quickly produce high-quality artemisinin that is not subject to seasonal and other growing conditions and that is comparable in cost to naturally-occurring artemisinin does exist.⁵⁴

Conclusion

The discovery of artemisinin by Tu Youyou and her team would seem to validate that the ethnobotanical approach to drug discovery can be successful. In this case, extensive study of the TCM literature helped produce the most effective drugs ever discovered for treating one of the most devastating diseases in history: malaria.

"The ethnobotanical and ethnomedical roots of the development of artemisinin demonstrate, beyond a doubt, both the profound history of traditional medicine and the interface of traditional medicine and contemporary Western scientific drug development," said Steven King, PhD, senior vice president of ethnobotanical research and sustainable supply at Jaguar Animal Health and member of ABC's Advisory Board (email, April 12, 2016).

King also said that artemisinin "indicates that careful attention to the ethnobotanical detail of how plant medicines are prepared can make all the difference in discovering bioactive molecules that can become important therapies for global public health. ... If [Tu and her team] had not carefully studied the ethnobotanical information, they might have given up on this plant and preparation."

Beginning in the 1990s, when King was at Shaman Pharmaceuticals Inc., he was part of a group that looked for new drugs based on an ethnobotanical approach. Those efforts eventually produced crofelemer, a natural compound isolated from the red latex of the South American tree *sangre de grado* (dragon's blood; *Croton lechleri*, Euphorbiaceae).⁵⁶ In 2012, crofelemer (trade name Fulyzaq) became the

second botanical, and the first orally administered botanical, to receive drug approval from the US Food and Drug Administration (FDA). The drug is used to treat HIV-associated diarrhea, and it demonstrates that, even decades after the discovery of artemisinin, plants and other natural sources should still be considered viable leads for new and effective drugs.

“The global large- and small-scale pharmaceutical research approach has shifted away from natural products and ethnobotanical information over the past 30 years, focusing rather on high throughput screening, genomics, and related approaches,” King said. The most often mentioned reason for this shift, according to King, is that the chemical diversity found in plants has been explored and hasn’t produced any new therapeutics. “This is not, by any means, fully accurate, but microorganisms, marine compounds, and extremophiles (organisms that thrive in extreme environments, such as hydrothermal vents in ocean trenches) continue to be of interest in the search for new drugs. It would be a wise idea to integrate the wisdom of traditional medicine with the latest advances in drug discovery and development. There are so many examples of new applications for ethnobotanically-derived therapeutics,” he said.

According to King, the Nobel Prize reinforces “that plant medicine has been, and continues to be, a critical part of the global management of human health. A plant-based medicine does not have to become, or lead to, a new drug to demonstrate its utility to human and animal health. ... Plants as medicines are part of the foundation of human health care worldwide, and will become more so in the 21st century.”

He also said that the Nobel Assembly’s recognition of Tu Youyou and artemisinin, as well as its recognition of avermectin, is “timely and symptomatic of a scientific community that is hopefully becoming more holistic and integrated.” HG

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Artemisinin: Mechanisms of Action

It is believed that artemisinin’s effectiveness is due largely to its unique endoperoxide bridge (i.e., two bonded oxygen atoms between two carbon atoms; C-O-O-C), which is contained within a six-membered ring. “The oxygen-oxygen bond in the endoperoxide bridge is somewhat stable, but not as strong as a carbon-carbon bond. Nonetheless, the endoperoxide bridge in artemisinin is very active when broken,” said Rodriguez. It is worth noting that artemisinin derivatives that lack this feature show no antimalarial activity.⁴⁴

It is also believed that heme* is responsible for catalyzing the cleavage (breakage) of the endoperoxide bridge.⁴⁴ During the trophozoite stage (the feeding stage) of the parasite’s life cycle (see previous sidebar), according to one estimate, *P. falciparum* ingests and digests about 70% of the hemoglobin (a protein that carries oxygen from the lungs to the body’s tissues) in an infected red blood cell (erythrocyte) in just a few hours. Hemoglobin is an important nutrient source for the parasite and enables its growth and maturation. As the parasite breaks down the hemoglobin, heme is released.^{57,58}

When the endoperoxide bridge is cleaved in the presence of ferrous iron from heme, each of the previously bonded oxygen atoms retains one of the two previously shared electrons (i.e., homolytic fission) and becomes a free radical (a highly reactive, short-lived atom, or group of atoms, with one or more unpaired electrons).^{44,59} The unstable compound then damages the microorganelles and membranes of the parasite, as well as the infected erythrocyte, causing the host’s immune system to eliminate the infected erythrocyte. The theory that free radicals mediate the death of the parasites is supported by the fact that the presence of antioxidants (free radical scavengers) blocks the antimalarial effects of artemisinin.⁴⁴

“You can imagine it like a dart sticking to a dartboard,” Rodriguez said. “In other words, the dartboard, in this case, could be a protein, an enzyme, and the dart is the small molecule that just jams that board, or that protein, and then it doesn’t function. ... It’s always been a battle of small molecules against macromolecules.”

He proposed another explanation for artemisinin’s effectiveness. “We’ve done some preliminary, but unpublished, research in which we show that artemisinin is capable of cleaving DNA,” he said. “In other words, artemisinin can remove a proton or a hydrogen from DNA that can lead to the eventual breakdown of DNA. ... If you have all these radicals just bombarding the DNA, it really messes it up.”

* Heme is a non-protein constituent of hemoglobin that contains, at its center, a ferrous iron atom (i.e., an iron atom with two more protons than electrons; Fe²⁺).

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Artemisia annua. Photo ©2016 Steven Foster



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Saffron: THE SALUBRIOUS SPICE

Emerging Research Suggests Numerous Health Benefits

By Linda Woolven and Ted Snider

Introduction

Since ancient times, saffron (*Crocus sativus*, Iridaceae) has been valued in the medical traditions of Persia, Greece, Egypt, and India. Strangely, though, it has largely been ignored by scientists and by the West — until now. The past dozen years has brought a flowering of research on this versatile and intriguing herb.

Saffron is the world's most expensive culinary botanical, and it may soon become known for its medicinal value as well. Perhaps the most interesting research on saffron has examined its effects on depression and Alzheimer's disease (AD). However, there has also been promising research on a host of other conditions, from erectile dysfunction (ED), premenstrual syndrome (PMS), and dysmenorrhea, to glaucoma, weight loss, and exercise.

The plant part used as a medicine and spice is the dried stigma from the flower. Saffron is expensive because each flower contains only three red, yellow, or golden yellow-orange stigmas, which are collected in the field and used. A small, but growing, body of research is exploring the possibility of using saffron extracts made not from the stigma, but from the petal. (The potency of stigma extracts and

petal extracts is relatively similar, and both preparations have been shown to produce antidepressant effects.) With more usable plant material to produce extracts, saffron could become a more readily available, and more affordable, medicinal herb.

The purpose of this review is to summarize the available evidence from clinical trials on the internal and topical uses of saffron. Together, these studies form an impressive and exciting body of research that suggests that saffron is a safe, effective, and multipurpose herb.

Saffron as Food and Medicine

Saffron's history as a culinary and medicinal plant stretches back to ancient times. It first appeared in a seventh century BCE Assyrian botanical dictionary in which it



Saffron *Crocus sativus*. Photo ©2016 Steven Foster

was indicated for breathing difficulties, painful urination, menstrual disorders, and “diseases of the brain” — the last two uses corresponding to some of the best-researched modern applications.¹ Though saffron is best known for its use in traditional Persian medicine, it also was used by the ancient Greeks and Egyptians, as well as in the Ayurvedic tradition of India.² Its traditional medical indications were many, and included cramps, asthma, menstrual conditions, liver disease, and pain.³

Iran is the world’s largest producer of saffron, and much of the modern pharmacological and clinical research on the herb has been conducted there in a number of research facilities, including major universities and hospitals.

Saffron’s mechanisms of action are not yet well understood, but they likely involve a number of compounds, such as safranal, crocin, and crocetin — carotenoids that are structurally similar to zeaxanthin, a carotenoid found in

many plants, as well as in the eye. (Carotenoids are photosynthetic pigments with strong antioxidant properties.)⁴

Despite the broad traditional uses of saffron, modern research has been scarce. Few studies have evaluated its traditional uses, and few modern herbal books have included saffron. However, this has changed in the past dozen years with recent clinical research focusing on Alzheimer’s disease, depression, reproductive health, eye health, weight loss, exercise, and other areas.*

Alzheimer’s Disease

A group of researchers in Iran has published two small studies on saffron and AD. The first was a double-blind, randomized, controlled phase 2 study comparing a saffron extract to donepezil. Donepezil is one of the most recently approved cholinesterase inhibitors, the leading class of Alzheimer’s drugs.

