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Search for Psychoactive Plant Drugs

Proposed Regulatory Framework for Cannabis

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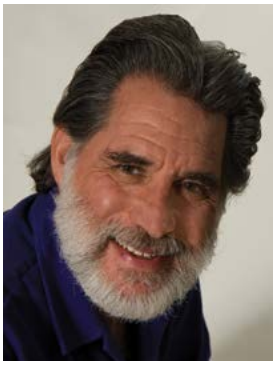

dear *reader*

Our herb profile in this issue is on tongkat ali, a Southeast Asian tree that has been used traditionally for a variety of purposes, including as an aphrodisiac, to enhance stamina, and for hypertension. Regular contributors Josef Brinckmann and Thomas Brendler provide an extensive review that documents the emerging pharmacological and clinical research that supports some of these historical ethnobotanical uses — another example of tradition converging with modern science. Human clinical trials on tongkat ali largely have focused on men's health issues, and evidence suggests that it may be a safe and potentially effective natural product for certain male sexual conditions.

In March, ABC announced the recipients of its annual Botanical Excellence Awards. The 2018 ABC James A. Duke Excellence in Botanical Literature Award went to our good friend Dennis McKenna, PhD, whom I have called for many years an "ethnopsychopharmacologist," one who studies the traditional and modern research on psychoactive plants, fungi, and other substances. In 2017, Dennis helped organize a historic conference that commemorated the 50th anniversary of a 1967 conference in San Francisco in which many of the luminaries of psychoactive substance research presented. The proceedings of both conferences were compiled in *Ethnopharmacologic Search for Psychoactive Drugs,* a two-volume set published in 2018. We present an edited version of Dennis' introduction to the book, wherein he describes his personal odyssey in the domain of psychoactive research and how his finding a copy of the 1967 conference proceedings early in his career guided his personal and professional research interests. This book was extensively reviewed by PhD candidate Lan Truong in *HerbalGram* issue 121.

And speaking of psychoactive plants, when many people of my generation started smoking grass in the 1960s (some of us never exhaled!), none of us could have predicted how pot-smoking and cannabis culture would evolve over the next 50 or so years. The medicinal and recreational uses of cannabis have created a huge regulated industry in many US states. In a guest editorial, Tami Wahl, an attorney with expertise in food and drug law and the cannabis industry, and Josef Brinckmann outline a proposed state-federal regulatory framework for cannabis in the United States, based largely on the US Department of Agriculture's programs for specialty crops.

As I write this column in May 2019, I am compelled to share a personal milestone. This month marks the 40th anniversary of my involvement in one case to help improve the quality of herbal products in the United States. Back in the late 1970s, some hucksters were selling a product mislabeled as "wild red American ginseng" to health food stores. The herb was not, in fact, ginseng (*Panax* spp.), but "canaigre" (*Rumex hymenosepalus*), or red dock, which grows in the deserts of the American Southwest. This was clearly a case of adulteration, mislabeling, and fraud. As the president of the Herb Trade Association (HTA, the now-defunct herb industry organization that preceded the American Herbal Products Association) at the time, I researched and documented these findings with the assistance of colleagues in HTA's "Policy Statement #1 – Canaigre." While the canaigre example marks a successful case of education and self-regulation by the then-nascent herb industry, some botanical materials, unfortunately, are still being adulterated. The diligence of and education by the responsible elements of the herb community must continue. HG

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

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Salvia divinorum
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Tongkat Ali

Eurycoma longifolia

Family: Simaroubaceae

By Josef Brinckmann and Thomas Brendler

INTRODUCTION

Eurycoma longifolia is a slow-growing evergreen plant that belongs to the quassia family (Simaroubaceae) of shrubs and trees, which includes 19 or 20 genera and more than 100 species with pantropical distributions.[1-3] There are only three known *Eurycoma* species and one subspecies[2]: *E. apiculata*, distributed in Peninsular Malaysia and Sumatra (Indonesia)[4]; *E. harmandiana*, which occurs in the border regions between Thailand and Laos[5,6]; *E. longifolia*, native to parts of southeastern Asia (Indonesia, Malaysia, Brunei Darussalam, Singapore, Thailand, Cambodia, Laos, and Vietnam)[7]; and *E. longifolia* subsp. *eglandulosa*, endemic to the Philippines.[8] It is difficult to differentiate *E. longifolia* from *E. apiculata*, though the latter typically has slightly bigger leaves[9] and usually short inflorescences or infructescences that point upward, whereas the fertile parts of *E. longifolia* are long and drooping.[10] Some Vietnamese compendia list *Crassula pinnata* (Crassulaceae) as a synonym of *E. longifolia*,[11] but *The Plant List* classifies *C. pinnata* as an unresolved name.[2]

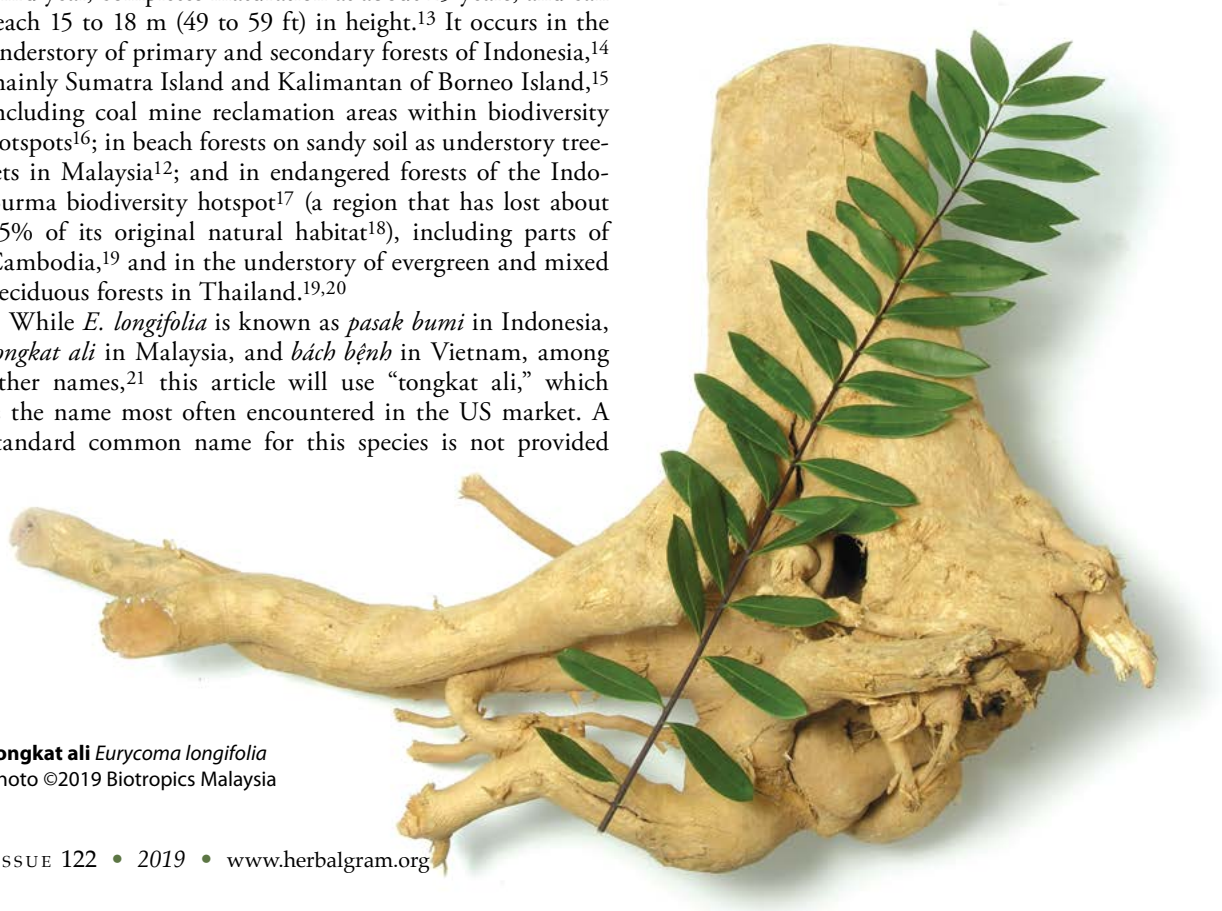
The *E. longifolia* tree is dioecious (male and female flowers occur on separate plants) with hairy, purplish-crimson, bell-shaped flowers.[12] The tree fruits after the second or third year, completes maturation at about 25 years, and can reach 15 to 18 m (49 to 59 ft) in height.[13] It occurs in the understory of primary and secondary forests of Indonesia,[14] mainly Sumatra Island and Kalimantan of Borneo Island,[15] including coal mine reclamation areas within biodiversity hotspots[16]; in beach forests on sandy soil as understory treelets in Malaysia[12]; and in endangered forests of the Indo-Burma biodiversity hotspot[17] (a region that has lost about 95% of its original natural habitat[18]), including parts of Cambodia,[19] and in the understory of evergreen and mixed deciduous forests in Thailand.[19,20]

While *E. longifolia* is known as *pasak bumi* in Indonesia, *tongkat ali* in Malaysia, and *bách bệnh* in Vietnam, among other names,[21] this article will use "tongkat ali," which is the name most often encountered in the US market. A standard common name for this species is not provided in the American Herbal Products Association's *Herbs of Commerce*, 2nd edition.[22] While some companies in Malaysia use the marketing name "Malaysian ginseng," the term "ginseng" is narrowly defined in US regulation (7 CFR §65.145 Ginseng) as ginseng root of the genus *Panax*.[23] As per US Code (21 USC §343(u) Ginseng), no herb or herbal ingredient may be labeled or marketed in the United States as "ginseng" unless it is derived from *Panax* species.[24]

Until recently, almost all of the commercial supply of tongkat ali was obtained from wild collection in forests of Indonesia, Malaysia, and Vietnam. In the early 2000s, commercial plantations were started in Malaysia.[25]

HISTORY AND CULTURAL SIGNIFICANCE

In 1822, Scottish botanist and medical practitioner William Jack (1795-1822), while employed as a surgeon with the East India Company, assigned the Latin name *Eurycoma longifolia* in volume II of *Malayan Miscellanies*.[26] The genus name *Eurycoma* stems from the Greek *eurys* meaning "large" and *kome* meaning "tuft of hairs,"[27] referring to its compound leaves that spiral out at the tip of its slender trunk in a large, dense rosette.[28] Jack described the small tree having leaves that are two feet long, thus the



Tongkat ali *Eurycoma longifolia*
Photo ©2019 Biotropics Malaysia

species name *longifolia*. In Latin, *longus* means "long" and *folia* means "leaf." Jack's 1822 monograph did not use the common name tongkat ali (which means "Ali's root") but listed a Malay name for the plant, *kayu kabal*, and stated that the tree is found in Singapore (at that time a British colony established in 1819) and in Tapanuli and Bencoolen (at that time possessions of the British Empire in Sumatra; now part of Indonesia).[26]

The cultural history of coffee (*Coffea arabica*, Rubiaceae) in Southeast Asia has intersected with that of tongkat ali. In the late 18th century, cultivated coffee ranked among the most important commodities for the colonial government in Tapanuli. British merchant ships loaded coffee at the port of Tapanuli until the trade was taken over by Dutch colonials in 1833.[29] Today, tongkat ali-based coffee and tea (*Camellia sinensis*, Theaceae) products are among the most common beverage combinations in the region.[30] Recently, analytical methods have been developed to identify tongkat ali extract when combined with coffee.[31] A novel food application was made in 2016, awaiting decision at the time of this writing, seeking approval for the use of tongkat ali root extract as a component of coffee beverages in the European Union (EU).[32]

In Brunei Darussalam and Singapore, preparations of *E. longifolia* (root, root bark, and/or leaf) are used for lowering blood pressure.[25] In Cambodian traditional medicine, the roots are used as an antidote against intoxication, and, when boiled or soaked in wine before drinking, to enhance human power. The Batak people of North Sumatra prepare a decoction of the roots that is used to enhance stamina and treat stomachache, fever, and malaria.[33] Men of the Kutai ethnic group in East Kalimantan, Indonesia, drink an infusion of the tap roots for backaches and an aphrodisiac effect.[34] For hundreds of years, traditional medicine practitioners of the isolated Lingga Malay people — a lineage descending from the former Riau-Lingga Sultanate, a monarchy that was recognized by the British and Dutch colonial empires — have protected their traditional formulations including *obat pahit*, which means "bitter medicine." Prepared as an aqueous decoction and taken as a "body energy keeper," obat pahit tea may contain up to 24 herbs, including roots of *E. longifolia*, *Bauhinia semibifida* (Fabaceae), *Cnestis palala* (Connaraceae), and *Rhodomyrtus tomentosa* (Myrtaceae), among others.[35]

In Malay medicine, tongkat ali roots are used for fever, boils, wounds, ulcers, syphilis, bleeding gums, and as medication after birth.[14] The bark is used as a vermifuge.[7] The Semelai people (population ca. 2,000) of Tasek Bera in Peninsular Malaysia prepare aqueous decoctions of tongkat ali root in combination with roots of *Iguanura wallichiana* (Arecaceae) and *Calamus insignis* (Arecaceae) as an aphrodisiac or to boost energy. Tongkat ali root is also decocted with whole plant of *Smilax calophylla* (Smilacaceae) or tuber of *S. myosotiflora* for similar purposes.[36] *Eurycoma longifolia* is among the most used plant species of the Temuan people, indigenous to parts of western Peninsular Malaysia, who prepare an aqueous decoction of the root that is taken orally to treat muscle pain and conditions related to diabetes and hypertension.[37] In Thai traditional medicine, the roots are used to treat sore throat and tonsillitis, for detoxification, and for their antipyretic, expectorant, anti-tuberculosis, anthelmintic, diaphoretic, and antimalarial actions. The bark is used as an antipyretic and antimalarial.[14] In Vietnam, the very bitter bark traditionally is used for indigestion.[7]

The first quality standards monograph for tongkat ali root appeared in volume I of the *Malaysian Herbal Monograph* in 1999,[38] which was significantly revised and updated in the currently valid 2015 edition.[39] Based in part on the *Malaysian Herbal Monograph*, the Department of Standards Malaysia published a specification developed by the Working Group on Phytopharmaceutical Aspect of Herbs for a freeze-dried aqueous extract of tongkat ali root.[40] In 2001, the Indonesian Institute of Sciences, Research Center for Chemistry published an initial monograph for quality control testing.[41] The Indonesian National Agency of Drug and Food Control included monographs (for *pasak*

Tongkat ali *Eurycoma longifolia*
Photo ©2019 Mokkie

bumi) in the *Acuan Sediaan Herbal* ("Manual of Herbal Drug Preparations") volumes VI (2011)[42] and VII (2012).[43] In 2013, a monograph for the extract was included in volume II of *Pedoman Teknologi Formulasi Sediaan Berbasis Ekstrak* ("Formulation Technology Guidelines for Herbal Drug Extract Preparations").[44] Despite these monographs, standardization of extracts and analytical testing has been hampered by the very high cost of the reference standard eurycomanone, and alternative methods are in development.[45-47]

CURRENT AUTHORIZED USES IN COSMETICS, FOODS, AND MEDICINES

In Vietnam, *E. longifolia* (bách bệnh) is included on the Ministry of Health's positive list of traditional herbal medicinal tonic drugs that are covered under the national insurance health fund.[48] In Malaysia, at the time of this writing, there are 56 registered traditional medicine products that list *E. longifolia* as an active ingredient. Most of the listings appear to be male enhancement drugs.[49] In volume VI of the Indonesian manual of herbal drug preparations, the extract of the root (*ekstrak pasak bumi*) is listed as an anticancer drug with a prescribed dosage of 300 mg, twice daily, with a maximum dosage of 1,000 mg daily.[42] Volume VII of the manual includes monographs for uses as a male infertility drug and as a male aphrodisiac drug.[43] For specific treatment of erectile dysfunction, Indonesia's new national formulary of traditional herbal medicines prescribes one 400-mg capsule of extract daily.[50]

In the United States, tongkat ali may be used as a component of dietary supplement products, which require notification with the US Food and Drug Administration (FDA) within 30 days of marketing if a structure-function claim is made.[51] In Canada, tongkat ali is regulated as an active ingredient of licensed natural health products (NHPs), which require pre-marketing authorization from the Natural and Non-prescription Health Products Directorate (NNHPD). At the time of this writing, there are 206 licensed NHPs in Canada that list *E. longifolia* as an active ingredient.[52] In the EU, there are some authorized applications for use of an extract of the root in cosmetic products, specifically for skin conditioning and skin protecting functions.[53] However, for oral ingestion, *E. longifolia* is presently classified as an unauthorized novel food in the EU. There has been a request for a determination as to whether it requires authorization under the Novel Food Regulation. According to EU regulatory authorities, *E. longifolia* was not used as a food or food ingredient in the EU before May 15, 1997, and, therefore, a pre-marketing safety assessment under the Novel Food Regulation is required.[54]

MODERN RESEARCH

The health benefits and traditional uses of tongkat ali root extract, namely its antimalarial, anticancer, antidiabetic, aphrodisiac, proandrogenic, and antimicrobial effects, have been confirmed in a wide range of investigations: laboratory research, animal models, and human clinical trials.[55-61] Tongkat ali's adaptogen-like phytoandrogenic properties make it a promising remedy to address a wide range of male sexual health-related ailments, from erectile dysfunction[62] to age-related loss of virility[59] and osteoporosis.[63] It may also provide a natural alternative to testosterone replacement therapy.[64]

Various chemical compounds have been isolated and characterized from the root, leaf, and stem including β-carboline alkaloids, such as canthin-6-one; squalene derivatives; triterpenes; biphenyl neolignans; and quassinoids, specifically lonilactone, eurycomanone, 13α(21)-epoxyeurycomanone, eurycomanol, eurycomalide A and B, eurycolactone, laurycolactone, and eurycomalactone.[55,65,66] The pharmacokinetics of tongkat ali have been addressed in a number of reviews.[56,30] There is very little evidence that tongkat ali interacts with conventional pharmaceutical drugs; most drug-metabolizing cytochrome P450 enzyme isoforms are not affected (up- or downregulated) by tongkat ali administration, making it a suitable adjuvant with low interaction potential in the treatment of various disease states.[67]

The major quassinoids in tongkat ali appear to be responsible for stimulating the release of free testosterone from its binding proteins and improving overall hormone profiles. The quassinoid eurycomanone also has been shown to stimulate spermatogenesis.[68] Recently, a number of compounds isolated from tongkat ali have demonstrated promising antiproliferative and cytotoxic effects, the latter by inducing apoptosis by up-regulating p53 (a tumor suppression protein) and Bax (a pro-apoptotic protein) and down-regulating Bcl-2 (an anti-apoptotic protein) expression.[65,69] Based on previous investigations (e.g., Varghese et al, 2013),[70] a number of NF-κB inhibitors responsible for tongkat ali's anti-inflammatory properties have been identified.[71]

Overall, tongkat ali has been shown to possess an excellent safety profile. Using rat models, scientists have investigated the oral toxicity of the branded tongkat ali root aqueous dry extract Physta® (Biotropics Malaysia Berhad; Shah Alam, Malaysia), which is also known as LJ100™ in the United States (distributed by HP Ingredients; Bradenton, Florida). Based on these experiments, researchers reported a median lethal dose (LD_{50}) of more than 2,000 mg/kg body weight (acute) and a no-observed-adverse-effect-level (NOAEL) greater than 1,000 mg/kg body weight (sub-acute).[72,73] The genotoxicity potentials of tongkat ali[72] and Physta[74] also have been investigated. No mutagenic, clastogenic, or histopathological changes were observed. Physta was not toxic to *Salmonella* strains at doses up to 5 mg/plate, and it did not alter relative polychromatic erythrocytes (PCEs) or increase incidence of micronucleated PCEs in a mouse peripheral blood cell micronucleus assay.[74]

Effectively all of the studies listed in Table 1 were conducted with Physta, which is manufactured using a patented hot-water extraction process. The studies are highly heterogeneous in power and quality. Results of early investigations were presented as papers or posters at international conferences and have never been fully published. This makes it almost impossible to fully describe, let alone evaluate, their

Table 1. Clinical Trials with Tongkat Ali Root Extract

Publication	Study Design	Interventions	Outcome
Hamzah & Yusof (2003)[79]	Randomized, controlled trial (RCT)	100 mg/d ELWSE* (n=7) or placebo (n=7); five weeks	ELWSE increased fat-free body mass, reduced body fat, and increased muscle strength and size
Tambi (2005)[80]	Observational (OBS)	200 mg/d, 400 mg/d, or 600 mg/d LJ100; no duration or number of participants given	Sexual Health Inventory for Men (SHIM) elevated, Aging Males' Symptoms (AMS) score lowered, no adverse effects
Talbott et al. (2006)[81]	RCT	100 mg/d ELWSE (n=15) or placebo (n=15); 24 hours	ELWSE significantly decreased cortisol levels and significantly increased testosterone levels
Sarina et al. (2009),[82] cited in Talbott et al. (2013)[73]	RCT	100 mg/d ELWSE (n=16) or placebo (n=15); 12 weeks	ELWSE increased muscle strength and led to bigger quadriceps muscles compared to placebo
Muhamad et al. (2010)[76]	RCT, crossover	150 mg/d ELWSE (n=6) or placebo (n=6); seven days, one-week washout, and seven days	No significant difference in endurance running capacity or lab parameters between groups
Tambi & Imran (2010)[83]	OBS	200 mg/d Physta (n=75); nine months	Significant improvement in sperm quality
Talbott et al. (2010)[84]	OBS	Combination of Physta, citrus peel extract (30% flavones), and green tea extract (30% catechins); eight weeks (n=46) and 12 weeks (n=29)	Significant improvement of cortisol/testosterone ratio, mood, vigor, fatigue, and depression scores
Tambi et al. (2012),[85] likely a subset from Tambi & Imran (2010)[83]	OBS	200 mg/d Physta (n=76); one month	Significant improvement in AMS score and serum testosterone concentration
Ismail et al. (2012)[86]	RCT	300 mg/d Physta (n=48) or placebo (n=43); 12 weeks	Significant increase of sperm volume and motility compared with placebo
Talbott et al. (2013)[60]	RCT	200 mg/d Physta (n=31) or placebo (n=32); four weeks	Significant improvement in some mood parameters, reduced cortisol, and increased testosterone status compared with placebo
Henkel et al. (2014)[87]	OBS	400 mg/d Physta (n=25; 13 male, 12 female); five weeks	Testosterone/cortisol ratio improved in men but not AMS score, AMS score significantly improved in women
Chen et al. (2014)[77]	RCT, crossover	400 mg/d Physta (n=7) or placebo (n=6); six weeks, three-week washout, and six weeks	No significant difference in testosterone/epitestosterone ratio, liver or renal function between groups
Udani et al. (2014)[88]	RCT	200 mg/d Physta + 100 mg/d *Polygonum minus* extract (10:1 DER) (n=12) or placebo (n=14); 12 weeks	Significant improvements in scores for Sexual Intercourse Attempt diary, Erection Hardness Scale, SHIM, and AMS
George et al. (2016)[89]	RCT	200 mg/d Physta (n=40) or placebo (n=41); four weeks	Significantly higher Scoring of Immunological Vigor (SIV) and T-cell count versus placebo
George et al. (2018)[78]	RCT	50 mg/d Physta + multivitamins (n=47) or placebo (n=39); six weeks (efficacy) and 12 weeks (safety)	Significant improvements in mood and stress levels, 12-Item Short-Form Health Survey, and immune parameters versus placebo

* *Eurycoma longifolia* water-soluble extract (ELWSE) = LJ100™ = Physta®

endpoints, methodologies, and results. It is likely that low dosage and/or short duration of supplementation led to failure in demonstrating beneficial effects in some of the studies,[75,76] the exception being the results published by Chen et al (2014).[77] Nonetheless, when considering the substantial body of traditional use and pre-clinical data, a positive benefit-risk ratio can be derived at least for the commercial product Physta, which has demonstrated an excellent safety profile in human trials, with the latest being George et al (2018),[78] which evaluated a combination of Physta and multivitamins. None of the studies reported adverse events linked to the use of the product.

ADULTERATION

Adulteration of tongkat ali products with synthetic pharmaceutical drug substances has been documented since the early 2000s and remains a serious concern, with potential impacts on human health and safety. In 2004, the Drug Control Authority of Malaysia issued a warning about the presence of the erectile dysfunction drug tadalafil in a product called Shitek Tongkat Ali Plus, which had a fraudulent marketing authorization number on the label.[90] In a separate case in 2012, tadalafil was detected in the gelatin capsules that the tongkat ali extract was filled into, but not in the extract itself. It was theorized that the adulteration was likely accomplished by adding tadalafil powder to gelatin during the manufacturing of the capsules.[91] In a 2015 study, researchers used a high-performance thin-layer chromatography (HPTLC) method to screen for the presence of three phosphodiesterase type 5 inhibitors (sildenafil, vardenafil, and tadalafil) and eight analogs in finished products. Of the 45 products screened, 31 were found to contain at least one of these compounds, including a product labeled as Tongkat Ali Power Plus (tablets) that tested positive for sildenafil.[92]

One study asserted that, due to the presence of bitter-tasting quassinoids, tongkat ali extracts that do not have a distinct bitter taste may likely be adulterated, with some containing no tongkat ali root extract at all, but rather tadalafil, sildenafil, or vardenafil.[60] This could also be considered economic adulteration because the erectile dysfunction active ingredients cost less than authentic extracts of tongkat ali root. A 2018 study, using DNA barcoding validated by high-performance liquid chromatography (HPLC) analysis, reported that only 37% of 11 sampled products (nine capsules, one tea, and one tablet) labeled as containing *E. longifolia,* purchased from retail shops in four different areas of Malaysia, were authentic.[93] However, the study compared the products in capsule, tea, or tablet form against an extract prepared from authenticated tongkat ali root. It was not stated whether the dosage of the extract or powder in the finished products took into consideration the dilution factor introduced by excipients or other ingredients.

In the United States, there have been several recalls of instant tongkat ali-coffee beverages including Kopi Jantan Tradisional Natural Herbs Coffee (Bestherbs Coffee; Grand Prairie, Texas) and Stiff Bull Herbal Coffee, due to the FDA's detection of desmethyl carbodenafil (a compound similar to sildenafil) in the products, and Caverflo Natural Herbal Coffee, due to FDA laboratory analysis confirming the presence of both sildenafil and tadalafil.[94,95] Furthermore, despite the Malaysian Ministry of Health's having banned *kopi jantan* ("male coffee") products spiked with erectile dysfunction drugs, brands like Kopi Jantan Tradisional, Kopi Tenaga Tok Lebai Plus, and Kopi Panggung Al-Ambiak remain popular and openly available in markets. The content of tongkat ali per serving is rarely stated on the labels of such products, which likely contain very low amounts of powdered root, not extract. In contrast, there are functional coffee products available that are labeled to contain 50 mg of clinically tested standardized extract per sachet (i.e., Nu-caffe from Biotropics Malaysia).

Due to shared or similar common names, inadvertent substitution may also occur. In Malaysia, other substances share the common name tongkat ali, some of which are also used for similar purposes, such as the fungus *Entomophthora apiculata* (Entomophthorales) and the roots of *Stemona tuberosa* (Stemonaceae),[96] *Polyalthia bullata* (Annonaceae), and *Goniothalamus* spp. (Annonaceae).[30]

SUSTAINABILITY AND

Tongkat ali *Eurycoma longifolia*
Photo ©2019 Biotropics Malaysia

FUTURE OUTLOOK

In the Malaysian state of Sarawak on Borneo Island, *E. longifolia*, known locally as *sengkayap*, became a protected plant in 1998 under Sarawak's Wild Life Protection Ordinance.[97,98] In 2003, *E. longifolia* was included in the list of medicinal genetic resources of Laos to be managed and protected as per the Prime Minister's decree on natural resources for medicines.[99] Known as *linátog* in the Tagalog language, *E. longifolia* subsp. *eglandulosa* is classified as an endangered species on the *National List of Threatened Philippine Plants*.[100]

Conservation and sustainability of the tongkat ali tree have been a concern for decades. As it is mainly the roots that are used, destructive harvesting by uprooting the entire tree was common. By the late 1990s, when overharvesting of wild populations became apparent, the Malaysian Ministry of Primary Industries formed a task force, taking actions to prevent extinction and promote cultivation.[101] Although the tree itself reaches maturity in about 25 years,[13] roots are generally harvested from trees of seven to 10 years' maturity. Nonetheless, Malaysia's National Forestry Council (NFC) began to promote development of the country's medicinal plant sector, including the popular, high-value tongkat ali. In this context of trade promotion for the root of a slow-growing tree, the Forest Research Institute Malaysia (FRIM) was tasked with shortening the root maturity period from seven years to five years.[102]

Tongkat ali *Eurycoma longifolia*
Photo ©2019 Biotropics Malaysia

Some Malaysian institutions have taken steps to manage, conserve, and determine sustainable use of wild tongkat ali populations. The Malaysian Agricultural Research and Development Institute (MARDI), for example, has implemented projects to ensure that maximum genetic diversity within the current wild population will be preserved and managed for future needs and the formation of cluster farms under the East Coast Economic Region of Malaysia for replanting.[9] The agronomical studies conducted by FRIM and genetic material conservation by MARDI provided resources to help enable successful tongkat ali cultivation and future sustainability. Replanting of deforested areas has been undertaken successfully in Sabah, Malaysia, with detailed forest management systems in place, which can provide suitable habitat for tongkat ali trees.[103] Additionally, in 2012, the first successful adventitious root induction for tongkat ali was reported, paving the way for potential mass production of root cultures in a bioreactor system.[104] (Adventitious roots are roots that arise from any nonroot plant tissue.) The Malaysian Nuclear Agency claims to have developed an advanced bioreactor technology facility, designed to mass produce root cultures that, they say, will be able to reduce the tongkat ali root maturing time from 7-10 years down to mere months.[105] In addition, pilot projects involving tongkat ali seed germination, seedling nurseries, and replanting in the forest have been initiated with indigenous communities to support sustainability (Annie George, senior manager at Biotropics Malaysia, email to T. Smith, April 5, 2019).

Indonesia and Malaysia are the main exporters of tongkat ali ingredients and products.[41] The species also ranks among the most important high-demand medicinal plants wild-collected from forests in Vietnam.[106] Tongkat ali is the highest volume and value wild-collected medicinal plant in Malaysia.[41] A 2001 supply and demand study estimated that about 21,000 kg were wild harvested in Malaysia annually and that domestic annual demand was about 54,189 kg by Malay traditional industries.[107] According to FRIM, in 2009, the sustainably produced supply of tongkat ali roots was estimated at about 100 tons (about 90,718 kg) annually. At that time, the government held 167 ha (413 acres) of tongkat ali tree plantations in Peninsular Malaysia, while the private sector operated 29 ha (72 acres), with a yield of about four tons (about 3,629 kg) of roots per ha.[108] As a result, the government of Malaysia has banned the export of viable tongkat ali raw material (roots) to prevent use of its plant genetic resources without prior informed consent.[109]

In 2010, the Malaysian Ministry of Health projected an annual 15% increase in tongkat ali demand and valued the overall tongkat ali market at 7 billion MYR (Malaysian Ringgits), or approximately $1.7 billion.[110] In Indonesia, extraordinarily high market prices continue to encourage increased exploitation of wild *E. longifolia* trees. In 2014, the export price for chipped root was reported to be nearly $250 per kg (about $550 per lb), and prices of extracts ranged from about $1,625 to $3,243 per kg (about $3,582 to $7,149 per lb), depending on the drug-to-extract ratio, compared to a price range of $375 to $900 per kg (about $827 to $1,984 per lb) for the same extracts in 2012, a tripling to quadrupling of extract prices in just two years. This increase appears to be related to the increasing scarcity of wild resources and increasing demand.[18]

Like many medicinal plants that have unique chemical compositions and corresponding pharmacological actions and that developed in a biodiverse forest ecosystem, future access may depend on protection and conservation of biodiversity hotspots. Efforts to conserve the genetic diversity of this species are underway in some parts of its range. Continuing to explore innovative methods for mass production of plant and root cultures is also important, and, in the future, may result in tongkat ali preparations of quality and effect comparable to those of mature wild tree roots. HG

References

1. Alves IABS, Miranda HM, Soares LAL, Randau KP. Simaroubaceae family: Botany, chemical composition and biological activities. *Rev Bras Farmacogn.* 2014;24(4):481-501.
2. *Eurycoma longifolia.* The Plant List (2013). Version 1.1. Available at: http://theplantlist.org/tpl1.1/record/kew-2805148. Accessed April 29, 2019.
3. Hua P, Thomas WW. Simaroubaceae. ku mu ke. In: *Flora of China: Oxalidaceae through Aceraceae.* Vol 11. St. Louis, MO: Missouri Botanical Garden Press; 2008:100-104.
4. Hassler M. World Plants: Synonymic Checklists of the Vascular Plants of the World (version April 2018). In: Roskov Y, Ower G, Orrell T, et al., eds. *Species 2000 & ITIS Catalogue of Life, 24th December 2018*. Digital resource at www.catalogueoflife.org/col. Leiden, the Netherlands: Species 2000: Naturalis; 2019.
5. Kanchanapoom T, Kasai R, Chumsri P, Yamasaki K. Quassinoids from *Eurycoma harmandiana*. *Phytochemistry.* 2001;57(8):1205-1208.
6. Sydara K, Xayvue M, Souliya O, Elkington BG, Soejarto DD. Inventory of medicinal plants of the Lao People's Democratic Republic: A mini review. *J Med Plants Res.* 2014;8(43):1262-1274.
7. Uphof JCT. *Dictionary of Economic Plants.* 2nd ed. New York, NY: Verlag von J. Cramer; 1968.
8. Lillo EP, Fernando ES, Lillo MJR. Plant diversity and structure of forest habitat types on Dinagat Island, Philippines. *J Asia Pac Biodivers.* 2018.
9. Nordin MS. Distribution of the population of tongkat ali (*Eurycoma* spp.) in Malaysia based on data taken from herbarium records. *Medicinal and Aromatic Plants.* 2014;3(2):155.

