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INTRODUCTION

Acerola is the common name assigned to two species in the tropical nance family (Malpighiaceae) — *Malpighia emarginata* and *M. glabra*. Both are called Barbados cherry and West Indian cherry by various sources that are not always in agreement as to which is which.¹,² Some sources even classify them as the same species.³

*Malpighia glabra* is a large shrub or small tree that can grow as tall as 20 feet (6.09 m).⁴ The pink or lavender flowers are succeeded by red drupes, i.e., stone fruits (fleshy fruits with one seed that do not split open upon maturation) sometimes referred to as acerola cherries. This species is native to the Lesser Antilles from St. Croix Island (US Insular Area) to Trinidad and Tobago, Curaçao (Netherlands), and Margarita Island (Venezuela), as well as neighboring northern South America into Brazil. *Malpighia glabra* was introduced to cultivation in Cuba, Jamaica, and Puerto Rico (US Insular Area).⁴

*Malpighia emarginata* also is a shrub or small tree that grows up to 20 feet tall.⁵ The flowers and fruit are very similar to *M. glabra*. *Malpighia emarginata* is indigenous to southern Mexico, Central America, and the northern region of South America. It was introduced to Brazil, now the world’s biggest producer, in the mid-20th century.⁵

The fruit of both species is used interchangeably and is round, bright red, one-half to one inch (1.25-2.5 cm) in diameter, with juicy, acidic pulp.⁴

HISTORY AND CULTURAL SIGNIFICANCE

Acerola fruit is high in vitamin C in the form of ascorbic acid.⁴ The fruit’s ascorbic acid content is dependent upon various factors including how and where the plant is grown, how much sunlight it receives, and at what stage of ripeness the fruit is harvested, as well as the individual plant’s genetic makeup. The amount of ascorbic acid can range from up to 4,500 mg per 100 g of edible fruit if harvested when still green, or 2,000 mg ascorbic acid per 100 g of edible fruit if harvested when very ripe. Acerola is surpassed in vitamin C content by very few sources, chief among them kakadu plum (*Terminalia latipes* ssp. *psilocarpa*, syn. *Terminalia ferdinandiana*, Combretaceae), camu-camu (*Myrciaria dubia*, Myrtaceae), and rose hips (*Rosa* spp., Rosaceae).⁶ As with many plants, some of the beneficial effects are diminished by heat. For example, jelly made from acerola may contain only 500 to 1,900 mg ascorbic acid per 100 g of fruit.⁴

*Malpighia glabra* juice is popular in Brazil, and the fruit is consumed as a natural remedy.⁷ The fruit has astringent,⁷,⁸ anti-inflammatory, stimulant, and diuretic properties.⁷ In Brazil, the fresh fruit is used for cardiovascular support,
diarrhea (Brazil, Guatemala), dysentery (Brazil, Venezuela), fever (Brazil, Mexico), wound healing (Brazil), and as nutritional support for convalescents and those who require treatment for anemia, high cholesterol, diabetes, liver conditions, rheumatism, and tuberculosis. It also has been used to treat hepatitis, breast conditions (Venezuela), and tenesmus (a symptom characterized by a sensation of constantly needing to pass stools although the colon is empty). In the United States, acriola is used as a food (e.g., juice) or as a component of dietary supplement products. For example, extracts of the whole fruit are found in vitamin C supplements, sometimes in combination with other sources of vitamin C such as ascorbic acid and/or sodium ascorbate.

The ripe fruit, which is pleasant to taste despite being slightly sour, is used in making jams, jellies, juice, ice cream, pies, and preserves, as well as for flavoring for cocktails. It also is used in making liqueurs.

**CURRENT AUTHORIZED USES IN COSMETICS, FOODS, AND MEDICINES**

For beverage food products, the United States Food and Drug Administration requires a minimum Brix Level* of 6.0 for acriola single-strength (100% juice) products. In its International Food Standards, Codex Alimentarius sets a minimum Brix Level of 6.5 for reconstituted acriola fruit juices and reconstituted acriola purée, and a minimum juice and/or purée content (% v/v) of 25.0% for acriola fruit nectars.

For conventional (non-organic) cultivation of acriola, the US Environmental Protection Agency has established maximum allowable limits for residues of various acaricides (e.g., bifenthrate), fungicides (e.g., azoxystrobin, fludioxonil), herbicides (e.g., carfentrazone-ethyl, glyphosate, paraquat), insecticides (e.g., buprofezin, chlorantraniliprole, fenpropathrin, imidacloprid, methoxyfenozide, spinetoram, spinosad, spirotetratam), and pesticides (e.g., pyriproxyfen). There are, however, more than 20 producers of certified organic acriola fruit listed in the United States Department of Agriculture National Organic Program (NOP) database of operators, most of which are situated in Brazil, but also in Costa Rica and Peru.

In Canada, acriola is classified as a medicinal ingredient and is listed as a complementary ingredient in the "Workout Supplements" monograph at a maximum daily dose of 48 g of fruit. At non-therapeutic dosages, other defined acriola substances are permitted for use as non-medicinal ingredients of licensed natural health products (NHPs). For example, acriola fruit juice, fruit juice concentrate, and/or fruit extract can be used as non-medicinal flavor-enhancing ingredients. Dried acriola fruit also may be used as a flavor enhancer or preservative antioxidant, except in vitamin C products. In such cases, acriola must be declared as a source of the medicinal ingredient vitamin C for oral vitamin C products, or for products making claims per the NHP Directorate vitamin C monograph, if the quantity of vitamin C provided is above the lower medicinal limit as stated in the monograph. At the time of this writing (August 2014), there were more than 250 licensed NHPs listing either "acriola" or "Malpighia glabra" as a medicinal ingredient and more than 120 licensed NHPs listing acriola as a non-medicinal ingredient.