* See Table e1, available at <http://cms.herbalgram.org/herbalgram/index.html>, for additional details about the studies mentioned in this article.

The dose of donepezil was 5 mg for four weeks, then 5 mg twice a day for 18 weeks; the dose of saffron extract was 15 mg a day for four weeks, then 15 mg twice a day for 18 weeks. The saffron (Green Plants of Life, IMPIRAN Co., Ltd.; Tehran, Iran) was prepared by extracting dried and milled stigmas with 80% ethanol at a 1:15 ratio. The extract was then dried. It contained 0.13-0.15 mg of safranal and 1.65-1.75 mg of crocin per 15 mg. Study participants had experienced cognitive decline for at least six months before the start of the study. Forty-seven people completed the study (24 in the saffron group; 23 in the donepezil group). The mean age was 72.7 in the saffron group and 73.9 in the donepezil group.

In this study, saffron was found to be as effective as donepezil. Scores on the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-CS) improved by 3.96 points in the saffron group and by 3.77 points in the donepezil group. The improvement was not significantly different between the two groups. Scores on the Clinical Dementia Rating Scale-Sums of Boxes (CDRS-SB) improved by 0.77 points in the saffron group and by 0.83 points in the donepezil group. Again, the improvement was not significantly different between the two groups. The changes in scores from baseline to 22 weeks were not statistically significant for either scale in either group, but the authors state that a three-point change in the ADAS-CS score, which both groups experienced, is clinically meaningful. While there was no statistical difference between saffron and donepezil, saffron did have an advantage in adverse events (AEs). Frequency of AEs was similar, but there was significantly more vomiting in the donepezil group.⁵

In another study, the beneficial effect of the saffron preparation did reach statistical significance. In this randomized, double-blind, placebo-controlled study of 46 people with probable AD, each person was given either a placebo or 15 mg of saffron extract (Green Plants of Life, IMPIRAN) twice a day for 16 weeks. Saffron stigmas were extracted in 80% ethanol, then dried. ADAS-CS and CDRS-SB scores improved significantly in the saffron group compared to placebo ($P = 0.04$ on both scales). On both scales, subjects improved in the saffron group, while those in the placebo

group continued to worsen (-3.69 and $+4.08$, respectively, on the ADAS-CS, and -0.67 and $+0.63$, respectively, on the CDRS-SB). There was no significant difference between saffron and placebo in AEs. The researchers said that saffron's mechanism in benefiting AD may be the inhibition of aggregation and deposition of amyloid β plaque in the brain.⁶

Depression

Saffron was used in traditional Persian medicine for treating depression, and depression is the condition for which saffron has the strongest scientific support in Iran.⁷ The initial evidence was provided by two small, double-blind studies. The first was a six-week, randomized, double-blind, placebo-controlled trial of 35 people with mild to moderate depression who were given either a placebo or 30 mg of saffron stigma extract (produced in 80% ethanol, then dried). The saffron extract used (Novin Zaferan Co.; Mashhad, Iran) was not standardized. At the end of the six-week study, the saffron group had a significantly greater improvement on the Hamilton Rating Scale for Depression (HAMD) ($P < 0.001$). The saffron was well-tolerated, and there was no significant difference in AEs between the saffron and the placebo groups.⁷

The second study was also a six-week, randomized, double-blind, placebo-controlled study of 40 people with mild to moderate depression that compared 30 mg of saffron petal extract to a placebo. The saffron was an 80% ethanol extract (identified by the Department of Cultivation and Development of the Institute of Medicinal Plants [DCDIMP]; Tehran, Iran). Once again, the saffron group's HAMD scores improved significantly more than those of the placebo group ($P < 0.001$). As in the first study, AEs were the same in both groups.⁸ An intriguing feature of this study is that it is one of the few to use saffron petal instead of saffron stigma. One systematic review has shown that saffron petal is as effective as saffron stigma for depression.⁹ Though saffron petal does not contain crocin, it does contain kaempferol, a flavonoid with antidepressant effects.¹⁰

The next studies on saffron and depression compared the herb to various antidepressant drugs. The first small study



A detail from the "Saffron Gatherers" fresco of the Xeste 3 building. It is one of many depicting saffron; they were found at the Bronze Age settlement of Akrotiri, on the Aegean island of Santorini. Image from *Le Musée absolu*, Phaidon, 2012.



was a randomized, double-blind trial that compared saffron extract (Novin Zaferan Co.) to the pharmaceutical tricyclic antidepressant imipramine. The study lasted six weeks and included 30 people, aged 18-55, with mild to moderate depression. The dose of imipramine was 100 mg per day; the dose of saffron was 30 mg per day. The saffron preparation was an 80% ethanol extract of dried and milled stigmas that was then dried. Improvement on the HAMD was significant in both groups ($P < 0.0001$) and there was no significant difference between groups ($P = 0.33$). Though saffron was not more effective than imipramine, it had fewer AEs, because dry mouth and sedation were significant in the imipramine group.⁹

In the next study, saffron was compared to a selective serotonin reuptake inhibitor (SSRI). In a six-week, randomized, double-blind study, 40 people, aged 18-55, with mild to moderate depression were given either 10 mg of fluoxetine twice a day, or 15 mg of saffron twice a day. The saffron extract was made from dried and milled stigmas extracted with 80% ethanol, and it was then dried. Each 15-mg capsule was standardized to 0.30-0.35 mg of safranalin. Both fluoxetine and saffron led to significant improvement on the HAMD. The 54% improvement with saffron was similar to the 65% improvement with fluoxetine ($P = 0.71$). While saffron was not more effective than fluoxetine, it trended toward a decreased incidence of sexual dysfunction ($P = 0.10$) and tremor ($P = 0.10$), but this was not statistically significant.¹¹

Saffron was compared to fluoxetine again in an eight-week, randomized, double-blind study of 38 people, aged 18-55, with mild to moderate depression who were given either 10 mg of fluoxetine twice a day or 15 mg of an 80% ethanol extract of saffron petals twice a day (morning and evening). The extract was standardized to 0.30-0.35 mg of safranalin. The saffron had a significant effect ($P < 0.0001$) on HAMD scores compared to baseline values, which was equal to the effect of fluoxetine (-12, or 54%, in the saffron group and -13.5, or 59%, in the fluoxetine group). In both groups, the remission rate was 25%, and there was no significant difference in the response rate to treatment (defined as at least a 50% decrease on the HAMD) between the two groups: 75% in the saffron group and 85% in the fluoxetine group responded to treatment.¹² The study was limited by the lack of a placebo control.

A third study, with a different population, compared saffron to fluoxetine. This study included people with mild to moderate depression who had undergone percutaneous coronary intervention (angioplasty) for coronary artery disease. This population was investigated because coronary artery disease is often associated with depression, and the procedure of percutaneous coronary intervention may also be associated with depression. In this small, randomized, double-blind, placebo-controlled study, 40 people were given either 40 mg of fluoxetine or 30 mg of saffron extract (SaffroMood; Green Plants of Life, IMPIRAN) each day for six weeks. The saffron extract was a dried 80% ethanol extract of stigmas. Each 15-mg capsule contained 0.13-0.15 mg of safranalin and 1.65-1.75 mg of crocin. The two treatments were found to be equally effective ($P = 0.62$), according to the HAMD. In both groups, the remission rate was

70%. A complete response was counted if the decrease on the HAMD was 50% or more; 85% of the saffron group had a complete response versus 80% of the fluoxetine group. There was no significant difference in the frequency of AEs, but two people in the fluoxetine group had to be excluded due to severe anxiety and suicidal thoughts.¹³

There have been two reviews of saffron preparations for the treatment of depression. The first was a meta-analysis of five randomized, controlled studies. The meta-analysis does not identify the preparations used, but a check of the references reveals that four of the studies used ethanol extracts of saffron stigmas and one used an ethanol extract of the petals. Two of the studies used placebos in the control arms, and three used antidepressant drugs. An antidepressant effect was found for saffron preparations compared to placebo, and saffron was shown to be as effective as the antidepressant drugs. Saffron was as safe as placebo and safer than imipramine.¹⁴

A systematic review of six high-quality clinical trials included the five studies mentioned in the previous paragraph and one additional study that had been conducted since publication of the first meta-analysis. This systematic review included 230 people with major depression. Two studies were randomized, double-blind, and placebo-controlled, and four were randomized, double-blind comparisons to antidepressant medications. Four of the studies used saffron stigma extract and two used saffron petal extract. In all six studies, the dose of saffron extract was 15 mg twice a day. In three of the studies, the saffron extract was standardized for crocin and/or safranalin; in the other three studies, there was no reported standardization. This review also found a large treatment effect for saffron preparations, compared to placebo, which was similar to the effect for antidepressant drugs. Interestingly, the review found that saffron stigma extracts and petal extracts had similar efficacy, according to HAMD scores (stigma extracts: reduction of 11.7-12.2; petal extracts: reduction of 12-14).¹⁰

The authors of the systematic review suggested that saffron's mechanism of action in treating depression may be due to its serotonergic, antioxidant, anti-inflammatory, neuroendocrine, and neuroprotective effects. It has been suggested that the serotonergic effect is due to saffron's ability to act like an SSRI. Saffron may also inhibit the reuptake of dopamine and norepinephrine.¹⁵

Reproductive Health

Saffron may be able to attenuate some of the sexual dysfunctions caused by SSRI antidepressants when the two are used conjunctively.¹¹ This is according to at least two studies, which found that subjects taking saffron preparations had significantly greater improvements in certain symptoms compared to those taking a placebo.