10. Tan AL, Nurnida MK, Tan HP. Notes on the morphological characteristics of *Eurycoma* spp. observed and its status in Peninsular Malaysia. In: *Program Book. Contributions of Flora Malesiana to the Welfare of People in Asia.* Bogor, Indonesia: 9th International Flora Malesiana Symposium; 2013:233-234.
11. Đỗ TL. *Những cây thuốc và vị thuốc Việt Nam.* Hà Nội, Việt Nam: Nhà Xuất Bản Y Học; 2004.
12. Chan LK, Su TS, Teo CKH. A preliminary study on the germination of *Eurycoma longifolia* Jack (tongkat ali) seeds. *Pertanika J Trop Agric Sci.* 2002;25(1):27-34.
13. Elhag HEEA, Sulaiman AZ, Azilah A. A Review on the Exraction Methods of Extracts and Phytochemicals from *Eurycoma longifolia* (Tongkat Ali Jack). In: Ibrahim Z, Pebrianti D, Mohamed N, Ghani SA, Geem CH, eds. *Proceedings of The National Conference for Postgraduate Research (NCON-PGR 2016).* Pekan, Pahang: Universiti Malaysia Pahang (UMP); 2016:253-259.
14. Ali RM, Samah ZA, Mustapha NM, Hussein N. *ASEAN Herbal and Medicinal Plants.* Jakarta, Indonesia: ASEAN Secretariat; 2010.
15. McCann G, Hsu YC. Animism and Traditional Knowledge Disappear in Virachey National Park, Cambodia. In: Verschuuren B, Furuta N, eds. *Asian Sacred Natural Sites. Philosophy and Practice in Protected Areas and Conservation.* London, UK: Routledge; 2016.
16. Tordoff A, Baltzer M, Fellowes J, Pilgrim J, Langhammer P. Key biodiversity areas in the Indo-Burma Hotspot: Process, progress and future directions. *J Threat Taxa.* 2012;4(8):2779-2787.
17. Hamidah S, Arifin YF, Fitriani A. Micro climate assessment of medicinal plant habitat for the first step of domestication. *Acad Res Int.* 2018;9(3):145-150.
18. Kartikawati SM, Zuhud EAM, Hikmat A, Kartodihardjo H, Fuadi M. Habitat preferences, distribution pattern, and root weight estimation of Pasak Bumi (*Eurycoma longifolia* Jack). *J Man Hut Trop.* 2014;20(1):43-50.
19. Trimanto T, Sofiah S. Exploration of flora diversity and recommending species for reclamation of coal mining with biodiversity concept in Besiq Bermai Forest, East Borneo. *J Trop Life Sci.* 2018;8(2):97-107.
20. Choon KK, ed. *Forest Ecology Study Final Technical Report.* Bangkok, Thailand: Forestry Research Center, Faculty of Forestry, Kasetsart University; 2004.
21. Tnah LH, Lee CT, Lee SL, Ng KKS, Ng CH, Hwang SS. Microsatellite markers of an important medicinal plant, *Eurycoma longifolia* (Simaroubaceae), for DNA profiling. *Am J Bot.* 2011;98(5):e130-e132.
22. McGuffin M, Kartesz JT, Leung AY, Tucker AO. *American Herbal Products Association's Herbs of Commerce.* 2nd ed. Silver Spring, MD: American Herbal Products Association; 2000.
23. United States Department of Agriculture. 7 CFR § 65.145 - Ginseng. In: *Code of Federal Regulations.* Washington, DC: US Government Printing Office; 2018.
24. Office of the Law Revision Counsel. 21 USC 343: Misbranded food. In: *United States Code.* Washington, DC: US House of Representatives; 2018.

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25. Handa SS, Rakesh DD, Vasisht K. *Compendium of Medicinal and Aromatic Plants - ASIA.* Vol II. Trieste, Italy: United Nations Industrial Development Organization and the International Centre for Science and High Technology (ICS-UNIDO); 2006.
26. Jack W. Descriptions of Malayan plants. In: *Malayan Miscellanies.* Vol II. Bencoolen: Sumatran Mission Press; 1822.
27. Craig J. *A New Universal Etymological Technological, and Pronouncing Dictionary of the English Language.* Vol I. London: Henry George Collins; 1848.
28. Forest Research Institute Malaysia. The rare sight of fruiting Tongkat Ali. 2014. Available at: www.frim.gov.my/the-rare-sight-of-fruiting-tongkat-ali/. Accessed April 29, 2019.
29. Agustono B, Junaidi. The Dutch colonial economic policy: Coffee exploitation in Tapanuli residency, 1849–1928. *KEMANUSIAAN Asian J Humanit.* 2018;25(2):49–71.
30. Rehman SU, Choe K, Yoo HH. Review on a traditional herbal medicine, *Eurycoma longifolia* Jack (tongkat ali): Its traditional uses, chemistry, evidence-based pharmacology and toxicology. *Molecules.* 2016;21(3):331.
31. Fadzil NF, Wagiran A, Mohd Salleh F, Abdullah S, Mohd Izham NH. Authenticity testing and detection of *Eurycoma longifolia* in commercial herbal products using bar-high resolution melting analysis. *Genes.* 2018;9(8):408.
32. Biotropics Malaysia Berhad. *Application for the Approval of Tongkat Ali Root Extract as a Novel Food.* Selangor, Malaysia: Biotropics Malaysia Berhad; 2016.
33. Silalahi M, Nisyawati. Etnobotani pasak bumi (*Eurycoma longifolia*) pada etnis Batak, Sumatera Utara. *Pros Sem Nas Masy Biodiv Indon.* 2015;1(4):743-746.
34. Saragih B. *Economic value of non-timber forest products among Paser Indigenous People of East Kalimantan*, Universiteit Leiden; 2011.
35. Fitmawati, Sofiyanti N, Roza RM, et al. Traditional medicinal formulation: Obat pahit from Lingga Malay ethnic in Riau Archipelago, Indonesia. *Biodiversitas.* 2017;18(3):1196-1200.
36. Wetlands International. *Living Pharmacies in Tasek Bera. A Wetland of International Importance in Malaysia.* Wageningen, The Netherlands: Wetlands International; 2006.
37. Azliza MA, Ong HC, Vikineswary S, Noorlidah A, Haron NW. Ethno-medicinal resources used by the Temuan in Ulu Kuang Village. *Stud Ethno-Med.* 2012;6(1):17-22.
38. Ismail Z, Ismail N, Lassa J. *Malaysian Herbal Monograph.* Vol I. Kuala Lumpur, Malaysia: Malaysian Monograph Committee; 1999.
39. Malaysian Herbal Monograph Committee. *Malaysian Herbal Monograph 2015.* Kuala Lumpur, Malaysia: Institute for Medical Research; 2015.
40. Department of Standards Malaysia. *Phytopharmaceutical Aspect of Freeze Dried Water Extract from Tongkat Ali Roots - Specfication (Malaysian Standard MS 2409:2011 / ICS: 67-040).* Cyberjaya, Malaysia: Department of Standards Malaysia, Ministry of Science, Technology and Innovation; 2011.
41. Brinckmann JA. *Market for Malaysian Natural Ingredients used in Cosmetic, Dietary Supplement and Pharmaceutical Products.* Putrajaya, Malaysia: Malaysian Herbal Corporation; 2007.
42. Direktorat Obat Asli Indonesia. *Acuan Sediaan Herbal.* Vol 6. 1 ed. Jakarta, Indonesia: Badan Pengawas Obat dan Makanan RI; 2011.
43. Direktorat Obat Asli Indonesia. *Acuan Sediaan Herbal.* Vol 7. 1 ed. Jakarta, Indonesia: Badan Pengawas Obat dan Makanan RI; 2012.
44. Badan POM RI (National Agency of Drug and Food Control of Republic of Indonesia). *Pedoman Teknologi Formulasi Sediaan Berbasis Ekstrak.* Vol 2. Jakarta, Indonesia: Direktorat Obat Asli Indonesia, Deputi Bidang Pengawas Obat Tradisional, Kosmetik Dan Produk Komplemen; 2013.
45. Khari N, Aisha AFA, Ismail Z. Reverse phase high performance liquid chromatography for the quantification of eurycomanone in *Eurycoma longifolia* Jack (Simaroubaceae) extracts and their commercial products. *Trop J Pharm Res.* 2014;13(5):801-807.
46. Zaini NN, Osman R, Juahir H, Saim N. Development of chromatographic fingerprints of *Eurycoma longifolia* (Tongkat Ali) roots using online solid phase extraction-liquid chromatography (SPE-LC). *Molecules.* 2016;21(5):583.
47. Yunianto P, Nurhadi N, Supriyono A. Isolasi, validasi metode dan optimasi awal proses ekstraksi senyawa penanda eurycomanon dari akar tanaman pasak bumi (*Eurycoma longifolia*). *Chim Nat Acta.* 2017;5(2):70-76.
48. Bộ Y tế Việt Nam. *VĂN BẢN PHÁP LUẬT KHÁC - VĂN BẢN HỢP NHẤT - THÔNG TƯ: Ban hành Danh mục thuốc đông y, thuốc từ dược liệu và vị thuốc y học cổ truyền thuộc phạm vi thanh toán của quỹ bảo hiểm y tế.* Hà Nội, Việt Nam: Bộ Y tế, Cộng hòa xã hội chủ nghĩa Việt Nam; 2018.
49. National Pharmaceutical Regulatory Agency. *Sistem Pendaftaran Produk & Perlesenan QUEST 3+.* Selangor, Malaysia: National Pharmaceutical Regulatory Agency, Ministry of Health Malaysia; 2019.
50. Menteri Kesehatan Republik Indonesia. *Peraturan Menteri Kesehatan Tentang Formularium Obat Herbal Asli Indonesia.* Jakarta, Indonesia: Menteri Kesehatan Republik Indonesia; 2016.
51. US Food and Drug Administration. Regulations on Statements Made for Dietary Supplements Concerning the Effect of the Product on the Structure or Function of the Body; Final Rule. *Federal Register.* 2000;65(4):1000-1050.
52. Natural and Non-prescription Health Products Directorate. *Licensed Natural Health Products Database (LNHPD).* Ottawa, ON: Health Canada; 2019.
53. European Commission. *Cosmetic ingredient (CosIng) database.* Brussels, Beglium: DG Internal Market, Industry, Entrepreneurship and SMEs; 2019.
54. European Commission. *Novel Food Catalogue.* Brussels, Belgium: European Commission; 2019.
55. Bhat R, Karim AA. Tongkat ali (*Eurycoma longifolia* Jack): A review on its ethnobotany and pharmacological importance. *Fitoterapia.* 2010;81(7):669-679.
56. Norhidayah Mohamed A, Vejayan J, Yusoff M. Review on *Eurycoma longifolia* pharmacological and phytochemical properties. *J Appl Sci.* 2015;15(6):831-844.
57. Han YM, Woo S-U, Choi MS, et al. Antiinflammatory and analgesic effects of *Eurycoma longifolia* extracts. *Arch Pharm Res.* 2016;39(3):421-428.
58. Lim TK. *Edible Medicinal and Non-Medicinal Plants: Volume 11 Modified Stems, Roots, Bulbs.* 1st ed. Switzerland: Springer International Publishing; 2016.
59. Thu HE, Mohamed IN, Hussain Z, Jayusman PA, Shuid AN. *Eurycoma longifolia* as a potential adoptogen of male sexual health: a systematic review on clinical studies. *Chin J Nat Med.* 2017;15(1):71-80.
60. Talbott SM, Talbott JA, George A, Pugh M. Effect of tongkat ali on stress hormones and psychological mood state in moderately stressed subjects. *J Int Soc Sport Nutr.* 2013;10(1):28.
61. Thu HE, Hussain Z, Mohamed IN, Shuid AN. Recent advances in antibacterial, antiprotozoal and antifungal trends of *Eurycoma longifolia:* A review of therapeutic implications and future prospects. *Curr Drug Targ.* 2018;19(14):1657-1671.
62. Kotirum S, Ismail SB, Chaiyakunapruk N. Efficacy of tongkat ali (*Eurycoma longifolia*) on erectile function improvement: Systematic review and meta-analysis of randomized controlled trials. *Complement Ther Med.* 2015;23(5):693-698.
63. Effendy NM, Mohamed N, Muhammad N, Naina Mohamad I, Shuid AN. *Eurycoma longifolia*: Medicinal plant in the prevention and treatment of male osteoporosis due to androgen deficiency. *Evid Based Complement Alternat Med.* 2012;2012:9.
64. George A, Henkel R. Phytoandrogenic properties of *Eurycoma longifolia* as natural alternative to testosterone replacement therapy. *Andrologia.* 2014;46(7):708-721.
65. Kuo P-C, Damu AG, Lee K-H, Wu T-S. Cytotoxic and antimalarial constituents from the roots of *Eurycoma longifolia*. *Bioorg Med Chem.* 2004;12(3):537-544.
66. Zakaria N, Mohd K, Hamil MSR, Memon DAH, Asmawi M, Ismail Z. Characterization of primary and secondary metabolites of leaf and stem extracts from *Eurycoma longifolia* Jack. *J Fundam Appl Sci.* 2017;9(2S):661-679.
67. Thu H, Hussain Z, Mohamed I, Shuid A. Exploring dynamic biomedical algorithm of *Eurycoma longifolia* Jack and its bioactive

phytochemicals: A review of pharmacokinetic and pharmacodynamic implications and future prospects. *Asian Pac J Trop Med.* 2018;11(2):89-97.
68. Low B-S, Das PK, Chan K-L. Standardized quassinoid-rich *Eurycoma longifolia* extract improved spermatogenesis and fertility in male rats via the hypothalamic–pituitary–gonadal axis. *J Ethnopharm.* 2013;145(3):706-714.
69. Thu HE, Hussain Z, Mohamed IN, Shuid AN. *Eurycoma longifolia,* a potential phytomedicine for the treatment of cancer: evidence of p53-mediated apoptosis in cancerous cells. *Curr Drug Targets.* 2018;19(10):1109-1126.
70. Varghese CP, Ambrose C, Jin SC, Lim YJ, Keisaban T. Antioxidant and anti-inflammatory activity of *Eurycoma longifolia* Jack, a tracitional medicinal plant in Malaysia. *Int J Pharm Sci Nanaotechnol.* 2013;5(4):1875–1878.
71. Tran TVA, Malainer C, Schwaiger S, et al. NF-κB Inhibitors from *Eurycoma longifolia*. *J Nat Prod.* 2014;77(3):483-488.
72. Li C-H, Liao J-W, Liao P-L, et al. Evaluation of acute 13-week subchronic toxicity and genotoxicity of the powdered root of tongkat ali (*Eurycoma longifolia* Jack). *Evid Based Complement Alternat Med.* 2013;2013:11.
73. Talbott SM. Chapter 53 - Human Performance and Sports Applications of Tongkat Ali (*Eurycoma longifolia*). In: Bagchi D, Nair S, Sen CK, eds. *Nutrition and Enhanced Sports Performance.* San Diego: Academic Press; 2013:501-505.
74. Ming YK, Zulkawi NB, Choudhary VK, Choudhary YK. Evaluation of the genotoxicity of *Eurycoma longifolia* aqueous extract (PHYSTA®) using in vitro ames test and in vivo mammalian micronucleus test. *Int J Pharm Pharm Sci.* 2014;6(4):652-657.
75. Kiew OF, Singh R, Sirisinghe RG, Suen AB, Jamalullail SMS. Effects of a herbal drink on cycling endurance performance. *Malays J Med Sci.* 2003;10(1):78-85.
76. Muhamad AS, Keong CC, Kiew OF, Abdullah MR, Lam CK. Effects of *Eurycoma longifolia* Jack supplementation on recreational athletes' endurance running capacity and physiological responses in the heat. *Int J Appl Sports Sci.* 2010;22(2):1-19.
77. Chen CK, Mohamad WMZW, Ooi FK, Ismail SB, Abdullah MR, George A. Supplementation of *Eurycoma longifolia* Jack extract for 6 weeks does not affect urinary testosterone: epitestosterone ratio, liver and renal functions in male recreational athletes. *Int J Prev Med.* 2014;5(6):728-733.
78. George A, Udani J, Abidin NZ, Yusof A. Efficacy and safety of *Eurycoma longifolia* (Physta®) water extract plus multivitamins on quality of life, mood and stress: a randomized placebo-controlled and parallel study. *Food Nutr Res.* 2018;62:10.29219/fnr.v29262.21374.
79. Hamzah S, Yusof A. The ergogenic effects of *Eurycoma longifolia* Jack: A pilot study. *Br J Sports Med.* 2003;37:464-470.
80. Tambi MI. Standardized water soluble extract of *Eurycoma longifolia* (LJ100) on men's health. In: *Abstracts of the 8th International Congress of Andrology*, 12–16 June 2005, Seoul, Korea. *Int J Androl* 2005;28(Suppl. 1):27.
81. Talbott S, Talbott J, Negrete J, Jones M, Nichols M, Roza J. Effect of *Eurycoma longifolia* extract on anabolic balance during endurance exercise. *J Int Soc Sports Nutr.* 2006;3(1):S32.
82. Sarina MY, Zaiton Z, Aminudin AHK, Nor AK, Azizol AK. Effects of resistance training and *Eurycoma longifolia* on muscle strength, lipid profile, blood glucose, and hormone level in middle-aged women. In: *Abstracts from 4th Asia-Pacific Conference on Exercise and Sports Science & 8th International Sports Science Conference.* Kuala Lumpur, Malaysia: Academy of Medicine of Malaysia; 2009.
83. Tambi MIBM, Imran MK. *Eurycoma longifolia* Jack in managing idiopathic male infertility. *Asian J Androl.* 2010;12(3):376-380.
84. Talbott S, Talbott J, Christopulos AM, Ekberg C, Larsen W, Jackson V. Ancient wisdom meets modern ailment - Traditional Asian medicine improves psychological Vigor in stressed subjects. *Prog Nutr.* 2010;12(1):64-69.

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85. Tambi MI, Imran MK, Henkel RR. Standardised water-soluble extract of *Eurycoma longifolia*, Tongkat ali, as testosterone booster for managing men with late-onset hypogonadism? *Andrologia.* 2012;44(Suppl 1):226–230.
86. Ismail SB, Wan Mohammad WMZ, George A, Nik Hussain NH, Musthapa Kamal ZM, Liske E. Randomized clinical trial on the use of PHYSTA freeze-dried water extract of *Eurycoma longifolia* for the improvement of quality of life and sexual well-being in men. *Evid Based Complement Alternat Med.* 2012;2012:10.
87. Henkel RR, Wang R, Bassett SH, et al. Tongkat ali as a potential herbal supplement for physically active male and female seniors—A pilot study. *Phytother Res.* 2014;28(4):544-550.
88. Udani JK, George AA, Musthapa M, Pakdaman MN, Abas A. Effects of a proprietary freeze-dried water extract of *Eurycoma longifolia* (Physta) and *Polygonum minus* on sexual performance and well-being in men: A randomized, double-blind, placebo-controlled study. *Evid Based Complement Alternat Med.* 2014;2014:10.
89. 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. *Phytother Res.* 2016;30(4):627-635.
90. Anon. Shitek Tongkat Ali Plus 400mg: Presence of tadalafil. *WHO Pharmaceuticals Newsletter.* 2004(3):2.
91. Venhuis BJ, Tan J, Vredenbregt MJ, Ge X, Low M-Y, de Kaste D. Capsule shells adulterated with tadalafil. *Forensic Sci Int.* 2012;214(1):e20-e22.
92. Do TTK, Theocharis G, Reich E. Simultaneous detection of three phosphodiesterase type 5 inhibitors and eight of their analogs in lifestyle products and screening for adulterants by high-performance thin-layer chromatography. *J AOAC Int.* 2015;98(5):1226-1233.
93. Abubakar BM, Salleh FM, Shamsir Omar MS, Wagiran A. Assessing product adulteration of *Eurycoma longifolia* (Tongkat ali) herbal medicinal product using DNA barcoding and HPLC analysis. *Pharm Biol.* 2018;56(1):368-377.
94. Glatter R. Viagra in your coffee? FDA recalls latest combo product. *Forbes.* July 21, 2017. Available at: www.forbes.com/sites/robertglatter/2017/07/21/viagra-in-your-coffee-fda-recalls-latest-combo-product/. Accessed April 29, 2019.
95. Caverflo.com Issues Voluntary Nationwide Recall of Caverflo Natural Herbal Coffee due to the Presence of Undeclared Active Pharmaceutical Ingredients and Undeclared Milk [press release]. Silver Spring, MD: US Food and Drug Administration; December 1, 2018.
96. Vejayan J, Mohamed AN, Zulkifli AA, Che Yahya YA, Munir N, Yusoff MM. Marker to authenticate *Eurycoma longifolia* (tongkat ali) containing aphrodisiac herbal products. *Curr Sci.* 2018;115(5):886-894.
97. Ministry of Natural Resources and Environment. *4th National Report to the Convention on Biological Diversity.* Putrajaya, Malaysia: Government of Malaysia; 2009.
98. Sarawak Government. *Laws of Sarawak. Wild Life Protection Ordinance 1998.* Kuching, Sarawak: Percetakan Nasional Malaysia Berhad; 1998.
99. Prime Minister's Office Lao People's Democratic Republic. *Decree on natural resources for medicines (pharmaceutical natural resources) No 155/PM.* Vientiane Capital Lao PDR: Prime Minister's Office; 2003.
100. Department of Environment and Natural Resources. *Updated National List of Threatened Philippine Plants and Their Categories.* Quezon City, the Philippines: Republic of the Philippines Department of Environment and Natural Resources; 2017.
101. Lee HS. Introducing the cultivation of medicinal plants and wild fruits in forest rehabilitation operations on former shifting cultivation sites in Sarawak Malaysia: Issues and challenges. *Southeast Asian Stud.* 2004;42(1):60-73.
102. Ali ARM, Norini H, Lim HF. The role of forestry research and development (R&D) institution in policy formulation and implementation: A Malaysian perspective. *Pertanika J Trop Agric Sci.* 2007;30(2):153-163.
103. Anon. Luasong tree replanting project a success. *Borneo Post Online.* December 5, 2018.
104. Hussein S, Ling APK, Ng TH, Ibrahim R, Paek KY. Adventitious roots induction of recalcitrant tropical woody plant, *Eurycoma longifolia*. *Romanian Biotechnol Lett.* 2012;17(1):7026-7035.
105. Rahim KA, Ibrahim R, Othman Z, Harun AR, eds. *A Compendium of R&D on Nuclear Technology Applications in Agriculture and Biosciences (1984-2014).* Selangor, Malaysia: Malaysian Nuclear Agency; 2014.
106. Hung TN, Chi VL. Country Status Report on Medicinal and Aromatic Plants in Vietnam. In: Paroda R, Dasgupta S, Mal B, Ghosh SP, Pareek SK, eds. *Expert Consultation on Promotion of Medicinal and Aromatic Plants in the Asia-Pacific Region: Proceedings, Bangkok, Thailand; 2-3 December, 2013.* Bangkok, Thailand: Asia-Pacific Association of Agricultural Research Institutions (APAARI); 2014:226-231.
107. Idris MAH, Haron N. Supply and demand of *Eurycoma longifolia* (tongkat ali) plants with few others. *J Trop Med Plants.* 2001;2(1):145-154.
108. Vijaindren A. Flaccid outlook for tongkat ali. *New Sunday Times.* 2009:16.
109. Jabatan Perkhidmatan Kuarantin dan Pemeriksaan Malaysia (MAQIS). *Prosedur Operasi Piawaian: Pemeriksaan Konsainan Herba yang Dieksport [Standard Operating Procedure: Consignment Inspection for Exported Herbs] [in Malay].* Putrajaya, Malaysia: MAQIS; 2014.
110. Wan-Muhammad-Azrul WA, Mohd-Farid A, Lee SY, Sajap AS, Omar D, Mohamed R. A survey on the occurrence of pests and diseases in tongkat ali (*Eurycoma longifolia*) plantations in Peninsular Malaysia. *J Trop For Sci.* 2018;30(3):362-375.

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American Botanical Council Hosts Annual Botanical Excellence Awards Ceremony

By ABC Staff

The American Botanical Council (ABC) hosted its 14th annual American Botanical Celebration and Awards Ceremony on March 6, 2019. The event took place at the Hilton Anaheim during the Natural Products Expo West trade show in Anaheim, California, and focused on ABC's 30th anniversary, which occurred in November 2018.

The ceremony is held each year to honor the recipients of the ABC Botanical Excellence Awards and celebrate the supporters of ABC's nonprofit educational mission. This year, more than 350 guests attended, including ABC Sponsor Members, Adopt-an-Herb participants, and supporters of the ABC-AHP-NCNPR Botanical Adulterants Prevention Program and the new Sustainable Herbs Program. Many members of ABC's Board of Trustees, Advisory Board, and Director's Circle also attended. Guests enjoyed lively conversation, vegetarian hors d'oeuvres, and cocktails.

Mark Blumenthal, ABC's founder and executive director, summarized ABC's accomplishments in 2018 and then introduced Jim Emme, the CEO of NOW Health Group, who received the 2018 ABC Champion Award for his generous support of ABC.

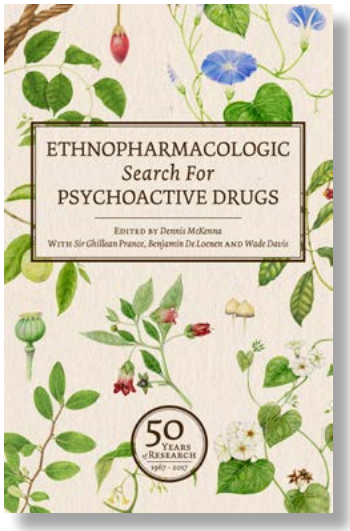
Blumenthal also presented the 2018 ABC Mark Blumenthal Herbal Community Builder Award to husband and wife Larry and Linnea Wardwell, who have been organizing and promoting herbal medicine conferences for more than 25 years.

Stefan Gafner, PhD, ABC's chief science officer, presented the 2018 Varro E. Tyler Commercial Investment in Phytomedicinal Research Award to GW Pharmaceuticals. Founded in 1998, the Cambridge, England-based company's focus is "to bring novel, cannabinoid-based prescription medicines to patients in areas of serious unmet need."[1]Alice Mead, vice president of US public policy and public affairs at Greenwich Biosciences (the US subsidiary of GW Pharmaceuticals), accepted the award on GW's behalf.

Gafner also introduced the recipient of the 2018 ABC Norman R. Farnsworth Excellence in Botanical Research Award: Otto Sticher, PhD, a professor, pharmacist, pharmacognosist, and natural products chemist from Switzerland. Sticher accepted the award via a prerecorded video.

The 2018 James A. Duke Excellence in Botanical Literature Award went to *Ethnopharmacologic Search for Psychoactive Drugs: 50 Years of Research*, Volumes I and II (ESPD50). *HerbalGram* Associate Editor Hannah Bauman presented the award to Dennis J. McKenna, PhD, the editor of ESPD50. Published by Synergetic Press, the book contains the proceedings of the groundbreaking 1967 ESPD symposium and the 50th anniversary symposium held in 2017.

Finally, the second annual ABC Fredi Kronenberg Excellence in Research and Education in Botanicals for Women's Health Award was presented by ABC Trustee Peggy Brevoort to Aviva Romm, MD, a midwife, herbalist, author, and Yale-trained physician who is a recognized expert in botanical medicine. Romm accepted the award via video.



Historic Compilation of Psychoactive Research Receives James A. Duke Botanical Literature Award

ABC gives the Duke Award annually to books that contribute significantly to the medicinal plant-related literature, and the fields of botany, taxonomy, ethnobotany, pharmacognosy, phytomedicine, and other related disciplines.

The Duke Award was created in 2006 to honor economic botanist and author James A. Duke, PhD, who died in December 2017. Duke's prestigious career achievements in economic botany and ethnobotany included decades of work at the United States Department of Agriculture and the authorship of more than 30 reference and consumer books. Among his many other activities and positions, he was also a co-founding member of ABC's Board of Trustees.

Public interest in the field of psychedelic and psychoactive substances is growing: Tourists travel in increasing numbers to the Amazon to partake in ayahuasca ceremonies, which involve a traditional psychoactive brew made of multiple Amazonian plants; more clinical studies are being conducted on the potential therapeutic benefits of psilocybin, a psychoactive compound from mushrooms

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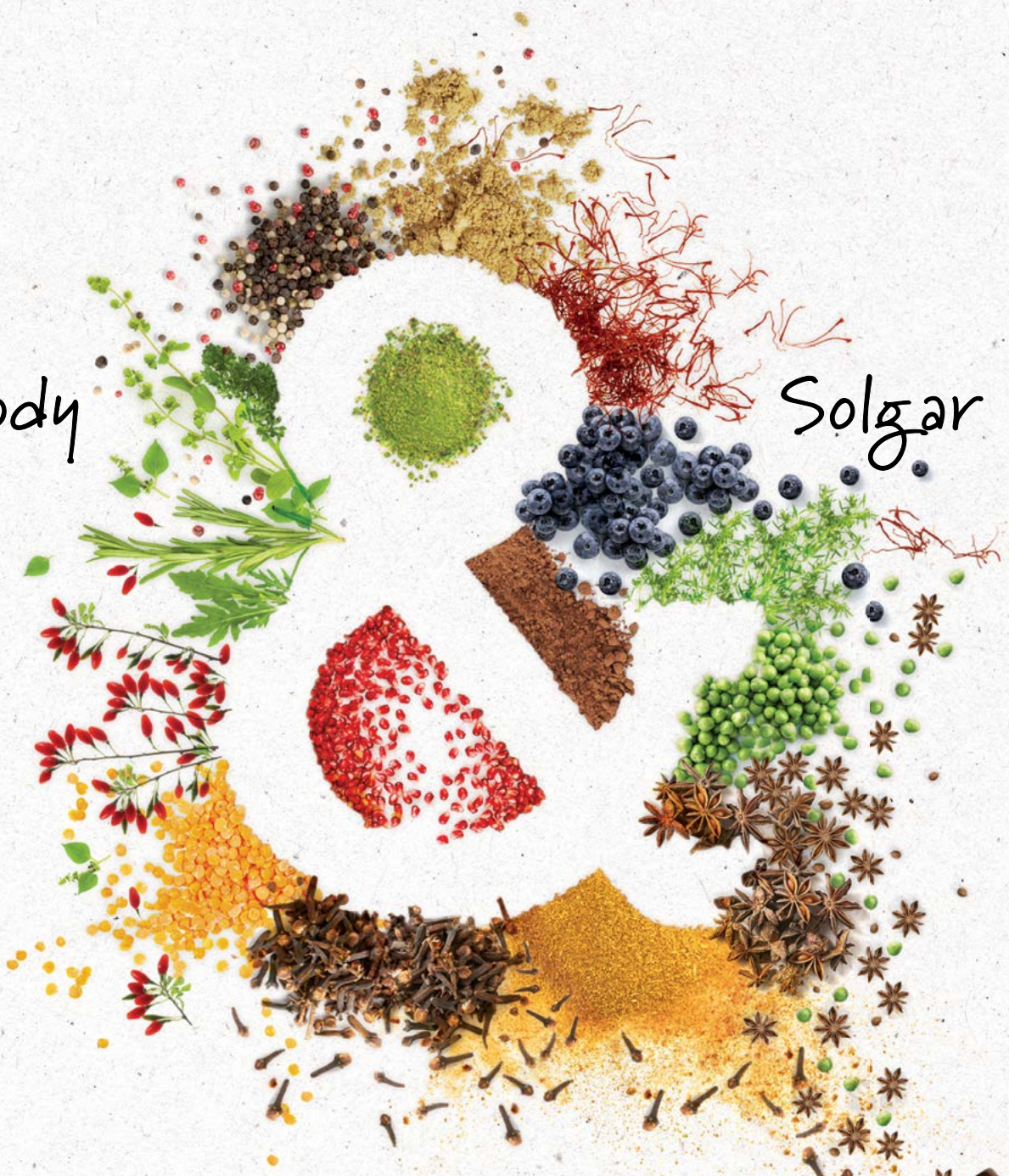

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in the genus *Psilocybe* (Hymenogastraceae) and other fungal genera; and an attempt to restrict access to kratom (*Mitragyna speciosa*, Rubiaceae), a botanical with pain-relieving properties, in the United States in 2016 caused such an outcry that the proposal was withdrawn.