In the European Union (EU), acriola fruit has been on the market as a food or food ingredient and was consumed to a significant degree prior to May 15, 1997; therefore, its presence in the EU market is not subject to the Novel Food Regulation No. 258/97. The European Food Safety Authority issued a scientific opinion on substantiation for health claims related to vitamin C, including those made for acriola fruit products. Proposed wording of acceptable claims for products containing acriola fruit at a daily amount equivalent to 12 mg vitamin C include the following: "Vitamin C can contribute to the reduction of tiredness and fatigue," "Vitamin C contributes to normal psychological functions," "Vitamin C contributes to the regeneration of the reduced form of vitamin E," "Vitamin C contributes to normal energy-yielding metabolism," "Vitamin C contributes to a normal function of the immune system," and "Vitamin C contributes to the protection of cell constituents from oxidative damage."

Several acriola ingredients are listed for use in cosmetic products by the European Commission Health and Consumers Directorate General. For example, “Malpighia Glabra Fruit,” “Malpighia Glabra Fruit Extract,” “Malpighia Glabra Fruit Juice” (juice expressed from the fruit), “Malpighia Glabra Fruit Water” (aqueous solution of the steam distillates obtained from the fruit), and “Hydrolized Acriola Fruit” (hydrolysate of the fruit derived by acid, enzyme, or other method of hydrolysis) all are listed as skin-conditioning substances; “Malpighia Emarginata Fruit Extract” and “Malpighia Emarginata Seed Extract” both are listed for hair- and skin-conditioning functions; and “Malpighia Emarginata Fruit Powder” is listed as an absorbent (takes up water- and/or oil-soluble dissolved or finely dispersed substances).

**MODERN RESEARCH**

In laboratory experiments, acriola has exhibited the following actions: acetylcholinesterase inhibition, antigentoxic, antioxidant, anti-inflammatory, free radical scavenging, inhibition of the formation of both alpha-glucosidase and advanced glycation end product, cytotoxic against tumor cell lines (human oral squamous cell carcinoma and human submandibular gland carcinoma), antibacterial, nitric oxide production inhibition, and antifungal.

Unfortunately, relatively few human clinical studies have investigated acriola’s medicinal benefits as it is consumed mainly as a food.

A clinical study published in 2011 explored the efficacy of a combination product in the treatment of recurrent upper respiratory tract infections in children. The product, Imoviral® Junior (100 mg 4% echinacoside from *Echinacea angustifolia* [Asteraceae], arabinogalactan [amount not stated], 265 mg acriola, 50 mg beta-glucan, 7 mg zinc [extraction method not stated]; Cristalfarma, Milan, Italy), was given to 37 children with recurrent pharyngotonsil-

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*Brix is a measurement of soluble solids in a liquid that can provide an approximate measure of sugar content.*
titis (inflammation of the pharynx and tonsils, characterized by sore throat) or otitis media (middle ear infection) at the dosage of one sachet per day (dissolved in water) for two weeks per month for three months. The cycle was repeated once and a follow-up was conducted at six months. The mean number of inflammatory episodes decreased from 3 ± 2.19 during the six months prior to treatment to 1 ± 0.93 during the six months following treatment. At the completion of the treatment, 77% of the children reported decreased frequency of chronic inflammation. Overall, parents expressed general satisfaction and a better quality of life for the children treated.

A 2012 single-stage, phase IV, prospective, non-comparative, open clinical study investigated a combination product intended to counteract the effects of skin aging. Twenty-nine women, 35 to 60 years of age, with skin phototypes I (pale, with light eyes and hair, who frequently burn and rarely tan) to III (darker white skin, who tan after initial burn) took two tablets per day with food for 120 days of Imedeen® (Biomarine Complex™, an extract of marine proteins and polysaccharides, and 14.8 mg LycoPhence GS™, composed of lycopene, grape seed extract, and 30 mg acerola extract; Ferrosan A/S; Copenhagen, Denmark). Concurrently, the subjects used Episol® SPF 15 lotion (Mantecorp Indústria Química e Farmacêutica Ltda.; Rio de Janeiro, Brazil) on the face, twice daily, in the morning and at lunch. Results obtained from analysis of clinical response assessment questionnaires showed that gradual and statistically significant clinical improvement in wrinkles, fine lines, redness, hydration, sebum, and smoothness was experienced with daily use.

In 2011, a crossover, experimental study in Japan investigated the bioavailability of ascorbic acid in humans. Healthy male volunteers (number not stated, aged 22 to 26 years, non-smokers not taking high-dose vitamin C supplements) took a single oral dose of ascorbic acid (50, 100, 200, or 500 mg with 100 ml distilled water). Blood was collected and centrifuged every half hour for three-and-a-half hours and at hours four, five, and six after the dose. Additionally, urine samples were collected and their volume recorded every one to two hours up to six hours after the dose. After an overnight fast, the same procedure was followed but with the subjects drinking 100 ml acerola juice (frozen mature fruit obtained from Nichirei do Brazil; Recife, Brazil) diluted with water containing 50 mg ascorbic acid. Results showed that acerola juice promoted the absorption of ascorbic acid in blood plasma and suppressed its excretion in urine better than ascorbic acid alone.

**FUTURE OUTLOOK**

The main production areas and trading centers for acerola fruit ingredients are in South American countries, particularly Brazil. Early 2014 market reports indicated flat demand for most fruit juices including acerola, which may be linked to negative publicity surrounding fruit juice consumption (due to their naturally occurring sugar levels). Prices for acerola fruit juice ingredients also have declined because the market is well supplied. Indicative prices from April through July 2014 were $1,150 to $1,200 per metric ton (CFR Rotterdam) for frozen single strength from Brazil and $3,000 to $3,100 per metric ton (FOB Santos) for origin frozen concentrate (20-22 brix clear) from Brazil.