Many SSRIs can cause sexual dysfunction, such as decreased desire and arousal. In particular, fluoxetine is associated with reduced sexual desire: 64.3% of women on fluoxetine reportedly experience this symptom.¹⁶

A randomized, double-blind, placebo-controlled study found that saffron can help women suffering from sexual dysfunction induced by fluoxetine. The study included 34 women, aged 18-45, who were suffering from major depres-

sion. All the women were taking 40 mg of fluoxetine a day and were experiencing various sexual dysfunctions. None of the women had experienced any sexual dysfunction before initiating fluoxetine treatment. Each subject added to her current treatment either 30 mg a day of saffron petal extract (Green Plants of Life, IMPIRAN) or a placebo for four weeks. The saffron was prepared by extracting dried and milled petal in 80% ethanol, then drying it. Each 15-mg capsule was standardized to 1.65-1.75 mg of crocin. Though the intervention section of the article first refers to the saffron material as “the stigma’s extract,” it later refers to it as “dried and milled petal” and “extract of petal.” So, this could be the third study to use the less expensive saffron petals, instead of the more expensive stigmas, although it is unclear. Compared to the placebo group, the women taking the saffron extract experienced significantly greater improvements in total Female Sexual Function Index (FSFI) ($P < 0.001$), and in the arousal ($P = 0.028$), lubrication ($P = 0.035$), and pain ($P = 0.016$) domains of the FSFI, but not in the desire ($P = 0.196$), satisfaction ($P = 0.206$), or orgasm ($P = 0.354$) domains. Frequency of side effects was similar between the two groups, but less frequent in the saffron group. This study suggests that saffron extract may be able to improve some of the sexual dysfunction symptoms caused by fluoxetine.¹⁷

Saffron can also help men suffering from sexual dysfunction caused by SSRIs. In a randomized, double-blind, placebo-controlled study, 30 men, aged 18-45, with major depression who were taking fluoxetine and experiencing sexual impairment were given either 15 mg of saffron stigma extract (Green Plants of Life, IMPIRAN) or a placebo twice a day for four weeks. The saffron was extracted in 80% ethanol, then dried. Each capsule was standardized to 1.65-1.75 mg of crocin. Researchers used the International Index of Erectile Function (IIEF-5) scale to gauge sexual function. After four weeks, the saffron group had significantly greater improvements in ED ($P < 0.001$), intercourse satisfaction ($P < 0.001$), and total IIEF-5

scores ($P < 0.001$) compared to the placebo group. Saffron did not significantly improve orgasm, overall satisfaction, or sexual desire compared to placebo. Impressively, 60% of the men taking saffron achieved a normal erectile function score on the IIEF-5 versus only 7% of those taking the placebo. The frequency of AEs was similar between the two groups.¹⁸

Saffron preparations may also be effective for sexual dysfunction not caused by antidepressant drugs. In an open-label study, 20 men with ED were given 200 mg of saffron for nine days and then 400 mg on the 10th day. The saffron used was an aqueous extract (plant part not specified) containing 19.7 mg/g of crocin and 0.25 mg/g of safranal (Novin Zaferan Co.). After 10 days of saffron treatment, subjects had significant improvements in rigidity ($P < 0.0001$) and size ($P < 0.0001$) compared to baseline scores, as measured by the Nocturnal Penile Tumescence (NPT) test. Total IIEF-5 scores also improved significantly after saffron treatment ($P < 0.001$). Mean IIEF-5 scores for erectile function, orgasmic function, sexual desire, intercourse satisfaction, and overall satisfaction increased significantly after saffron treatment ($P < 0.0001$). Saffron led to more frequent ($P < 0.0001$) and longer-lasting erections (p-value not reported). There were no major AEs.¹⁹ These are impressive results after only 10 days of treatment, but the study was small, there was no control, and it was not blinded.

A second study looked at men suffering from ED and lower urinary tract symptoms (LUTS) due to benign prostatic hyperplasia (BPH). The study was randomized, but it is not clear if it was blinded. One hundred twenty-nine men over the age of 50 were given either 320 mg of saw palmetto (*Serenoa repens*, Arecaceae) berry extract alone or in combination with 120 mg Masson’s pine (*Pinus massoniana*, Pinaceae) bark extract and 100 mg of saffron extract (IDIProst Gold; idiPharma; Aci Bonaccorsi, Italy), for three months. Additional details about the extracts were not provided. The combination



Saffron *Crocus sativus*. Photo ©2016 Liné

product produced a significantly greater improvement in the International Prostate Symptom Score (IPSS) compared to saw palmetto alone ($P < 0.001$). The combination also produced greater improvement in ED, as evidenced by significantly greater improvement on the IIEF-5 ($P < 0.003$). Saw palmetto berry extract alone did not improve ED. Quality of life, as measured by the Short Form Health Survey (SF-36), also improved significantly more in the combination group ($P < 0.001$). There were few AEs.²⁰ The inclusion of the pine bark extract in this study makes it difficult to establish the role of the saffron, because the patented extract of French maritime pine (*P. pinaster*) bark, which is known commercially as Pycnogenol (Horphag Research; Geneva, Switzerland), also has been reported to improve ED.²¹

Diabetes is a major risk factor for ED. In a novel study, saffron was shown to help ED when applied topically. This one-month, double-blind, placebo-controlled study asked 50 diabetic men with ED to apply a “pea-sized” amount of either a topical saffron gel or a placebo gel 30 minutes before intercourse for one month. The saffron gel consisted of 1% saffron (the paper does not specify the plant part used, or if it was an extract) in a starch-based gel (School of Pharmacy, Shahid Beheshti University of Medical Sciences; Tehran, Iran). The saffron gel significantly improved ED compared to placebo on the IIEF-5 ($P < 0.001$).²²

Saffron can help other aspects of reproductive health as well. At least two studies have explored saffron’s efficacy for menstrual conditions. A randomized, double-blind, placebo-controlled study investigated saffron’s ability to alleviate symptoms of PMS. The study included 47 women, aged 20 to 45, who suffered from PMS. They were given either a placebo or 15 mg of saffron extract twice a day (morning and evening) for two menstrual cycles. The saffron was made from dried and milled stigma that was extracted with 80% ethanol and then dried (identified by the DCDIMP). Compared to placebo, the saffron significantly improved the symptoms of PMS, according to the Total Premenstrual Daily Symptoms Rating (TPDSM) scores ($P < 0.0001$). In the saffron group, 76% of participants responded to treatment, compared to 8% in the placebo group, a significant difference ($P < 0.0001$). Not surprisingly, given the research on saffron and depression, the saffron preparation also significantly decreased depression on the HAM-D ($P < 0.0001$) — the secondary endpoint of the study — and did so significantly better than the placebo ($P < 0.001$). In addition, 60% of the saffron group responded to treatment, according to HAM-D scores, compared to only 4% of the placebo group ($P < 0.0001$). There was no significant difference in AEs between groups.²³

The second study related to female reproductive health used a combination saffron product. One hundred eighty students, aged 18-27, who suffered from dysmenorrhea (painful menstruation), were given either a placebo, 500 mg of highly purified saffron combined with celery (*Apium graveolens*, Apiaceae) seed and anise (*Pimpinella anisum*, Apiaceae; presumably the seed), or mefenamic acid three times a day, for three days, starting from the onset of bleeding or pain. (Mefenamic acid is a nonsteroidal anti-inflammatory drug [NSAID] commonly used for dysmenorrhea.)