All of the sessions at the 2017 symposium were live-streamed on Facebook to an audience of more than 100,000 people, and ESPD50 is currently in its third print run to meet consumer demand.

McKenna commented: "Many discoveries were made in the five decades between the 1967 symposium and the 2017 symposium. The topics covered were timely then, and are even more timely now, as the habitats and cultures that are the holders of the knowledge are disappearing rapidly.... Science has always looked to nature for psychoactive remedies that may be used to alleviate human suffering. It is my hope that these symposium volumes will inspire a new generation of young investigators to continue this quest."

Blumenthal praised McKenna and his colleagues for their accomplishment. "This two-volume set is a major contribution to the world's literature on psychoactive plants and fungi," he said. "The growing body of compelling clinical research on compounds from psychoactive plants and fungi to provide remedies for a variety of existential and medical conditions continues to underscore the need for more research in this vital area. It is clear that many psychoactive plants and fungi and their compounds will become welcome medicines of the future, and that future is not far off.

"Dr. McKenna and his colleagues are to be commended for their pioneering work in this area," Blumenthal continued. "I am certain that Dr. Duke would strongly approve of ABC's choice of these books to receive his eponymous award."

Michael J. Balick, PhD, a respected ethnobotanist and vice president for botanical science and director and philecology curator at the Institute of Economic Botany at the New York Botanical Garden, agreed. As a member of the ABC Board of Trustees, Balick served on the selection committee for the Duke Award. "Dr. McKenna has compiled, in a single reference, a remarkable collection of scholarship relating to plants and fungi that indigenous cultures have used to 'enter the other world,'" he noted, "and in doing so, he has created a resource that will serve a generation of scholars who are interested in this fascinating relationship among botanicals, phytochemicals, and people. This is especially interesting as he has included many papers of historical importance based on the first symposium 50 years prior. Bravo to Dennis and his colleagues for organizing the meeting that led to this publication and, as editor, for bringing it to fruition."

Professor Otto Sticher Receives Norman R. Farnsworth Excellence in Botanical Research Award

ABC presents this annual award, named in honor of the celebrated Professor Norman R. Farnsworth, PhD, to an individual who has made significant research contributions in the fields of pharmacognosy, ethnobotany, ethno-

Otto Sticher, PhD, recipient of the ABC Norman R. Farnsworth Excellence in Botanical Research Award. Photo ©2019 American Botanical Council

pharmacology, or other scientific disciplines related to medicinal plants. Farnsworth, who died in 2011, was a highly published and internationally renowned research professor of pharmacognosy, a senior university scholar in the College of Pharmacy at the University of Illinois at Chicago, and one of the founding members of ABC's Board of Trustees.

Sticher, professor emeritus of pharmacognosy at the Swiss Federal Institute of Technology in Zürich, Switzerland (ETH Zürich), is best known for his pioneering work on the chemistry of plant compounds known as iridoids. He also has made extraordinary contributions to the development of analytical methods for quality control of herbal medicines and to the knowledge of the chemistry and medicinal properties of many extracts and isolates from plants, bacteria, and marine organisms.

For more than 50 years, Sticher has been at the forefront of research in the fields of ethnobotany and ethnopharmacology, natural products drug discovery, and analytical chemistry. He published what may have been the first HPLC-UV (high-performance liquid chromatography-ultraviolet) analytical method to measure ginsenosides in ginseng (*Panax* spp., Araliaceae), and established a ginkgo (*Ginkgo biloba*, Ginkgoaceae) extract fingerprint, which includes the separation of 33 ginkgo flavonoids.

According to Gafner: "The latter is not only an amazing piece of liquid chromatography, but also one of the first papers to consider evaluating the quality of an herbal extract not by a single marker compound, but by the entirety of its chemical composition, or fingerprint."

The impact of Sticher's many scientific contributions goes well beyond his more than 400 scientific papers, book chapters, and books (most notably the textbook *Pharmakognosie – Phytopharmazie*, which is now in its 10th edition). He taught and mentored many students, and some of the most prominent natural products researchers (e.g., Kurt Hostettmann, PhD; Ikhlas A. Khan, PhD; A. Douglas Kinghorn, PhD; Gabriele M. König, PhD; Beat Meier, PhD; and Fabio Soldati, PhD) worked in his laboratories at ETH Zürich.

Sticher has received numerous awards and recognitions, including the Egon-Stahl-Award in Gold from the Society for Medicinal Plant and Natural Product Research (GA) in 2014 and an honorary doctorate from the University of London in 2002. In March 2014, the *Journal of Natural Products* published a special edition in his honor.

Gafner also noted: "Professor Sticher was one of the pioneers in using HPLC to measure the composition of plant extracts. Examples of his earliest work include the HPLC analysis of licorice [*Glycyrrhiza glabra*, Fabaceae] saponins or the bitter principles in gentian [*Gentiana* spp., Gentianaceae] in 1977. But while his research publications most often focus on the chemical or quality aspects of plants, he has a much broader view of herbal medicine quality, which he has passed on to several generations of pharmacy students through training in botanical identification, macroscopic and organoleptic analysis, and botanical microscopy. Besides being an exceptional scientist, he is known to colleagues and friends mainly as a kind and honest human being, a true gentleman."

Sticher wrote: "I am very pleased and grateful to receive the 2018 ABC Norman R. Farnsworth Excellence in Botanical Research Award. I would like to thank the American Botanical Council for honoring me with this award. Over the years, our research group at the ETH Zürich had a close scientific collaboration with the group created by Norman Farnsworth at the University of Illinois at Chicago (UIC). This resulted in an ongoing exchange of visitors between ETH and UIC. By fostering such collaborations, Norman Farnsworth helped to build bridges internationally among scientists in the field of traditional botanical medicine."

GW Pharmaceuticals Receives ABC Tyler Award for Phytomedicinal Research

The ABC Tyler Award was created to honor one of the most respected educators in late-20th century herbal medicine and pharmacognosy. Varro E. Tyler, PhD, who died in 2001, was vice president of academic affairs at Purdue University and dean of the College of Pharmacy and Pharmaceutical Sciences at Purdue for 20 years. He was the senior author of six editions of a leading pharmacognosy textbook and numerous other professional and popular books and academic articles. Tyler, an early member of ABC's Board of Trustees, encouraged scientific and product integrity and envisioned a rational phytomedicinal health care sector that valued the proper evaluation of botanical products' quality, safety, and efficacy.

"GW Pharmaceuticals is extremely honored to receive this prestigious award recognizing our many years of cutting-edge research in the field of cannabis-derived medications," said Justin Gover, CEO of GW. "Professor Tyler was a great pioneer in the field of pharmacognosy, and, like him, we believe that plants, like cannabis, have vast therapeutic potential. Our work demonstrates that, with rigorous research and the advent of new scientific techniques, the cannabis plant can form the basis for new prescription medicines that have the potential to make a meaningful impact on patients' lives. We are committed to continuing our research into the therapeutic applications of cannabis and cannabinoids for many years to come."

GW is especially known for the development of two phytomedicines from cannabis (*Cannabis sativa*, Cannabaceae). The first is Sativex®, a standardized complex botanical mixture delivered as an oromucosal spray that has been approved in more than 25 countries outside the United States to treat multiple sclerosis-related spasticity. According to the company, Sativex is the world's first cannabis-derived prescription medicine. Sativex contains equal parts of cannabidiol (CBD, the most-studied non-intoxicating

compound in cannabis) and tetrahydrocannabinol (THC, the main intoxicating compound in cannabis). The US Food and Drug Administration (FDA) has not approved Sativex. But, according to Mead, GW expects to begin a phase 3 clinical trial in the United States later in 2019. The trial will investigate Sativex's effects in patients with multiple sclerosis, and the company hopes it will lead to FDA approval.

The second is Epidiolex®, a standardized oil-based CBD oral solution. In June 2018, the FDA approved Epidiolex for the treatment of seizures associated with Dravet syndrome and Lennox-Gastaut syndrome, two rare, severe, early-onset forms of epilepsy, both with frequent, difficult-to-control seizures of multiple types. Epidiolex is the first drug approved by the FDA for the treatment of Dravet syndrome and is also the first cannabis-derived prescription medicine available in the United States. Additionally, it represents a new class of anti-seizure medication.

The FDA's approval was prompted, at least partly, by three randomized, double-blind, placebo-controlled clinical trials on Epidiolex (all funded by GW). In these trials, patients in the Epidiolex group experienced statistically significant reductions in seizure frequency compared to those taking placebo. Importantly, these patients otherwise had been unable to achieve seizure control with their standard treatment regimens.

According to Mead, GW has invested more than $1 billion on research and development. The company is also developing other cannabinoid product candidates, with a focus on neurological conditions.

GW grows its cannabis in greenhouses that control temperature, humidity, and lighting, and the company does not use pesticides or fungicides. The company has bred a proprietary chemovar (chemical variety) of cannabis that has higher levels of CBD and lower levels of THC. It has been growing the plants in-house for more than 20 years.

Gafner said: "The clinical work by GW Pharmaceuticals has led to effective therapeutic agents to reduce spasticity in multiple sclerosis patients and treat Lennox-Gastaut and Dravet syndromes. However, the impact of its research cannot be measured solely by the patient benefits. The company's pioneering work on *Cannabis sativa* has helped to destigmatize the plant and opened the door for additional research, which will hopefully lead to treatment successes for other diseases in which effective therapies are desperately needed."

Aviva Romm Receives ABC Fredi Kronenberg Excellence in Botanicals for Women's Health Award

The award was named in honor of distinguished researcher, educator, and longtime ABC Board of Trustees member Fredi Kronenberg, PhD, who died in April 2017. Kronenberg dedicated her professional life to the study of medicinal plants and phytomedicines for women's health conditions and was particularly interested in phytoestrogen-containing botanicals, such as black cohosh (*Actaea racemosa*, Ranunculaceae), for the treatment of menopause symptoms.

Aviva Romm, recipient of the ABC Fredi Kronenberg Excellence in Research and Education in Botanicals for Women's Health Award.
Photo ©2019 American Botanical Council

"Fredi was brave in both her life and her death," Romm said in a recorded acceptance speech. "As a scientist, she charted territory in medicine that can only be called pioneering. Her work was part of creating recognition for herbal medicine, which paved a pathway that has allowed herbal medicine to have a place on the modern map of health care."

Kronenberg was a champion of integrative medicine and co-founded the Richard and Hinda Rosenthal Center for Complementary and Alternative Medicine (CAM) at Columbia University — the first CAM program at an Ivy League school and the first government-funded CAM research and educational center. For 10 years, she also co-directed an onsite five-day continuing education course for physicians and other health care providers interested in botanical medicine.

"In a larger medical culture in which women's wisdom has historically been suppressed, women healers and scholars marginalized, and in which men of science have been considered king, modern herbal medicine is a culture that is distinctly unique," Romm said. "Women's wisdom, knowledge, tradition, and skills are honored and respected. It's as part of a legacy of women in science and herbal medicine that I am profoundly honored to ... accept [this award]."

For more than three decades, Romm has focused on providing herbal medicine options for women and children that are based on a combination of traditional knowledge and modern scientific and clinical data. In her practice, she uses a holistic approach that takes into account an individual's environment, diet, lifestyle, and many other factors to address the root causes of chronic health conditions. Previously, Romm served as both the president of the American Herbalists Guild and medical director of the American

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Herbal Pharmacopoeia.

Like Kronenberg, Romm has been actively involved in herbal medicine curricula for students and practitioners. She is the co-founder of the Yale Integrative Medicine Curriculum and has created online professional training programs in integrative and herbal medicine. Romm is also a botanical industry consultant, sought-after speaker, and member of multiple advisory boards. She is the founder of DharmaMoms, a nonprofit that works to reduce maternal mortality in the United States and high-risk countries.

"ABC is pleased to recognize Dr. Romm with the ABC Fredi Kronenberg Award for her excellent work in the area of botanicals and women's health," said Blumenthal. "Aviva's interests, expertise, and passion in this area are wholly in line with those of Dr. Kronenberg, making her a natural choice for this award."

Romm is the author of seven books on natural medicine, including *Botanical Medicine for Women's Health* (Elsevier, 2010), which received the ABC James A. Duke Excellence in Botanical Literature Award in 2010. The second edition of the textbook was published by Elsevier in 2018. In addition, Romm is the author of *The Adrenal Thyroid Revolution* (Harper One, 2017) and a contributing author of the *American Herbal Products Association's Botanical Safety Handbook*, 2nd edition (CRC Press, 2013). She has written dozens of articles for major publications, including *USA Today*, *The Boston Globe*, and *Prevention*, and has shared her botanical knowledge as a returning guest on "The Dr. Oz Show."

Last year, the inaugural ABC Fredi Kronenberg Award was given to Tieraona Low Dog, MD, a leading expert in integrative medicine and women's health. Low Dog said: "A warm and heartfelt congratulations to Aviva Romm, MD, a dear friend and colleague, on receiving the ABC Fredi Kronenberg Award. Aviva has the rare gift of being a gifted clinician, teacher, and writer. Her book *Botanical Medicine for Women's Health* was a major contribution to the field, as were her many years leading the American Herbalists Guild. Dr. Kronenberg would be delighted."

Both Romm and Low Dog were guest editors of *HerbalGram* issue 121, a special issue dedicated to Kronenberg, which focused on botanicals in women's health.

Jim Emme Named ABC Champion for 2018

The ABC Champion Award was created to recognize individuals who have been outstanding supporters of ABC and have helped the organization promote and achieve its nonprofit research and educational mission, whether through monetary support or contributions of time. The generosity of ABC's friends and members is vital to ABC's continued success and growth.

"Jim Emme is a particularly giving and supportive person," said Blumenthal. "He is quick to see the potential and value of an ABC initiative. In fact, because of Jim, NOW Health Group was the first company to underwrite ABC's newest initiative, the Sustainable Herbs Program partnership, which ABC announced last November. Over the years, Jim has answered many a call to support ABC's efforts. He is a true 'champion' of our nonprofit educational mission and efforts."

Emme has more than 20 years of experience in the natural products industry. In 1995, he joined NOW Foods as plant manager and became COO some years later before being promoted to the role of president and CEO of NOW Health Group. He has been a key player in NOW Health Group's global expansion efforts and instrumental in developing its operational resources and facilities in North America. His food science education combined with decades of experience in the design and management of food manufacturing and distribution operations make Emme stand out in the dietary supplement industry. He is on the Natural Products Association Board of Directors and is involved with the Alliance for Natural Health and the Economic Development Authority of Western Nevada, among other organizations.

Emme thanked ABC for the award, stating: "NOW is proud to support the American Botanical Council and honored by this recognition. My first introduction to botanicals education was when my sister Dorie gave me her copy of an issue of *HerbalGram* in the early 1980s. As a food scientist, I was impressed with the details. How would I have known that my bootleg copy of *HerbalGram* would be the gateway to my interest in natural products? Just as ABC is dedicated to helping people live healthier lives through the science-based, responsible use of herbs, NOW's mission is to provide products and services that empower people to lead healthier lives, so we are aligned in passion and purpose. I look forward to

Jim Emme, recipient of the 2018 ABC Champion Award.
Photo ©2019 American Botanical Council

working with Mark and his great staff for many years to come."

Linnea and Larry Wardwell Receive ABC Mark Blumenthal Herbal Community Builder Award

This annual award is given to individuals who have played a significant role in creating a sense of community among herbalists, botanical researchers, members of the herb and natural products communities and industries, and others who work in the area of medicinal and aromatic plants.

The Wardwells have contributed significantly to the herbal education of tens of thousands of people and have helped build and strengthen the herbal community. Through their company, Herbal Educational Services, they organize and promote the annual Medicines from the Earth conference in Black Mountain, North Carolina, and the annual Southwest Conference on Botanical Medicine at the Southwest College of Naturopathic Medicine in Tempe, Arizona. Additionally, they have recorded most of the presentations at these conferences and compiled extensive conference proceedings, making them available via their company — what Blumenthal calls "an important and highly useful herb educational resource." Many of these recordings and proceedings are part of approved continuing education modules for health professionals.

Larry (left) and Linnea (center) Wardwell, recipients of the 2018 ABC Mark Blumenthal (right) Herbal Community Builder Award.
Photo ©2019 American Botanical Council

"Linnea and Larry Wardwell have given so much of their heart and soul to these conferences to ensure that there are the highest quality presenters for the best learning experience for the attendees," said Ric Scalzo, founder of Gaia Herbs, the primary sponsor of the Medicines from the Earth conference since its inception. "They have acted lovingly and consciously out of a deep sense of stewardship – for the earth, for the plants, and for conference attendees who have become part of the herbal community."

Herbalist, author, and founder of herb company Herbalist & Alchemist, David Winston, who has been a teacher at almost every Medicines from the Earth conference, lauded the Wardwells.

"I cannot think of many people in the [US] herbal community more deserving of the ABC Mark Blumenthal Herbal Community Builder Award than Linnea and Larry Wardwell," said Winston. "Quietly behind the scenes, Linnea, Larry, and their staff have planned and supervised two of the most important clinically oriented [US] herbal conferences since the 1990s. Through these conferences, they have brought together the foremost teachers of clinical herbalism, naturopathic medicine, functional medicine, traditional Chinese medicine, Tibetan medicine, and Ayurveda with thousands of eager students, many of whom are health professionals. In order to make this vital information more available, they have also produced yearly proceedings and recordings for both conferences that are a testament to both ancient healing traditions and the most up-to-date research in the herbal world.

"Few people have had such a profound impact on herbal education as the Wardwells," Winston continued, "and it is time for them to step out from behind the computer and receive our sincere gratitude and congratulations for their dedication to making herbal medicine a safe and effective part of so many people's lives."

Blumenthal said: "I feel deeply grateful to be one of the teachers who has been invited to speak at the Medicines from the Earth conference numerous times in the beautiful mountains of western North Carolina. One of the most important aspects of this conference that has continued to impress me, aside from the beautiful forest and the amazing herbal teachers, is the fact that so many people continue to return to the conference year after year. To me, this is an important form of community building.

"It is highly fitting that Linnea and Larry would be involved in botanical medicine education," added Blumenthal. "A relevant anecdote: Linnea's mother, an avid organic gardener back in the 1950s, named her daughter after the renowned 18th-century Swedish botanist Carl von Linné (Linnaeus), the father of the botanical binomial nomenclatural system used in all modern scientific literature." HG

Reference

1. History & approach. GW Pharmaceuticals website. Available at: www.gwpharm.com/about/history. Accessed April 3, 2019.

ABC Publishes Monograph on BCM-95 (Curcugreen) Turmeric Rhizome/Curcumin Extract Preparation

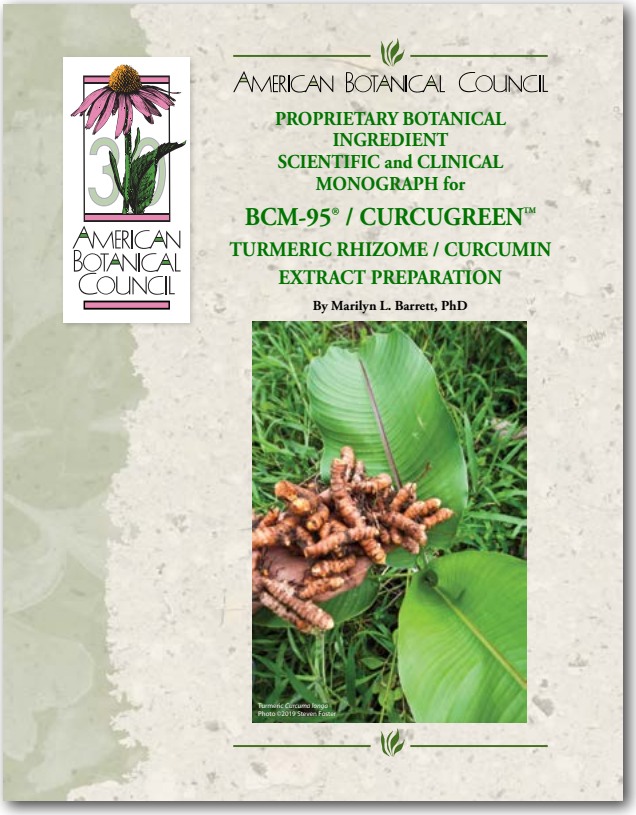
Monograph summarizes pharmacological and clinical research on proprietary, patented curcumin extract

By ABC Staff

The American Botanical Council (ABC) recently published an ingredient-specific monograph on BCM-95® (also marketed as Curcugreen™), a proprietary patented extract made from the rhizome of the popular spice and medicinal plant turmeric (*Curcuma longa*, Zingiberaceae).

Turmeric rhizome (root) contains several biologically active compounds called curcuminoids, with curcumin as the most prominent. BCM-95 is a unique preparation of standardized curcuminoids that is blended with the essential oil of turmeric, which, according to the manufacturer, assists in absorption of the preparation and enhances its biological activities and health benefits.

Dietary supplements made from turmeric rhizome powder and concentrated and/or standardized rhizome extracts (often referred to in trade as "curcumin") are some of the top-selling herbal dietary supplements in the United States and worldwide. Turmeric and curcumin were the top-selling dietary supplement ingredients in natural food retail outlets in the United States from 2013 to 2017, and the fifth top-selling ingredients in mainstream retail outlets in 2017 (the last year for which complete sales data are available).



BCM-95 is formulated by Arjuna Natural Ltd. of Kerala, India, in an environmentally sustainable manner and exclusively distributed in the United States and Canada by EuroPharma USA of Green Bay, Wisconsin, for the natural food and health practitioner channels.

Clinical research on BCM-95 has examined its potential benefits for mental health, joint health, immune health, pain, and cancer. The BCM-95 monograph includes detailed descriptions of 13 human clinical trials and a table that summarizes them. The monograph also reviews numerous pharmacological and toxicological studies, lists US and international patents, and contains 90 references. The BCM-95 extract preparation has a total of more than 50 published scientific and clinical studies, according to EuroPharma.

The monograph was written by Marilyn L. Barrett, PhD, a research and consulting pharmacognosist, and was peer reviewed by various medicinal plant specialists with knowledge of turmeric and curcumin.

"It is a pleasure to work with the American Botanical Council and to support its mission of educating the public about the science behind herbal medicine," said Barrett. "The BCM-95 monograph is a snapshot in time of the scientific information on this proprietary extract of curcumin, and it is an indication of the ever-expanding scientific literature on herbal preparations."

ABC Founder and Executive Director Mark Blumenthal commented: "A significant part of ABC's research and educational mission is to acknowledge the clinical research conducted on specific commercial botanical ingredients and phytomedicinal products. ABC encourages and welcomes such research.

"Botanical ingredients and the products made from them can vary widely," he continued, "due to the range of chemical compounds in plants, the processing methods used, and other variables. Accordingly, it is fitting for ABC to report the published research that has been conducted on proprietary botanical ingredients like BCM-95 and acknowledge companies' investments in such research. This monograph can be a highly useful resource for health professionals, researchers, and others interested in the health benefits of turmeric."

Terry Lemerond, founder and president of EuroPharma USA, explained that BCM-95's other trademark name, Curcugreen, is based on the environmentally sustainable production processes used to make it. "Our partners in India chose the name Curcugreen to reflect their ongoing sustainability efforts, which include exclusive use of solar power in the manufacturing process, rainwater harvesting, and cutting-edge waste purification treatment practices. They also plant up to 50 acres of trees per year as part of their green initiative.

"The entire extraction process for BCM-95/Curcugreen uses only food grade solvents," Lemerond continued, "and there are absolutely no synthetic ingredients added to artificially affect absorption. BCM-95/Curcugreen relies on the patented turmeric essential oil process for both enhanced health benefits and improved absorption. BCM-95 contains only ingredients that are typically found in the rhizome (root) of the turmeric plant."

Lemerond added: "We use BCM-95 in both our CuraMed and Curamin line of products because we believe it is the best in the world. Our relationship with our partners in India provides us with exclusivity in the retail health food and health care practitioner's channel. We are very excited to see the compelling scientific information on BCM-95 (Curcugreen) curcumin gathered into this detailed monograph."

Turmeric *Curcuma longa*
Photo ©2019 Steven Foster

The BCM-95 (Curcugreen) monograph is the fifth ingredient- or product-specific monograph published by ABC. Previous monographs can be accessed on the ABC website.

The 27-page document also contains a two-page Clinical Overview section that summarizes the therapeutic and clinical data on the extract. The publication was developed through an unrestricted educational donation by EuroPharma USA. ABC's production and distribution of the monograph is for educational purposes only and is not an endorsement of the ingredient or products made from it, the manufacturer, importers, or distributors of the ingredient. HG

James A. Duke Inducted into New Hope Network's Hall of Legends

By Hannah Bauman

On March 7, 2019, the New Hope Network posthumously inducted famed ethnobotanist and author James A. Duke, PhD, into its Hall of Legends. The Hall of Legends recognizes some of the greatest contributors to the natural products industry and their efforts to bring health and wellness to consumers. Helen Lowe Metzman, chief gardener at Duke's four-acre Green Farmacy Garden in Fulton, Maryland, since 2006, and Mark Blumenthal, American Botanical Council (ABC) founder and executive director, accepted the award on behalf of the Duke family. The ceremony occurred during the Natural Products Expo West tradeshow in Anaheim, California.

In her acceptance speech, Metzman remembered Duke as "an amazing man who spoke in poetry and prose" and revealed that after his death on December 10, 2017, and in accordance with his final wishes, some of his ashes were spread in the Peruvian rainforest, under the guidance of a shaman. Some of his ashes also were buried in Duke's herb garden in June 2018 as part of a celebration of life that was attended by more than 100 friends, colleagues, and family members and was sponsored by ABC and the Maryland University of Integrative Health.

Duke, who was a co-founder of ABC, had a distinguished career in economic botany, including more than 35 years at the US Department of Agriculture (USDA), and traveled extensively to the Amazon, Panama, Puerto Rico, China, and many other places to study indigenous plant use. During his tenure at the USDA's Agricultural Research Service, he created and maintained "Dr. Duke's Phytochemical and Ethnobotanical Databases," a vital research tool for botanists and chemists. He also authored or co-authored dozens of books that aimed to introduce both academic and consumer audiences to herbal medicine practices and traditional remedies.

In Blumenthal's acceptance speech, he said: "I wish everyone could have met Jim. He was the kind of person who stands out in your life…. You find subtle ways in which they shaped and affected you." Blumenthal also recalled that Duke was "a man who walked humbly; most of the time barefoot…. He just carried a small little satchel when he went down there [to the Peruvian Amazon] with just a few pairs of shorts and a T-shirt, not all the backpacks and stuff that the hippie environmental herbalists had."

Herbalist, author, and ABC Board of Trustees member Steven Foster added: "This accolade is well-deserved for a scientist and herb expert who bridged the gap between science and popular understanding of medicinal plants, while raising the importance of using botanicals as an integral aspect of a healthy lifestyle."

HerbalGram honored Duke's life with articles by Metzman and Foster in issue 117.[1,2] HG

References

1. Metzman HL. From the Desk of James A. Duke. *HerbalGram*. 2018;117;40-43. Available at: http://cms.herbalgram.org/herbalgram/issue117/hg117-feat-JAD-fromdeskof.html. Accessed March 8, 2019.
2. Foster S. James A. Duke — A Life of Botanical Bounty. *HerbalGram*. 2018;117:44-57. Available at: http://cms.herbalgram.org/herbalgram/issue117/hg117-feat-JAD-alifeofbot.html. Accessed March 8, 2019.

James A. Duke
Photo ©2019 Steven Foster

Adoptions by BOTALYS and Euromed Support ABC's Adopt-an-Herb Program

By Connor Yearsley

The American Botanical Council (ABC) recently announced the adoptions of two botanicals through its Adopt-an-Herb research and education program: Asian ginseng (*Panax ginseng*, Araliaceae) by BOTALYS, a Belgium-based company that specializes in botanical ingredients and unique cultivation methods; and milk thistle (*Silybum marianum*, Asteraceae) by Euromed, a Spain-based herbal products research and development company.

These adoptions support ABC's extensive HerbMedPro database, ensuring that this unique research and educational resource remains up to date for researchers, health professionals, industry members, students, consumers, and other members of the herbal and dietary supplements and natural medicine communities.

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 265 herbs, spices, medicinal plants, and fungi.

BOTALYS Adopts Asian Ginseng

According to Gaelle Stockman, marketing communications manager of BOTALYS, the company's adoption of Asian ginseng constitutes "a great opportunity to increase the scientific knowledge" about this important plant. "We did not choose ginseng as a key botanical by coincidence," Stockman wrote. "It helps people adapt to our challenging 21st-century lifestyle."

She added that Asian ginseng has many health benefits. "Ginseng not only mildly stimulates the central nervous system, but it also modulates the immune and endocrine systems. It also works as a stress reliever, helping us live dynamically and serenely," she wrote.

ABC Founder and Executive Director Mark Blumenthal said: "ABC is deeply grateful to the people at BOTALYS for their adoption of Asian ginseng on ABC's robust and unique HerbMedPro database. Asian ginseng has a long reputation as a major herb in traditional Chinese medicine and also in the West in the past 50 years as a premium tonic and adaptogenic herb. The adoption by BOTALYS will enable ABC to provide increased benefit to the international herb and medicinal plant community by ensuring that the HerbMedPro database is constantly maintained to reflect the most recent scientific and clinical publications on Asian ginseng."

About Asian Ginseng

Asian ginseng is a slow-growing deciduous perennial that is native to eastern Asia, primarily China and the Korean Peninsula, where it has been used for at least 2,000 years. It is now rare in its original range but is cultivated extensively in China, Japan, Korea, and Russia. *Panax ginseng* is one of about a dozen species in the genus *Panax*, all but two of which are found in Asia.

The genus name *Panax*, derived from the Greek *pan*, for "all," and *akos*, for "cure," reflects the 18th-century Western perception of the plant's traditional use, though it was not actually used as a "cure-all" or panacea, according to Harvard University botanist Shiu-Ying Hu, PhD (1908-2012). Instead, the use of ginseng root was limited and specific in traditional Chinese medicine (TCM). The species

Asian ginseng *Panax ginseng*
Photo ©2019 Steven Foster

name *ginseng* loosely means "essence of the earth in the form of a man" or "man essence."

The earliest known written record of Asian ginseng reportedly is from *The Divine Husbandman's Classic of Materia Medica* (*Shen Nong Ben Cao Jing*), which was written during the Han Dynasty (206 BCE–220 CE). Centuries later, Pierre Jartoux (1669-1720), a French Jesuit missionary, provided the first account of Asian ginseng by a Westerner after he encountered the plant on a mapping expedition in China in 1708 and 1709. He wrote: "Nobody can imagine that the Chinese and Tartars would set so high a value on this root, if it did not constantly produce a good effect. Those that are in health often make use of it, to render themselves more vigorous and strong." His account propelled European interest in the plant and led to the European discovery of American ginseng (*P. quinquefolius*).

Ginseng roots traditionally have been used as a tonic and adaptogen (a substance that increases the state of non-specific resistance to stress). It is suggested their greatest value may be their normalizing, restorative effects on the whole body, rather than effects on specific body organs/systems or for specific diseases. Most of Asian ginseng's effects are attributed to a mixture of saponins called ginsenosides.