One of the NOP certified organic producers of acerola is “Fazenda Amway Nutrilite Do Brasil Ltda – Nutribotânica” (Ubajara, Brazil), also affiliated with Trout Lake Farm LLC (Trout Lake, Washington). Fazenda Nutribotânica is the largest Nutrilite® farm, producing acerola fruit year-round on 1,660 hectares, and providing 100% of the natural ascorbic acid used in Nutrilite products. Since 1999, the Fazenda Nutribotânica farm has been inspected and certified by Instituto Biodinâmico. In addition to operating under organic agriculture standards, the farm has implemented biodynamic standards and has Demeter biodynamic certification. Fazenda Nutribotânica claims to be the world’s largest grower of certified organic and biodynamic acerola fruit.

In collaboration with Nutrilite, the Brazilian Agricultural Research Corporation — or EMBRAPA (Empresa Brasileira de Pesquisa Agropecuária) — developed a new

*Acerola Malpighia glabra. Photo ©2014 Steven Foster*
acera variety known as “BRS 366 Jaburú,” which yields 100 kg of fruit per plant annually, corresponding to about 57 metric tons per hectare.34 EMBRAPA states that this is an approximately 20% higher yield than the second most productive variety known as Minería. The fruits are picked green, when the vitamin C levels are twice that of the ripe fruit. According to EMBRAPA, the new cultivar has a competitive advantage over others because it is well suited to both manual and mechanized harvesting.34 Other sources report that the average yields for acera in the Brazilian northeast are 40 or more tons per hectare compared to 25 tons in other regions.35

The total area of acera cultivation in Brazil is estimated to be more than 10,000 hectares, with the highest production occurring in the northeastern state of Bahia, followed by the nearby northeastern states of Pernambuco, Ceará, and Paraíba.36 Annual fruit production in Brazil is approximately 33,000 metric tons. About 37% to 43% of the annual crop is exported, with primary destination markets comprising the United States, Germany, France, and Japan.

According to natural products industry insiders, a significant amount of the global supply of acera material is reportedly adulterated with exogenous L-ascorbic acid, some of which may be chemically synthesized and/or produced from genetically engineered starting materials. For many years, L-ascorbic acid had been produced mainly by chemical synthesis (Reichstein process), but there are now biotechnological approaches, e.g., involving an epiphytic bacterium Erwinia herbicola (Enterobacteriaceae) strain genetically engineered to contain a gene from the Gram-positive bacterium Corynebacterium spp. (Corynebacteriaceae), which converts glucose to 2-ketogulonic acid and can then be converted to ascorbic acid, among other novel biotech methods.37 Methodologies to determine the presence or absence of biotech or synthetic L-ascorbic acid in acera products have been developed and validated, including Isotope Ratio Mass Spectrometry (13C-IRMS-AOAC 998.12).38 It is recommended that buyers of natural acera ingredients and products work with independent laboratories applying this methodology in order to verify authenticity.

Although the so-called “super fruit” market is somewhat crowded, and acera berries compete in this arena against other more popular Brazilian exports such as açai (Euterpe oleracea, Arecaceae) berries, the market for all things organic and biodynamic continues to grow. With an increasing number of certified organic acera operations, this is an area that may grow faster than conventional acera product demand. There is also a growing niche for non-synthetic, food-based vitamin products for which acera powders and extracts can play a role as a source of natural, plant-based vitamin C. HG

—Gayle Engels and Josef Brinckmann

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17. EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA): Scientific opinion on the substantiation of health claims related to vitamin C and reduction of tiredness and fatigue (ID 139: 2622), contribution to normal psychological functions (ID 140), regeneration of the reduced form of


An unusual confluence of events during the editorial cycle for this issue resulted in several articles that pertain to tobacco, a plant that seldom receives coverage in these pages as it typically is not considered a medicinal plant, although it does enjoy a respected reputation in Native American ethnobotany.

Concern about the Ebola virus has prompted much media coverage, but there is a lack of reporting on an experimental Ebola treatment drug made using a species of low-nicotine tobacco. Our own Tyler Smith reports on the beneficial potential of this plant-produced treatment as well as purported herbal “cures” for the virus.

In January 2014, the CBS newsmagazine 60 Minutes ran a report about former Virginia governor Robert McDonnell and allegations of impropriety with respect to a donor, Jonnie R. Williams Sr. Williams’ company, Star Scientific, produced a “dietary supplement” called Anatabloc®, made from a minor tobacco alkaloid called anatabine and marketed for its anti-inflammatory properties. Though media coverage of McDonnell and his wife has been widespread, there has been scant reporting on Anatabloc itself. Accordingly, we present Tyler Smith’s article focusing on the interesting legal and regulatory aspects of the issue, particularly since the Dietary Supplement Health and Education Act — celebrating its 20th anniversary as we go to press — specifically excludes tobacco (and constituents thereof) as an ingredient in dietary supplements. And, since we suspect that most people in the herb and dietary supplement community are not familiar with anatabine, we have posted online a technical review of alkaloids in general, with a focus on anatabine chemistry, toxicology, and pharmacology by Jay Pierotti, a tobacco chemistry expert. (Jay’s article is available on the ABC website at http://cms.herbalgram.org/herbalgram/issue104/HG104-feat-AnatabineScience.html.)

One of the biggest areas of concern among health professionals and public health officials regarding herb safety is hepatotoxicity and whether or not a particular herb or herbal formulation is associated with an increased risk of liver dysfunction. Herbs including chaparral, comfrey, and, more recently, kava, have come under scrutiny as we have reported over the years. However, there are challenges and anomalies in reporting on herbs and potential hepatotoxicity, as ABC’s Chief Science Officer Stefan Gafner and I elucidate in an extensive article on this subject.

In discussing herb safety, the question often arises as to how much safety-related information should appear on the labels of commercial herbal products sold as dietary supplements. Expanding on an article he wrote in HerbalGram #56, attorney Paul Rubin and colleagues — experts in food and drug law — have contributed a guidance article for industry members about crafting safety-related information on herb product labels. This article is a must-read for people in the business of producing herb products.