The women were followed for two to three menstrual cycles. There was a statistically significant reduction in pain and duration of pain in the herbal combination group ($P < 0.001$) and the mefenamic acid group ($P < 0.01$) compared to baseline, but the improvement was significantly greater in the herbal combination group.²⁴ Given that saffron was administered in combination with two other herbs, it is difficult to isolate the effectiveness of saffron in this study.

Eye Health

Another promising area of saffron research is eye health. A leading cause of blindness, glaucoma is caused by increased pressure within the eye, known as intraocular pressure. In this randomized, double-blind, placebo-controlled study, 34 people with primary open-angle glaucoma, who were being treated with timolol and dorzolamide eye drops, added either an oral aqueous extract of saffron stigma (East Sorkhfam Saffron Co.; Gonabad, Razavi Khorasan, Iran) or a placebo. The saffron capsule contained 30 mg of concentrated powdered extract, and was taken once a day. After three weeks, there was a significantly greater improvement in the saffron group ($P = 0.013$) compared to placebo. At the end of the four-week study, intraocular pressure was virtually unchanged in the placebo group, but, in the saffron group, intraocular pressure dropped significantly ($P = 0.001$). There were no AEs for either group.²⁵

Saffron has also been shown to help age-related macular degeneration (AMD). In an open-label study, researchers gave 20 mg a day of saffron stigma to 29 people with AMD for 15 months (Zaffit; Hortus Novus; L’Aquila, Italy). At this dose, the supplement was presumably an extract. Compared to baseline, the saffron preparation led to a significant increase ($P < 0.01$) in focal electroretinogram (fERG), an assessment of macular function, and a significant improvement in mean visual acuity ($P < 0.01$). All 29 participants reported improved vision, especially contrast and color perception, reading ability, and vision at low light.²⁶

A second study on saffron and AMD was randomized, double-blind, and placebo-controlled. It included 25 people, aged 54 to 85, with AMD who were given either a placebo or 20 mg of saffron for three months. No information is provided about the saffron supplement; though, at a dose of 20 mg, it is presumably an extract. fERG improved significantly in the saffron group ($P < 0.001$) but not in the placebo group. The difference between the two groups was significant ($P < 0.01$). Visual acuity improved in 80% of the saffron group but in 0% of the placebo group. The improvement in visual acuity was significant ($P < 0.01$). There were no AEs.²⁷

Weight Loss

In a less-explored area of research, saffron has demonstrated the ability to reduce snacking and promote weight loss. One study included 60 healthy, mildly overweight women. It was randomized, double-blind, placebo-controlled, and lasted eight weeks. Subjects took either a placebo or Satiereal (Inoreal Ltd.; Plérin, France), which the manufacturer describes as a novel patented extract of saffron stigma.²⁸ The saffron supplement contained 176.5 mg of saffron taken

in two doses: one at breakfast and one at dinner. Subjects' caloric intake and exercise frequency were not restricted. The women in the saffron group lost significantly more weight than those in the placebo group: 2.19 lbs versus 0 lbs ($P < 0.01$). The women in the saffron group had their snacking reduced by 55% compared to a 28% reduction in the placebo group, a significant difference ($P < 0.05$). Feelings of satiety increased in the saffron group. On the General Index of Food Craving, the saffron group experienced an improvement in the "hunger" and "snacking" dimensions, compared with the placebo group ($P < 0.05$). The saffron supplement was well-tolerated.²⁹

Exercise

Delayed onset muscle soreness (DOMS) is the pain and discomfort that may be felt for a few days after strenuous exercise. It is experienced as stiffness, tenderness, and pain during physical activity. DOMS is problematic for people in training because, aside from the discomfort, it can limit exercise and training. In a randomized, double-blind, placebo-controlled trial, 39 sedentary men were given a placebo, 300 mg of dried saffron powder (plant part not specified), or 75 mg of the NSAID indomethacin for 10 days, starting one week before exercise and continuing for three days. The placebo group experienced severe pain for three days after the exercise, but pain in the saffron group was 11.2 times lower than baseline scores after 24 hours. Pain in the indomethacin group took three days to disappear, but the saffron group had no pain after 48 hours ($P < 0.001$). The researchers concluded that dried saffron is more effective than indomethacin for DOMS.³⁰

Systematic Reviews

There have been three recent reviews of saffron research. One is a systematic review of 12 randomized, controlled trials of saffron or saffron combination products. Six of the studies were on depression, one was on PMS, four were on sexual dysfunction and infertility, and one was on weight loss and snacking behavior. The review does not provide details about the preparations used, but an analysis of the references reveals that numerous preparations were used: seven studies used saffron stigma extracts; two depression studies used saffron petal extracts; one study on fluoxetine-induced sexual dysfunction did not specify whether the extract was of stigmas or petals; one used a standardized, but unspecified, extract; and the other also was unspecified. The reviewers conclude that the data from these studies support the efficacy of saffron for depression, PMS, sexual

dysfunction, and excessive snacking. They say that the strongest clinical evidence exists for saffron as a treatment for depression. They also note that, in the studies comparing saffron to antidepressants, the pharmaceutical drugs caused more sedation/drowsiness, headaches, dry mouth, constipation, and sexual dysfunction compared to saffron. The reviewers conclude that the data support saffron's efficacy for ED, despite their inclusion of one negative open-label study that compared a dried 80% ethanolic extract of saffron petal with the ED drug sildenafil.³

A second review article concluded that saffron can improve cognition (comparable to donepezil), can help treat mild to moderate depression (comparable to imipramine) and AMD, can significantly improve symptoms of PMS, improve fluoxetine-induced sexual dysfunction in men and women, and can significantly decrease lipoprotein oxidation.⁴



Saffron *Crocus sativus*. Photo ©2016 Steven Foster

The third review concluded that saffron is effective for depression, and is more effective than placebo and as effective as donepezil for AD.³¹ It found evidence that saffron can help with weight loss and reduce snacking, and that it is superior to placebo and similar to standard treatments for PMS. The review included two studies on AD, six on depression, one on ED, one each on PMS and dysmenorrhea, and one on weight loss, all of which are discussed above. It also identified one study that suggested that saffron does not help male infertility caused by idiopathic low sperm count.³² Another study included in the review found that saffron may have short-term immunomodulating effects.³³

The review included two promising studies on saffron for cardiovascular health. The first was a double-blind, placebo-controlled trial that concluded 400 mg of saffron stigma (at this dose, presumably not an extract) produced a statistically significant lowering of standing systolic blood pressure and arterial blood pressure. However, according to the authors, the improvements were not clinically significant.³⁴ The second cardiovascular study found that 50 mg of saffron dissolved in milk, when administered twice a day to a group of 20 people (10 of whom had heart disease), decreased susceptibility to lipoprotein oxidation.³⁵

Two studies provided limited evidence that saffron can benefit the skin. The first showed that a 0.3% dry extract of saffron stigma in a cream, lotion, or face powder can lighten skin via shining and depigmentation. However, the methodology of the study was not adequately reported.³⁶ The second study was an open-label, randomized, controlled trial that found improvement in itching with a topical application that included saffron. However, the 0.025% saffron extract is one of 11 ingredients in the formula, so it is not possible to make any conclusions about the efficacy of saffron itself.³⁷ Finally, the review concluded that saffron has a “high safety level.”

Conclusion

The recent research from Iran on this traditionally used plant strongly suggests that saffron, the most expensive spice on the market, may also have significant medicinal value. Additional research on the efficacy of petal extracts, compared to the more commonly used stigma extracts, may lead to more of the botanical being used in medicinal preparations, thus making it more accessible and possibly decreasing the historically high price. If replicated and confirmed by researchers in other countries, this growing body of research could lay the foundation for saffron to take a place among other important medicinal plants used for a variety of physical and psychological conditions. HG

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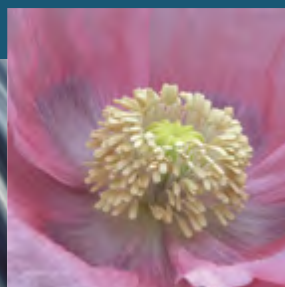
day Guide to Medicinal Herbs and Their Use (2006), *The Family Naturopathic Encyclopedia* (2011), and *Sex & Fertility: Natural Solutions* (2012), all published by Fitzhenry and Whiteside Limited. They also publish *The Natural Path newsletter*. Woolven and Snider can be reached on their blog at www.thenaturalpathnewsletter.com

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Phytopharmacy: An Evidence-Based Guide to Herbal Medicinal Products by Sarah E. Edwards, Inês da Costa Rocha, Elizabeth M. Williamson, and Michael Heinrich. Chichester, UK: Wiley-Blackwell; 2015. Softcover, 403 pages. ISBN: 978-1-118-54356-6. \$70.00.