About BOTALYS

Based in Ath, Belgium, BOTALYS was established in 2011 as Green2Chem, a consulting company that specialized in food and biotechnology and conducted preliminary research on vertical farming cultivation methods (in which plants are grown in stacked layers) to produce hydroponically grown plants. In 2018, with its new large-scale indoor vertical farm, the company changed its name to BOTALYS. It produces botanicals and ingredients for the food supplement, cosmetics, and pharmaceutical industries. It also values preserving the environment.

The company produces HRG80™, a pure and highly bioactive powder of *P. ginseng* root that contains 12% total ginsenosides, of which 80% are claimed to be bioactive. BOTALYS cultivates ginseng hydroponically in a sterile environment using a new vertical farming method. According to the company, this method enables it to grow bioactive plants that are difficult to cultivate with traditional agricultural methods. Ginseng plantlets are grown in a water solution, and, after harvesting, the roots are steam-cooked (with no extraction solvents) and then air-dried and ground into powder.

This cultivation method combines ancestral Asian knowledge with state-of-the-art technology. BOTALYS controls the process from beginning to end and claims it can ensure full traceability for each batch of ginseng produced. It also certifies that HRG80 is completely free of contaminants (e.g., pesticides, mycotoxins, and solvents) and not genetically modified or irradiated. According to the company, its production capacity will increase from 500 kg of Asian ginseng in 2018 to 2.2 metric tons by the end of 2019. For more information, visit www.botalys.com.

Euromed Adopts Milk Thistle

"We highly regard the work done by the American Botanical Council and believe the Adopt-an-Herb Program is an ideal channel to communicate to a growing and diverse global audience the vast amount of scientific and clinical research on milk thistle," wrote Andrea Zangara, scientific marketing manager of Euromed.

Blumenthal added: "ABC is deeply grateful to our good friends at Euromed for their adoption of milk thistle on ABC's highly useful HerbMedPro database. This adoption is quite fitting since Euromed is known internationally for its pioneering leadership in producing its clinically tested standardized milk thistle extract."

Stefan Gafner, PhD, chief science officer of ABC, commented: "Milk thistle extract is one of the main botanical ingredients to maintain liver health. The effects of silymarin have been researched extensively, and we are grateful to Euromed for helping to make this research available in an easily accessible manner through our HerbMedPro database. This will be a great resource for health care professionals and other people with interest in this important medicinal plant."

About Milk Thistle

Native to the Mediterranean region, milk thistle is an herbaceous annual or biennial that has been naturalized around the world. It belongs to the sunflower family (Asteraceae) and is one of two known species in its genus, along with *S. eburneum*. The plant can grow to five feet and is recognizable by its thistle-like, purple-pink flowers with spiny bracts (specialized or modified leaves) and large, prickly, lobed, rosette-forming leaves. In many places, milk thistle is a common wayside plant and may be invasive.

The leaves have distinctive white blotches along the veins and exude a white fluid when crushed, hence the name "milk." The genus name *Silybum* derives from the Greek *silybon*, meaning "tassel" or "tuft." The species name *marianum* owes to the plant's symbolic association with the Virgin Mary.

First-century Greek physician Dioscorides, to whom the genus name is attributed, prescribed the leaves to treat snakebites. Also in the first century, Roman naturalist Pliny the Elder noted that the plant's juice, mixed with honey, was used for "carrying off bile," which may be the first mention of the plant's liver-related uses. In her treatise *Physica* (ca. 1150), German herbalist and mystic Hildegard von Bingen wrote about the uses of milk thistle. Centuries later, the 17th-century English herbalist Nicholas Culpeper wrote that the plant is effectual "to open the obstructions of the liver and spleen, and thereby is good against the jaundice."

The leaves have been eaten in a way similar to artichokes (*Cynara* spp., Asteraceae), and the seeds, when roasted, have been brewed as a coffee (*Coffea* spp., Rubiaceae) substitute. In Europe, the plant has been cultivated as a vegetable and for ornament. The seeds also have been used traditionally as a galactagogue to increase production of breast milk. Seed extracts have validated benefits for hepatitis, cirrhosis, and

jaundice. They also have been used both preventively and curatively to protect the liver from toxins, including alcohol, aspirin, acetaminophen, heavy metals, and the death cap mushroom (*Amanita phalloides*, Amanitaceae).

Silymarin, a mixture of flavonolignans obtained from the seeds (technically fruits), can neutralize harmful free radicals that result from metabolism of toxic substances. It also has shown the ability to stimulate synthesis of liver-protective bile salts and alter cell membrane permeability, which prevents toxins from entering liver cells. Additionally, silymarin can increase production of glutathione, an antioxidant that is important for liver detoxification.

About Euromed

Based in Mollet del Vallès, Spain, Euromed was founded in 1971 by the German pharmaceutical group Madaus to ensure vertical integration and superior quality for its leading phytomedicine, a standardized milk thistle extract, and for other phytomedicines. Plantations were established, and the whole supply chain was integrated and verticalized. Since then, Euromed has grown into a leading global botanical manufacturer, and has maintained milk thistle extract as one of its flagship products, according to Zangara.

Now, a sustainable farming program in Central Europe yields milk thistle fruits used to produce Euromed's milk thistle extract, which is indicated for liver support. Traceability begins with seed selection and identification of growing areas. Plants and seeds are collected from several places and then planted. From the most desirable plants, the primary flowers are isolated to prevent cross-pollination of any kind, and then self-fertilized, which leads to uniform quality, according to Zangara.

Biannually, the fields are audited to confirm there is no contamination of the soil or groundwater. The harvesting machinery helps preserve the chemistry of the seeds that are used in the production of Euromed's extract. Steps are taken to prevent cross-contamination by pollutants, pesticides, and aflatoxins during the harvest and drying processes. After that, the raw material is dried, packaged, coded, and shipped to Euromed's Innovation Center in Barcelona, where it is tested by the company's quality control department with internationally recognized laboratory methods. According to Zangara, this testing results in consistent quality from batch to batch and year to year, to assure biological activity, as per Euromed's PhytoProof quality seal. Euromed's standardized milk thistle extract has been clinically studied over the past few decades in more than 5,500 patients worldwide.

About Adopt-an-Herb and HerbMedPro

BOTALYS and Euromed are among the 59 US and international companies that have supported ABC's educational efforts to collect, organize, and disseminate reliable, traditional, and science-based information, including clinical studies, on herbs, medicinal plants, and other botanical- and fungal-based ingredients through the Adopt-an-Herb program. This program encourages companies, organizations, and individuals to "adopt" one or more specific herbs for inclusion and ongoing maintenance in the HerbMedPro database. To date, 64 herbs have been adopted.

Milk thistle
Silybum marianum
Photo ©2019 Steven Foster

Each adopted herb is continuously researched for new scientific articles and botanical, chemical, pharmacological, toxicological, and clinical studies, ensuring that its HerbMedPro record stays current and robust. Access to the studies is conveniently organized by publication type, with each study condensed to a one-sentence summary with a link to the study's official abstract on PubMed (the US National Library of Medicine's free-access database) or other publicly accessible database.

HerbMedPro is available to ABC members at the Academic level and higher. Its "sister" site, HerbMed, is available to the general public at no cost, with access to 25-30 herb records from the larger HerbMedPro database. In keeping with ABC's position as an independent research and education organization, herb adopters do not influence the scientific information that is compiled for their respective adopted herbs. HG

Botanical Adulterants Prevention Program Publishes Grape Seed Extract Laboratory Guidance Document

50th BAPP publication discusses analytical methods to authenticate grape seed extracts and detect adulteration with PAC-rich extracts from other plants

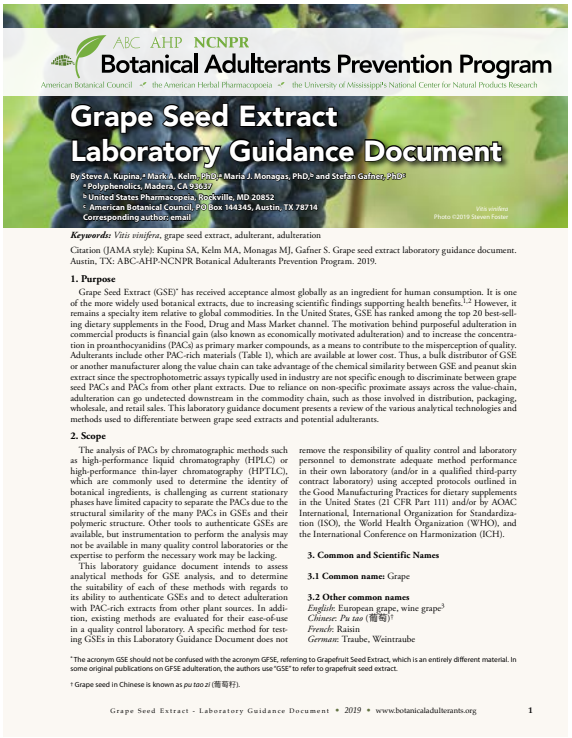
By ABC Staff

The ABC-AHP-NCNPR Botanical Adulterants Prevention Program (BAPP) has published a new Laboratory Guidance Document (LGD) on grape (*Vitis vinifera*, Vitaceae) seed extract (GSE). The new guidance document is the 50th peer-reviewed publication from the program.

In human clinical trials, GSEs have been shown to improve parameters related to cardiovascular health. Despite these promising results, GSE dietary supplements were not among the 40 top-selling botanical dietary supplement ingredients in US mainstream or natural retail outlets in 2017, according to *HerbalGram*'s herb market report.[1]

Grape seeds are a rich source of proanthocyanidins (PACs), to which many of the commercially available bulk ingredients are standardized. Despite the relatively low cost of grape seeds, which are byproducts of the juice and wine industries, PACs from other plant species often are used as economic adulterants. These include, for example, PACs derived from peanut (*Arachis hypogaea*, Fabaceae) skin or Masson's pine (*Pinus massoniana*, Pinaceae) bark.

The availability of these lower-cost PACs combined with the difficulties in unambiguously identifying the source material of PAC-rich extracts has made it easier for GSE adulteration to occur for the financial gain of some suppliers.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Botanical Adulterants Prevention Program
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Grape Seed Extract
Laboratory Guidance Document

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

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1. Purpose

Grape Seed Extract (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 health benefits.[1,2] However, it remains a specialty item relative to global commodities. In the United States, GSE has ranked among the top 20 best-selling dietary supplements in the Food, Drug and Mass Market channel. The motivation behind purposeful adulteration in commercial products is financial gain (also known as economically motivated adulteration) and to increase the concentration in proanthocyanidins (PACs) as primary marker compounds, as a means to contribute to the misperception of quality. Adulterants include other PAC-rich materials (Table 1), which are available at lower cost. 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 grape seed PACs and PACs from other plant extracts. Due to reliance on non-specific proximate assays across the value-chain, adulteration can go undetected downstream in the commodity chain, such as those involved in distribution, packaging, wholesale, and retail sales. This laboratory guidance document presents a review of the various analytical technologies and methods used to differentiate between grape seed extracts and potential adulterants.

2. Scope

The analysis of PACs by chromatographic methods such as high-performance liquid chromatography (HPLC) or high-performance thin-layer chromatography (HPTLC), which are commonly used to determine the identity of botanical ingredients, is challenging as current stationary phases have limited capacity to separate the PACs due to the structural similarity of the many PACs in GSEs and their polymeric structure. Other tools to authenticate GSEs are available, but instrumentation to perform the analysis may not be available in many quality control laboratories or the expertise to perform the necessary work may be lacking.

This laboratory guidance document intends to assess analytical methods for GSE analysis, and to determine the suitability of each of these methods with regards to its ability to authenticate GSEs and to detect adulteration with PAC-rich extracts from other plant sources. In addition, existing methods are evaluated for their ease-of-use in a quality control laboratory. A specific method for testing GSEs in this Laboratory Guidance Document does not remove the responsibility of quality control and laboratory personnel to demonstrate adequate method performance in their own laboratory (and/or in a qualified third-party contract laboratory) using accepted protocols outlined in the Good Manufacturing Practices for dietary supplements in the United States (21 CFR Part 111) and/or by AOAC International, International Organization for Standardization (ISO), the World Health Organization (WHO), and the International Conference on Harmonization (ICH).

3. Common and Scientific Names

3.1 Common name: Grape

3.2 Other common names
English: European grape, wine grape[3]
Chinese: *Pu tao* (葡萄)†
French: Raisin
German: Traube, Weintraube

*The acronym GSE should not be confused with the 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.

† Grape seed in Chinese is known as *pu tao zi* (葡萄籽).

Grape Seed Extract - Laboratory Guidance Document • 2019 • www.botanicaladulterants.org 1

Routine analytical methods using chromatography (e.g., high-performance liquid chromatography; HPLC) generally are not suitable for separating the larger PAC molecules in grape seed. High-resolution mass spectrometry (MS) is useful to determine the molecular weight distribution of PACs, but such equipment is not available in many industry quality control laboratories. In addition, genetic methods (DNA testing) may not be successful because of the extensive processing that leads to DNA fragmentation and the interference of PAC-rich extracts with enzymatic processes such as the polymerase chain reaction. For these and other reasons, it is often difficult to determine if grape seed is the source of an extract.

The new LGD was written by Steve Kupina, director of quality and technology at botanical ingredient manufacturer Polyphenolics; Mark Kelm, PhD, director of research and development at Polyphenolics; Maria Monagas, PhD, scientific liaison for dietary supplements and herbal medicines at the United States Pharmacopeia; and Stefan Gafner, PhD, chief science officer of the American Botanical Council (ABC) and technical director of BAPP.

The LGD evaluates the usefulness of published analytical methods to detect GSE adulteration, and summarizes the main advantages and disadvantages of each method regarding its suitability for use in a quality control laboratory. In addition, the document details the chemical composition of grape seed, potential confounding species, and known adulterants. The GSE LGD was peer-reviewed by 25 international experts from third-party contract analytical laboratories and the herbal industry.

Gafner explained: "There is a reason why BAPP's most recent laboratory guidance documents on cranberry and GSEs have dealt with PAC-rich ingredients. Materials that contain PACs are often difficult to authenticate, and many suppliers have been using inappropriate tests based on spectrophotometric methods as a means to document the authenticity. Many of the lessons learned from GSE adulteration may be applied to the verification of the identity of other ingredients that contain condensed tannins.

As such, this LGD may not only benefit those working with GSEs, but also those whose duty it is to verify the identity of condensed tannin-containing plant materials such as cinnamon bark, apple fruit, or pine bark extracts."

Mark Blumenthal, ABC founder and executive director and BAPP founder and director, said: "The program's 50th peer-reviewed publication is a new milestone for BAPP that speaks to the high output of the program, and it shows our continued commitment to the high quality and reliability of our extensively peer-reviewed publications. That is, the GSE LGD reflects both the quality and quantity of our research and educational efforts to provide responsible members of the herb and dietary supplement industries worldwide with authoritative resources that can help them properly authenticate botanical raw materials, extracts, and essential oils, as well as detect those that may be adulterated."

The GSE LGD is the eighth publication in the series of LGDs published by BAPP. As with all publications of the program, LGDs are freely accessible to all ABC members, registered users of the ABC website, and all members of the public on the program's website (registration required). HG

Grape
Vitis vinifera
Photo ©2019 Steven Foster

Reference

1. Smith T, Kawa K, Eckl V, Morton C, Stredney R. Herbal supplement sales in US increase 8.5% in 2017, topping $8 billion. *HerbalGram*. 2018;119:62-71. Available at: http://cms.herbalgram.org/herbalgram/issue119/hg119-herbmktrpt.html. Accessed April 1, 2019.

ADOPT-AN-HERB

HerbMedPro™ PROGRAM

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

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

HerbMedPro provides online access to abstracts of scientific and clinical publications on more than 250 commonly used medicinal herbs. A free version, HerbMed®, is available to the general public and includes access to 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 122, or by email at denise@herbalgram.org.

AMERICAN BOTANICAL COUNCIL

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layn USA	**Monk Fruit** *Siraitia grosvenorii*	Pharmatoka	**Cranberry** *Vaccinium macrocarpon*
travel medic travelmedic.net	**Kratom** *Mitragyna speciosa*	ECOSO DYNAMICS	**Devil's Claw** *Harpagophytum* spp.
DIANA Performance from nature FOOD	**Acerola** *Malpighia* spp.	Terry Naturally EuroPharma	**Turmeric** *Curcuma longa*
CONTAINS Zembrin	**Sceletium** *Sceletium tortuosum*	YOUR LOGO	**Plant name** *Scientific name*

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EMBRIA Health Sciences — **EpiCor® Fermentate** *Saccharomyces cerevisiae*

JIAHERB essentials of nature — **Rhodiola** *Rhodiola rosea*

neem BIOTECH A ZALUVIDA COMPANY. — **Garlic** *Allium sativum*

Artichoke *Cynara cardunculus* Scolymus Group

DMH ingredients — **Baobab** *Adansonia digitata*

Rooibos *Aspalathus linearis*

Friends of the Honey Bee — **Propolis**

YOUR LOGO — **Plant name** *Scientific name*

KP Authentic Botanical Extracts — **Senna** *Senna alexandrina*

Soladox BOTANICALS — **Black Chokeberry** *Aronia melanocarpa*

Elderberry *Sambucus nigra*

Stinging Nettle *Urtica dioica*

natural Factors — **Echinacea** *Echinacea* spp.

ARTEMIS INTERNATIONAL — **Purple Corn** *Zea mays*

FOUR ELEMENTS — **Lemon Balm** *Melissa officinalis*

afrigetics BOTANICALS — **Bulbine** *Bulbine natalensis*

BRASSICA — **Broccoli** *Brassica oleracea* Broccoli Group

DownUnder enterprises — **Tea Tree** *Melaleuca alternifolia*

Aromatics INCORPORATED — **Peppermint** *Mentha x piperita*

HERBALIFE — **Aloe Vera** *Aloe vera*

Natural Health International Conscious | Leading | Empowering — **Maca** *Lepidium meyenii*

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Kratom Research Grant: NIDA Gives University of Florida $3.5 Million to Study Southeast Asian Tree

By Connor Yearsley

In December 2018, the US National Institute on Drug Abuse (NIDA) awarded researchers at the University of Florida (UF) College of Pharmacy a $3.5-million, two-year grant to study the therapeutic and abuse potential of alkaloids from the leaves of the Southeast Asian tree kratom (*Mitragyna speciosa*, Rubiaceae).[1]

Kratom has received a significant amount of media coverage in the past several years and was featured in an extensive cover article in *HerbalGram* issue 112,[2] with a follow-up article in issue 119.[3] The species is a tropical evergreen tree that can grow to 25 meters (82 feet) tall and whose broad leaves produce compounds with opioid-like effects. It is native to Thailand, Malaysia, and other Southeast Asian countries, where leaf preparations have been used in traditional medicine for centuries. Now, an estimated three million to five million Americans use kratom regularly (as powders and teas) for many purposes, including to manage fibromyalgia and other chronic pain conditions (sometimes as an alternative to prescription opioids), recover from alcoholism, and cope with post-traumatic stress disorder (PTSD). There is interest in the potential for new pharmaceutical therapeutics derived from the leaves, either as single compounds or whole-plant preparations, to become safe and effective pain-relievers and opioid recovery aids.[2,3]*

Researchers at the University of Florida College of Pharmacy who were awarded the $3.5-million, two-year grant. From left to right: Jenny Wilkerson, Francisco Leon, Bonnie Avery, Christopher McCurdy, Lance McMahon, Jay McLaughlin, Joanna Peris, and Takato Hiranita

Unlike grants in which only the principal investigators control all the studies, the NIDA grant is a cooperative agreement between UF in Gainesville, Florida, and NIDA, which is one of the 27 institutes and centers that form the US National Institutes of Health (NIH). NIDA will therefore coordinate and plan studies with UF researchers led by Christopher McCurdy, PhD, professor of medicinal chemistry in the college; Lance McMahon, PhD, professor and chair of the college's department of pharmacodynamics; and Bonnie Avery, PhD, clinical professor of pharmaceutics in the college. According to McCurdy, NIDA has set a goal of evaluating 11 kratom alkaloids, although it is possible that more may be isolated and analyzed (oral communication, February 7, 2019).

The research will investigate the alkaloids' pharmacodynamics, or what the compounds do to the body (e.g., their mechanisms of action), and their pharmacokinetics, or what the body does to the compounds (how they are absorbed, distributed to tissues, metabolized, and ultimately eliminated from the body).

According to McMahon, $3.5 million is "huge" for a preclinical grant that does not involve human subjects, and it will allow the researchers to combine chemistry and pharmacology in a way that has not yet been possible for this plant.

UF researchers will collaborate with Eurofins, an international company based in Brussels, Belgium, with numerous analytical and research laboratories in the United States. Eurofins conducts comprehensive, but preliminary, screening of activity at numerous potential receptor targets and catalytic enzymes. The company will analyze if and how the kratom alkaloids interact with about 100 targets in the central nervous system. This work will be done in isolated tissue, which allows cells to be manipulated more selectively than is possible in whole, live animals. UF researchers will then perform much more in-depth analysis (dose and concentration response func-

* In November 2017, the FDA identified 36 deaths associated with the use of kratom-containing products.[4] In most, if not all, of these cases, it is difficult or impossible to establish a causal relationship between kratom and the deaths. Many of these cases also involved other substances, but to the FDA this means that potentially lethal interactions could occur when kratom is used with other substances. A 2019 study[5] (authored by UF researchers) showed that drug-drug interactions mediated by liver enzymes could be problematic for mitragynine, as they can be for most drugs. UF researchers have a pending grant proposal that would further investigate potential kratom-drug interactions.

tions), as well as whole-animal (rodent) pharmacology, therapeutic, and adverse effect profile testing.

"So, we will get a better picture of what these alkaloids are doing individually, and then we will look at those in terms of their ability to produce pharmacological effects similar to those of opioids," McCurdy said.

"We are essentially taking a symphony orchestra and taking out [some] of the individual instruments in that orchestra and looking at what they are responsible for in terms of the overall song," he continued, adding that the compounds will eventually be analyzed in different combinations. "But that is not the initial goal of the grant." The initial goals are to isolate the alkaloids in adequate quantities, purify them, and then perform the pharmacodynamic and pharmacokinetic studies.

Most of the past scientific literature has focused on mitragynine, one of kratom's major alkaloids, and some has focused on 7-hydroxymitragynine, a minor alkaloid, according to McCurdy. "But people have not paid much attention to any of the other alkaloids that are present in the plant," he said. "For instance, paynantheine and speciogynine are two other…major alkaloids within the plant matrix, and nobody has really investigated those. So, this grant is obviously going to help advance the understanding of [some of] the other compounds in the plant, along with furthering the understanding of mitragynine and 7-hydroxymitragynine."

McCurdy, who has been studying the plant for about 15 years, also mentioned that most of the focus on the activity of kratom alkaloids has been centered on opioid receptor interactions, but the grant will enable a more complete understanding of the compounds' other activities. "We really think that these alkaloids are special and different from the traditional opioids…because of their…polypharmacology, meaning that they interact with so many more targets than just opioid receptors," he said. "And some of those other target action sites may be why they [seem to have a] better safety profile, because some of those targets may be implicated in helping with blockade of respiratory depression, or easing withdrawal symptoms, or improving mood.

"Mitragynine interacts with serotonin receptors, which would be involved with mood improvement, and adrenergic receptors, which would be involved in reducing withdrawal symptoms that we might see from opioids," McCurdy continued. "It also interacts with opioid receptors, and so, by slightly activating the opioid receptors, it could somewhat attenuate the withdrawal that people go through when they start to move off of prescription opioids."

McCurdy thinks it is possible that kratom-derived therapeutics, as single medications, could be used for opioid withdrawal or helping people to stay off of traditional opioids (e.g., morphine, hydrocodone, and oxycodone), which normally requires multiple medications. "Maybe these alkaloids and their polypharmacologic mechanisms could be very interesting from a single-drug standpoint," he said. "A single drug that could be used to treat withdrawal symptoms is much more attractive.... You would not have as many drug interactions to worry about."

Kratom is controversial, partly because of a lack of data about its safety and abuse potential; disagreement about

Kratom *Mitragyna speciosa*
Photo ©2019 The Healing East

whether it is helping the opioid epidemic or contributing to it; the fact that such a large number of Americans are using it to self-medicate, without guidance from trained medical professionals; and a lack of quality control for many available kratom products.[2,3]

Amid the controversy, the NIDA grant was not necessarily unexpected. "I almost want to say I'm not surprised at all," McMahon said. "In these institutes — and I can tell you this from great experience working with the NIDA — these are first and foremost scientists. They want to objectively understand the chemistry, pharmacology, and human behavioral effects of drugs. They definitely appreciate the fact that their mission is to try to mitigate the public health consequences of drug abuse… but I think that there is a very strong sense among most NIDA program officials that the science is paramount."

NIDA will use the results of the research in discussions with US Food and Drug Administration (FDA) officials about whether kratom should be placed in a schedule of the Controlled Substances Act, which would likely limit access to the plant.

NIDA will use the results of the research in discussions with US Food and Drug Administration (FDA) and US Drug Enforcement Administration (DEA) officials about whether kratom should be placed in a schedule of the Controlled Substances Act, which would likely limit access to the plant. "We won't have pretty much anything to do with the regulatory aspects or side of it," McCurdy said. "I don't think the government is softening on [kratom] at all, but I do think that the government is being wise to listen to the public outcry to get some science-based information behind this. And it is putting its money into that and really trying to collect some of the scientific data to understand if there is abuse potential and if there is medical potential."

McMahon thinks the "floodgates are going to open. I think you are going to see a pretty major increase in funding of kratom-related research. That is a prediction. We don't have any hard evidence to support that prediction, but, if…the NIDA wants to generate science, it is going to be increasing funding in this area."

Although the grant might have significant implications for government opinion and actions regarding kratom, that won't be a distraction. "As scientists…you try to objectively design experiments that yield objective data that can speak for themselves," McMahon said. "So, in that sense, there's no pressure. We will do the best we can, and the experiments will speak for themselves…. Now, we are also human…. We want the best possible outcome for the public, whatever that is.

"And, if it is determined that this is a safe product, or a safe chemical class, and its access is increased, then great," McMahon added. "If…, from the data we generate, it is determined that [kratom] is more dangerous than we thought, then, obviously, we would hope that, in terms of protecting the public, the appropriate decisions would be made, in terms of access."

This grant could also help lay the groundwork for future kratom-related developments, possibly including human clinical trials. "The hope is that, if things can move in the proper direction, maybe within three to five years there might be some clinical trials," McCurdy said. "It all depends on support. It costs a lot of money to do all the studies that are required by the FDA to move to the investigational new drug, or IND, stage.

"We are investigating the options and opportunities to move toward human clinical trials," McCurdy added. "That would take separate funding mechanisms and separate researchers to come onboard with us, as well. But, those are things that we would like to see, ultimately. I believe the NIDA would like to see that."

The grant may also have implications for the eventual development of standardized kratom products, because it is

Researchers at the University of Florida College of Pharmacy who were awarded the $3.5-million, two-year grant. Bonnie Avery (left) and Christopher McCurdy (right). Photo ©2019 University of Florida

Kratom *Mitragyna speciosa*
Photo ©2019 Thor Porre

necessary to understand what the individual alkaloids are doing separately and together before an informed decision on standardization can be made. "That is something I have been interested in for a long, long time," McCurdy said. "Part of the problem with that is there is still no control over the plant material, where it is coming from, and how it is getting into the US marketplace. When we tried to develop kratom for human clinical trials before, we ran into this problem because we don't know the chain of custody of the biomass. We don't know if the biomass has been exposed to certain [contaminating] chemicals.

"Even if you do have a reliable source, there is little to nothing known about the monthly changes in the plant chemistry," McCurdy continued. "You have a wet season and a dry season, essentially, in the tropical monsoonal forest, and the alkaloid contents would probably be very different between the rainy season and the dry season. They could differ between times of day even…. There is a lot of understanding that has to be done on the plant chemistry side before we can even think about making a consistent, standardized [drug] product."

He said that it would be possible to do a batch harvest at a certain time, standardize the formulation, and do a clinical trial with that formulation, but the FDA will require consistent batch-to-batch comparativeness. "And that is going to be difficult to attain…until we can get a solid and reliable source of biomass. There are potential farmers to work with in Thailand, Malaysia, and other countries. Now that Thailand has decriminalized kratom, it may be a place that we could identify someone to partner with…. But it is a much more complex question than just creating a standardized formulation."

McMahon thinks it is important to emphasize that the UF researchers appreciate the value of kratom. McCurdy added: "We want to understand the plant. We believe in the plant. We believe that there are potential medical benefits to this plant. But somebody has to do the science to support that. That is what we are here to do."

David J. Kroll, PhD, a professor of pharmacology at the University of Colorado School of Pharmacy who has reported on kratom for Forbes.com, wrote: "The UF kratom research team wisely tailored its proposed work on kratom to this NIDA research funding mechanism. Some kratom researchers have been waiting for a specific NIH call for applications to investigate kratom's pharmacology and potential therapeutic uses" (email, March 26, 2019).

"But the UF team proactively responded to an existing NIDA request for applications (RFA) titled, 'Development of Medications to Prevent and Treat Opioid Use Disorders and Overdose,'" Kroll continued. "Therefore, they framed the cooperative research project to understand the botanical components in the context of preventing and treating opioid use disorders, a medical indication for which some consumers are already using kratom to self-medicate, much to the dismay of the FDA. But I think this approach may keep regulators at bay until the benefits and risks of kratom constituents can be well-understood, as outlined in the UF project." HG

References

1. Baltich D. UF College of Pharmacy receives $3.5 million NIDA grant to bolster kratom research. University of Florida Health website. December 10, 2018. Available at: https://ufhealth.org/news/2018/uf-college-pharmacy-receives-35-million-nida-grant-bolster-kratom-research. Accessed March 14, 2019.
2. Yearsley C. Kratom: Medicine or Menace? *HerbalGram*. 2016;112:46-59. Available at: http://cms.herbalgram.org/herbalgram/issue112/hg112-feat-kratom-med-men.html. Accessed March 14, 2019.
3. Yearsley C. Kratom Crackdown: FDA Intensifies Warnings with Limited, Inconclusive Data. *HerbalGram*. 2018;119:56-60. Available at: http://cms.herbalgram.org/herbalgram/issue119/hg119-legreg-kratom.html. Accessed March 14, 2019.
4. Statement from FDA Commissioner Scott Gottlieb, MD, on FDA advisory about deadly risks associated with kratom. FDA website. November 14, 2017. Available at: www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm584970.htm. Accessed March 14, 2019.
5. Kamble SH, Sharma A, King TI, León F, McCurdy CR, Avery BA. Metabolite profiling and identification of enzymes responsible for the metabolism of mitragynine, the major alkaloid of *Mitragyna speciosa* (kratom). *Xenobiotica*. 2019. doi: 10.1080/00498254.2018.1552819.

Meta-analysis Shows Saw Palmetto Extract as Effective as Standard Drugs for Lower Urinary Tract Symptoms Associated with Benign Prostatic Hyperplasia

Reviewed: Vela-Navarrete R, Alcaraz A, Rodríguez-Antolín A, et al. Efficacy and safety of a hexanic extract of *Serenoa repens* (Permixon®) for the treatment of lower urinary tract symptoms associated with benign prostatic hyperplasia (LUTS/BPH): systematic review and meta-analysis of randomised controlled trials and observational studies. *BJU Int.* 2018;122(6):1049-1065. doi: 10.1111/bju.14362.

By Anne Louise Merrill

Study Details: At a Glance	
Study Design	Systematic review and meta-analysis
Included Studies	27 studies (15 RCTs and 12 observational)
Study Length	1 to 60 months
Intervention	320 mg/day of saw palmetto extract Permixon (Pierre Fabre Médicament; Castres, France)
Control	Various
Disclosures	Pierre Fabre Ibérica S.A. provided funding for the review and meta-analysis, and three of the 17 authors have received research funding or monetary reimbursements from Pierre Fabre. Four of the 27 studies were funded by companies affiliated with Pierre Fabre, and 23 provided no information about funding.

As men age, the risk of developing lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia (BPH) increases. LUTS associated with BPH (LUTS/BPH) can significantly decrease quality of life, increase health care costs, and lead to other morbidities. Treatment options include α-1 blockers, 5-α-reductase inhibitors (5ARIs), muscarinic receptor antagonists, phosphodiesterase 5 inhibitors, and phytomedicines.