About three years ago, due to concern over the possible excessive levels of some industrial solvents in herbal extracts, we embarked on a project to produce a reference book on solvents used in the manufacture of botanical extracts, which will be published soon by ABC. We present an article on methanol — a potentially toxic alcohol used as a solvent — by Deepak Mundkinajeddu and Amit Agarwal of Natural Remedies Pvt. Ltd. in India, a manufacturer of botanical extracts. In their article, they demonstrate that people consume more naturally occurring methanol in common foods than the amount allowed by international authorities for use as solvents for supplements and pharmaceuticals.

Additionally, we profile our good friend Heather Oliff, who has been writing HerbClips for ABC for more than 15 years — producing over 1,100 thus far! Heather is a valuable part of ABC’s prolific scientific publications team, and we truly appreciate her contributions to the botanical medicine community. (If you are not reading HerbClips every two weeks, or accessing them through ABC’s online database, then you’re missing out on a unique educational resource. HerbClip is available to all ABC members at the Academic Level and higher.)

Finally, a tip of the ABC hat to two herb organizations that are celebrating milestone anniversaries this year: The American Herbalists Guild is observing its 25th anniversary, and, in the UK, the National Institute of Medical Herbalists is celebrating 150 years since its founding in 1864. Both organizations are dedicated to helping foster increased education and professionalism among people who advise on the judicious and responsible use of herbal preparations in selfcare and healthcare.
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Star-Crossed: The Rise and Fall of Anatabloc®
By Tyler Smith

In September, a federal jury found former Virginia governor Robert McDonnell guilty of 11 felony counts of corruption for his dealings with Jonnie R. Williams Sr., the founder of the dietary supplement company Rock Creek Pharmaceuticals, formerly known as Star Scientific. Over a period of two years, McDonnell and his wife, Maureen, accepted more than $177,000 in gifts and loans in exchange for promoting Williams’ supplements, including Anatabloc® and CigRx®, both of which contain anatabine, a minor constituent of the tobacco plant and other plant species. This compound was the subject of a December 2013 warning letter from the US Food and Drug Administration, which stated that the products did not meet the legal definition of a dietary supplement. Williams resigned as CEO shortly thereafter, and in August 2014, Rock Creek Pharmaceuticals announced that it was reassessing its supplement business and halted sales of Anatabloc and CigRx. McDonnell, whose sentencing is scheduled for January 6, 2015, could face up to 10 years of prison time for his crimes.

Perspectives about the Potential Hepatotoxicity of Various Herbs, Including Green Tea Extract
By Stefan Gafner, PhD, and Mark Blumenthal

As more people in the United States use herbal dietary supplements, the Drug-Induced Liver Injury Network (DILIN) also has reported a larger percentage of liver injuries related to dietary supplements. Media reporting has interpreted these findings with sensationalist and sometimes inaccurate headlines, disseminating misleading information to the general public. It is not clear what caused the recent jump in numbers for supplement-induced hepatotoxicity, but according to the DILIN, the large number of case reports from the bodybuilding category seems to be one of the contributing factors. Another factor may be the growing population using dietary supplements. Frequent issues surrounding case reports of herbal supplement-induced liver injury include inadequate reporting methods that fail to properly establish causality, the absence of analytical testing to determine if the supplement was adulterated, or users’ failure to consume the recommended dosage. As more data are accumulated on the effects of herbal dietary supplements on the liver, a clearer picture will emerge on their relative safety, as well as potential risks that they may pose to a consumer’s health.
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Tobacco Nicotiana tabacum. Photo ©2014 Steven Foster
HerbClip Author Profile: Heather S. Oliff, PhD

Prolific HerbClip author Heather Oliff, PhD, celebrates 15 years with the American Botanical Council (ABC). HerbClips are peer-reviewed research summaries and clinical trial reviews published twice a month as an ABC member benefit. ABC recently announced the publication of the 500th issue. Dr. Oliff has been writing HerbClips since 1999.

At an average of about six per month, Dr. Oliff has written more than 1,120 HerbClips since 1999—a considerable percentage of the overall total of over 5,800. Primarily, Dr. Oliff writes about neurological disorders and topics related to aging, ginkgo (Ginkgo biloba, Ginkgoaceae), and black cohosh (Actaea racemosa, Ranunculaceae). The HerbClips she authors frequently are used as the basis for HerbalGram Research Reviews, expanding her extensive publication history with ABC.

During Dr. Oliff’s first few years writing for ABC, HerbClips still were printed and mailed to members instead of their current electronic form. “I would receive a large envelope in the mail every month with around 20 HerbClips,” she recalls. “I was happy when HerbClip went electronic because the ABC website has a great search engine and I don’t need to store all of those hard-copies.” (Currently, 15 HerbClips are released electronically every two weeks to ABC members at the Academic level and above.)

“All of us here at ABC, including thousands of our members in the United States and around the world, really owe Heather a major debt of gratitude,” said ABC Founder and Executive Director Mark Blumenthal, who also serves as HerbalGram and HerbClip editor-in-chief. “Heather has produced a significant part of ABC’s educational content. Not only does she produce excellent work, but she is also highly consistent and reliable. She’s a real pleasure to work with,” he added, “and is an editor’s dream!”

Dr. Oliff earned her doctorate in pharmacology and toxicology from the University of California at Irvine. After four years of post-doctoral research at the same institution, she decided to pursue medical writing full time and formed her own company, Science Consulting Group, LLC.

“My first client was a nutritional supplement manufacturer,” she said. “They encouraged me to go to the Natural Products Expo and that’s where I met ABC and got them as my second client.” She has worked on other projects for ABC over the years, including collaborating with Blumenthal on several monographs, such as the ABC Product-Specific Monograph on Sinupret® (Bionorica; Neumarkt, Germany) and the forthcoming revision of the extensive ABC Product-Specific Monograph on Pycnogenol® (Horphag Research; Geneva, Switzerland).