This is a welcome new addition to the modern literature on herbal medicine, written by a prestigious team of authors. It is pitched as a guide for health professionals who are not already converted to the benefits of herbs. All authors are based in pharmacy schools, and the target audience is indicated in the title. The book's aim is to help people who know little about herbs make better judgments when they encounter patients who are inclined to take them. Included in the audience are "expert patients" (the term is formally used by the National Health Service in the United Kingdom for patients, usually with chronic disease, who are offered more discretion in determining their treatment plan, perhaps as the hub of a network of health professionals).

This last point indicates that the book is clearly directed to a UK audience (which is made clear in the "How to Use" section). There is much in the introduction about the complexities of European regulation of herbs, either as medicines or as food supplements ("botanicals"). Thus, the book's relevance to readers in other regions is limited. However, it is still an important addition to bookshelves around the world.

The average pharmacist, physician, or nurse in the United States might be surprised that some of these things are considered medicines at all and that many products include official Patient Information Leaflets (PILs). They may also be moderately impressed by the quality of the information available about clinical judgments on the use of these medicines. The authors discuss the use of "phytomedicine" in conventional medical and pharmaceutical practices in mainland Europe as well. Reflecting this for a wider audience is a useful service.

The vast majority of the text is devoted to 115 monographs running from açai (*Euterpe oleracea*, Arecaceae) to yohimbe (*Pausinystalia johimbe*, Rubiaceae), using the common English names as titles. Each monograph opens with a status position at the top right, denoting the medicinal status and the authors' own rating system of the evidence base. A quick count indicates that just over half of the herbs in the list have medicinal status. Most are "traditional herbal remedies," meaning the product has been registered in the UK as a traditional herbal medicinal product. (This requires a full pharmaceutical dossier of quality, a full safety assessment and monitoring procedure, and a "traditional use" indication, based on an agreed plausible claim for a self-limiting condition suitable for self-medication that has been applied for at least 30 years). Seven monographs relate to herbs that have been used in fully licensed medicines, an earlier regulatory route for products that could demonstrate evidence of efficacy as well as meet other pharmaceutical requirements.



The rating system goes up to five stars (actually leaves). This top level denotes that the herb is on the UK market with full marketing authorization and has a widely acknowledged evidence base of clinical trials and meta-analyses. There are only five monographs that earn this rating: cannabis (*Cannabis sativa*, Cannabaceae), which is available in the UK only by prescription; chili/capsicum (*Capsicum annuum*, Solanaceae); colloidal oatmeal (*Avena sativa*, Poaceae) as a topical; peppermint (*Mentha x piperita*, Lamiaceae) leaf oil; and senna (*Senna alexandrina*, Fabaceae) fruit

and leaf.

Monographs with four leaves have "robust" clinical evidence. These are: centella (*Centella asiatica*, Apiaceae; also called gotu kola) herb; German chamomile (*Matricaria chamomilla*, Asteraceae) flower; echinacea (*Echinacea* spp., Asteraceae) herb and root; ginkgo (*Ginkgo biloba*, Ginkgoaceae) leaf extract; hawthorn (*Crataegus monogyna*, Rosaceae) leaf, flower, and fruit; horse chestnut (*Aesculus hippocastanum*, Sapindaceae) seed extract; ispaghula/psyllium (*Plantago ovata*, Plantaginaceae) seed husk; ivy (*Hedera helix*, Araliaceae) leaf; kalmegh (*Andrographis paniculata*, Acanthaceae) herb; lavender (*Lavandula* spp., Lamiaceae) oil; linseed/flaxseed (*Linum usitatissimum*, Linaceae); pelargonium (*Pelargonium sidoides*, Geraniaceae) root; St. John's wort (*Hypericum perforatum*, Hypericaceae) herb; and saw palmetto (*Serenoa repens*, Arecaceae) berry, which downplays the resounding negativity of the latest Cochrane review.¹

A remarkable reflection of the idiosyncrasies of the regulatory process is that neither centella nor hawthorn have medicinal status (the latter because there are no agreed upon indications for minor self-limiting conditions suitable for self-medication, since hawthorn is used for cardiac conditions).

Two monographs have a skull-and-crossbones icon denoting an overriding caution: butterbur (*Petasites hybridus*, Asteraceae), in spite of the fact that there are medicinal products with low-pyrrolizidine alkaloids available across Europe, and graviola (*Annona muricata*, Annonaceae). Generally, as expected, the default position in the monographs is that if there is little evidence of safety, herbs are not recommended during pregnancy and lactation, and often not for children either.

The monograph structure provides the key headings expected and found in other therapeutic dossiers. With many monographs to cover in a portable reference book, and an audience that is not likely to compound prescriptions for an individual patient, the detail in each monograph is less than in a text designed for herbal practitioners. Similarly, conclusions are based on evidence rather than traditional practice and reputation. In the ginger monograph, for example, the "Indications/Uses" summary hints at the overwhelming worldwide, historical reputation of this remedy for cold-induced respiratory and digestive conditions, but the rest of the monograph focuses on indications

(e.g., nausea) based on clinical research and other scientific evidence.

There are also a smaller number of citations than one would see in a European Scientific Cooperative on Phytotherapy (ESCOP) or American Herbal Pharmacopoeia (AHP) monograph. In this text, the many hundreds of possible citations for St. John's wort have been reduced to 20, for example. However, it seems that the focus is on relevance to this audience and systematic reviews rather than comprehensiveness. Papers are generally up-to-date with the 2013 cut-off for this edition. This is entirely appropriate for the target audience.

It would be helpful in future editions to have an index or two. A list of botanical and drug names would be useful,

and, for some in the target audience, it could be helpful to list the evidence ratings and medicinal status. Future editions might also refer to regulatory status outside the UK and Europe, to help broaden the appeal of the text. HG

—Simon Mills

**Herbal Practitioner, Author
Exeter, England**

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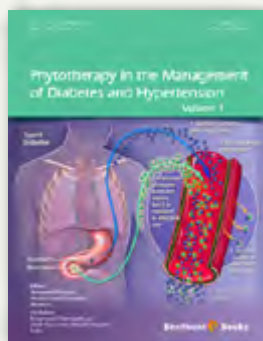
Phytotherapy in the Management of Diabetes and Hypertension, Volume 1* by Mohamed Eddouks and Debasprasad Chattopadhyay, eds. Dubai, UAE: Bentham Science; 2012. E-book, 249 pages. ISBN: 978-1-60805-014-7. \$59.00.

From the onset, the editors of this compilation of research papers set an ambitious goal: “to [provide] success in the management of diabetes and hypertension through plant-based therapeutics and dietary intervention.”

Chapter 1 accounts for almost a quarter of the e-book and presents an overview of what the authors of this section call cellular nutrition and nutritional medicine, as they relate to diabetes and its complications. Initially, there is an interesting historical overview of major discoveries related to diabetes, which is presented in a standard and concise way. General symptoms and diagnostic guidelines for the disease are also provided. The authors then describe the biochemical pathophysiology of diabetes in simple terms, and cover the broad mechanisms of glucose handling and insulin action. The rest of the chapter focuses primarily on nutrition and nutritional medicine. The authors' approach to nutritional medicine, however, is a bit haphazard and somewhat opinionated.

The first chapter also includes informative, general tables on minerals and vitamins, but the authors then highlight alpha-lipoic acid, omega-3 fatty acids, and chromium without clearly establishing the rationale for their selections. One table presents graded evidence for the beneficial actions of omega-3 fatty acids in diabetes, yet it fails to provide references or the rationale for the grading. Another table details nutrition requirements and sources of “major” phytonutrients, vitamins, and minerals, but, there too, the selections are not justified and thus appear random. Similarly, the last table in the chapter lists “Symptoms and Solutions for Some Health Problems with Nutritional Medicine” that leaves the reader wondering how and why the listed components were chosen.

Chapter 2 explores the intimate relationship between diabetes and hypertension. It begins by repeating the classifications of the two types of diabetes and then provides the general biochemistry of carbohydrate metabolism and insulin action. A significant portion of this chapter is devoted to reactive oxygen species (ROS), their sources, and their role in the pathogenesis of diabetes and atherogenesis (the formation of plaques in



the arteries). Hypertension is then discussed with a focus on nutritional factors, such as sugar and salt as contributors to the condition. A number of botanicals and natural products that can be useful for treating hypertension are then described, but, again, without a rationale for the selections or references supporting the claims.