Saw palmetto (*Serenoa repens*, Arecaceae) berry has a long history of use for LUTS/BPH, and saw palmetto extracts have been evaluated in numerous randomized controlled trials (RCTs). However, systematic reviews and meta-analyses of these RCTs have produced conflicting results. One explanation is that some meta-analyses have included different types of saw palmetto extracts. As noted by the authors of this meta-analysis: "The current European LUTS/BPH EAU (European Association of Urology) guidelines propose that different brands of phytotherapy should be assessed individually because differences in potency mean that results cannot be extrapolated from one brand to another."

To draw better conclusions about the efficacy and tolerability of one brand of saw palmetto extract on LUTS/BPH, these authors conducted an exhaustive systematic review and meta-analysis of studies that evaluated a daily dose of 320 mg of saw palmetto as a hexanic extract (Permixon®; Pierre Fabre Médicament; Castres, France).

Study Design

The Cochrane Library, ISI Web of Knowledge, MEDLINE, and Scopus databases were searched using the terms "*Serenoa repens*," "saw palmetto," "*Sabal serrulata*," "Permixon," "benign prostatic hyperplasia," "BPH," "prostatic adenoma," "prostatic hypertrophy," "lower urinary tract symptom," and "LUTS," in combination with keywords such as "efficacy," "tolerability," and "outcome." Bibliographic reference lists from related articles were hand-searched. All RCTs, non-randomized controlled trials, case-control studies, and prospective observational studies (OSs) up to April 2017 were included if they reported data on the selected outcomes and evaluated 320 mg/day of Permixon.

Two researchers working independently evaluated the results for inclusion in the review, and a third researcher resolved disagreements. The Meta-analysis of Observational Studies in Epidemiology (MOOSE) protocol was used to perform the meta-analysis, and the findings were reported using Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) recommendations. Included studies were evaluated using the Downs and Black Quality Index (DBQI) checklist, which ranks study quality on a scale from 0 to 27, with higher numbers reflecting better quality.

The researchers extracted these data from the studies: International Prostate Symptom Scores (IPSSs), peak urinary flow (Q_{max}), frequency of nocturia, quality of life (QoL; question 8 of the IPSS) ratings, prostate volume, and sexual function questionnaire responses. Adverse event (AE) and adverse drug reaction (ADR) reporting were considered for the safety analysis. Mean decreases in IPSS of at least 3.1 were considered clinically relevant. For the statistical analysis, numerical data (IPSS, nocturia, QoL, and Q_{max}) were expressed as mean pre-post treatment differences (MDs). ADRs were expressed as proportions. Sensitivity analyses excluded studies that did not provide standard deviations (SDs) or standard errors (SEs). Heterogeneity among the studies was assessed using the I^2 statistic.

Funnel plots were used to assess publication bias and forest plots were used to display results. Subgroup analyses of data from studies lasting one year or longer were conducted to evaluate long-term effects.

Included Studies

Included in the meta-analysis were 27 studies (15 RCTs and 12 OSs), with a total of 5,800 patients allocated as follows: Permixon (n = 3,926); α-1 blockers (n = 775; tamsulosin [n = 377], unspecified [n = 398]); 5ARIs (n = 578; finasteride [n = 484], unspecified [n = 94]); placebo (n = 301); control group (no treatment; n = 190); and gestonorone caproate (n = 30).

ADR data were extracted only from one RCT and one OS because the efficacy data lacked precision. The studies were published between 1983 and 2016. The sample sizes ranged from 10 to 1,713 participants. Treatment durations ranged from one month to 60 months, with the most frequent study duration of three months. DBQI scores ranged from three to 25; most of the studies with low DBQI scores were conducted in the 1980s and early 1990s before the publication of the first Consolidated Standards of Reporting Trials (CONSORT) guidelines in 1996.

Permixon vs. Placebo

The seven RCTs that evaluated Permixon compared to placebo did not report IPSS data and were of moderate quality, with DBQI scores ranging from six to 15. Meta-analysis showed that Permixon significantly improved nocturia with 0.64 fewer voids per night ($P < 001$). Meta-analysis of the four studies that reported Q_{max} data indicated Permixon significantly increased peak urine flow by 2.75 mL/s ($P = 0.014$). There was no significant heterogeneity or publication bias found for the nocturia and Q_{max} data.

Permixon vs. α-1 Blockers

Two RCTs and one OS compared Permixon to α-1 blockers and reported IPSS data; all three studies were of high quality, with DBQI scores between 19 and 25. Although the improvement in mean IPSS was greater with Permixon, the difference between groups was not statistically significant ($P = 0.35$). Two RCTs compared Permixon to the α-1 blocker tamsulosin and reported nocturia and Q_{max} data; there were no significant differences between groups for either measure at the end of the studies. Similarly, two studies found no significant difference between Permixon and α-1 blockers in the effect on prostate-specific antigen (PSA) levels ($P = 0.60$).

Saw palmetto *Serenoa repens*
Photo ©2019 Steven Foster

Permixon vs. 5ARIs

Two RCTs compared the effects of Permixon and 5ARIs on IPSS and PSA values. Mean IPSS improvement did not differ significantly between the groups (P = 0.30). However, 5ARIs significantly reduced PSA values (P < 0.001), while there was no change with Permixon. No heterogeneity was observed for either outcome.

Overall Changes from Baseline

Analysis of the change from baseline data in this meta-analysis showed that Permixon significantly improved IPSS, Q_{max}, nocturia, QoL, and prostate volume, but not PSA levels, while having no effect on sexual function (P = 0.64). Compared to baseline, and accounting for any potential publication bias or outliers, there was a mean improvement of –5.38 points in IPSS (P < 0.001); mean increase of 2.26 mL/s in Q_{max} (P < 0.001); mean reduction of 1.56 voids per night (P < 0.001); mean QoL score increase of 1.07 points (P < 0.001); and mean prostate volume reduction of –2.36 mL (P < 0.001). The effect on PSA was not clinically significant.

When comparing the results of the RCTs and OSs, there was no statistically significant difference between the two types of studies when analyzing for IPSS, Q_{max}, or QoL. However, there was a significant difference between study types for nocturia and prostate volume; there was only one OS that reported nocturia, and, for prostate volume, the five OSs reported significantly different findings.

Long-term Studies

Meta-analysis of the data from the three studies with a treatment duration of one year or longer showed there was a mean improvement in IPSS of –6.06 points (P < 0.001) from baseline in the Permixon group, or –4.85 points (P < 0.01) after exclusion of outliers. Q_{max} increased 2.29 mL/s (P < 0.001), or 1.81 mL/s (P < 0.01) after excluding outliers. QoL improved 1.31 points (P < 0.001) with no heterogeneity among the studies; and prostate volume decreased by 5.37 mL (P = 0.034). Two of these studies measured PSA levels; there was no significant change in PSA levels with Permixon (P = 0.18) and no heterogeneity.

Safety

The four types of ADRs with a mean incidence of more than 1% were gastrointestinal disorders (3.8%), nausea and vomiting (2.6%), hypertension (1.2%), and tinnitus (1.2%). Long-term use of Permixon was safe and well-tolerated. There was a lower incidence of ejaculation disorders with Permixon compared to the α-1 blocker tamsulosin in one long-term study (P = 0.001).

Conclusion

This systematic review and meta-analysis found that a dose of 320 mg of Permixon daily was superior to placebo and comparable to α-1 blockers and short-term treatment with 5ARIs on most relevant outcomes, including clinically significant improvements in IPSS, and equivalent efficacy to α-1 blockers on Q_{max}. When compared to baseline, Permixon was associated with a clinically significant improvement in QoL.

The authors commented that in "an increasingly polymedicated population, such as elderly men affected by LUTS/BPH, the availability of an effective treatment with a very low rate of ADRs and very limited drug interactions is of relevance." They also emphasized that potency has been shown to vary considerably between brands of saw palmetto extracts, and these results cannot be generalized to other preparations.

Acknowledged limitations of this review include the low quality and relatively short duration of some studies. HG

Meta-analysis Supports Antidepressant Activity of Saffron

Reviewed: Yang X, Chen X, Fu Y, et al. Comparative efficacy and safety of *Crocus sativus* L. for treating mild to moderate major depressive disorder in adults: a meta-analysis of randomized controlled trials. *Neuropsychiatr Dis Treat*. May 21, 2018;14:1297-1305. doi: 10.2147/NDT.S157550.

By Heather S. Oliff, PhD

Study Details: At a Glance	
Study Design	Meta-analysis
Included Studies	Seven double-blind, randomized, controlled clinical trials
Study Length	Various
Intervention	Various saffron petal and stigma preparations
Control	Antidepressant or placebo
Disclosures	None

Major depressive disorder (MDD) is a common, sometimes serious mood disorder that may require long-term treatment. Pharmaceutical antidepressants can reduce depressive symptoms, but they are not effective in some patients and often have adverse side effects that are difficult to tolerate. Additional safe and effective therapies are needed. Saffron (*Crocus sativus*, Iridaceae) dried flower stigma is one of the world's most expensive spices. Saffron has antioxidant, anti-inflammatory, and antidepressant activities. Clinical trials performed with both saffron stigma and flower petal extracts suggest that saffron may be a safe and effective alternative to synthetic antidepressants. The purpose of this systematic review and meta-analysis was to investigate the efficacy and safety of saffron extract preparations in adults with MDD.

Researchers at The First Affiliated Hospital of Chongqing Medical University in Chongqing, China, searched PubMed, Embase, the Cochrane Library, Web of Science, and ClinicalTrials.gov databases from inception to September 20, 2017, using the search terms "saffron," "crocus," "crocus sativus," "depression," "depressive," "mood disorder," and "affective disorder." Literature citations from relevant publications were hand-searched. Included trials were double-blind, randomized trials that used a synthetic antidepressant or placebo control, enrolled adults with a diagnosis of MDD receiving monotherapy, and were published in any language. Trials that enrolled patients with depression that was secondary to a physical disease or enrolled a small number of patients (N < 10) were excluded. Methodological quality was assessed using the Cochrane Collaboration's risk of bias tool. The primary outcome was the mean overall change in depression symptoms from baseline to the end of the intervention. Secondary outcomes were remission rates (defined as the proportion of patients with Hamilton Depression Rating Scale [HAM-D] scores less than seven at the end of the studies), response rates (the proportion of patients with at least a 50% reduction in HAM-D scores from baseline), and dropout rates.

A total of 128 unique articles were identified, and seven trials met the criteria to be included in the meta-analysis. Patients (N = 316) had depression of mild-to-moderate severity at baseline, according to HAM-D and Beck Depression Inventory (BDI) scores. Saffron dosages were 15-30 mg/day (n = 1 trial), 30 mg/day (n = 5), and 100 mg/day (n = 1). Control agents used in the trials included placebo (n = 3), fluoxetine (n = 2), imipramine (n = 1), and citalopram (n = 1). Treatment duration ranged from six to 12 weeks. All trials were conducted in Iran, and results were published from 2004 to 2017.

In the combined analysis (as well as in each of the individual trials), depression symptoms improved significantly more in the saffron group compared to the placebo group ($P = 0.001$). Saffron was about as effective as synthetic antidepressants in improving depression symptoms, with no significant difference found between the groups.

Remission and response rates were reported in only two trials that used synthetic antidepressants as controls. No significant differences in remission and response rates were found between the saffron and synthetic antidepressant groups at the end of these two trials. No difference in dropout rates was found between the saffron and placebo or synthetic antidepressant groups.

The quality of the trials was rated as moderate. Heterogeneity among the placebo-controlled studies was high, and most of the variation was due to treatment duration and dosage. Heterogeneity among antidepressant-controlled studies was rated as mild. Saffron "did not increase" the risk of adverse events compared to placebo and synthetic antidepressants (no data were reported).

The authors conclude that "saffron was effective for treating MDD and had comparable efficacy to synthetic antidepressants" and therefore "could be considered as an alternative to CBT [cognitive behavioral therapy] or synthetic antidepressants." The authors noted that commercial saffron is expensive, which may limit medicinal use. One of the trials included in this meta-analysis tested saffron petals instead of saffron stigma and found antidepressant effects. Petals are much less expensive than stigmas, which could facilitate more widespread use of the species for medicinal purposes.

There are several limitations to this meta-analysis. The number of eligible trials and the overall sample size were small. All studies were conducted in one country, mostly by the same group of investigators. It may be difficult to extend the results of this study to other populations. The authors stated that more well-designed studies with longer treatment durations and inclusion of different ethnic groups are needed. Further studies of the petals of saffron would also be useful. HG

Fig and Flixweed Improve Symptoms of Irritable Bowel Syndrome with Constipation

Reviewed: Pourmasoumi M, Ghiasvand R, Darvishi L, Hadi A, Bahreini N, Keshavarzpour Z. Comparison and assessment of flixweed and fig effects on irritable bowel syndrome with predominant constipation: A single-blind randomized clinical trial [Published online September 11, 2018]. *Explore*. doi: 10.1016/j.explore.2018.09.003.

By Shari Henson

Individuals with irritable bowel syndrome (IBS) have bloating and abdominal pain or discomfort that can lead to work absences, increased health care expenses, and decreased quality of life. Constipation-predominant IBS (IBS-C) is defined as constipation accompanied by abdominal pain, which typically can be relieved by a bowel movement. Flixweed (*Descurainia sophia*, Brassicaceae) seed and fig (*Ficus carica*, Moraceae) fruit are rich in soluble and insoluble fiber. They have a long history of use in Iranian traditional medicine for constipation and other gastrointestinal problems. The authors conducted a single-blind, randomized clinical trial to examine the effects of flixweed and fig on symptoms of IBS-C and on the inflammation marker C-reactive protein (CRP).

Fig *Ficus carica*
Photo ©2019 Steven Foster

Patients aged 18 to 70 years who were referred to the gastrointestinal research center of Isfahan University of Medical Sciences or to private medical practices in Isfahan, Iran, and were diagnosed with IBS-C were eligible for the study. The 150 patients chosen for the study were randomly and equally assigned to the flixweed, fig, or control group for the four-month intervention study. According to group assignment, patients took 30 g of dried flixweed or 45 g of dried fig with a glass of water before breakfast and before lunch daily, or continued with their normal diet in the control group. Anthropometric indices were measured at baseline and at the end of the study. Dietary intake and physical activity were evaluated, and all patients were monitored for any adverse effects during the study.

Study Details: At a Glance	
Study Design	Single-blind, randomized controlled trial
Participants	142 men and women diagnosed with IBS-C
Study Length	Four months
Intervention	30 g of dried flixweed or 45 g of dried fig twice daily
Control	Normal diet
Disclosures	None declared

Flixweed *Descurainia sophia*
Photo ©2019 Radio Tonreg

The authors used the IBS Severity Scoring System (IBS-SSS) at baseline and at the end of the study to assess frequency and severity of abdominal pain, severity of abdominal distention, dissatisfaction with bowel movements, and interference of IBS with life in general. Total scores were rated as mild, moderate, or severe, with higher scores indicating greater severity. The Bristol Stool Chart was used to determine the frequency of bowel movements and hard stools. The effects of IBS on quality of life were measured by examining the patients' answers to 34 questions about dysphoria, interference with activity, body image, health concerns, food avoidance, social reactions, sexual concerns, and relationships. Higher scores indicated better quality of life.

Of the 50 patients in the flixweed group, one patient lost interest in completing the study, and one patient withdrew because of influenza. In the fig group, one patient did not consume the fig product as instructed, and three patients were not interested in completing the study. In the control group, one patient moved, and one patient did not want to complete the study. The number of patients who completed the study totaled 142, with 48 each in the flixweed and control groups and 46 in the fig group. No adverse effects were reported during the study.

At baseline, the mean age of the patients was approximately 57.6 years, 75% of the patients were women, and 65% had moderately severe IBS-C. The three groups were similar in terms of dietary intake, physical activity, and anthropometric measures at baseline and at the end of the study.

The authors report that total IBS-SSS scores significantly improved in the flixweed and fig groups compared with baseline and with the control group ($P < 0.05$ for each). All individual items, except for abdominal pain severity, significantly improved in both the fig and flixweed groups compared with baseline and with the control group at the end of the study ($P < 0.05$ for each). Although abdominal pain severity improved in both the flixweed and fig groups compared with baseline, the improvement was not statistically significant. Improvements in defecation and hard stool frequency in both intervention groups were significant compared with the control group ($P < 0.05$ for each). Overall quality of life significantly improved in both intervention groups after four months compared with baseline and with the control group ($P < 0.05$ for each). Comparing the improvements observed in the fig and flixweed groups, no significant differences were found in overall IBS-SSS score, IBS symptoms, or quality of life. CRP levels did not significantly change in any of the three groups.

According to the authors, limitations of the study include the lack of a placebo group, the use of only CRP as a marker of inflammation, and the focus only on the fiber component of fig and flixweed and how it affected IBS-C symptoms.

The authors concluded that "consumption of flixweed and fig among IBS-C patients may have positive effects on IBS-C symptoms, and that these natural products could be considered as a safe therapy for this syndrome." HG

Comparative Clinical Study on Quince for Gastroesophageal Reflux Disease during Pregnancy

Reviewed: Shakeri A, Hashempur MH, Mojibian M, Aliasl F, Bioos S, Nejatbakhsh F. A comparative study of ranitidine and quince (*Cydonia oblonga* Mill) sauce on gastroesophageal reflux disease (GERD) in pregnancy: a randomised, open-label, active-controlled clinical trial [Published online March 19, 2018]. *J Obstet Gynaecol*. doi: 10.1080/01443615.2018.1431210.

By Mariann Garner-Wizard

Study Details: At a Glance	
Study Design	Two-phase, randomized, open-label, controlled trial
Participants	Phase one: 229 pregnant women Phase two: 137 pregnant women
Study Length	Phase one: 2 weeks Phase two: 4 weeks
Intervention	10 mg of concentrated quince fruit extract after each meal daily
Control	150 mg of ranitidine twice daily
Disclosures	None declared

Gastroesophageal reflux disease (GERD) can occur in men and women at any age but is most common in pregnant women. GERD usually presents as heartburn and may be treated with diet and lifestyle changes. In addition, histamine-2 receptor antagonists (H2RAs) like ranitidine (Zantac®; Chattem Inc.; Chattanooga, Tennessee) may also be prescribed. Ranitidine is the only H2RA whose efficacy in pregnancy-related GERD has been established, but concerns remain about its safety in this population. Traditional Iranian medicine (TIM) offers other approaches to pregnancy-related GERD as symptomatically described in TIM literature. Ibn Sina (Avicenna; ca. 980-1037) and other early TIM practitioners used quince (*Cydonia oblonga*, Rosaceae), or *safarjal*, in formulas for GERD. In TIM, quince is used as a gastric tonic, appetite enhancer, and remedy for nausea, vomiting, and epigastric pain. Quince also is said to have a protective effect on the fetus and is used specifically for pregnant women in other traditional medicine systems.

The authors conducted a two-phase, randomized, active-controlled, open-label, parallel group clinical trial that compared ranitidine to quince sauce (QS; a concentrated quince fruit extract) in pregnant

Quince *Cydonia oblonga*
Photo ©2019 Dietrich Krieger

women with GERD. This is the first study of the efficacy of QS in pregnant women with GERD, according to the authors.

The first phase included 229 pregnant women aged 18-35 years with gestational age of 12-34 weeks and who had at least one GERD symptom more than once weekly for four weeks, and attended the Mojibian Outpatient Clinic (Yazd, Iran) between April 2015 and January 2016. Participants received 15-minute lessons on lifestyle and diet changes from a trained general practitioner and were assessed at baseline and two weeks. No additional details about the lifestyle or diet modifications were provided. A General Symptom Score (GSS) and Major Symptom Score (MSS) were computed for each woman based on symptom severity, intensity, and frequency. Patient responses to treatment were analyzed by calculating a Symptom Score Reduction Ratio (SSRR). "Complete" responders were defined as having an SSRR of at least 75% by the end of the study, and "fair" responders were defined as having an SSRR between 25% and 49% by the end of the study. After two weeks, 79 women (34.5%) had responded completely or fairly to the lifestyle modifications.

The second phase included patients who did not respond to lifestyle modifications after two weeks (SSRR less than 25%), were experiencing heartburn, and had not received any GERD medication for a week before beginning the second-phase study protocol. Thirteen initial subjects were lost to follow-up before randomization, leaving 137 to be randomized as follows: 68 received 150 mg of ranitidine twice daily and 69 received 10 mg of QS* after each meal daily for four weeks.

QS was prepared from fruit purchased at a Tehran market by the Faculty of Pharmacy at Tehran University of Medical Sciences in Iran. Preparation involved heating quince juice pressed from fresh pulp. QS was standardized for its total polyphenols (3.16 mg/1 g QS) as gallic acid equivalents (GAEs). Quality control measures included screening for heavy metals and bacterial contamination. QS was refrigerated during the study.

Baseline demographic and clinical characteristics of the two study groups were similar; however, baseline GSSs were somewhat worse in the ranitidine group. During the study, eight participants in the ranitidine group were lost to follow-up and four discontinued participation (three because of adverse events [AEs]). Data from 56 were analyzed. In the QS group, three participants were lost to follow-up and two discontinued treatment (one because of worsening symptoms). Data from 64 were analyzed.

GSS values in both study groups improved during the study. At the two-week data collection point, there was a significant difference in GSS favoring QS (P = 0.036). At four weeks, the difference between groups was not significant (P = 0.074). When major symptoms were analyzed individually, heartburn in those who received QS was significantly lower at two weeks (P = 0.03) and four weeks (P = 0.04) compared to those who received ranitidine. Other major symptoms showed no significant between-group differences at any time point. After two weeks of treatment, a significantly greater percentage of subjects in the QS group responded completely compared to the ranitidine group (P = 0.03). At week two, 28.1% of patients in the QS group had attained complete response compared to 12.5% of those taking ranitidine. However, the difference between groups at week four was not significant (P = 0.37). There were slightly fewer non-responders at the end of the study in the ranitidine group than the QS group. QS was well-tolerated, and no AEs were reported.

QS previously has been compared to omeprazole (Prilosec OTC®; Procter & Gamble; Cincinnati, Ohio), a proton pump inhibitor used for GERD, in pediatric patients with similar results as this study. In this study, QS performed as well as ranitidine and worked more rapidly. QS is inexpensive and can be used easily at home. Studies with a longer follow-up period and objective outcome measures are recommended. HG

* A reviewer of this article noted that the QS dosage used in this study appears to be unusually small. The authors of the journal article did not respond to requests to confirm the dosage.

Reflections on a Book that Changed My Life

By Dennis J. McKenna, PhD

Editor's note: *A previous version of this article was published in the second volume of* Ethnopharmacologic Search for Psychoactive Drugs *(ESPD; Synergetic Press, 2018), a collection of papers based on presentations made at the ESPD symposium in Buckinghamshire, England, in June 2017. This symposium was the 50th anniversary commemoration of the first ESPD symposium held in San Francisco in 1967. Present at the initial conference were some of the leading pioneering researchers who initiated much of the modern chemical, ethnopharmacological, and ethnobotanical investigations of various plants and non-botanical materials with known psychoactive uses in native cultures. The two-volume set was awarded the 2018 ABC James A. Duke Excellence in Botanical Literature Award, as described on page 18 of this issue. An earlier version of this article was published in the September 2018 issue of HerbalEGram.*

The First Ethnopharmacologic Search for Psychoactive Drugs Symposium (San Francisco, 1967)

In 1967, a landmark symposium in the history of psychedelic substances was held in San Francisco, California, under the sponsorship of the US National Institute of Mental Health (NIMH). The title of the invitational symposium was "Ethnopharmacologic Search for Psychoactive Drugs" (ESPD), and a volume of the proceedings was published under the same name later that year and sold through the US Government Printing Office (GPO; now called the US Government Publish-

ing Office).[1] The volume, now out of print, has become a classic reference in the ethnobotanical literature.

This was probably the first time that an interdisciplinary group of specialists, ranging from ethnobotanists to neuroscientists, gathered in one place to share their findings on a topic of widespread interest at the time: the use of psychoactive plants in the context of indigenous and non-Western societies. In 1967, the word "psychedelic"* had not yet become stigmatized. There were still expectations in the psychiatric and neuroscientific communities that these little-known and curious agents, used for centuries in the ethnomedicine and rituals of traditional cultures, might yield new healing substances that could be used in our own troubled society and serve as important tools for exploring the human mind.

The roster of attendees at the 1967 symposium reads like a Who's Who of ethnopharmacology: John Daley, PhD; Daniel Efron, MD, PhD; Daniel X. Freedman, MD; Bo Holmstedt, MD, PhD; Nathan Kline, MD; Richard Schultes, PhD; Alexander Shulgin, PhD; Stephen Szára, MD; R. Gordon Wasson; Andrew Weil, PhD; and many others. Only a few of the researchers who attended the original symposium are still alive, and, of those, even fewer remain active in the field. Their work contributed to making the first ESPD symposium one of the most unusual and interdisciplinary scientific convocations ever organized.

Originally, follow-up symposia were planned to be held about every 10 years. That time frame, it was thought, was sufficient to accommodate the stately progress of scientific research, yet frequent enough to enable researchers in various specialties to come together in a collegial environment to share research results in a timely fashion.

After the summer of 1967, the political winds shifted, and psychedelic substances soon became demonized, feared, and banned. The federal government did not want to sponsor any similar symposia. In fact, its sponsorship of the original symposium, as valuable as it was for the dissemination of research findings, became an embarrassment, and, as a result, no follow-up symposia were held. The symposium proceedings were available for a time from the GPO but eventually went out of print, closing that particular chapter in the history of psycho-ethnopharmacology.

In the 50 years that have passed since the first symposium, numerous federal administrations have come and gone. Our recent past and current administrations, along with most of their affiliated institutions, remain as far from developing a viable, realistic drug policy today as they were then. A new generation of researchers, many inspired by the giants at the first conference, has continued to investigate the outer limits of psycho-ethnopharmacology. Some outstanding discoveries have been made, and the work continues. At the same time, there has been a change in public and medical perception of psychoactive substances. There is now a renaissance in psychedelic research around the world, and the therapeutic potential of some of these agents is being reinvestigated. While psychedelic substances have become less stigmatized than in the past, they remain controversial. Much work in this field remains unfinished, and the most significant discoveries may still lie in the future.

Their work contributed to making the first ESPD symposium one of the most unusual and interdisciplinary scientific convocations ever organized.

Ayahuasca *Banisteriopsis caapi*
Photo ©2019 Steven Foster

* According to the US National Institute on Drug Abuse, a psychedelic is a substance that "distorts perception, thought, and feeling." A psychoactive substance is defined more generally as a substance that has a "specific effect on the brain."[2]

ESPD50 cover art ©2019 Synergetic Press

How ESPD Changed My Life — Summer 1968

When the first ESPD symposium was held in 1967, I was 16 years old, a bored teenager living in a small town in western Colorado. More than anything, I longed to escape my dreary life and travel to San Francisco, the Mecca for the counterculture and the epicenter of the psychedelic revolution. My late brother, Terence, a lifelong friend and mentor, had escaped our soft prison a few years earlier and was a student at Berkeley at the time. We were both just beginning to discover the wondrous world of psychedelics, and we agreed that they were the most fascinating things that we had encountered in our young lives. The fascination we felt continued to guide our interests and even careers for the rest of our lives.

In 1967, while we were fascinated by psychedelics and wanted to immerse ourselves in the counterculture, neither of us had much of a clue about them. Terence was living in Berkeley, and I managed to get away from my small town and visit him during the height of the Summer of Love. Neither of us was aware of the obscure private symposium that had taken place in San Francisco just a few months earlier.

Like most of our like-minded contemporaries, we had no context in which to understand the emergence of these compounds into mass consciousness in the 1960s. Timothy Leary, PhD, had transformed from a mild-mannered Harvard researcher to the Messiah of LSD, and although much of his message resonated with us, we were slow to plunge full tilt into the hippie movement. This was partly because we identified as intellectuals and, to some degree, were put off by the distinctly anti-intellectual trappings of hippie culture. We thought there had to be more to psychedelics than their superficial depictions in the mass media, but we had no idea where to find a more in-depth and balanced perspective.

Sometime in 1968, while we were busy trying to sort all this out, two books surfaced in our world. These works provided deep background context in which psychedelics made sense to us. One of these books was Carlos Castaneda's *The Teachings of Don Juan: A Yaqui Way of Knowledge* (University of California Press, 1968), which described the author's apprenticeship with a Yaqui shaman.[3] Although it was later discovered that much of Castaneda's work is highly fictionalized, if not completely fabricated, we did not know that at the time.

For me, at least, that book was influential because it provided a cultural context for psychedelics based on traditions older and richer than anything I had encountered in mass media sources. It made clear that there was nothing new about psychedelics. In fact, these sacred plants and fungi had been used in indigenous shamanic practices for hundreds, if not thousands, of years. While Castaneda's book was not scientific, or even accurate, it gave me insights into shamanism, a set of practical methodologies and beliefs involving the use of these materials for healing and the exploration of consciousness. Terence gave me a copy of the first edition of *The Teachings of Don Juan* for my 18th birthday in 1968; it was a very special gift. I still have it, and I still cherish it.

The proceedings of the first ESPD symposium were published some months after the symposium under the sponsorship of the Psychopharmacology Research Branch of the NIMH.[4] A rather worn copy came into my possession in the summer of 1968. I dropped whatever I was reading and devoured the book from cover to cover. This book provided the perfect balance to *The Teachings of Don Juan*. While that work had made me aware of the cultural contexts related to the indigenous uses of psychedelics, the *Ethnopharmacologic Search for Psychoactive Drugs* was even more influential, because through it I became aware that this discipline — ethnopharmacology, or more specifically psycho-ethnopharmacology — was a real field of scientific investigation. Moreover, it was my first introduction to people like Schultes, Holmstedt, Shulgin, Wasson, and others, who became iconic figures in my personal pantheon, and in some cases, as with Schultes and Shulgin, mentors and friends.

The realization that real science was being pursued in this field was a revelation to me, partly because it opened the possibility that one day I, too, might be able to achieve a place in this exclusive fellowship. At first, I thought I would be able to prove to my parents that I was serious about psychedelics and not just a confused hippie in search

of cheap thrills, but they were not very reassured. However, over the years, they came to recognize the merits of my chosen career.

Two Decades Later

The shabby volume of that first edition resides on my shelf to this day. While I don't remember exactly how it came into my hands, I remember very well how my second copy came to me in 1986. I had completed my PhD at the University of British Columbia in 1984 under the supervision of Neil Towers, PhD, another lifelong mentor and friend. My thesis was an ethnopharmacological investigation of the ethnobotany, chemistry, and pharmacology of ayahuasca (*Banisteriopsis caapi*, Malpighiaceae) and another hallucinogen, a relatively more obscure preparation known as *oo'koey*, derived from *Virola* (Myristicaceae) species. Though derived from entirely different botanical sources, both ayahuasca and oo'koey were orally active tryptamine hallucinogens, and my thesis was a comparative study of their active constituents and pharmacology.

After the completion of my thesis in early 1984, I moved to San Diego, California, and began the first of three post-doctoral research projects. About a year after I moved, my thesis publications came out, and one attracted the attention of Juan Saavedra, MD, a researcher at NIMH. When Saavedra requested a reprint of my publication on ayahuasca in the *Journal of Ethnopharmacology*,[4] I was surprised. I recognized his name from an early paper he had published with Julius Axelrod, PhD, on the endogenous synthesis of the psychoactive compound DMT (dimethyltryptamine) in rat and human brains.[5] (Axelrod later won the Nobel Prize in Physiology or Medicine for his work on mechanisms of neurotransmission.)

Figuring it was a long shot, I enclosed a letter with my signed reprint, timidly enquiring if there might be a chance I could come to NIMH and work with him on endogenous tryptamines. A few weeks passed, and one day I received a kind reply. He thanked me for my reprint and mentioned that he had been in the Amazon in 1979 with Schultes and Towers, my mentor, along with a dozen other researchers on the research vessel *Alpha-Helix*, operated by the Scripps Institution of Oceanography. He informed me that there was a fellowship opportunity at the National Institute of General Medical Sciences called the Pharmacology Research Associate Training (PRAT) program that was targeted to young investigators who wanted to expand their scientific training outside their field of specialization. He said it was a perfect fit for me and encouraged me to apply. I did, was accepted into the program, and began my second post-doc in the fall of 1986 in the hallowed environs of the Laboratory of Clinical Pharmacology at NIMH.