Writing for HerbClip, she says, helps keep her up to date on the latest advances in the field. She also enjoys the opportunity to expand her knowledge of herbal medicine by learning about an herb that is unfamiliar to her or that is in the beginning stages of clinical development.

“My specialty because of my education background is neuroscience,” she said, “but I don’t solely write neuroscience anymore. I find that in [the herbal] industry, they just care that you’re not biased against the industry. … By being able to write for this industry, I’ve been able to increase my knowledge about all clinical indications. This gives me an opportunity to really learn about multiple diseases and body systems and therapeutic methods.”

Dr. Oliff lives in California with her husband and two daughters and enjoys spending time with her family. “I live not too far from Disneyland, so for fun, we go quite frequently,” she said. She also enjoys traveling and cooking, though she does not claim any signature dish but rather favors trying out different recipes and new cuisines.

Her daughters currently are not impressed with her expansive publication credits, but she thinks that could change soon, especially with her very own magazine profile. “I think my younger daughter finally gets it,” she said, “because my older daughter was flipping through HerbalGram #102 to see what boring thing I had written, and my younger daughter said, ‘You wrote in that magazine? ’” This family audience, however, is tough to please. She went on to ask, “Well, how many subscribers are there, like, ten?”

“Heather’s consistency, dedication, and willingness to hone her writing craft have helped make HerbClip the educational and informative program that it is today,” said Lori Glenn, HerbClip managing editor. “I am delighted to have her as one of the HerbClip writers and am thrilled to be celebrating her longevity!”

—Hannah Bauman
Distinguished Scientist John Cardellina Joins ABC-AHP-NCNPR Botanical Adulterants Program

The ABC-AHP-NCNPR Botanical Adulterants Program (BAP) is pleased to announce the addition of John H. Cardellina II, PhD, as Chief Technical Consultant and Associate Editor of the BAP. Dr. Cardellina is a renowned, highly respected natural products and botanicals expert. He most recently worked in research and development at McCormick & Co., Inc., where he conducted research on spice and herb quality and the development of new flavors.

The BAP is an international educational joint venture led by three nonprofit organizations: the American Botanical Council (ABC), the American Herbal Pharmacopoeia (AHP), and the National Center for Natural Products Research (NCNPR) at the University of Mississippi.

“I am excited to rejoin this important effort by ABC, AHP, and NCNPR,” said Dr. Cardellina. “Adulteration is a growing problem in the supplement and food/flavor industries. Whether intentional or unintentional, adulteration is a serious disservice to consumers. I believe the Botanical Adulterants Program is a vitally important step in combating this problem, while simultaneously educating manufacturers, suppliers, researchers, and other interested parties.”

From 2002 to 2007, Dr. Cardellina served as an expert chemist in the Screening Technologies Branch of the National Cancer Institute (NCI). Prior to that, he was vice president of botanical science and regulatory affairs at the Council for Responsible Nutrition (CRN), a leading industry trade group. Dr. Cardellina developed CRN’s comprehensive botanicals agenda, intended to guide member companies in the manufacture of safe, high-quality, beneficial herbal products. Before joining CRN in April 1998, he was a senior investigator and head of the Natural Products Chemistry Section of the NCI’s Laboratory of Drug Discovery, Research and Development.

Dr. Cardellina has published more than 195 scientific papers in peer-reviewed professional journals and has lectured extensively on issues related to natural products research and botanical products. He is a member of the American Chemical Society and the American Society of Pharmacognosy (ASP), for which he served as president from 2000 to 2001. Dr. Cardellina is on ABC’s scientific advisory board and is chair of the board of directors of the American Herbal Pharmacopoeia and the board of directors of the ASP Foundation.

“John has an impressive knowledge of natural products, and a good understanding of the issues with regard to authentication and the challenges it poses to the dietary supplement industry,” said Stefan Gafner, PhD, ABC’s chief science officer and technical director of the Botanical Adulterants Program. “He is a highly respected scientist and expert editor — he currently serves as book review editor of the Journal of Natural Products. It is a privilege to be working with John on the Program.”

In addition to other publications on adulteration of specific botanical ingredients and extracts, Dr. Cardellina will be working on a Lab Guidance Document for analytical methods to authenticate so-called “grapefruit seed extract” (GFSE) and to detect synthetic antibacterial compounds that frequently have been found in analyses of GFSE, per an extensive review article published by the Program in HerbalGram #94 in 2012.1

“We are deeply grateful for Dr. Cardellina’s association with the Botanical Adulterants Program,” said Mark Blumenthal, founder and executive director of ABC and director of the Program. “John was involved previously with the Program in its first year and authored the review of 10 analytical publications showing that grapefruit seed extract is adulterated with synthetic commercial disinfectants. We welcome his extensive experience to help move our Program forward.”

Professor Ikhlas Khan, PhD, associate director of the NCNPR at the University of Mississippi, said, “John is a well established authority in natural products. He is a wonderful person, but unwavering when it comes to science and the facts. His unbiased approach towards the issue of adulteration will certainly strengthen the Program.”

According to Roy Upton, director of AHP, “John brings a wealth of expertise and experience from the world of medical research and pharmacognosy. He has been a valued AHP director for several years and his further contributions to the Adulterants Program will be of immense value.”

Reference
International Dietary Supplement Trade Alliance Endorses Botanical Adulterants Educational Program

IADSA to Support ABC-AHP-NCNPR Botanical Adulterants Program, International Herbal Quality Control Initiative

The International Alliance of Dietary/Food Supplement Associations (IADSA) has endorsed the ABC-AHP-NCNPR Botanical Adulterants Program, an international consortium of nonprofit organizations, analytical laboratories, industry members, professional scientists, and others that advises industry, health professionals, and researchers about the various challenges related to adulterated herb and botanical ingredients sold in commerce.