Chapter 3 continues exploring the relationships among diabetes, hypertension, and cardiovascular diseases. After statements about diabetes statistics and gene-environment interactions, the chapter presents concise paragraphs that address the influence or involvement of stress, aging, sedentary lifestyle, obesity, dyslipidemia (an abnormal amount of blood lipids), and microalbuminuria (an elevated amount of the protein albumin in urine). The prominent biomarkers for atherosclerosis and hypertension in people with diabetes are then discussed. Surprisingly, the chapter also focuses on the dynamic and electrokinetic parameters of red blood cell membranes — a topic that includes references to the authors' own work. Lastly, lifestyle modifications and genetic susceptibility (gene polymorphisms) are briefly covered.

The first three chapters make up more than half of the book and provide useful background on nutrition, diabetes, hypertension, and cardiovascular diseases, though the material is somewhat simplistic and the selected topics are sometimes a bit random.

The remainder of the book covers the main subject matter, namely phytotherapy for diabetes and hypertension. Chapter 4 is written by Nigerian researchers and begins with concise, yet redundant sections on the classification, epidemiology, pathophysiology, and treatment of diabetes. The authors then describe 18 plants as useful monoherbal antidiabetic therapies. These stem mostly from Indian (several from Ayurveda) and Arabic traditional medicine, with a few plants from West Africa, Asia, and Latin America also included. Among the better-known plants mentioned in this chapter are fenugreek (*Trigonella foenum-graecum*, Fabaceae), Asian ginseng (*Panax ginseng*, Araliaceae), bitter melon (*Momordica charantia*, Cucurbitaceae), and prickly pear (*Opuntia ficus-indica*, Cactaceae). Unfortunately, many of the references are out-dated and some are of questionable scientific quality. In the last portion of the chapter, the authors present several interesting polyherbal preparations originating principally from India/Ayurveda.

References are more recent, but, in one case, the only citation refers to the website of an Indian pharmaceutical company.

In Chapter 5, the e-book's editors review the transition of blood sugar-regulating plants from folkloric to modern, science-based applications. After discussing ethnobotany and different worldviews of various traditional medicine systems, the reader is again presented with brief definitions and classifications of diabetes. The chapter then surveys botanicals used for the treatment of diabetes around the world. The selections were apparently based on the number of citations for the plants' antidiabetic effects, though a clear description of the actual parameters used is not provided. Again, "classical" hypoglycemia-mitigating plants, such as ginseng and bitter melon, are described with more updated references, considering the publication date of the e-book (2012). The author then covers several classes of compounds with references to their biodiversity, mechanisms of action, and potential toxicity. The chapter concludes with a review of *in vivo* (animal-based) and *in vitro* (cell-based) methods that will be helpful for students and new researchers in the field.

Chapter 6, "Phytotherapy of Hypertension in Morocco," was also written by the editors. After a concise introduction of hypertension, its causes, and general pathophysiology, the chapter systematically discusses plants used for hypertension, as identified in a Moroccan ethnobotanical survey. The plants are organized alphabetically in their respective families, and information about their botanical properties, ethnobotanical studies, and hypotensive activities is clearly presented.

Unfortunately, for several plants, studies on their uses for hypertension are either lacking or solely based on preclinical experiments. It is surprising that, even for the plants with the most compelling evidence, certain crucial references are missing. In the case of garlic (*Allium sativum*, Amaryllidaceae), for example, the authors list a Cochrane review concerning

garlic and the common cold, but fail to cite a meta-analysis for garlic and hypertension that was published around the same time.¹ Similarly, for olive (*Olea europaea*, Oleaceae) products, the authors concentrate on olive leaf extracts but do not detail the well-described benefits of olive oil (e.g., a reduced risk of developing cardiovascular conditions such as hypertension) as a crucial part of the Mediterranean diet.

In the final chapter, the editors present a general overview of processes involved in the discovery of plant-derived drug leads, from extraction to structure elucidation.

The contents of the e-book are unfortunately already a bit outdated, given that this field is evolving so rapidly. Nevertheless, the book can be useful for students and researchers with a new interest in herbals who are looking for an overview of diabetes and hypertension in the realm of phytotherapy, as well as general approaches to research in this field. However, contemporary researchers will be left somewhat disappointed if they want an updated and well-documented review of the most prominent herbs used for diabetes and hypertension around the globe, notably those supported by more recent clinical evidence. HG

* Volume 2 of *Phytotherapy in the Management of Diabetes and Hypertension* was published in December 2015.

—Pierre S. Haddad, PhD
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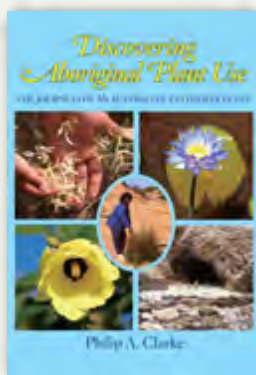
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Discovering Aboriginal Plant Use: The Journeys of an Australian Anthropologist by Philip A. Clarke. Rosenberg Publishing; Kenthurst, Australia; 2014. Hardcover, 192 pages. ISBN: 9781925078220. \$49.95.

While Philip Clarke, PhD, writes of "discovering Aboriginal plant use" as an Australian anthropologist, it is noteworthy that he dedicates the book to "all ethnobotanists." This is understandable. He writes that from early on in his career as a museum-based anthropologist, he chose "to use ethnobotany as the window through which to better understand Aboriginal Australia." With glossy 8.5×11-inch pages, the book bears a superficial resemblance to coffee-table publications that are often stereotyped as including beautiful illustrations with limited text. This is not the case with this book.

Given Clarke's anthropological training, ethnobotanical orientation, diverse professional experiences over a 30-year career, and many "journeys" through the Australian landscape, which he carefully recorded in his field journals, *Discovering Aboriginal Plant Use* is a well-written, informative, and beautifully illustrated book. It is indeed a wonderful introduction to



discovering the natural regional environments of Native Australian cultures and plant-use traditions in southeastern Australia, the arid interior, and the monsoonal northern regions. With respect to the organization of the book, these broad geographical regions are divided into chapters, with each chapter having four or five subsections dealing with specific locations.

Clarke, whose background also includes biology and geography, began his career in 1982 working with Native Australian ethnographic collections of the South Australian Museum. At the time, his research interests focused on plant foods, medicines, and materials for making artifacts, but over the course of a career that included work as a museum assistant, collection manager, registrar, curator, and head of anthropology, his interests would broaden to include Native Australian perception and land use. It is this broad view to which the reader is treated in this work.

I found particularly interesting the extent to which the author wove a basic understanding of the representation of Aboriginal material culture in diverse collections across Australia.

lia into his account of natural regional environments with their different cultures and plant-use traditions. It is in this context that issues of native title claims and heritage projects are also dealt with in this work. The topic of Native Australian medicinal plant use is discussed throughout the book and will be of special interest to readers of this publication.

The successful combination of geography, anthropology, and ethnobotany makes this book an important contribution to the literature that is suitable for general readers and a wide variety of scholars. In addition to its many excellent photographs and a useful map, the book will be particularly valuable to students

and researchers because the author has provided nine pages of endnotes, 11 pages of references, two extensive indexes of common names and scientific names, and 12 pages of a detailed general index. HG

—John Rashford, PhD
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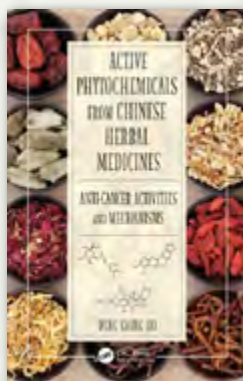
Active Phytochemicals from Chinese Herbal Medicines: Anti-Cancer Activities and Mechanisms by Wing Shing Ho. Boca Raton, FL: CRC Press; 2016. Hardcover, 178 pages. ISBN: 978-1-4822-1986-9. \$139.95.

Exploration of the anticancer actions of herbal medicines and phytochemicals is an active field of pharmacology, particularly in China where modern investigation of traditional Chinese medicine (TCM) is proceeding rapidly. Many phytochemicals from TCM herbs have anticancer activities, including the promotion of apoptosis (i.e., normal, programmed cell death — a kind of cell “suicide”). Apoptosis is a focus of this volume by Wing Shing Ho, PhD, a professor at the Chinese University of Hong Kong who has been writing in this field for more than a decade.