I had been in the lab for less than two weeks when Saavedra pointed to an upper shelf in a cabinet in the lab. He said there was a box up there containing some research chemicals that he and Axelrod had used in their research on endogenous tryptamines. He suggested that I go through it and see if there was anything useful, and to send the rest to the hazardous waste disposal center on the National Institutes of Health campus. I didn't waste any time; I stayed late one afternoon until most of my fellow workers had called it a day, then got up on the bench and retrieved the box. Inside, I found a mint-condition copy of the *Ethnopharmacologic Search for Psychoactive Drugs*! How many years it had languished on the shelf next to that box of chemicals I had no idea, but it had clearly never been opened.

Recipient of the 2018 ABC James A. Duke Excellence in Botanical Literature Award

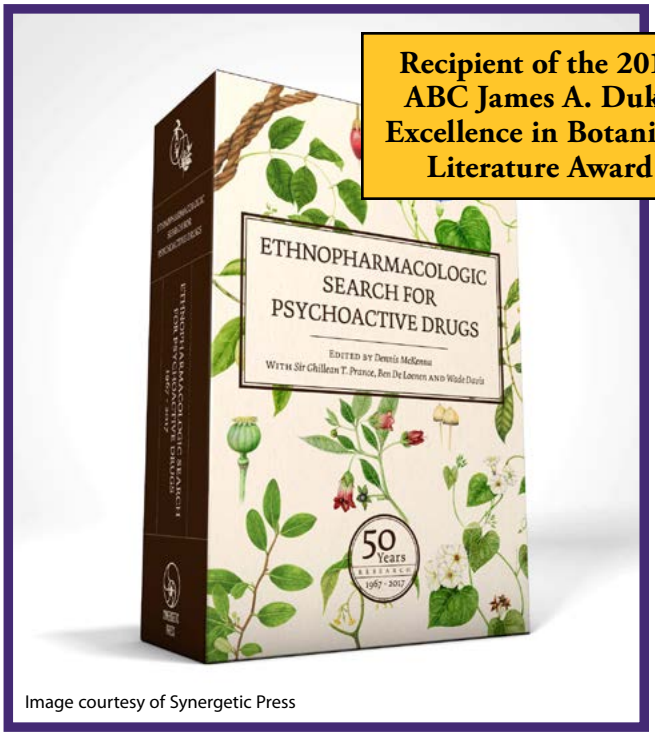
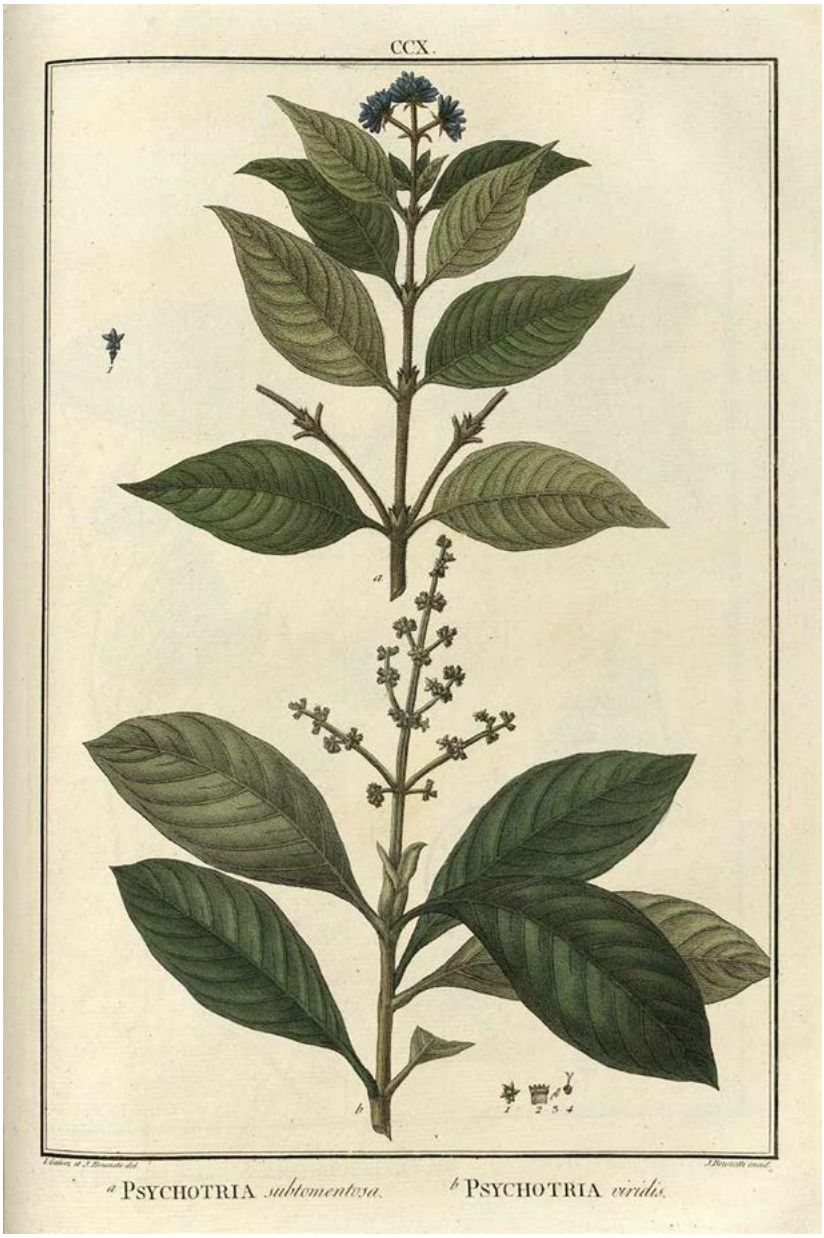


Image courtesy of Synergetic Press

Here I was, just beginning my post-doctoral studies in the heart of NIMH, the very institution where the original ESPD symposium had originated, and suddenly, the book that had so enthralled me as a curious teenager magically reappeared. How cool was that? I took it as a very good omen. It quietly disappeared into my library, where it sits beside my first copy from 1968. Some of those research chemicals turned out to be interesting as well. Along with a couple of vials of DMT and 5-methoxy-DMT, there was an interesting assortment of other derivatives, such as 5,7-dihydroxy-DMT, 6-methoxy-DMT, and so on. I kept those for many years, but never found the courage to personally bioassay them.

ESPD Returns: 50 Years Later

So, that is the story of my personal history with this book. It has haunted most of my professional career. It opened my eyes to the science of ethnopharmacology, and later, I was fortunate to meet and befriend some of the people who presented at that 1967 symposium. Though its contents



Pyschotria viridis from H. Ruiz and J. Pavón's *Flora Peruviana, et Chilensis*, Vol 2. Madrid, Spain: Typis Gabrielis de Sancha; 1799.

are dated now, that book influenced my life and career in profound ways, and I am sure that my career in ethnopharmacology, such as it has been, would never have happened had I not encountered that obscure tome in the summer of 1968.

I wanted to organize a follow-up symposium for many years. In fact, I first drafted a proposal about it in 1995, hoping to stage it in 1997, the 30th anniversary of the San Francisco symposium. It never happened for various reasons, mostly due to lack of funds, time, and an appropriate venue. In 2017, the 50th anniversary of the ESPD, all of those necessary elements came together almost miraculously.

I hope that the commemorative symposium and the publication of both symposium volumes, 1967 and 2017,[6] will attract the attention of younger investigators working in the field of ethnopharmacology and inspire them to continue this valuable work. There is still more — much more — to be discovered. I hope that the quest represented in the book's title — *Ethnopharmacologic* ***Search*** *for Psychoactive Drugs* — will be carried on by a new generation, who one day will report their discoveries to the world at a future ESPD symposium. I also hope that it will not take another 50 years!

Significant Discoveries of the Last 50 Years

Psycho-ethnopharmacology has not stood still over the last 50 years. Significant discoveries have been made and are still being made. The 50th anniversary ESPD conference in 2017 included presentations on some of the most interesting discoveries of those decades but must necessarily omit many others that are just as worthy. Though it's not my intention to discuss them in any detail, a few are worth mentioning in brief.

Ayahuasca Admixtures — The importance of the many ayahuasca admixtures had not received much attention in 1967. Some of Schultes' students were reporting on the use of the DMT-containing admixtures that give ayahuasca its psychedelic properties, but most of this work was not published until 1968 or later.[7] Interestingly, the word *Psychotria* occurs only once in the entire 1967 edition. This genus includes *Psychotria viridis* (Rubiaceae), the most widely used ingredient in ayahuasca admixtures. In the 1980s, Luis Eduardo Luna, PhD, and I also published on the many other species that are occasionally used in these admixtures.[8,9**] Many of these remain poorly investigated, in terms of both their chemistry and their pharmacology. For a later publication,[10] I screened many of these species using neuroreceptor-binding assays as part of a broad sampling of reported plants with potential anti-dementia and anti-schizophrenic activities. I contributed a condensed version of that paper ("Ethnopharmacology Meets the Receptorome: Bioprospecting for Psychotherapeutic Medicines in the Amazon Rainforest") in the final section of the 2017 symposium volume.[6]

** This paper originally was published in Spanish in the *Journal America Indigena* in 1986.[8] An English translation was published as a chapter in an anthology, *Ethnobotany: Evolution of a Discipline* (Dioscorides Press, 1995).[9]

Salvia divinorum
Photo ©2019 Steven Foster

Ayahuasca *Banisteriopsis caapi*
Photo ©2019 Steven Foster

Kava *Piper methysticum*
Photo ©2019 Steven Foster

***Salvia divinorum* and Salvinorin A** — Although ethnographic reports of the use of this member of the mint (Lamiaceae) family in Mazatec shamanism date back to at least the 1930s,[11,12] it was not discussed during the 1967 symposium. The primary active constituent, the diterpene salvinorin A, was isolated and characterized in the 1990s,[13] and its potent activity as a highly selective kappa-opioid receptor agonist was described in 2002.[14] This initial discovery has led to a flurry of research on the chemistry and pharmacology of salvinorin A and its analogs. More than 30 papers on salvinorin A have been published since (for a review, see Cunningham et al, 2011[15]). Ethnopharmacologist Michael Heinrich, PhD, and his student, Ivan Casselman, contribute a retrospective on this interesting plant ("Ethnopharmacology – From Mexican Hallucinogens to a Global Transdisciplinary Science") in the 2017 volume.[6]

Kava (*Piper methysticum*) — The term "kava" refers to both the plant in the pepper (Piperaceae) family and the mildly psychoactive beverage prepared from its roots. Kava

Mitragyna speciosa illustration from W. Haan et al.'s *Verhandelingen over de natuurlijke geschiedenis der Nederlandsche overzeesche bezittingen*, Vol 2. Leiden, the Netherlands: in Commissie bij. S. en J. Luchtmans en C.C. van der Hoek; 1839.

was reported on during the first ESPD symposium (see "Session II" in the 1967 volume), but much additional work has been done on this plant in subsequent decades. It is now widely available as a dietary supplement, and its anxiolytic, muscle-relaxant, and sedative properties have made it a popular alternative to pharmaceuticals such as benzodiazepines (for a review, see LaPorte et al, 2011[16]).

Kratom (*Mitragyna speciosa*) — The leaf of this Southeast Asian tree in the madder (Rubiaceae) family is the source of mitragynine and related alkaloids that are mu-opioid receptor agonists. The plant can cause mild addiction like any source of opioids, but in traditional contexts it often is used as an alternative to opium, and as a way to gradually end dependence on opium and heroin. The kratom alkaloids do not seem to cause respiratory depression, unlike heroin and other opioids, and hence show promise as a less toxic, and less addictive, analgesic. Kratom was not illegal in the United States when I first wrote this chapter in 2017, but was identified as a "drug of concern" by the US Drug Enforcement Administration in 2005 and may be scheduled under the Controlled Substances Act in the near future. At the same time, some investigators, such as Christopher McCurdy, PhD, have urged that it not be prohibited because it may enable many opioid addicts to overcome their habits.[17,18] McCurdy reported on his research and the current "state of the art" with respect to kratom ("Kratom (*Mitragyna speciosa*) as a Potential Therapy for Opioid Dependence") in the second section of the 2017 symposium volume.[6]

Iboga (*Tabernanthe iboga*) and Ibogaine — Iboga, sometimes spelled eboga, is a West African plant in the Apocynaceae family that is used in traditional initiation rites in the spiritual discipline of Bwiti in Gabon. In those rites, young men and women, coming of age as adults, undergo an initiation in which they consume large — sometimes nearly lethal — amounts of iboga root. They experience a deep trance, sometimes lasting up to 36 hours, during which they often claim to experience visits from their ancestors and are initiated and given ancestral wisdom. Ibogaine, the major alkaloid, has received recognition and notoriety because it is effective for the treatment of opioid and other addictions.[19] Although a Schedule I controlled substance in the United States, it is unregulated in many countries and is used in treatment centers in various parts of the world, especially Mexico.[20] Kenneth Alper, MD, a leading authority on the chemistry and pharmacology of ibogaine, contributes "The Iboga Project: Urban Ethnomedicine for Opioid Use Disorder" in the second section of the 2017 symposium volume.[6]


Kanna *Sceletium tortuosum*
Photo ©2019 Tommi Nummelin

Kougoed (*Sceletium tortuosum*) — Kougoed, also called channa or kanna, is a South African succulent in the Aizoaceae family whose roots contain a spectrum of alkaloids with central nervous system activities. Some, such as mesembrenone, mesembrine, and mesembrenol, are potent serotonin-reuptake inhibitors and phosphodiesterase 4 inhibitors. These are only three of more than 30 alkaloids that have been isolated from the plant; the pharmacological properties of most have not been thoroughly characterized.[21] In the second section of the 2017 symposium volume, Nigel Gericke, MD, reports on his research with *S. tortuosum* ("Kabbo's !Kwaiń: The Past, Present and Possible Future of Kanna") that has led to the commercial development of Zembrin® (HG&H Pharmaceuticals; Johannesburg,


Iboga *Tabernanthe iboga*
Photo ©2019 Ji-Elle

Although obviously neither botanical nor fungal, psychoactive and psychedelic amphibians – frogs and toads – have attracted attention recently as potentially therapeutic.

South Africa), a natural herbal anxiolytic and antidepressant sold as a dietary supplement.[6]

Jurema (*Mimosa hostilis* syn. *Mimosa tenuiflora*) and Yuremamine — This Brazilian tree in the legume (Fabaceae) family has long been known as the source of *Vinho da Jurema*, a psychoactive beverage that contains DMT as its main active constituent. However, it has been an ethnopharmacological enigma because DMT is not orally active unless potentiated by a monoamine oxidase inhibitor (MAOI). Yet, no plants with MAOI activity have been reported to be added to the mixture in traditional shamanism. Recently, a novel compound, yuremamine, was isolated from the roots of jurema at about the same concentration as DMT.[22] This compound has an interesting structure, in that the structure of DMT is "caged" within the larger molecule, and it may be a prodrug that is converted to DMT in vivo. The initially proposed structure has been challenged, and total synthesis has so far been elusive.[23] It may also be an MAOI itself, and thus could potentiate the DMT. So far, there have been no human bioassays of this compound, so its pharmacological properties in a pure form are unknown.


Giant leaf frog *Phyllomedusa bicolor*
Photo ©2019 Bernard Dupont

***Acacia* spp. and Tryptamines** — The large genus *Acacia* (Fabaceae) has proven to be an unusually rich source of DMT and other psychoactive tryptamines. At the time of the first ESPD conference in 1967, the tryptaminic *Acacia* species were unknown to science. The earliest reference in PubMed is Wahba and Elkheir (1975).[24] Since then, tryptamines have been detected in more than 60 species of *Acacia*, as documented in the review paper "Australian Psychoactive Acacia Species and their Alkaloids" by Snu Voogelbreinder in the second section of the 2017 symposium volume.[1] Many more *Acacia* species contain unidentified alkaloids, and phenylethylamines, ß-carbolines, tetrahydroisoquinolines, pyridines, and other structural classes have been reported. Interestingly, much of what science knows about the chemistry of psychoactive *Acacia* species is due to investigations by amateur scientists who have conducted research outside conventional academic channels, and, as a result, much of it does not appear in the peer-reviewed literature.


Acacia sp.
Photo ©2019 Forest & Kim Starr

Frog and Toad Medicines — Although obviously neither botanical nor fungal, psychoactive and psychedelic amphibians — frogs and toads — have attracted attention recently as potentially therapeutic. Among these are the so-called sapo medicine, more properly termed kambô, from *Phyllomedusa bicolor* (the giant leaf frog), a frog containing a variety of neuroactive peptides in its skin secretions. This species is used by the Matsés (Mayoruna) tribe as hunting magic, and taking "sapo" is becoming a popular pastime among tourists in Peru. So far, the peptides identified include phyllocaerulein (hypotensive), phyllomedusin (tachykinin, a potent vasodilator and secretagogue), phyl-

lokinin (a potent arterial smooth muscle dilator), and several delta-opioid-selective peptides, the deltorphins, as well as mu-opioid-active peptides, the dermorphins. Many of these compounds may have therapeutic potential, and the neuroactive peptides are only a part of this rich peptide cocktail. For reviews and more information see Erspamer et al (1993),[25] Daly et al (1992),[26] and den Brave et al (2014).[27]

In addition to the *Phyllomedusa* peptides, the poison of *Bufo* species contains psychedelic tryptamine derivatives, either bufotenine or 5-methoxy-DMT, and its use has gained popularity in various neo-shamanic practices. Although the subjective effects of *Bufo* poison were first reported by Weil and Davis (1994),[28] there is little evidence that these species were ever used as psychedelic medicines in any ethnomedical or shamanic tradition. A comprehensive review of the use of *Bufo* species as sources for psychedelics, and a discussion of some of the controversies surrounding this practice, can be found in Lyttle et al (1996).[29]

Old Yet New: Harmine and Related ß-carbolines — Harmine is the major ß-carboline and MAOI in the ayahuasca vine. Harmine is an "old" alkaloid, meaning that it has been known for many years, having first been identified in the seeds of Syrian rue (*Peganum harmala*, Nitrariaceae) by chemist J. Fritsch in 1847, more than 10 years before ayahuasca came to the attention of science as a result of explorer Richard Spruce's discovery in 1858. However, recent investigations have shown that even old alkaloids can still harbor secrets. New research has shown that harmine and some of its derivatives can display a diverse array of biological activities. It has been shown to have antimicrobial, antidiabetic, antidepressant, antitumor, neuroprotective, and other effects. It interacts with a number of neuroreceptors, including 5-HT_{2A}, 5-HT_{2C}, imidazoline, and dopamine transporter receptors. Significantly, it recently has been shown to be a potent inhibitor of DYRK1A, a kinase involved in a variety of intracellular signaling functions related to cell proliferation and neurogenesis, and has been shown to potently stimulate proliferation of neural cell progenitors, an effect linked to its inhibition of DYRK1A.[30] For recent reviews on the pharmacology of harmine and other ß-carbolines, see Cao et al (2007),[31] Patel et al (2012),[32] and the paper by Dale Millard ("Broad Spectrum Roles of Harmine in Ayahuasca") in the first section of the 2017 symposium volume.[6]

Conclusion

This article comprises a brief summary of some of the most significant discoveries in psycho-ethnopharmacology in the five decades since the first ESPD symposium in 1967. These findings are only a small sampling of the discoveries that have been made in the last 50 years. The 2017 ESPD symposium — and the publication of the proceedings as a two-volume set that includes a reprinting of the 1967 symposium proceedings — demonstrates that the field of psycho-ethnopharmacology is far from a dead or dying discipline. It is potentially more vibrant than ever. There are still exciting discoveries to be made in years to come. In today's world, no science can thrive without financial support and academic legitimacy. It is my hope that the publication of this symposium volume will bring a measure of both to this field, and will inspire and excite the next generation of psycho-ethnopharmacologists.

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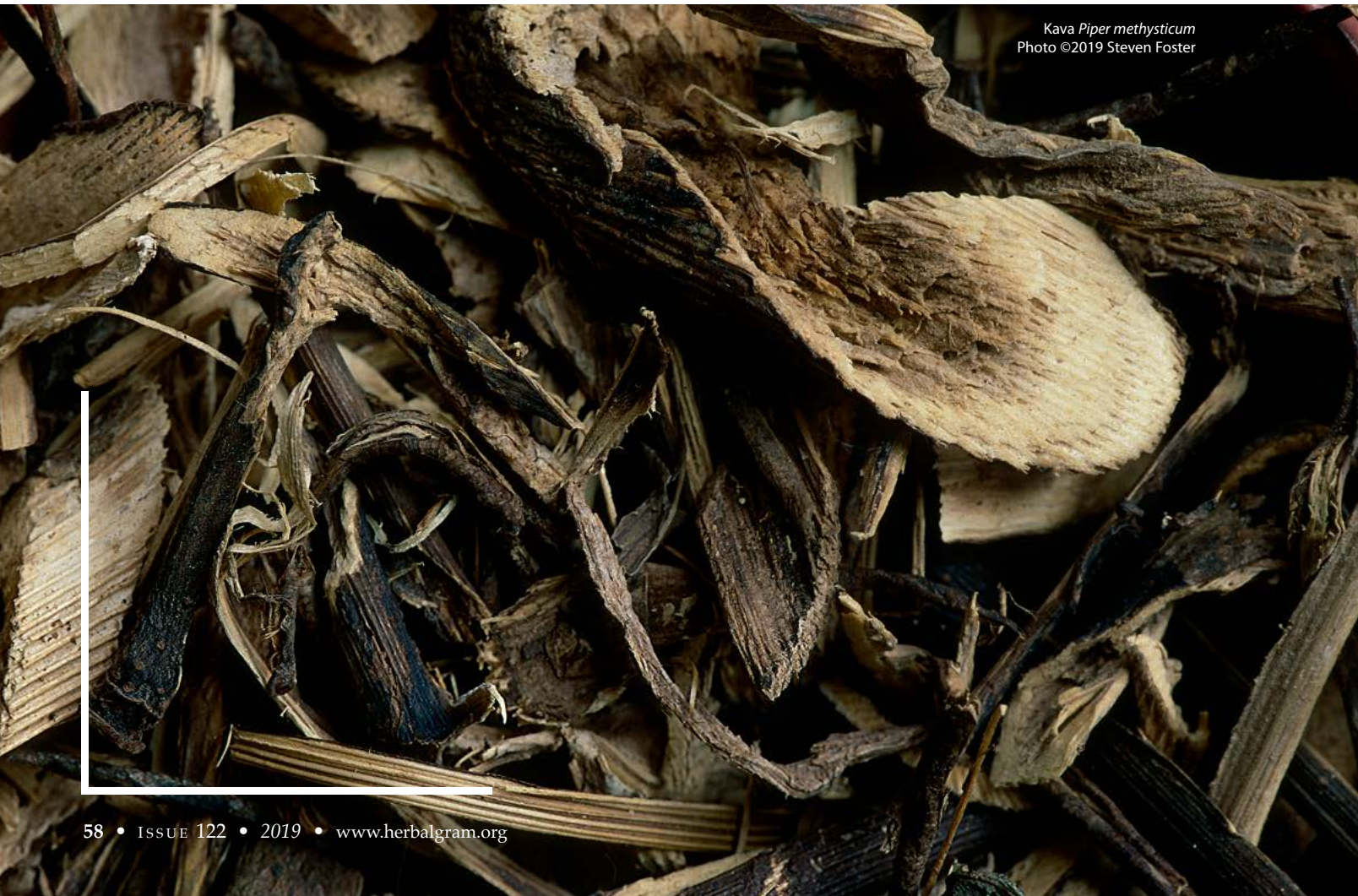
2002 to 2017. In 2017, he organized and presented a conference in the UK, the "Ethnopharmacologic Search for Psychoactive Drugs: 50 Years of Research," to commemorate the original ESPD conference in San Francisco in 1967. The symposium proceedings of both conferences were published by Synergetic Press in 2018.

References

1. Efron DH, Holmstedt B, Kline NS, eds. Ethnopharmacologic Search for Psychoactive Drugs – 1967. Workshop Series of Pharmacology Section, NIMH No. 2. Sponsored by Pharmacology Section, Psychopharmacology Research Branch, National Institute of Mental Health. Public Health Service, US Department of Health, Education, and Welfare. Public Health Service Publication No. 1645, US Government Printing Office; 1967.
2. Commonly used terms in addiction science. National Institute of Drug Abuse website. Available at: www.drugabuse.gov/publications/media-guide/glossary. Accessed September 19, 2018.
3. Castaneda C. 1968. *The Teachings of Don Juan: A Yaqui Way of Knowledge*. Berkeley, CA: University of California Press; 1968.
4. McKenna DJ, Towers GHN, Abbott FS. Monoamine oxidase inhibitors in South American hallucinogenic plants: tryptamine and beta-carboline constituents of ayahuasca. *Journal of Ethnopharmacology*. 1984;10:195-223.
5. Saavedra JM, Axelrod J. Psychotomimetic N-methylated tryptamines: formation in brain in vivo and in vitro. *Science*. 1972;175(4028):1365-1366.
6. Prance GT, McKenna DJ, de Leonen B, Davis W, eds. *Ethnopharmacologic Search for Psychoactive Drugs: 50th Anniversary Symposium Volume*. Santa Fe, NM: Synergetic Press; 2018.
7. Pinkley HV. Plant admixtures to ayahuasca, the South American hallucinogenic drink. *Lloydia*. 1969;32:305-314.
8. McKenna DJ, Luna LE, Towers GHN. Ingredientes biodinamicos en las plantas que se meszclan al ayahausca. Una farmacopea tradicional no investigada. *America Indigena*. 1986;46:73-101 (Spanish with English abstract).
9. McKenna DJ, Luna LE, Towers GHN. Biodynamic constituents in ayahuasca admixture plants: an uninvestigated folk pharmacopoeia. In: von Reis S, Schultes RE, eds. *Ethnobotany: Evolution of a Discipline.* Portland, OR: Dioscorides Press; 1995.
10. McKenna DJ, Ruiz JM, Hoye TR, Roth BR, Shoemaker AP. Receptor screening technologies in the evaluation of Amazonian ethnomedicines with potential applications to cognitive deficits. *Journal of Ethnopharmacology*. 2011;134, 475-492.
11. Johnson JB. Some notes on the Mazatec. *Revista Mexicana de Estudios Antropologicoa*. 1939;3:142-156.
12. Johnson JB. The elements of Mazatec witchcraft. *Etnologiska Studier*. 1939;9:128-150.
13. Valdés LJ. *Salvia divinorum* and the unique diterpene hallucinogen, Salvinorin (divinorin) A. *Journal of Psychoactive Drugs*. 1994;26:277-83.
14. Roth BL, Baner K, Westkaemper R, et al. Salvinorin A: a potent naturally occurring nonnitrogenous kappa opioid selective agonist. *Proceeding of the National Academy of Sciences USA*. 2002;18:11934-11939.
15. Cunningham CW, Rothman RB, Prisinzano TE. Neuropharmacology of the naturally occurring kappa-opioid hallucinogen salvinorin A. *Pharmacological Reviews*. 2011;63:316-347.
16. LaPorte E, Sarris J, Stough C, Scholey A. Neurocognitive effects of kava (*Piper methysticum*): a systematic review. *Human Psychopharmacology*. 2011;26:102-111.



Kava *Piper methysticum*
Photo ©2019 Steven Foster

17. Ward J, Rosenbaum C, Hernon C, McCurdy CR, Boyer EW. Herbal medicines for the management of opioid addiction: safe and effective alternatives to conventional pharmacotherapy? *CNS Drugs*. 2011;25:999-1007.
18. Babu KM, McCurdy CR, Boyer EW. Opioid receptors and legal highs: *Salvia divinorum* and Kratom. *Clinical Toxicology (Philadelphia)*. 2008;46:146-152.
19. Alper KR. 2001. Ibogaine: a review. The alkaloids. *Chemistry and Biology*. 2001;56:1-38.
20. Brown TK. Ibogaine in the treatment of substance dependence. *Current Drug Abuse Reviews*. 2013;6:3-16.
21. Gericke N, Viljoen AM. Sceletium — a review update. *Journal of Ethnopharmacology*. 2008;119:653-663.
22. Vepsäläinen JJ, Auriola S, Tukiainen M, Ropponen N, Callaway JC. Isolation and characterization of yuremamine, a new phytoindole. *Planta Medica*. 2005;71:1053-1057.
23. Calvert MB, Sperry J. Bioinspired total synthesis and structural revision of yuremamine, an alkaloid from the entheogenic plant *Mimosa tenuiflora*. *Chemical Communications (Cambridge)*. 2015;51:6202-6205.
24. Wahba KSK, Elkheir YM. Dimethyltryptamine from the leaves of certain *Acacia* species of northern Sudan. *Lloydia*. 1975;38:176-177.
25. Erspamer V, Erspamer GF, Severini C, et al. Pharmacological studies of 'sapo' from the frog *Phyllomedusa bicolor* skin: a drug used by the Peruvian Matses Indians in shamanic hunting practices. *Toxicon*. 1993;31:1099-1111.
26. Daly JW, Caceres J, Moni RW, et al. Frog secretions and hunting magic in the upper Amazon: identification of a peptide that interacts with an adenosine receptor. *Proceedings of the National Academy of Sciences USA*. 1992;89:10960-10963.
27. den Brave PS, Bruins E, Bronkhorst MW. *Phyllomedusa bicolor* skin secretion and the Kambô ritual. *The Journal of Venomous Animals and Toxins Including Tropical Diseases*. 2014;20:40.
28. Weil AT, Davis W. *Bufo alvarius*: a potent hallucinogen of animal origin. *Journal of Ethnopharmacology*. 1994;41:1-8.
29. Lyttle T, Goldstein D, Gartz J. Bufo toads and bufotenine: fact and fiction surrounding an alleged psychedelic. *Journal of Psychoactive Drugs*. 1996;28:267-290.
30. Dakic V, Maciel RM, Drummond H, Nascimento JM, Trindade P, Rehen SK. Harmine stimulates proliferation of human neural progenitors. *Peer J*. 2016;4:e2727.
31. Cao R, Peng W, Wang Z, Xu A. Beta-carboline alkaloids: biochemical and pharmacological functions. *Current Medicinal Chemistry*. 2007;14:479-500.
32. Patel K, Gadewar M, Tripathi R, Prasad SK, Patel DK. A review on medicinal importance, pharmacological activity and bioanalytical aspects of beta-carboline alkaloid "harmine." *Asian Pacific Journal of Trop Biomedicine*. 2012;2:660-664.

A Modern State-Federal Framework for a Regulated US Cannabis Industry

By Tami Wahl and Josef Brinckmann

Cannabis *Cannabis sativa*
Photo ©2019 Steven Foster

Summary

Based on the regulatory situation for cannabis (*Cannabis* spp., Cannabaceae) in the United States, the premise of this proposed federal framework is to create a regulatory model specific to a plant-based end product that can be used for both social and therapeutic purposes. Cannabis products currently are being regulated at the state level, with the exception of US Food and Drug Administration (FDA)-approved drug products such as Epidiolex® (GW Pharmaceuticals; Cambridge, UK).

The proposed framework, by design, defers to the existing state-regulated infrastructures by leaving state autonomy intact to the greatest degree possible, with minimal federal entanglement. Importantly, the framework also sets forth that the federal interface would be conducted via the US Department of Agriculture (USDA) and the cannabis plant would not be a federally scheduled substance. The full paper explains why this proposed dynamic is integral to the long-term success of the regulated cannabis market, and addresses why commonly cited frameworks, such as the alcohol and tobacco models, are not appropriate for a modern cannabis market. The scope of the proposed framework does not include the production, manufacture, or regulation of no- or low-THC hemp* or any crop cultivated under the provisions of the Agriculture Improvement Act of 2018 (the 2018 Farm Bill).[1]

The cannabis plant has a long history of human use for different purposes and is one of hundreds of botanicals with therapeutic properties supported by clinical data and traditional use. The proposed framework is a 21st-century pathway to market for plant-based products that respects the efforts of the states and balances an appropriate federal intersection with long-term market interests. This article is taken from a longer paper by the authors and has been revised for *HerbalGram*. The full paper, as referenced in this article, can be accessed at https://tinyurl.com/cannabisframework.

* The 2018 Farm Bill defines the term "hemp" as "the plant *Cannabis sativa* L. and any part of that plant, including the seeds thereof and all derivatives, extracts, cannabinoids, isomers, acids, salts, and salts of isomers, whether growing or not, with a delta-9 tetrahydrocannabinol concentration of not more than 0.3 percent on a dry weight basis."[1]

The public and political sentiment toward cannabis within the United States has changed dramatically over the past several years. The United States has a vibrant regulated cannabis industry that has been built on more than 46 intrastate markets. Today's emergent regulated landscape is a new consideration when discussing how best to approach contemporary cannabis policy. Because the United States has a robust regulated intrastate cannabis market — where a majority of the country's population now resides in a jurisdiction with some type of regulated market — the conversation is ripe to review federal cannabis policy.