IADSA, an international organization of trade associations composed of suppliers and manufacturers of dietary supplements, gave notice of its support in a letter dated August 3, 2014, from IADSA Executive Director Simon Pettman to Mark Blumenthal, founder and executive director of the nonprofit American Botanical Council (ABC) and general manager of the ABC-AHP-NCNPR Botanical Adulterants Program. In the letter, Pettman said of the decision, “...IADSA is constantly seeking ways in which to improve standards within the global industry and demonstrate that dietary supplements are a category of products that deserve the trust of decision-makers in government. We consider that your program will help us move forward on both these objectives and in time will provide real consumer benefits.”

According to its website, IADSA has 49 member associations, representing thousands of companies worldwide.

Adulteration refers to the accidental or intentional substitution or dilution of a material with an undisclosed lower-cost ingredient, thereby giving the consumer or user a false sense of the value of an ingredient or product containing such an adulterated ingredient.

The ABC-AHP-NCNPR Botanical Adulterants Program is a coalition of three American nonprofit groups: ABC, the American Herbal Pharmacopoeia (AHP), and the University of Mississippi’s National Center for Natural Products Research (NCNPR), with more than 130 other American and international parties supporting and cooperating with the Program.

“The endorsement of our Program by IADSA signifies not only the global nature of the problem of adulteration in the botanical supply chain, but also represents the concerns of many responsible, forward-thinking members of the herb and dietary supplement industry in 33 countries regarding this significant problem, and their confidence in and cooperation with the educational work we are doing,” said ABC’s Blumenthal. “IADSA’s involvement constitutes a quantum leap in the Program’s level of activity,” he added.

“IADSA supports this excellent program to bring safe and authenticated botanicals to consumers globally,” said Peter Zambetti, chairman emeritus of IADSA and director of global business development at Capsugel, the world’s largest manufacturer of gelatin capsules used in the manufacture of dietary supplements and pharmaceuticals.

“IADSA’s endorsement of this Program is a significant development for us, and helps to ensure that we have the prospect of success on an international basis, connecting organizations pursuing similar aims,” said Stefan Gafner, PhD, ABC’s chief science officer and technical director of the Botanical Adulterants Program. “We look forward to working with more botanical quality control experts from other organizations and scientists in the international arena,” he added.

According to Michelle Stout, treasurer of IADSA and regulatory policy director at Amway, one of the world’s largest producers of dietary supplements, “Authenticity of a botanical impacts its quality which directly impacts its efficacy and safety. The ABC-AHP-NCNPR Botanical Adulterants Program is an important initiative for building standards to ensure that the botanicals used in supplements are authentic and free from any deliberate or accidental adulteration.”

IADSA’s endorsement of the ABC-AHP-NCNPR Botanical Adulterants Program follows similar endorsements made last year by the international Society for Medicinal Plant and Natural Product Research (known by its German acronym, GA) and the American Society of Pharmacognosy (ASP). The GA and ASP are the two largest organizations of professional researchers in the field of medicinal plants and drugs of natural origin.

To date, the ABC-AHP-NCNPR Botanical Adulterants Program has published five extensively peer-reviewed and referenced articles on the history of adulteration, the adulteration of the herbs black cohosh (Actaea racemosa, Ranunculaceae) and skullcap (Scutellaria lateriflora, Lamiaceae), and adulteration of extracts of bilberry (Vaccinium myrtillus, Ericaceae) fruit and grapefruit (Citrus x paradisi, Rutaceae) seed. These open-access articles are available on the Program’s webpage: www.herbalgram.org/adulterants.

The Program also publishes a quarterly newsletter, “The Botanical Adulterants Monitor,” that highlights new scientific publications related to botanical authenticity and analysis to detect possible adulteration, recent regulatory actions, and Program news. Additional publications from the Program are being scheduled for release in the coming weeks and months.
Join more than 130 responsible companies, laboratories, nonprofits, trade associations, media outlets, and others in the international herb and natural products/natural medicine community.

Become a valued underwriter of the ABC-AHP-NCNPR Botanical Adulterants Program, a multi-year, supply chain integrity program providing education about accidental and intentional adulteration of botanical materials and extracts on an international scale.

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

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**Underwriters, Endorsers, and Supporters of the ABC-AHP-NCNPR Botanical Adulterants Program**

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*By acknowledging the generous support of these companies and organizations, ABC, AHP, and NCNPR are not endorsing any ingredients or products that may be produced or marketed by them.*
New Guidance from US Patent and Trademark Office Restricts Patent Eligibility for Natural Products

American Society of Pharmacognosy Submits Public Comments


This 2014 guidance, which may be revised and reissued, incorporates changes in determining eligibility of natural products meant to align current procedure with the Supreme Court’s rulings in the cases Association for Molecular Pathology v. Myriad Genetics, Inc. (2013) and Mayo Collaborative Services v. Prometheus Laboratories (2012). In the former, the Supreme Court decided specifically that human DNA — more than 4,300 genes of which previously had been patented — was not eligible for patent because “[a] naturally occurring DNA segment is a product of nature and not patent eligible merely because it has been isolated.” According to the USPTO’s new guidance, products submitted for patent protection now must be “markedly different” from what exists in nature, meaning that chemicals that are merely isolated from natural sources are forthwith ineligible for patent.


“ASP is concerned that the present interpretation of the Guidance may have the inadvertent outcome of hindering the development of new medicines,” the organization wrote, adding that between the years of 1981 and 2010, just 36% of all drugs were “purely synthetic structures that were derived without reliance on natural products.” Further, ASP noted in its comments that “70% of clinically used antibiotics are naturally derived from natural sources” and that USPTO’s new guidance will “impede future drug discovery and development.”