This book is aimed at an academic pharmacology audience. It presupposes detailed understanding of the biochemical bases for anticancer mechanisms, and provides a good deal of scholarly information in this area. However, due to a number of limitations in the text, chiefly poor editing and organization, the book achieves only moderately well, at best, its purpose of providing an in-depth look at the anticancer pharmacology of TCM herbal constituents.

The book has nine chapters on topics such as “Combination of Cancer Drugs,” “Therapeutic Benefits of Phytochemicals,” “Mechanism of Cancer Drug Action,” “Inhibition of Cancer Growth by Herbal Medicines,” and “Exploration of Herbal Medicine.” It contains two color plates on the mechanism of apoptosis, and an appendix listing the 26 phytochemicals discussed in depth in the book, with their structures, chemical formulas, physical properties, plant sources, and therapeutic classes. Altogether, about 70 phytochemicals are mentioned in the text, some only in passing.

The book does not pretend to offer a full listing of TCM phytochemicals with anticancer activities. It features detailed discussions of apoptosis-promoting compounds, and other compounds with preclinical anticancer actions, including gambogic acid, berberine, tetrandrine, and others (mostly ones studied by Ho and colleagues). The chapter on mechanisms of cancer drug actions features a thorough discussion of apoptosis. However, other important anticancer mechanisms of phytochemicals, such as anti-angiogenic and anti-inflammatory activities, receive short shrift, and immunomodulatory activity is treated only sporadically. The final chapter on future explo-



ration of herbal medicine points to some interesting emerging research directions.

A number of problems mar the usefulness of the book. The English language style is generally good, but awkward sentence structures appear regularly. There are problems in technical proofreading, including referring to the plant family Fabaceae as a “species” and a major error related to the combination index, or CI, of the Chou-Talalay formula for detecting synergism and antagonism in drug combinations. (If a CI is less than 1, synergism is indicated. If a CI equals 1, an additive effect is shown, and if a CI is greater than 1, antagonism is detected. The text indicates both synergism and antagonism as “CI value > 1.”)

In addition, the organization of the text appears haphazard in many places. Chapters are divided into titled sections, but the section titles often bear little resemblance to their contents. The section “Application of Chinese Medicine in Pediatric Populations” makes one reference to a pediatric study in a section that focuses on herbs with multiple therapeutic targets and physician communication about herbal medicines. This pattern occurs throughout the book and is quite disconcerting to the reader.

General issues surrounding the use of TCM phytochemicals in cancer treatment are discussed in several spots, but a consistent viewpoint is not manifested. Although the author frequently discusses combining TCM herbs with conventional treatments, one section curiously dismisses integrative medicine as “futile.” There are substantial sections on herbs used for cardiovascular disease and dementia. While cardiovascular herbs might be helpful in overcoming cardiac toxicity from cancer drugs, this possibility is not really addressed in the data presented. If the author wanted to suggest that anti-dementia herbs might manage treatment-related cognitive deficits, no effort is made to elucidate this link.

The editors of this volume have done few favors to the author by allowing such disorganization to go uncorrected. It detracts substantially from the usefulness of the book, leaving only the few sections with in-depth discussions of apoptotic mechanisms of various phytochemicals as the interesting nuggets of this publication. HG

—Charlotte Gyllenhaal, PhD
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Adolf Nahrstedt

1940-2015

Professor Adolf Nahrstedt, Dr. rer. nat., Dres. h.c.*, of the University of Muenster, passed away at age 75 at the St. Franziskus Hospital in Muenster, Germany, on January 7, 2016, after a long battle with prostate cancer.

Nahrstedt was born in Northeim/Harz, Lower Saxony, Germany, on August 9, 1940. He studied pharmacy and food chemistry at the University of Freiburg and received his PhD in 1971. Shortly after his habilitation (the highest academic qualification conferred after earning a research doctorate) in 1976, he was appointed as an associate professor at the Technical University of Braunschweig. He was made a full professor at the University of Muenster in 1986.

Beyond his activities as a professor, Nahrstedt accepted various appointments within the University of Muenster administration, as well as duties outside of academia. He served as vice-dean and was elected dean of the College of Chemistry and Pharmacy. He was a long-serving member of the Pharmacopoeia Commission of the Federal Institute for Drugs and Medical Devices (Bundesinstitut für Arzneimittel und Medizinprodukte, BfArM), and a board member of the German Society of Phytotherapy (GPhyt). He was also an honorary member of the European Academy of Natural Medicine, and a recipient of the Rudolf Fritz Weiss Award from the German Society of Phytotherapy and the Varro E. Tyler Prize from the American Society of Pharmacognosy (ASP). He holds honorary doctorates from Ovidius University of Constanta in Romania and the University of Mahasarakham in Thailand.

Nahrstedt's research interests included the biochemistry of secondary metabolites in plants and insects (especially the cyanogenic glycosides), as well as the phytochemistry of traditional herbal drugs and plant physiology. His work resulted in a significant increase in the scientific knowledge pertaining to these subjects. He discovered many new structures of cyanogenic and non-cyanogenic nitrile glycosides from all over the plant kingdom, and thoroughly investigated cyanogenic compounds in moths and butterflies.

Nahrstedt is probably best known for his major contributions to the study of St. John's wort (*Hypericum perforatum*, Hypericaceae) and its active constituents. His research provided further evidence that the accompanying substances in a plant extract contribute to the effects of an herbal medicinal product through their interactions with active agents. There have been several examples in the literature showing that such co-effectors improve not only the solubility but also the bioavailability of single compounds. Unfortunately, most investigations on this topic give little, if any, information, or just speculative information, about the mechanisms



of interaction and the compounds involved. Perhaps Nahrstedt's biggest achievement is that he could identify potential co-effectors in St. John's wort extracts. He demonstrated that procyanidin B2 and hyperoside can influence the biopharmaceutical properties of hypericin, one of the compounds that contributes to the antidepressant activities of St. John's wort.

However, St. John's wort is just one of the many botanicals on which Nahrstedt focused during his career. He also studied kava (*Piper methysticum*, Piperaceae), black cohosh (*Actaea racemosa*, Ranunculaceae), *Cistus* species (Cistaceae), hawthorn (*Crataegus* spp., Rosaceae), devil's claw (*Harpagophytum procumbens*, Pedaliaceae), English ivy (*Hedera helix*, Araliaceae), willow (*Salix* spp., Salicaceae), artichoke (*Cynara scolymus*, Asteraceae), ginger (*Zingiber officinale*, Zingiberaceae), English walnut (*Juglans regia*, Juglandaceae), horse chestnut (*Aesculus hippocastanum*, Sapindaceae), witch hazel (*Hamamelis virginiana*, Hamamelidaceae), celandine (*Chelidonium majus*, Papaveraceae), and rue (*Ruta graveolens*, Rutaceae). He published more than 200 research and review articles, and numerous book chapters. Fifty PhD theses and two habilitation theses were finalized under his supervision.

Nahrstedt was a longtime member of the ASP, as well as the Society of Medicinal Plant and Natural Products Research (GA). The GA in particular paid high tribute to Nahrstedt because of his valuable advice and substantial contributions to the GA advisory board. He also contributed to many important scientific discussions in nearly all fields of phytotherapy and phytochemistry. His most notable service to the GA, however, was undeniably his editorial activities for its official journal, *Planta Medica*. Nahrstedt was associated with the journal for more than 30 years, first as co-editor (1983-1992), later as editor-in-chief (1993-2004), and, until his death, as senior editor (2005-2015). In recognition of his outstanding service, the GA bestowed him with an honorary membership in 2005.

Those who were fortunate enough to know Nahrstedt professionally will always respect and admire him for his incredible knowledge of and ability to teach pharmacognosy. Those who knew him personally have appreciated his direct, gently teasing, but sympathetic personality. Science and teaching were his major interests, and many scientists all over the world learned about pharmacognosy from his lectures, books, and many reprints. Nahrstedt will be deeply missed in the scientific community, not only as a great colleague, but also as a true friend. HG

—Veronika Butterweck, PhD
Professor, School of Life Sciences
Institute for Pharma Technology
University of Applied Sciences Northwestern Switzerland
Muttenz, Switzerland

* *Doctor rerum naturalium* and *Doctor honoris causa*, respectively. Both of these designations are used frequently in European countries, including Germany and Austria. Dr. rer. nat. is a post-graduate degree comparable to a PhD, while the latter is an honorary degree.