Understanding the historic, albeit winding, road to 2019 provides useful guidance as to what the map to the future could look like. Similar to female hop (*Humulus lupulus*, Cannabaceae) flowers that are used in therapeutic products such as sleep aids and alcoholic beverages such as beer,[2] the cannabis plant possesses various psychoactive, physiological, and therapeutic properties. Therefore, this paper sets forth the position that the plant should be subject to an appropriate regulatory framework rather than as a controlled substance under the Controlled Substances Act (CSA). The proposed framework also sets forth a limited federal interface to ensure minimal disruption to the existing state-regulated industry, with the states retaining a majority of control over their respective programs. The states should also remain active participants in developing the direction of US cannabis policy. The proposed framework is designed to advance both innovation and inclusion by incorporating forward-thinking principles to ensure the regulated industry is diverse and allows access to all interested stakeholders. Finally, the framework allows entry into the global market, fosters responsible use, and subjects the market to minimal federal standards and technical assistance (for crop quality assurance and export marketing support) as needed to support the long-term integrity of the regulated industry.

States Retain Autonomy

The proposed federal framework sets forth as a foundational premise that state interests must be protected and at the forefront. The stakeholders that faced the greatest risk by engaging in these state-authorized "laboratories of democracy" should reap the benefits from laying the foundation for a multi-billion dollar regulated industry that serves both patients and consumers.

The significant investments made by the individual states to enact their programs — coupled with the considerations that the state programs are comprehensive and have been generally successful — underscore the importance of a federal interface that causes minimal disruption to the existing regulated markets. As explained in Section IV of the authors' full paper, the market vulnerabilities faced by the industry due to the design of the individual state programs are being addressed on the state level, and other market vulnerabilities (e.g., market stability, production and marketing controls [referred to as "volume controls" in USDA guidelines], pesticide use, solvent use, etc.) could be resolved with technical assistance via the federal government. The federal interface would be less of a primary authoritative regulator and, instead, would provide the needed technical assistance for the state-regulated markets.

The proposed federal model allows individual states to decide if a regulated cannabis market is appropriate for their state. The only federal override of this measure is that a state must recognize a valid prescription for medical cannabis regardless if such state has implemented a regulated medical cannabis program. This mandate is included to resolve the issue of "patient refugees," where patients seeking medical cannabis have relocated from their home jurisdiction that does not have a regulated medical program to a jurisdiction that does.

Thus, the individual state frameworks would largely remain intact, with the additional administrative responsibility of engagement with the federal interface and the advisory committee, both as defined below.

Federal Interface

This proposed framework delegates primary federal oversight of the regulated cannabis market to the USDA. After reviewing the strengths and vulnerabilities of the intrastate markets, the authors of this article found that the most common need was technical assistance, which is a service already provided through USDA programs for other crops (e.g., hops).

Concerning cash commodity crops (e.g., food, cosmetics, fiber, and medicine), the USDA has the technical expertise to work with plant material and help create market stability for plant-based products. Because of this expertise, and that the USDA currently operates in all 50 states and US territories, it is the best-suited federal agency to work in collaboration with the relevant state regulatory agencies and the individual state stakeholders in the cannabis industry. Furthermore, the USDA has Cooperative Extension System offices situated in each land-grant university (LGU; there are one or more LGUs in each state and territory that provide a network of scientists, extension staff, and volunteers to carry out USDA programs) as well as Farm Service Agency offices operating in each state.[3] The Agriculture Marketing Service (AMS) within the USDA is particularly well-suited to serve as the proposed federal interface.

This paper sets forth the position that the plant should be subject to an appropriate regulatory framework rather than as a controlled substance under the CSA.

The AMS was created in the late 1930s to facilitate "the efficient, fair marketing of US agricultural products, including food, fiber, and specialty crops."[4] The AMS engages with industry-driven initiatives that support particular agricultural sectors with technical assistance. The reach of the expertise within AMS is vast and extends to both domestic and global markets. AMS is versed in specialty crops that are experiencing rapid growth, as is the case with cannabis. This growing sector would benefit from technical assistance to help stabilize the market. As noted by AMS on the role and value of its services:

> AMS quality standards, grading, certification, auditing, and inspection are voluntary tools and services that industry can use to help promote and communicate quality and wholesomeness to consumers. These services assist businesses in differentiating themselves from their competition.
>
> Examples of USDA grades include USDA Prime, USDA Grade A, and US No. 1. Annually, AMS grades, audits, certifies and/or inspects over $150 billion worth of agricultural products, ensuring the quality of domestic goods and helping American farms and businesses export goods.[5]

The services provided by AMS include:

- Establishing data collection practices
- Collecting production and price data
- Distributing statistical data
- Inspection services
- Establishing standards and quality grading systems
- Calculating supply and demand levels
- Marketing and branding efforts
- Research efforts
- Enforcement measures with impact
- Establishing good agricultural and collection practices (GACPs) for an industry
- Monitoring and facilitating import/export transactions
- Providing scientific and analytical support
- Monitoring pesticide use (the Environmental Protection Agency approves crop-specific pesticides for human and/or animal food crops)

One attractive consideration for the state-regulated cannabis industry to work with AMS is the expertise of AMS on how to position unique crops as regional specialties. This branding ability is highly desirable as a means to establish a single recognizable grading system and secure the place of US cannabis-based products in a rapidly developing global market. This type of branding, marketing, and development of standards will drive interest from investors and buyers for US products and, ideally, when the United States enters the global market, demand for US products will already exist. AMS possesses the requisite expertise in international market intelligence for exported crops, which should help US farmers secure market share prior to the United States' entering the global market. AMS could facilitate the positioning of state-branded products (e.g., "California-grown") from the US-regulated market as high-value regional specialty crops.

Another appealing trait of the AMS is its existing expertise to navigate multiple pathways to market for finished products. The regulated cannabis industry is composed of products for medical use and patient populations, adult-use and social consumers, and veterinary use for pets and livestock.[6] The USDA understands plant material and is able to develop programs that are tailored to the specific plant and end user(s).

Finally, several of the current state-regulated cannabis markets already include the state counterpart to USDA. Examples include the Utah Department of Agriculture and Food ("the agency responsible for implementing and enforcing many of the new cannabis-related laws"[7]) and the Oregon Department of Agriculture, which works with two other state agencies that are the lead regulators for Oregon's medical and adult-use programs.[8] State departments of agriculture commonly address issues such as pesticide limits, fertilizer use, and cultivation practices.[9-11] The AMS is the obvious complement to state regulatory agencies.

This proposed framework delegates primary federal oversight of the regulated cannabis market to the US Department of Agriculture (USDA).

The range of industries with which AMS engages is extensive and includes various fruits, cotton (*Gossypium* spp., Malvaceae), dairy products, eggs, lumber, plant oils, specialty crops (e.g., medicinal herbs), and vegetables. The relationship between AMS and the American ginseng (*Panax quinquefolius*, Araliaceae) root and spearmint (*Mentha spicata*, Lamiaceae) essential oil industries are prime examples of the inherent value that AMS can bring to an industry.

The American ginseng plant is used both in culinary and medicinal applications, and the marketplace is highly competitive to the point that federal legislation was introduced in 2002 that banned the use of the name "ginseng" in US commerce unless the plant material is from the genus *Panax*.[12-14] The AMS currently works with ginseng producers in Wisconsin and has developed grading standards for American ginseng and Asian ginseng (*P. ginseng*). The US standards for quality grades of cultivated ginseng roots developed by AMS are fit for purpose[15] and have helped create a dynamic marketplace. The net result is that ginseng marketed with a "Wisconsin Ginseng Seal®" fetches a premium in foreign markets, particularly in the People's Republic of China. The Ginseng Board of Wisconsin is managed by an elected board of seven Wisconsin ginseng producers. The board functions under a marketing order managed by the Wisconsin Department of Agriculture, Trade & Consumer Protection.[16]

Spearmint is another popular plant with culinary and therapeutic applications that is cultivated in various regions of the United States. AMS has engaged with producers of spearmint in Idaho, Oregon, Nevada, Utah, and Washington. The producers are organized under the Far West Spearmint Oil Administrative Committee, and AMS is authorized to support research and promotion programs, and volume control (supply and demand). Accounting for more than 50% of total global production of spearmint oil, the northwestern United States (the "Far West") is the premier spearmint-producing area in the world.[17]

The previous two examples provide a preview of the potential benefits for a single-crop industry. The regulated cannabis industry would benefit greatly from a defined grading structure, and possible marketing order volume controls,[18,19] among the other services offered by AMS.

Additionally, the illicit market will continue to thrive until the price point within the regulated cannabis market is approachable. Access to a quality product in a regulated market is critical for reducing (and ultimately eliminating) the illicit market.

Cannabis *Cannabis sativa*
Photo ©2019 Steven Foster

It is also relevant that USDA has played a supportive role for industrial hemp farmers in different states in the past. The *Yearbook of the United States Department of Agriculture 1895*, for example, provided guidance to farmers on agricultural methods for the *Cannabis sativa* crop.[20] It is worth noting that the state of Kentucky was the predominant industrial hemp-farming state in the 19th century and, in the summer of 2018, US Senate Majority Leader Mitch McConnell of Kentucky pushed to allow more US farmers to grow hemp legally, which could play a role in meeting the production demands for high-value cannabidiol (CBD). Most Kentucky growers are already geared toward CBD production as opposed to growing hemp as a fiber crop.[21] The USDA understands and has the plant expertise for both industrial hemp and the cannabis plant. AMS will reengage with hemp farmers in 2019, as the 2018 Farm Bill (Section 10113) directs the USDA to issue regulations and guidance for a commercial hemp production program.

Logistically, under AMS guidelines, the cannabis plant would be considered a specialty crop, and the cost for states to partner with AMS would be absorbed by the state regulatory agencies and stakeholders. The AMS is currently structured to engage with an industry on a voluntary basis; however, under the proposed framework, engagement with AMS by the states that have regulated markets would be a mandate.†

The eight-decade-long evolution of US cannabis regulation largely has been defined by the unjustified treatment and a lack of willingness by federal authorities to either correct course or objectively review evidence on the plant. Due to this history, the authors sought viable alternatives outside the FDA to take the lead as the federal interface. However, the key deciding factor to structure the proposed framework within the USDA was the department's breadth of expertise, specifically within the AMS, in working with plants and crops. The state programs have existing infrastructures, and the AMS is equipped to engage with these existing state markets via regulatory agencies and individual stakeholders to create long-term market stability while continuing to drive innovation without over-commercialization.

Advisory Committee

An elected advisory committee (AC) is envisaged to act as the authoritative intermediary between the states and the federal interface. It is further proposed that the AC should consist of nine individuals, with seven representatives from the state perspective (including industry stakeholders) and two from the federal perspective, at least one of whom must be from the AMS. The AC would serve as experts of the regulated cannabis industry and field inquiries and concerns from state and federal stakeholders.

The AC would be responsible for:

- adopting or establishing baseline quality and laboratory standards, scientifically valid analytical methods — possibly in collaboration with the United States Pharmacopeia (USP),** American Herbal Pharmacopoeia (AHP), AOAC International, NSF International, or ASTM International — and minimum labeling requirements;
- creating a national educational message/tagline/symbol (e.g., "Smart Colorado"); and
- establishing social equity measures that merge innovation and inclusion (e.g., gender analysis on each policy issued).

The execution of the above three items will be instrumental in maintaining integrity in the regulated industry. Most importantly, an impactful educational campaign is critical for the responsible use of cannabis-based products and to thwart potential societal harms from uninformed consumption and misuse. Education is central to all industries and product categories; however, in light of the decades of misinformation about cannabis, a clear and sound educational message is all the more important.

Other areas of interest and concern that may be addressed by the AC include targeted research efforts, community re-investment measures, diversity and inclusion measures, and other social justice issues. The latter two have been addressed to varying degrees by local and state authorities; however, at a minimum, these matters could be referenced as part of the AC's charter. The AC must include the appropriate expertise and balance of perspectives to ensure the US-regulated cannabis market is as robust as possible while continuing to honor and support the existing state platforms.

Diversity and Small Business Provision

The regulated industry was built by individual efforts that over time joined forces in garnering support for a reasonable path forward. Today, the domestic and global regulated cannabis industry is experiencing hyper-growth. With such growth, promises of high returns on investments are rampant, which in turn has attracted larger players to seize the potential benefits. However, the efforts that built the industry must be considered when developing the path forward.

Education is central to all industries and product categories; however, in light of the decades of misinformation about cannabis, a clear and sound educational message is all the more important.

As a measure to ensure the industry maintains diversity and a range of business sizes, the proposed federal framework will include a section to protect and secure an opportunity for these interests to remain competitive in the regulated market. Furthermore, the inclusion of a provision to protect the roles of diversity and small businesses in the regulated industry is another

† At a minimum, a state's engagement with AMS would be a mandate prior to global entry.

** As discussed in the full paper, the United States Pharmacopeia (USP) is developing a quality standards monograph for the verification of the composition, identity, quality, purity, and strength of cannabis flower and preparations made from it for its *Herbal Medicines Compendium*. The USP is an authoritative standards-setting organization whose compendia are incorporated into regulations in many countries.

means of honoring the existing individual state structures and the participating stakeholders and acknowledging the impact from the historic treatment of the plant.

Some municipalities, like Oakland, California, are experimenting with cannabis licensing scenarios that aim to address racial inequity and take into consideration the failed war on drugs that disproportionately incarcerated the impoverished and minority communities. As reported in *USA Today*, Oakland's "Equity Applicant" system "aims to help poor, longtime Oakland residents — including those with convictions for illegally selling marijuana — get started in a business that otherwise has remained stubbornly white, male and middle class across the USA."[22]

As such, the city of Oakland now requires that at least half of all cannabis permits for cultivators, delivery-only dispensaries, distributors, testing laboratories, manufacturers, and transporters must be issued to Equity applicants:

- Equity — Applicants who qualify for fee waivers plus technical and financial assistance based on income level and residential location or cannabis conviction.
- General — All other applicants. A General applicant who incubates an Equity applicant by providing them with three years of free rent and security measures, has priority over other General applicants.[23]

The success of these types of licensing scenarios†† has yet to be fully realized; however, the Oakland program has met challenges in the early days of its program.[24,25] The advantage of local jurisdictions' retaining autonomy over the marketplace within their border is that experiments with different types of social equity models can be undertaken to find the most appropriate and effective path forward. A requirement in the federal framework that acknowledges the importance of these measures bolsters local and state efforts, which is the intended design of the federal framework.

†† San Francisco is another example of a local jurisdiction with a social equity program.

Cannabis *Cannabis sativa*
Photo ©2019 Michael Fischer

Also of interest, the term "small business" does not have a universal, accepted definition and has been in large part defined by individual industries. For example, the US Small Business Administration (SBA) develops size standards per economic activity sector or industry.[26] In addition to the number of employees and average annual receipts, the SBA requires a small business to meet several other criteria, including:

- being organized for profit,
- having a place of business in the United States,
- operating primarily in the US market or making a significant contribution to the US economy,
- being independently owned/operated, and
- not being dominant within one's industry on a national level.

Depending on the industry, the SBA defines a small business as having no more than 1,500 employees and less than $38 million in average annual receipts.

Another example of how small businesses can be defined is identified in regulations from a modern piece of legislation regarding food safety standards. Under the Food Safety Modernization Act (FSMA),[27] categories for "small businesses" and "very small businesses" were established to account for businesses with typically smaller budgets, fewer employees and resources, and limited bandwidth. Under FSMA, generally a small business is defined as a business with fewer than 500 employees.[28]

The primary point is that the term "small business" can go beyond a sole proprietor operating a business from her or his home. The range of parameters on how to define a small business is vast, and appropriate criteria to reflect the regulated cannabis industry will need to be identified by the AC. Possible measures for the AC to consider as a means to protect small businesses include a reduced tax rate, or additional tax credits for meeting the defined criteria of a small business. Measures that call for the reduction of or exemption from quality control standards should only be allowed if product integrity and safety are not compromised. The critical consideration is that small business interests are protected and that barriers to enter the market for smaller entities are not excessive.

Eligibility for Insurance Coverage

Of great relevance is that data from the US-regulated programs support the eligibility of medical cannabis for insurance coverage. The 46-plus medical cannabis programs currently serve more than two million patients,[29] and the cost for the medicines received via the state programs has been absorbed 100% out-of-pocket by the patient. The individual patient has been paying out of pocket for her or his medical cannabis since 1996, when California enacted a medical program.

Since that time, data have suggested that regulated cannabis markets correlate with positive health outcomes and reduced health care costs:

- States with medical cannabis programs have a 25% lower opioid mortality rate.[30]
- Availability of medical cannabis has correlated with reductions in Medicare Part D spending.[31]
- Medical cannabis laws are associated with significant reductions in opioid prescribing in the Medicare Part D population.[32]

An example of data generated from a state-specific program with notable effect comes from the Minnesota medical cannabis program. Minnesota enacted a medical cannabis program in 2014 and is considered a fairly conservative program. Recently released data from the Minnesota Department of Health, the agency that oversees Minnesota's medical cannabis program, demonstrated that patients with "difficult-to-control pain of moderate and high levels reported medical cannabis provided significant relief."[33,34] The data also indicated a reduction or elimination of opioid use by half of the participants after six months of use of medical cannabis.

> As this article sets forth a proposed federal framework specific to cannabis-based products that are also subject to a state regulatory model, there is no additional need for the cannabis plant to remain on any schedule within the CSA.

Opioids are commonly prescribed for pain[35] and, in light of the opioid crisis faced by the United States right now,[36] the promising early data on the use of medical cannabis for the treatment of pain are quite notable. This is even more true considering that more than 25 of the US medical cannabis programs list "pain" (with varying types of pain including moderate-to-severe, severe, chronic, intractable, and debilitating) as a qualifying condition. The use of medical cannabis instead of opioids for the treatment of pain continues to gain momentum on the state level as certain states even have enacted legislation as a means to reduce the use of opioids[37] or have expanded their existing medical cannabis programs to include qualifying conditions that could be treated with an opioid.[38]

Hence, medical cannabis programs appear to correlate with improved health outcomes and decreased health care costs. The above is one example that demonstrates

the potential role of medical cannabis in the opioid crisis. The state programs have several qualifying conditions and there is a confidence among the scientific and medical community that other conditions can successfully be treated with cannabis. To date, medical cannabis has been established as a safe and effective treatment for certain conditions and thus should be eligible for insurance coverage.[39,40]

Scheduled Status of Cannabis

With the implementation of a federal framework to interface with the existing state-regulated markets, the cannabis plant should be removed from the CSA. This proposed federal framework is not a legalization measure. Individual states retain the autonomy to determine what type of regulated market is appropriate for their individual state, and the proposed federal framework is structured to defer to the state-led initiatives. Both AMS and the AC will ensure that the state programs provide adequate instruction and oversight of cannabis-based products.

If a state does not have a regulatory framework that provides a pathway to bring a cannabis-based product to market, then such product would not be allowed in that jurisdiction but for the mandate to recognize a medical cannabis product that was obtained via a valid prescription in a jurisdiction with a regulated medical program.

Each of the five schedules of the CSA have certain criteria that must be met before a substance is placed in a schedule, and each schedule is based on the premise that there is a need to regulate a substance. As this article sets forth a proposed federal framework specific to cannabis-based products that are also subject to state regulatory models, there is no need for the cannabis plant to remain in any schedule of the CSA.

Even without a specific federal framework for cannabis-based products, the plant should not be included in Schedule I of the CSA. This is in part due to the lack of

Cannabis *Cannabis sativa*
Photo ©2019 Lode Van de Velde

proper review of the plant before the plant was scheduled in 1970,[41] and, more importantly, the well-established medicinal value and safety profile of the plant. The criteria for a substance to be placed in Schedule I and II are:

(1) Schedule I. —

- (A) The drug or other substance has a high potential for abuse.
- (B) The drug or other substance has *no currently accepted medical use* in treatment in the United States.
- (C) There is a *lack of accepted safety* for use of the drug or other substance under medical supervision.

(2) Schedule II. —

- (A) The drug or other substance has a high potential for abuse.
- (B) The drug or other substance has a currently accepted medical use in treatment in the United States or a currently accepted medical use with severe restrictions.
- (C) Abuse of the drug or other substances *may lead to severe psychological or physical dependence*.[42]

As explained in the full paper under the section titled "Evidence and Science of the Plant," there is ample evidence to support the medical applications of the plant, and it has an accepted safety profile. The remaining schedules of the CSA are less restrictive than Schedules I and II, but they are still based on the premise that the substances need to be controlled. As stated, with a federal framework designed for cannabis-based products there is not a need for the plant to be scheduled.

The pathway to market for cannabis-based products in the United States will be determined by the individual state frameworks, which are subject to the standards developed by the AC and the requirements identified by the AMS. The state-regulated pathway to market for cannabis-based products will coexist with the drug pathways under the FDA.

Funding Mechanism

Funding for the federal interface with AMS (and the AC, if needed) will be absorbed by the individual state programs.

Use of Technology

As is practical, both the AMS and the AC are encouraged to use modern technology platforms to facilitate the tracking, collection, and analysis of data. Public health trends and additional therapeutic uses of cannabis can be determined with methodical monitoring and collection of data from the state-regulated markets. Blockchain is one example of modern technology that may facilitate review of real-time data. The concept of big data to better inform health research and patient outcomes is gaining momentum. Other types of analytic data are driving innovation to meet patient and consumer demands. The use of modern technologies to understand consumer and patient uses of the plant along with any impacts on society will be instrumental in keeping pace with burgeoning market influences (e.g., consumer demands, investment opportunities, global interests, and overall market growth).

The breadth of expertise within the USDA, and specifically the AMS, in working with plants and crops was a key deciding factor to structure the proposed framework with the USDA as the federal interface.

In sum, the guardrails for the proposed framework are not overly prescriptive, yet are intended to provide adequate structure and substance to the federal interface to ensure the long-term vitality of the regulated cannabis industry.

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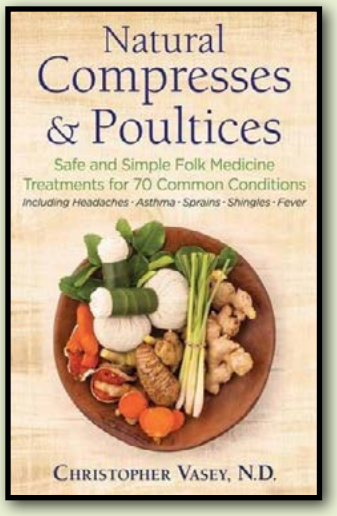
References

1. One Hundred Fifteenth Congress of the United States of America. Agriculture Improvement Act of 2018. Public Law 115-334. January 3, 2019. Available at: www.govinfo.gov/content/pkg/BILLS-115hr2enr/pdf/BILLS-115hr2enr.pdf.
2. Zhou ZK, Bartholomew B. Cannabaceae. In: Wu ZY, Raven PH, Hong DY, eds. *Flora of China.* Vol 5. Science Press, Beijing, and Missouri Botanical Garden Press, St. Louis; 2003:74-75.
3. United States Department of Agriculture. *USDA Local Offices.* Washington, DC: USDA. Available at: www.outreach.usda.gov/USDALocalOffices.htm. Accessed April 13, 2019.
4. United States Department of Agriculture Agricultural Marketing Service. *About AMS.* Washington, DC: USDA. Available at: www.ams.usda.gov/about-ams. Accessed April 13, 2019.
5. United States Department of Agriculture Agricultural Marketing Service. *Services.* Washington, DC: USDA. Available at: www.ams.usda.gov/services. Accessed April 13, 2019.

6. Lau E. Cannabis for veterinary patients gets research attention, funding. Stigma begins to lift but legal questions persist. *VIN News Service.* March 29, 2018.
7. Utah Department of Agriculture and Food. *Cannabis Laws.* State of Utah. Available at: www.ag.utah.gov/cannabis-information.html. Accessed April 13, 2019.
8. Oregon Department of Agriculture. *Cannabis (marijuana).* ODA. Available at: www.oregon.gov/ODA/agriculture/Pages/Cannabis.aspx. Accessed April 13, 2019.
9. Washington State Department of Agriculture. *Pesticide and Fertilizer Use for the Production of Marijuana in Washington.* Olympia, Washington: WSDA. Available at: https://agr.wa.gov/pestfert/pesticides/pesticideuseonmarijuana.aspx. Accessed April 13, 2019.
10. Illinois Department of Agriculture. *Medical Cannabis Pilot Program - Frequently Asked Questions.* Springfield, Illinois: IDA. Available at: www2.illinois.gov/sites/mcpp/Documents/mcppfaq-Updated-2-19-15.pdf. Accessed April 13, 2019; 2015.
11. Colorado Department of Agriculture. *Cannabis Pesticide Education.* Broomfield, Colorado: CDA. Available at: www.colorado.gov/pacific/agplants/cannabis-pesticide-education. Accessed April 13, 2019.
12. Senate and House of Representatives of the United States of America. *Farm Security and Rural Investment Act of 2002, Public Law 107-171, §10806(b), Ginseng Labeling.* Washington, DC: US Government Publishing Office; May 13, 2002.
13. United States Department of Agriculture. 7 CFR § 65.145 - Ginseng. In: *Code of Federal Regulations.* Washington, DC: US Government Printing Office; 2018.
14. Office of the Law Revision Counsel. 21 USC 343: Misbranded food. In: *United States Code.* Washington, DC: US House of Representatives; 2018.
15. United States Department of Agriculture Agricultural Marketing Service. *United States Standards for Grades of Cultivated Ginseng.* Washington, DC: USDA; 2012.
16. Ginseng Board of Wisconsin (GBW). Marathon, Wisconsin: GBW. Available at: www.ginsengboard.com/. Accessed October 9, 2018.
17. Far West Spearmint Oil Administrative Committee. *Marketing Order.* Kennewick, Washington: Far West Spearmint Oil Administrative Committee. Available at: www.farwestspearmint.org/marketing-order.html. Accessed October 9, 2018.
18. Wells J. Washington has more pot than it can smoke. CNBC.com. February 11, 2015.
19. Stangel M, Shepherd K. Oregon Grew More Cannabis Than Customers Can Smoke. Now Shops and Farmers Are Left With Mountains of Unwanted Bud. It turns out Oregonians are good at growing cannabis—too good. *Willamette Week.* April 19, 2018.
20. United States Department of Agriculture. *Yearbook of the United States Department of Agriculture 1895.* Washington, DC: Government Printing Office; 1896.
21. Chicago Lewis A. Mitch McConnell: Drug warrior, CBD champion? *Rolling Stone.* June 29, 2018.
22. Hughes T. California city to use pot shops to fight racial inequities. *USA Today.* August 1, 2017.
23. Special Activity Permits Office. *Cannabis Permits.* Oakland, California: The City Administrator's Office. Available at: www2.oaklandnet.com/government/o/CityAdministration/cannabis-permits/index.htm. Accessed April 13, 2019.
24. Taylor Jr. OR. Oakland's marijuana equity program is hurting those it was supposed to help. *San Francisco Chronicle.* July 15, 2018.
25. Wolfe L. Oakland's weed equity program not helping intended recipients. *Reason.* July 19, 2018.
26. US Small Business Administration. Title 13: Business Credit and Assistance. Part 121: Small Business Size Regulations. In: *Code of Federal Regulations.* Washington, DC: Government Printing Office; 2018.
27. US Food and Drug Administration. *FDA Food Safety Modernization Act (FSMA).* Silver Spring, Maryland: US Food and Drug Administration. Available at: www.fda.gov/food/guidanceregulation/fsma/. Accessed April 13, 2019.
28. US Food and Drug Administration. 21 CFR Parts 1, 11, 16, 106, 110, et al. Current Good Manufacturing Practice, Hazard Analysis, and Risk-Based Preventive Controls for Human Food; Final Rule. *Federal Register.* 2015;80(180):55908-56168.
29. Americans for Safe Access. *Medical Marijuana Access in the United States – A Patient-Focused Analysis of the Patchwork of State Laws. 2018 Annual Report.* Washington, DC: Americans for Safe Access; 2018.
30. Bachhuber MA, Saloner B, Cunningham CO, Barry CL. Medical cannabis laws and opioid analgesic overdose mortality in the United States, 1999-2010. *JAMA Intern Med.* 2014;174(10):1668-1673.
31. Bradford AC, Bradford WD. Medical marijuana laws reduce prescription medication use in Medicare Part D. *Health Aff (Millwood).* 2016;35(7):1230-1236.
32. Bradford AC, Bradford WD, Abraham A, Bagwell Adams G. Association between US state medical cannabis laws and opioid prescribing in the Medicare Part D population. *JAMA Intern Med.* 2018;178(5):667-672.
33. Zdechlik M. Analysis: Medical cannabis users find pain reduction. *MPR News.* March 1, 2018.
34. Mulcahy M, Erickson J. What are we learning about medical marijuana? *MPR News.* March 6, 2018.
35. Dowell D, Haegerich TM, Chou R. CDC guideline for prescribing opioids for chronic pain — United States, 2016. *MMWR Recomm Rep.* 2016;65(No. RR-1):1-49. doi: http://dx.doi.org/10.15585/mmwr.rr16501e15581.
36. US Department of Health and Human Services. *HHS Acting Secretary Declares Public Health Emergency to Address National Opioid Crisis.* Washington, DC: US Department of Health and Human Services; October 26, 2017.
37. Wall C. Rauner signs bill legalizing medical marijuana as opioid alternative. *ABC 7 Eyewitness News.* August 28, 2018.
38. New York State Department of Health. *New York State Department of Health Announces Opioid Replacement Now a Qualifying Condition for Medical Marijuana.* Albany, New York: New York State Department of Health; July 12, 2018.
39. MacCallum CA, Russo EB. Practical considerations in medical cannabis administration and dosing. *Eur J Int Med.* 2018;49:12-19.
40. National Academies of Sciences, Engineering, and Medicine. *The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research.* Washington, DC: The National Academies Press; 2017.
41. United States Commission on Marihuana and Drug Abuse. *Marihuana: A signal of misunderstanding; First report.* Washington, DC: US Government Printing Office; 1972.
42. US Drug Enforcement Administration. 21 USC. 812 - Schedules of controlled substances. In: *United States Code.* Washington, DC: US Government Printing Office; 2012.

New Book Profiles

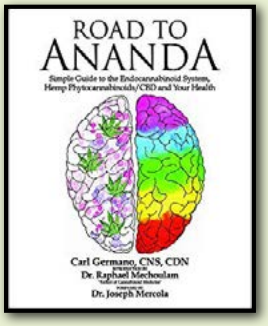
***Natural Compresses & Poultices: Safe and Simple Folk Medicine Treatments for 70 Common Conditions* by Christopher Vasey. Rochester, VT: Healing Arts Press; 2019. ISBN: 9781620557372. Softcover, 144 pages. $14.99.**



Poultices are gentle, effective, and time-honored herbal remedies that are easy to make at home. These simple preparations can be used for minor complaints such as pain and inflammation, congestion, mild fever, and more. This guide includes 70 recipes for poultices and compresses, with directions on how to prepare the materials and use the treatment, whether it is most effective hot or cold, and the proper duration of the treatment. The text also discusses the mechanisms behind the effectiveness of these treatments, which can be an integral part of a home first-aid kit.

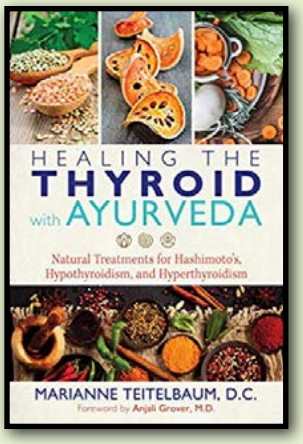
***Healing the Thyroid with Ayurveda: Natural Treatments for Hashimoto's, Hypothyroidism, and Hyperthyroidism* by Marianne Teitelbaum. Rochester, VT: Healing Arts Press; 2019. ISBN: 9781620557822. Softcover, 288 pages. $16.99.**

Focusing on diseases that affect the thyroid, Marianne Teitelbaum, DC, combines the ancient Indian practice of Ayurveda with modern research in this guide for practitioners and consumers. Teitelbaum draws from more than 30 years of her Ayurvedic practice to outline basic principles of diagnosis and treatment, and also explains the underlying causes of thyroid malfunction. The text discusses the use of herbs, dietary recommendations, and detoxification methods not only for specific thyroid conditions but also for symptoms common to these conditions, such as insomnia, depression, fatigue, hair loss, and weight gain.