According to former ASP president and American Botanical Council Advisory Board member John Cardellina, PhD, the USPTO’s current guidance—should it stand—would have a devastating impact on the United States’ position in the global drug development market (email, September 29, 2014). “If the US is the only country to adopt such a short-sighted policy, the American position in the global drug development market would be severely impaired, if not crippled,” he wrote.

“Given that roughly 75% of the pharmaceuticals in use today are natural products or natural product derived/inspired,” added Dr. Cardellina, “the rest of the world would leave the US in its ‘laboratory dust.’ Further, I would envision US pharmaceutical companies moving their headquarters and operations out of the US to seek haven in countries without such an ill-advised patent policy.”

The USPTO defines “natural products” as “[c]hemicals derived from natural sources (e.g., antibiotics, fats, oils, petroleum derivatives, resins, toxins, etc.); foods (e.g., fruits, grains, meats and vegetables); metals and metallic compounds that exist in nature; minerals; natural materials (e.g., rocks, sands, soils); nucleic acids; organisms (e.g., bacteria, plants and multicellular animals); proteins and peptides; and other substances found in or derived from nature.”

In determining patent eligibility, three questions are utilized:

1. Is the claimed invention directed to one of the four statutory patent-eligible subject matter categories: process, machine, manufacture, or composition of matter?
2. Does the claim recite or involve one or more judicial exceptions (abstract ideas, laws of nature/natural principles, natural phenomena, and natural products)?
3. Does the claim as a whole recite something significantly different than the judicial exception(s)?

Judicial exceptions, according to the guidance, “reflect the judicial view that … fundamental tools of scientific and technological work are not patentable.”

In order to illustrate the “significantly different” element of a claim, the USPTO guidance states that “(1) the claim includes elements or steps in addition to the judicial exception that practically apply the judicial exception in a significant way, e.g., by adding significantly more to the judicial exception; and/or (2) the claim includes features or steps that demonstrate that the claimed subject matter is markedly different from what exists in nature (and thus not a judicial exception).”

Under these guidelines, a newly discovered plant-derived chemical alone would not be eligible for patent; however, a novel process for extracting the chemical or a structurally and/or functionally different derivative of the chemical could be. Process claims including specific doses, administration lengths, and patient types also could be considered “[b]ecause the specific dosage and treatment period limitations narrow the scope of the claim, others are not substantially foreclosed from using [the natural product] in other ways.”

A variety of natural products have been patented in the past. For scientists and the pharmaceutical and dietary supplement industries — among others — the new guidance may result in decreased monetary incentive to discover and/or develop new beneficial natural products.

Intriguingly, ASP mentions penicillin in its public comments’ section on the history of patented natural products. Alexander Fleming, the Scottish scientist credited with discovering...
penicillin in 1928, did not pursue a patent on the natural antibiotic.4 “I did not invent penicillin. Nature did that,” he said.4 Andrew Moyer later patented a process for penicillin mass production in the United States.5

Under the USPTO’s new guidelines, penicillin certainly would not be patent-eligible in the United States today. According to natural products attorney Ashish Talati, it is possible that even Moyer’s process for mass production could be ineligible for patent protection under the 2014 guidelines. “However,” he said, “methods using recombinant cells may still be patentable if the organisms are structurally altered, assuming that the method meets the standards of novelty and non-obviousness” (email, September 26, 2014).

According to Talati, US patent seekers may be wise to focus on methods and processes rather than natural product compositions by themselves, at least for right now.

“[T]he impact of the weakening of eligibility for many classes of natural materials should not be minimized,” said Talati. “Until the USPTO issues its revised guidelines, current strategies may include relying on novel synthetic analogues of natural materials (a common practice in pharmaceutical research), or inclusion of non-natural components in order to patent a new composition or formulation.” Talati continued, “In any case, the expected revised guidelines (anticipated by the end of 2014) will hopefully, at a minimum, clarify what approaches may be best employed going forward, if not expand the options to a more reasonable framework.”

Talati, Dr. Cardellina, and ASP characterize USPTO’s interpretation of the aforementioned Supreme Court ruling on Myriad as overly broad. “The USPTO guidelines surprised observers by expanding the holding to compositions found in nature, and even novel combinations of such compositions, though still welcoming applications for methods of using such compositions,” said Talati. “This has struck many observers, he added, “as an overreach precluding patents on truly innovative discoveries.”

Where, then, is a reasonable place for the line to be drawn? “If such an isolated composition, or combination of natural compositions,” proposed Talati, “is truly ‘new and useful’ (the standard set forth in the patent statutes), I think the USPTO should consider that rather than apply a per-se rule.”

“We assert that the association of a novel bioactivity with a previously unknown discrete chemical entity derived from a natural source should be sufficient evidence of the ‘hand-of-man’ to allow composition of matter claims based on its chemical structure and the associated biological activity,” stated ASP in its comments, which concluded: “We believe that such an interpretation will be consistent with the Supreme Court decision by limiting the broad claims associated with patents on genes as in Myriad while still allowing for discrete composition of matter claims on bioactive natural product chemicals.”

“No matter what the final guidance is, there will be displeased, negatively affected parties,” said Dr. Cardellina. “However,” he continued, “I think it is imperative that USPTO revises this guidance to permit patents on natural products, including proteins/peptides, discovered to have impacts on human society not to be anticipated by their mere presence in the producing organism, whether that organism is a microbe, plant, or invertebrate.”