Devan Shah

1962-2016

Pioneering specialty tea distributor Devan Shah, CEO of International Tea Importers (ITI), passed away unexpectedly on April 3, 2016. Shah greatly influenced and strengthened the fledgling specialty tea (*Camellia sinensis*, Theaceae) industry in the United States, and it is now a multi-billion-dollar industry. The US is currently the third largest tea importer in the world behind Russia and Pakistan. Shah's visionary thinking and tireless efforts grew from his early interest in the Indian tea industry, and, through ITI, he sought to support the world's tea market with education and empowerment.

Shah was born in Mumbai, India, and grew up in the southern city of Coimbatore. The youngest of six children, he spent his early summers on his brother-in-law's tea plantation in Coonoor, in the Nilgiri mountains in India's southern state of Tamil Nadu. This exposure to the tea business would influence the trajectory of his career: After earning a degree in business, he became an assistant to a tea broker before immigrating to the United States in 1989.

"None of us in the world of tea would be where we are were it not for Devan," said James Norwood Pratt, Shah's longtime "tea brother" and author of *The Ultimate Tea Lover's Treasury*, which was published by Shah in 2011. "When he arrived in this country [the US], the tea trade was not just sleepy. It was comatose. ... Nobody in America, me included, knew anything whatsoever about south Indian tea."

Recognizing an opportunity, Shah quit his job at an electronics company and founded India Tea Importers in 1990. The small enterprise began with six chests of tea, stored in his father-in-law's garage, and grew slowly under his leadership. Along with his wife Reena, he acquired a tea room in California in 1994, determined to sell his high-quality product to the trendsetters and tastemakers in Beverly Hills.

"Meanwhile, I was far from the only person Devan was educating about tea," said Pratt. "Right from the outset, ... Devan Shah played a decisive role in developing [the US's] tastes in tea." According to Pratt, Shah was responsible for the popularity of chai tea in the US, which was relatively unknown before then. Using black tea from India, Shah worked with tea blenders in Oregon to create a ready-to-drink version of chai.

Since its introduction state-side, chai tea has truly been embraced by Americans, turning it from a little-known regional Indian blend of tea and spices into a cultural juggernaut and household staple. According to the *HerbalGram* tea market report for 2014, sales of bagged chai tea in the US rose 15% from 2013, while sales



of loose chai tea blends increased by almost 20%.¹ Shah's vision for the US tea market had taken off with a success that exceeded all expectations.

In 2002, India Tea Importers was renamed International Tea Importers to better reflect the global nature of the market and the addition of teas from China and other regions. In contrast to the six starting crates, ITI currently imports more than 600 different types of tea, and creates its own blends and flavors as well.

In an ITI catalog from 2011, Shah wrote: "Tea, the most romantic of beverages, has certainly come a long way in the United States. ... Today, the United States is buying more tea than ever, there are more businesses than ever retailing tea, and the world at large is more attentive than ever before to the tea trends we nurture and originate."

Shah's educational efforts and constant drive ensured that this growing market would continue to find new footholds and flourish. In recognition of his contributions to the tea industry, he received the 2013 Cha Jing Lifetime Achievement Award from *World Tea News*.

ITI will continue under the leadership of Shah's daughter, Bianca. She had worked closely with her father before his passing, and her brother, Brendan, will serve as the company's chief technology officer. Shah is also survived by his wife, Reena, the president of ITI. Through his family, Shah's lifelong passion for tea continues on for future generations to enjoy.

"He did his utmost to educate us in excellence, not only in our tea life but in our whole life," said Pratt in his eulogy to Shah. "Such was his unmistakable integrity and generosity, his enthusiasm and powerful positive energy, his endless helpfulness and constant effort to bring us into a higher awareness of what he saw and knew was possible." HG

—Hannah Bauman

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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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Hibiscus spp., Malvaceae

Hibiscus is a genus of shrubby, flowering plants native to Southeast Asia and naturalized in warm, tropical climates around the world.¹ The genus includes hundreds of species and cultivars, notably *H. rosa-sinensis* and *H. sabdariffa*. The ingredient labeled “hibiscus” in medicinal and herbal products and teas is typically *H. sabdariffa*. The showy blossoms make this plant a prized addition to landscapes, but the calyces and seeds are the parts used most often in medicinal preparations. The calyces of *H. sabdariffa* contain high amounts of fiber and antioxidant anthocyanins, and have shown cardiovascular benefits, particularly blood pressure-lowering effects. Hibiscus extracts can be applied topically and are a popular addition to cosmetics.

Andrea Opel Abbott-Ganuza is the winner of this issue's photo finish contest. She is a Florida Master Naturalist, graduate of Permaculture Miami, student of Ayurveda, yoga teacher, amateur photographer, integrative health coach, and creator of SomaBotanics. Photo taken in Punta Gorda, Florida, with an Apple iPhone 5s.

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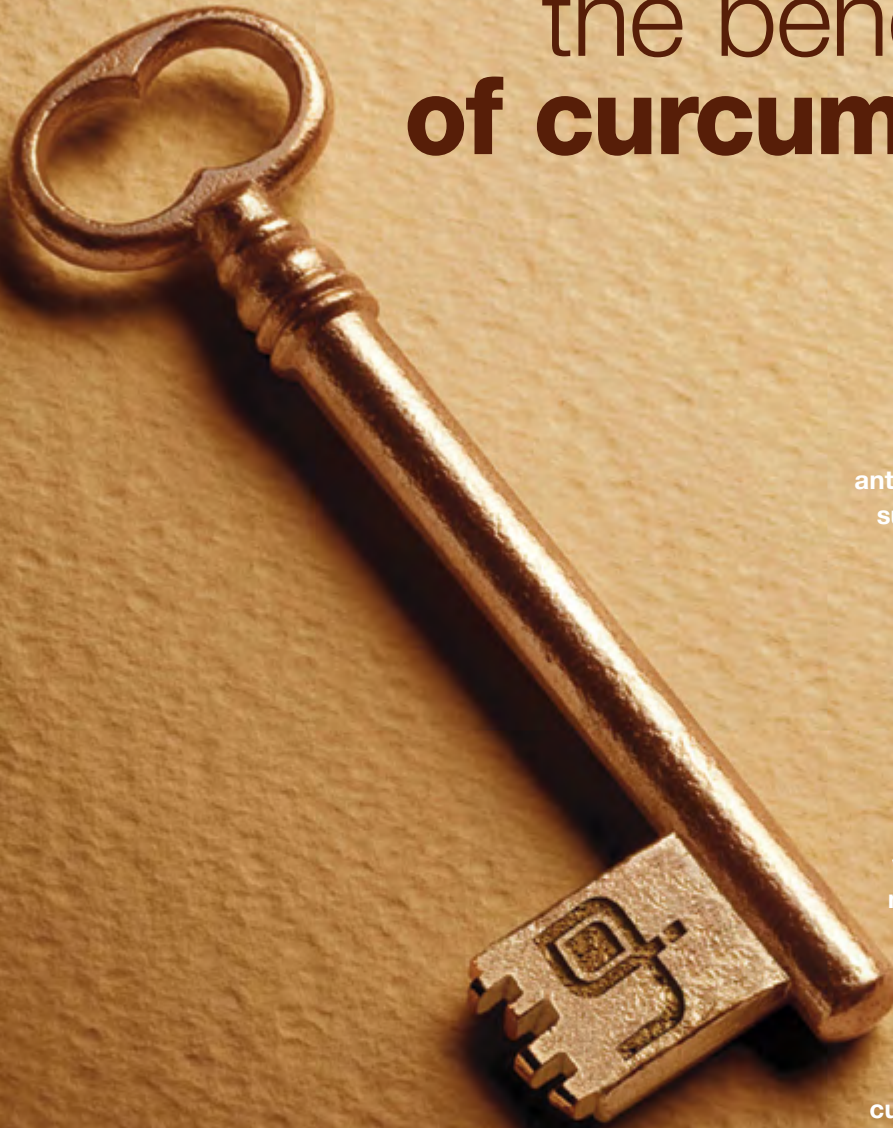


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Meriva[®] improved the treadmill walking performance of subjects by more than 200% in just two months.

Furthermore, **Meriva**[®] showed a significant improvement in individuals with eye challenges.

To discover more about how **Meriva**[®] unlocks the benefits of curcuminoids, visit indena.com today.



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BIOAVAILABLE CURCUMIN

These statements have not been evaluated by the Food and Drug Administration. These products are not intended to diagnose, treat, cure, or prevent any disease.

Marketers of finished products containing the ingredients described herein are responsible for determining whether the claims made for such products are lawful and in compliance with the laws of the country in which they will market the products.