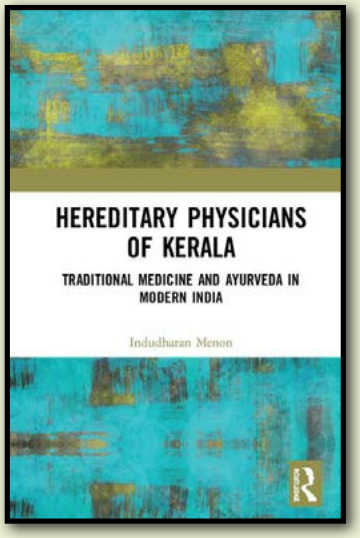


***Road to Ananda: Simple Guide to the Endocannabinoid System, Hemp Phytocannabinoids/CBD and Your Health* by Carl Germano. Broken Arrow, OK: Healthy Living Publishing; 2018. ISBN: 9780578447926. Softcover, 107 pages. $21.65.**

Supplement industry veteran and nutrition author Carl Germano pushes past the still-lingering stigma attached to the cannabis (*Cannabis* spp., Cannabaceae) plant to define and explain the endocannabinoid system of the human body. This physiological system modulates the body's response to inflammation, stress, and more, and is a growing area of study. Germano claims that this system can help one attain a state of bliss known as *ananda* in Sanskrit, or what is called homeostasis in the West. With an introduction by famed cannabis pioneer Raphael Mechoulam, PhD, *Road to Ananda* makes the case for cannabis preparations as an integral part of botanical medicine and the key to a full spectrum of wellness.



***Hereditary Physicians of Kerala: Traditional Medicine and Ayurveda in Modern India* by Indudharan Menon. London, UK: Routledge; 2019. ISBN: 9781138617308. Hardcover, 238 pages. $140.00.**



This book examines the history and evolution of Ayurveda and other indigenous Indian medical traditions and contrasts them with the practices and demands of modern India. The author draws from his extensive fieldwork to explore Kerala's remaining traditionally trained hereditary practitioners (folk healers, poison therapists, Sanskrit-speaking Muslim Ayurvedic practitioners, and Brahman Ashtavaidyan physicians) and examines the geographical, historical, sociocultural, ethnographic, and regional contexts in which they developed. This book will be useful to researchers and scholars of medical anthropology, health and social medicine, sociology and social anthropology, and Indian history.

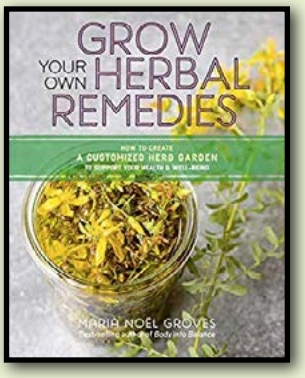
Chocolate: Superfood of the Gods **by Linda Woolven and Ted Snider. Twin Lakes, WI: Lotus Press; 2018. ISBN: 9780940676497. Softcover, 228 pages. $15.95.**

This text explores the reported benefits of chocolate and cacao (*Theobroma cacao*, Malvaceae) for heart health, cognition, and symptoms associated with multiple conditions and disease states, including type 2 diabetes. The authors cite clinical trials and discuss flavonoids and other phytochemicals present in chocolate. Chocolate's history, production, and mythology also are discussed. In addition, the book includes recipe ideas for incorporating chocolate and cocoa into the diet in creative ways. The extensive references provide further information for readers who seek to learn more about this "superfood."

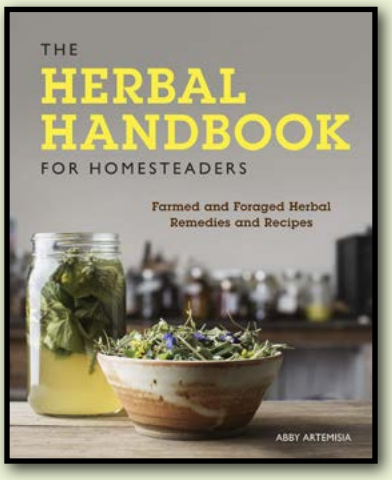
The Herbal Handbook for Homesteaders: Farmed and Foraged Herbal Remedies and Recipes **by Abby Artemisia. London, UK: Voyageur Press; 2019. ISBN: 9780760361863. Softcover, 160 pages. $24.99.**

Those on a quest to be self-reliant will appreciate the information in *The Herbal Handbook for Homesteaders*, particularly about the use of herbal medicine for pets and children. The book includes practical techniques and covers remedies such as poultices for minor injuries, flea washes and insect repellents for animals, and immune-boosting syrups and teas for cough, sore throat, and other ailments. The book is divided into sections such as "Bug Repellents and Skin Soothers" and "Allergies and Pain." Also included are several recipes for wild greens such as dandelion (*Taraxacum officinale*, Asteraceae), medicated vinegar, household cleaning spray, and pickles. Ethical and sustainable wild-harvesting is emphasized.

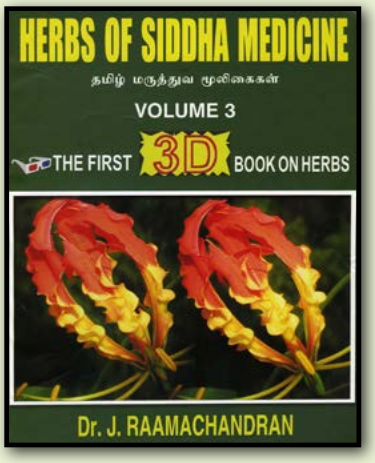
Grow Your Own Herbal Remedies: How to Create a Customized Herb Garden to Support Your Health and Well-being **by Maria Noël Groves. North Adams, MA: Storey Publishing; 2019. ISBN: 9781635860139. Softcover, 336 pages. $24.95.**



This text invites readers to grow herbal remedies from seed and provides 23 examples of "remedy gardens" that feature four or five common, easy-to-grow botanicals targeted to specific body systems. Clinical herbalist and teacher Maria Noël Groves also includes recipes that use these plants and instructions for how to prepare tinctures and capsules. The last section of the book contains plant profiles for each herb mentioned and extensive resources for further reading, conversion charts, and information about where to purchase supplies. With instructions from seed to harvest to preparation, Groves guides the reader through each stage of growth of medicinal herbs.

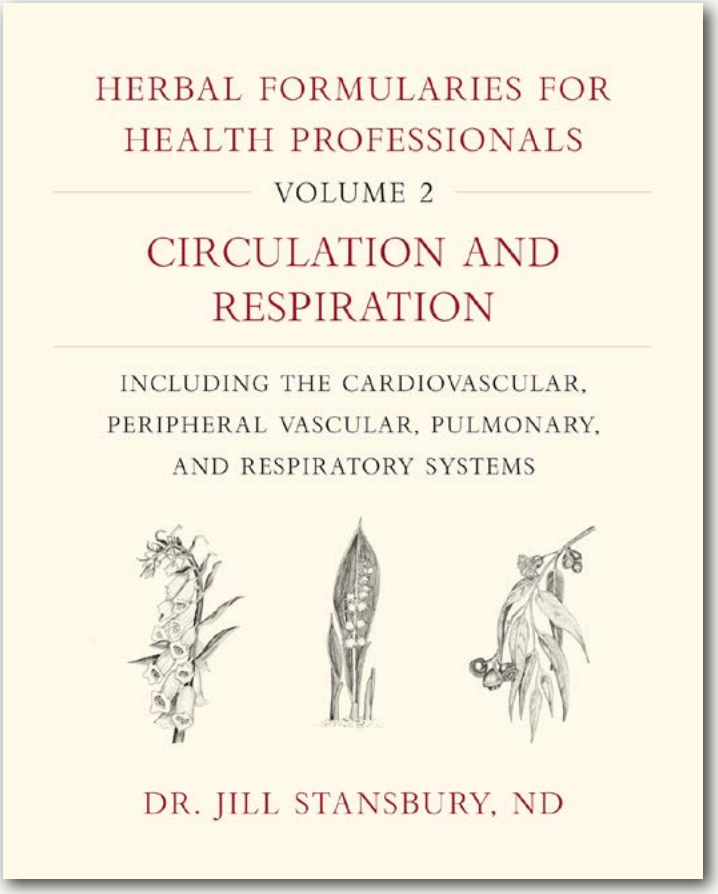


Herbs of Siddha Medicine**, Volume 3, by J. Raamachandran. Chennai, India: Murugan Siddha Marundhagam; 2018. ISBN: 9788190612326. Hardcover, 612 pages. $50.00.**



Herbs of Siddha Medicine is the third volume in a series of identification guides with pictures that can be viewed in 3D by using the provided glasses. This volume contains information about 100 botanicals used in Siddha medicine, a traditional healing practice from the southern state of Tamil Nadu, India. Organized alphabetically by Latin binomial, each two-page spread includes a list of phytochemicals present, the plant's medicinal properties, a detailed physical description, history and methods of use, and pictures. The herbs are identified by their common names in several languages, including Tamil, Hindi, Sanskrit, and English.

Herbal Formularies for Health Professionals, Volume 2: Circulation and Respiration, including the Cardiovascular, Peripheral Vascular, Pulmonary, and Respiratory Systems by Jill Stansbury. White Mountain Junction, VT: Chelsea Green Publishing; 2018. Softcover, 256 pages. ISBN: 9781603587983. $44.95.



Volume two of *Herbal Formularies for Health Professionals* by Jill Stansbury, ND, confirms that this planned five-volume series represents a major contribution to the literature on the practice of herbal medicine in the 21st century. Written by one of North America's foremost experts in naturopathic herbal medicine, the series should be essential reading for naturopathic students and on the shelves of all practitioners who use medicinal plants. This volume covers treatments and *materia medica* related to the cardiovascular, peripheral vascular, pulmonary, and respiratory systems in a similar way to the impressive coverage of digestion and elimination in volume one, also published in 2018. Volume three will cover endocrinology; volume four, neurology, psychiatry, and pain management; and finally, volume five, immunology, orthopedics, and otolaryngology.

The author is an internationally known naturopathic physician with decades of both clinical experience and experience teaching herbalists and naturopaths. This allows her to explain potentially obscure knowledge in a very approachable way. She served as the chair of the Botanical Medicine Department of the National University of Natural Medicine in Portland, Oregon, for more than 20 years, and remains on the faculty, teaching and leading ethnobotany field courses in the Amazon.

Continuing with the format that worked so well in volume one, this book addresses herbal treatment of pathologies that affect circulation and respiration. The opening is a cogent exploration of Stansbury's perspective on health and wholeness, which leads into a synthesis of three broad approaches to healing: modern naturopathic medicine (and its Eclectic roots), current phytotherapy, and traditional Chinese medicine (TCM). This is presented in a way that both practitioners and advanced students will find enlightening. The first chapter, titled "The Art of Herbal Formulation," is, by itself, a reason to get the book, as it explores one of the most abstruse areas of herbal medicine with clarity and insight that will be especially appreciated by teachers (and their often-confused students!).

The breadth of the coverage of cardiovascular and peripheral vascular systems starts with generalized treatments for support of the systems, followed by protocols for hyperlipidemia and atherosclerosis, angina and coronary artery disease, hypertension and hypotension, congestive heart failure, and arrhythmias. Approaches to vascular insufficiency are particularly well-developed with protocols for peripheral and cerebral problems, as well as capillary fragility and telangiectasia (spider veins). Specific pathologies discussed include Raynaud's syndrome, anemia, hemochromatosis (hereditary excessive iron absorption), venous congestion, and varicosities. Stansbury's work experience in the Andes Mountains informs a section on heart stress at high altitudes.

Throughout the book, there is a solid foundation of physiological and pharmacological rationale for the herbs used, and the author relates every formula to pathophysiology and the healing process. The author's synthesis of medical science with insights of naturopathy is truly refreshing and reflects her recognition that in the face of a patient's needs, all approaches are complementary.

There is a large *materia medica* suggested for cardiovascular conditions. This might surprise readers familiar with the anemic list proposed by modern phytotherapy or supported by evidence-driven medicine. It must be remembered that we only have "evidence" if the science has looked at a specific herb, and only a handful of the herbal *materia medica* has been assessed in clinical trials. The relevance and use of 125 herbs for cardiovascular health care are explored, with a number of important herbal issues discussed in more depth in call-out sections. These sidebars include "*Viscum album* for the Heart" (which addresses the use of European mistletoe), "*Centella asiatica* against Fibrosis" (which addresses the use of gotu kola), "Herbal Flavonoids for Protecting the Vasculature," "Fibrinolytic Botanicals," "Solid Extracts for Varicosities," and many more.

Chapter three, "Creating Herbal Formulas for Respiratory Conditions," is a breath of fresh air! Treatments for respiratory problems are a strength of herbalism, but not presented adequately in most current texts. Stansbury has again presented a successful marriage of well-established traditional protocols with phytotherapy and TCM.

Chapter three starts with "Creating Topical Applications for Lung Complaints," which covers essential material that often is overlooked. The chapter continues with sections on formulas for coughs and altered breath sounds, dyspnea (difficult breathing), hemoptysis (coughing of blood or blood-containing mucus), allergic rhinitis, acute and chronic bronchitis, cystic fibrosis, emphysema, pleurisy, asthma, chronic obstructive pulmonary disease (COPD), and more.

The respiratory *materia medica* discusses an impressive 170 herbs. A unique and invaluable feature is the discussion that focuses on their relevance to a particular system. For example, the subtleties of yarrow's (*Achillea millefolium*, Asteraceae) indications for the cardiovascular system are differentiated from the respiratory indications. This is yet another example of the insights of clinical practice being applied to the challenges of education.

Throughout the book, there are plentiful examples of formulas, how to make them, and, possibly of more importance, how to use them. The book is not only replete with such useful, one might say irreplaceable, techniques, but also abounds with formulations widely used by the Eclectics but that are now almost forgotten. This collective loss of memory is not because they do not work, but usually they require medicine-making skills no longer found in pharmacies. Hopefully, the information in the book will encourage "old-time" practitioner self-sufficiency. Another refreshing aspect is the author's presentation and usage of important herbs that seem to have gone out of fashion. There are a number of reasons for such trends, but the overriding issue is therapeutic relevance, not market availability.

Herbal Formularies for Health Professionals is a major work that should be appreciated by those involved in the practice or teaching of herbal medicine. In the hands of clinicians such as Jill Stansbury, herbal medicine has a bright future in 21st-century health care. HG

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Principal Scientist, Traditional Medicinals
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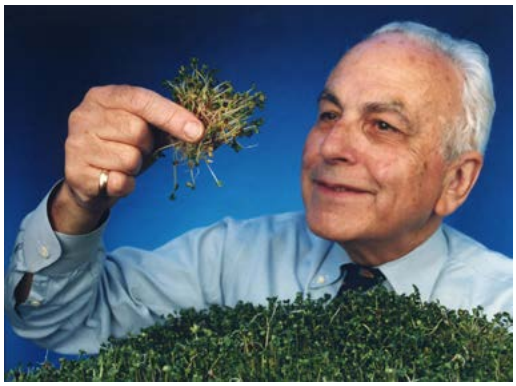
Paul Talalay 1923–2019

By Hannah Bauman



Internationally renowned pharmacologist Paul Talalay, MD, died on March 10, 2019, in Baltimore, Maryland, at the age of 95. Talalay was known for the study of cancer-preventive compounds in food, particularly glucoraphanin and sulforaphane from broccoli (*Brassica oleracea*, Brassicaceae) crowns and sprouts.

Talalay was born on March 31, 1923, in Berlin, Germany. Previously, his Russian-Jewish parents fled Russia following the revolution of 1917. In 1933, after Adolf Hitler's appointment as chancellor, Talalay's parents again faced the rise of anti-Semitism and obtained, at extraordinary cost, illicitly issued Haitian passports for the family. Talalay and his family left Berlin on his 10th birthday and traveled through Belgium before settling in England. Talalay received his primary education at Bedford School in Bedford, England, where he learned to speak English and developed a love of science.

The threat of war in 1940 once again prompted the family to move. Despite missives from the German government warning of German Jews carrying Haitian passports, the Haitian consulate in England renewed their passports, and the Talalay family embarked on a 10-day journey on the *SS Samaria* across the Atlantic Ocean to the United States. Since German submarines patrolled the waters, the passengers on the *Samaria* lived in "blackout" conditions and were forbidden to go on deck after dark or have any source of light. Ships traveled in convoys for protection in numbers, and one of the ships in their convoy was sunk by a German torpedo.

After the Talalay family settled in New York City, New York, Paul Talalay attended the Massachusetts Institute of Technology in Cambridge, Massachusetts, where he earned a bachelor's degree in biophysics in 1944. From 1944 to 1946, he attended the University of Chicago medical school, where he conducted research under Charles Huggins, MD. Huggins' research on how hormone treatment could alter the course of metastatic prostate cancer changed the way scientists viewed the development and treatment of cancer and eventually earned him the 1966 Nobel Prize in Physiology or Medicine. Under Huggins' supervision, Talalay also learned to view cancer treatment and prevention in a different light, and the experience influenced his course of study. After two years, he left Chicago to complete his degree at the Yale School of Medicine at Yale University in New Haven, Connecticut. He earned his MD in 1948.

After completing surgical training as a house officer at the Massachusetts General Hospital, Talalay returned to Huggins at the University of Chicago in 1950 as an American Cancer Society-Damon Runyon Fund Postdoctoral Fellow to study steroid hormones and their effects on prostate cancer. Later that same year, he was promoted to assistant professor, and then to professor of biochemistry and medicine at the Ben May Laboratory for Cancer Research at the university. In 1952, he took a brief sabbatical to Cambridge, England, where he met his wife Pamela, who was studying for her PhD in biochemistry.

Talalay remained at the University of Chicago until 1963, when he moved to Johns Hopkins University in Baltimore as chairman of the Department of Pharmacology and Experimental Therapeutics. In this position, he founded one of the first Medical Scientist Training (MD-PhD) Programs in the country, recruited and nurtured many outstanding faculty members and students, and guided the school of medicine's overall academic program. Colleagues referred to his tenure from 1963 to 1975 as "legendary."[1]

In 1973, Talalay received a Guggenheim Fellowship and returned to England. The experience of working in a laboratory full-time prompted him to resign his directorship of the department and pursue scientific study of his own interests. Upon his return from England, Johns Hopkins University named him the John Jacob Abel Distinguished Service Professor of Pharmacology and Experimental Therapeutics, a title he held until his death.

Talalay's research on "chemoprotection" was, at the time, counter to prevailing medical opinion, which maintained that cancer could not be prevented. Nevertheless, he changed direction from cancer treatment to cancer prevention, and his focus turned to phytochemicals in plants. Talalay not only believed cancer could be prevented, but he preferred the active term "protection."

After spending more than a decade developing a precise, quantitative laboratory assay capable of rapidly and reliably measuring enzyme protective activity, Talalay's research team saw a breakthrough with the identification and isolation of sulforaphane present in broccoli, which appeared to interact with proteins in cells that prevented the spread of cancer. Studies using animal models subsequently confirmed these findings, and Talalay and his colleagues published their research in 1992.[2] Following this discovery, he founded the Brassica Chemoprotection Laboratory, now known as the Lewis B. and Dorothy Cullman Chemoprotection Center, at Johns Hopkins. The center soon expanded its focus from broccoli and took an interdisciplinary approach to investigating the preventive properties of other substances, such as honey and moringa (*Moringa oleifera*, Moringaceae), for a broad look at chronic conditions in addition to cancer. With colleagues around the world, they extensively studied the biochemical cellular pathways to understand the natural processes of cell protection.

In 1997, Talalay; his colleague Jed Fahey, ScD, from Johns Hopkins; and his son Tony Talalay founded Brassica Protection Products under a licensure agreement from Johns Hopkins. The company formulates products using broccoli seeds and sprouts, which were found to contain much higher concentrations of the precursor of sulforaphane than mature broccoli crowns, and released its first nutritional supplement and food ingredient, SGS™ (later rebranded as TrueBroc®), in 2001. Brassica Protection Products received the American Botanical Council's 2016 Varro E. Tyler Commercial Investment in Phytomedicinal Research Award for the company's research on and promotion of the benefits of broccoli, which also include actions against *Helicobacter pylori* bacteria and elimination of airborne pollutants from the body.

Despite his focus on broccoli and its constituents, Talalay often cautioned against pinning all one's hopes on a single compound. "We try to avoid hype," he was quoted as saying.[3] "A diet of mostly plant-based foods, in moderation, is the best protection you can obtain."

In addition to his long career in the laboratory, Talalay served as an associate editor of *The Journal of Biological Chemistry* from 1962 to 1966. He also earned one of the first lifetime professorships of the American Cancer Society, which helped fund his research. He was a member of the National Academy of Sciences, the American Philosophical Society, and the American Academy of Arts and Sciences. In addition, the MD-PhD student library at the Johns Hopkins school of medicine bears his name, as does an award given by the university to PhD candidates as a part of Young Investigators' Day, an initiative he also founded.

In his personal life, Talalay was perhaps most proud of his walk-on roles in several films by Baltimore legend John Waters, including an appearance as a man exiting an X-rated film theater in the 1981 film "Polyester." His students also delighted in their professor's screen "career." Paul Talalay is survived by his wife Pamela, children Tony, Susan, Rachel, and Sarah, four grandchildren, and many beloved nieces and nephews. HG

References

1. Anft M. A Nibble of Prevention. *Johns Hopkins Magazine*. April 2008. Available at: http://pages.jh.edu/~jhumag/0408web/talalay.html. Accessed April 18, 2019.
2. Zhang Y, Talalay P, Cho CG, Posner GH. A major inducer of anticarcinogenic protective enzymes from broccoli: isolation and elucidation of structure. *Proc Natl Acad Sci USA*. 1992;89(6):2399-2403.
3. Paul Talalay and Jed Fahey. Institute for Basic Biomedical Sciences website. Available at: www.hopkinsmedicine.org/institute_basic_biomedical_sciences/about_us/scientists/Talalay_Fahey.html. Accessed April 18, 2019.

Koji Nakanishi 1925–2019

By Hannah Bauman

Koji Nakanishi, PhD, professor emeritus of chemistry at Columbia University, died on March 28, 2019, at age 93, in New York City, New York, after a brief illness. Nakanishi focused on the isolation and study of bioactive compounds and the development of spectroscopic methods for identification.

Natural product chemist Michael Tempesta, PhD, who completed two post-doctoral sessions under Nakanishi's tutelage, commented: "For those of us close to the natural products chemistry, bioorganic chemistry, and many other life sciences/healing fields, it was clear that Koji was unique among scientists and researchers. His ability to bridge the disciplines and encourage others in the pursuit, as well as the development, of many new techniques for determination of structural features in stereochemical situations was fundamental" (email, April 2, 2019).

Born in Hong Kong on May 11, 1925, Nakanishi earned his bachelor's degree in chemistry from Nagoya University in Japan in 1947. He earned a Fulbright scholarship, reportedly the first awarded to a Japanese student following World War II, and studied at Harvard University in Cambridge, Massachusetts, under Louis Fieser, PhD, from 1950 to 1952. After completing his Fulbright program, he returned to Nagoya University for his PhD, which he earned in 1954. His teaching career began shortly after, and he served as an assistant professor at Nagoya until 1958.

Nakanishi taught as a professor of chemistry at two of Japan's most prestigious universities: the Tokyo University of Education (now known as the University of Tsukuba) in Tsukuba from 1958 to 1963 and Tohoku University in Sendai from 1963 to 1969. One of his students at the Tokyo University of Education, Satoshi Omura, PhD, received the Nobel Prize in Physiology or Medicine in 2015 jointly with William C.

Campbell, PhD, for their discoveries concerning a novel therapy against infections caused by roundworm parasites.

Nakanishi began to take a global approach to his research at this time and was a founding member and the first director of research at the International Centre of Insect Physiology and Ecology in Nairobi, Kenya, in 1969, the same year he joined the faculty of Columbia University. In 1980, Columbia named him Centennial Professor of Chemistry, a title he held until his death.

In 1967, Nakanishi used his pioneering methods of isolation and identification to elucidate the structure of ginkgolides from *Ginkgo biloba* (Ginkgoaceae). The effects of ginkgo extract on neurological disorders would become a major research focus for his team in the chemistry department at Columbia. He also studied bioactive compounds from other sources, including illudins produced by some mushrooms and taxine alkaloids from yew (*Taxus* spp., Taxaceae). Other research interests included the study of toxins from insects and single-celled organisms; retinal proteins to determine the cause and progression of macular degeneration; and the development of mass spectrometric protocols to sequence membrane proteins.

During his tenure at Columbia, Nakanishi served as the chairman of the chemistry department from 1987 to 1990, mentored more than 300 doctoral students, and published approximately 750 papers. From 1979 to 1991, he served as the first director of the nonprofit Suntory Institute for Bioorganic Research (now known as the Suntory Foundation for Life Sciences) in Osaka, Japan, and assisted the Brazilian government with the establishment of the Institute of Medicinal and Ecological Chemistry in São Paulo. He published his autobiography, *A Wandering Natural Products Chemist* (American Chemical Society), in 1991. In addition to his academic papers and autobiography, Nakanishi also authored, co-authored, or edited eight more books on spectroscopy and natural products research and served on the editorial board of *Phytomedicine* from 1997 to 2016.

From 2001 to 2003, Nakanishi served as the director of chemistry at the University of Arizona's Biosphere 2 project in Oracle, Arizona. Biosphere 2, a research facility and academic center focused on earth sciences, contains a glass-domed building that simulates five different biomes, including rainforest and savannah, and allows students at the undergraduate and graduate levels to study the chemistry of plants grown in these conditions without ultraviolet light.

Nakanishi received many recognitions, awards, and honors over his six-decade career. The first, awarded in 1954, was the Award in Pure Chemistry from the Chemical Society of Japan (CSJ). Other notable awards include: the Centenary Prize from the Royal Society of Chemistry in 1978/1979; the first Norman R. Farnsworth Research Achievement Award from the American Society of Pharmacognosy (ASP) in 1985; the Imperial Prize of the Japan Academy in 1990; the William H. Nichols Medal Award from the American Chemical Society (ACS) in 1992; the King Faisal International Prize for Science in 2003; and the Silver Medal Award from the International Society of Chemical Ecology in 2007.

Perhaps the most significant honor was the foundation of the Nakanishi Prize, which was jointly established by the ACS and CSJ in 1995. This was the first award from the ACS to bear a person's name and was created "to recognize and stimulate significant work that extends chemical and spectroscopic methods to the study of important biological phenomena."[1] The award is presented in alternating years by ACS or CSJ.

Nakanishi also has been recognized with honorary issues of the journals *Chirality* (1997), *Heterocycles* (1998), and *Bioorganic and Medicinal Chemistry* (2005). He was a fellow of the American Academy of Arts and Sciences, the New York Academy of Sciences, ASP, the Accademia Nazionale delle Scienze in Italy, and the American Association for the Advancement of Science. He received honorary degrees from Williams College, Georgetown University, and Uppsala University; honorary professorships from Shanghai Institute of Materia Medica and Tohoku University; and honorary memberships to the Pharmaceutical Society of Japan, CSJ, and the Japanese Biochemical Society.

In his personal life, Nakanishi was an amateur magician who enjoyed performing sleight-of-hand tricks during parties, faculty meetings, and academic conferences.

Tempesta recalled his mentor's good nature: "Koji as a person was humorous and kind, and his genius was openly shared with all his students, colleagues, and friends on a daily basis for many decades. His love of magic and the ability to perform spontaneous shows under many unusual circumstances were most likely the origin of Koji's need to combine new spectroscopic techniques when determining structures of compounds from very interesting natural sources — to have the final results appear 'like magic.'… He will be missed by those of us fortunate enough to have spent time together with him during the journey."

Koji Nakanishi was preceded in death by his wife Yasuko, and is survived by his children Keiko and Jun, grandchildren Aya, Kenji, and Pico, and a great-granddaughter. HG

Reference

1. Nakanishi Prize. American Chemical Society website. Available at: www.acs.org/content/acs/en/funding-and-awards/awards/national/bytopic/nakanishi-prize.html. Accessed April 10, 2019.

Michael Bettler 1944–2019

By Laura S. Achenbaum

Master gardener, herb retailer, and herb educator and leader Michael Donel Bettler died on March 28, 2019, surrounded by loved ones.

Born in Oklahoma City, Oklahoma, on June 11, 1944, to Marcellus and Ellen (née Reed) Bettler, Michael was the younger of two children. His older brother, David Bettler, precedes him in death, as does his beloved wife of 45 years, Lucia Ferrara Bettler.

Raised primarily in Houston, Texas, Bettler attended Lamar High School and began his undergraduate education at Stephen F. Austin State University in Nacogdoches, Texas. A life-long traveler, he left school to join the US Peace Corps in 1967 and served two years in Niger, where he managed a well water pump installation program, taught water conservation and sanitation, created vegetable gardens, and adventured alongside the Tuareg people.

Upon his return to the United States, Bettler enrolled at the University of St. Thomas in Houston, where he met and married the love of his life, Lucia. After completing a degree in English, he went on to professionally teach English as a Second Language (ESL), which allowed him to share his love for language with students from diverse colleges, universities, and private corporations.

In partnership with his wife, Bettler was the co-owner of Lucia's Garden, a gift and herbal shop that operated in Houston for more than 30 years. Through the shop, he drew from his life's work and from his training as a Harris County Master Gardener to teach extensively about gardening, herb growing, medicinal herbs, and the language of flowers. Bettler was a member of the Texas Community College Teachers Association, TexTESOL, and the International Herb Association. He was also a member and past president of the Texas Herb Growers and Marketers Association.

Bettler was a highly creative person who appreciated art in its many forms. He was an accomplished photographer, poet, hobbyist cartographer, and aficionado of the Sunday funnies. He loved to travel and had a deep appreciation for the Earth and all it has to offer. His quest for knowledge and his love of folklore and symbolism made him a consummate mentor and teacher. Perhaps most of all, he will be remembered for his quick wit and humor. It was often hard to tell if a story he told was true, embellished, or the stuff of imagination. At the end of the day, however, such details didn't matter: His stories were always good and usually ended with a full-belly laugh.

Michael Bettler leaves behind a legacy of family and friends who cherish him. A memorial service celebrating Bettler's life was held on May 4, 2019, at the Live Oak Friends Meeting House in Houston, Texas. HG

Publications

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

Australian Journal of Herbal Medicine: Quarterly publication of the National Herbalists Association of Australia (founded in 1920). Deals with all aspects of Medical Herbalism, including latest medicinal plant research findings. Regular features include Australian medicinal plants, conferences, conference reports, book reviews, rare books, case studies, and medicinal plant reviews. AUD/$96 plus AUD/$15 if required by airmail. National Herbalists Association of Australia, P.O. Box 696, Ashfield, NSW 1800, Australia.

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

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Bloodroot
Sanguinaria canadensis, Papaveraceae

Native to eastern North America, bloodroot is among the first wildflowers to bloom beginning in late winter to early spring. It can grow to 10 inches tall, has a single basal leaf, and prefers semi-shaded woods with moist, acidic, humus-rich soil.[1] The species belongs to the poppy family (Papaveraceae) and is the only member of its genus. Both the genus name *Sanguinaria*, which derives from the Latin word for "blood," and the common name "bloodroot" owe to the plant's bright red sap.[2] Native Americans have used the roots to treat sore throats, cough, and wounds, among other conditions, and as a source of dye.[3] The main active compounds are alkaloids, primarily sanguinarine, which was used briefly in a toothpaste and mouthwash (Viadent®; Vipont Laboratories; Fort Collins, Colorado) to fight plaque, but was removed from the products due to concerns about potential long-term oral toxicity.[1-2] The species is subject to leaf blight from *Alternaria* and *Botrytis* fungi, root rot from *Pythium* parasites, and foraging by animals like deer.[1]

References

1. Bloodroot (*Sanguinaria canadensis*). United Plant Savers website. Available at: www.unitedplantsavers.org/bloodroot-sanguinaria-canadensis. Accessed September 28, 2017.
2. Gracie C. Bloodroot: An Understandable Misnomer. New York Botanical Garden website. April 20, 2013. Available at: www.nybg.org/blogs/plant-talk/2013/04/science/bloodroot-an-understandable-misnomer/. Accessed September 28, 2017.
3. Moerman DE. *Geraniums for the Iroquois: A Field Guide to American Indian Medicinal Plants*. Algonac, MI: Reference Publications; 1981.

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1.Belcaro G. et al. Eur. Rev. Med. Pharmacol. Sci. 2017; 2.Pellegrini L. et al. Eur. Rev. Med. Pharmacol. Sci. 2016; 3. Ernst E. BMJ. 2008.

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