—Ash Lindstrom

References
**Expand Your Herbal Library. It’s as easy as ABC!**

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

- **Principles and Practice of Phytotherapy, 2nd ed.** by Kerry Bone and Simon Mills, 2013. This newly updated edition is divided into three key parts. The first defines the underlying principles and knowledge base of modern phytotherapy; the second explores the role of plants as therapeutic agents in a clinical setting; and the third contains 50 detailed herbal monographs. The book focuses on a modern clinical approach including how and when to use specific herbs in response to approximately 100 modern ailments. Covers traditional use and scientific research, safety, and effective dosage. Foreword by ABC Founder and Executive Director Mark Blumenthal. Hardcover, 1056 pages. $125.00 ($112.50 ABC Member Price)

- **Handbook of Plant Food Phytochemicals: Sources, Stability and Extraction** by Brijesh K. Tiwari, Nigel P. Brunton, and Charles Brennan, 2013. This handbook provides an overview and evaluation of the occurrence, significance, and factors affecting phytochemicals in plant foods. Evaluation of the evidence for and against the quantifiable health benefits being imparted is expressed in terms of the reduction in the risk of disease conferred through the consumption of foods that are rich in phytochemicals. Hardcover, 526 pages. $205.95 ($185.37 ABC Member Price)

- **Essential Oil Safety: A Guide for Health Care Practitioners, 2nd ed.** by Robert Tisserand and Rodney Young, 2014. This almost totally rewritten new edition is an extensive text on essential oil-drug interactions that also provides detailed essential oil constituent data. It includes 400 detailed essential oil profiles and almost 4000 references. New chapters on the cardiovascular, digestive, nervous, respiratory, and urinary systems are included. Softcover, 592 pages. $96.95 ($87.26 ABC Member Price)

- **Green Tea Polyphenols: Nutraceuticals of Modern Life** by Lekh R. Juneja, Mahendra P. Kapoor, Tsutomu Okubo, and Theertham P. Rao, eds., 2013. Each chapter of this compilation addresses a specific aspect of recent research and development of green tea polyphenols. Topics covered include history, processing, chemical composition, biochemical and physicochemical characteristics, as well as a discussion of the properties of green tea polyphenols, including metabolism, bioavailability, safety, and health benefits. Hardcover, 348 pages. $129.95 ($117.00 ABC Member Price)

- **Fighting Multidrug Resistance with Herbal Extracts, Essential Oils, and Their Components** by Mahendra Rai and Kateryna Kon, 2011. This essential reference discusses herbal extracts and essential oils used or under investigation to treat MDR infections, as well as those containing antimicrobial activity that could be of potential interest in future studies against MDR microorganisms. This book provides important coverage of mechanism of action, the advantages and disadvantages of using herbal extracts, essential oils and their components, and more to aid researchers in effective antimicrobial drug discovery. Hardcover, 296 pages. $129.95 ($117.00 ABC Member Price)
American Herbal Pharmacopoeia Announces Development of Osha Monograph

The American Herbal Pharmacopoeia (AHP), in collaboration with United Plant Savers (UpS), has commenced production of a monograph and therapeutic compendium for osha (Ligusticum porteri, Apiaceae) root, an herb with extensive traditional use among native tribes in the western part of North America.1 While many species in the Ligusticum genus have been called “osha,” L. porteri is considered “true osha”2; other common names include bear medicine, bear root, Colorado cough root, Porter’s lovage, Porter’s licorice-root, Porter’s wild lovage, loveroot, mountain lovage, Indian parsley, mountain ginseng, nipo, and chuchupate.3

Osha has extensive ritual significance in addition to its medicinal uses. Primarily used for upper respiratory infections, osha also has been traditionally indicated for headaches, fevers, infections, and wound care. A member of the Apiaceae (or carrot) family, osha’s root is the primary medicinal component of the plant. It is sold in a variety of forms, including whole roots, dried or fresh; root tincture; liquid herbal extract; and capsules containing root powder.2,3

Following a grant from the American Herbal Products Association (AHPA) Education and Research Foundation to Kelly Kindscher, PhD, to conduct a sustainability study recording the impact of wild collection on osha populations, AHP noted that no monograph on the herb exists. “This was due to [an] observed increasing trend of osha use in industry and long-term concerns regarding the sustainability of the botanical due to it being a high elevation herb that has thus far resisted a number of attempts to [cultivate it commercially],” wrote AHP President Roy Upton (email, August 25, 2014). “From these discussions, and because of the importance of osha in indigenous North American herbal traditions, AHP believes it was a great candidate for a monograph.”

Though there are no official export controls in place, osha is considered a “species at risk” of overharvest by UpS4 due to its limited, high-elevation growing area and lack of commercial cultivation. Dr. Kindscher’s research, an ongoing multiyear project, seeks to determine the status of osha populations in the wild as well as the impact of root harvest and optimal harvest rates to maintain long-term viability.3 As the market use of the plant trends upwards, Upton hopes that the forthcoming monograph will serve as an important resource to members of the industry, researchers, herbalists, ethnobotanists, growers, and wildcrafters.

In addition to addressing conservation concerns, the monograph also will note the possibility of adulteration. “[T]here has been reported adulteration of osha, including with other species of Ligusticum, which may legitimately be used interchangeably, and the highly toxic poison hemlock [Conium maculatum, Apiaceae] and water hemlock [Cicuta douglasii, Apiaceae],” wrote Upton. The similarity in appearance among members of the Apiaceae family can lead to unintentional adulteration as well.

Currently, AHP is seeking donors and sponsors for the completion of the monograph, which has a total projected budget of $14,700. This would mark the 36th monograph published by AHP, following its historic cannabis monograph in December 2013.

—Hannah Bauman

References
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 nearly 250 commonly used medicinal herbs. A free version, HerbMed, is available to the general public. HerbMed features 20 to 30 herbs from HerbMedPro that are rotated on a regular basis with an emphasis on adopted herbs. HerbMedPro is available as a member benefit to all ABC members at the Academic Membership level and up.

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

Beginning in 2008, the Adopt-an-Herb Program has grown to include 28 companies and 30 adopted herbs. Parties interested in taking part in the Adopt-an-Herb Program are invited to contact ABC Development Director Denise Meikel at 512-926-4900, extension 120, or by email at denise@herbalgram.org.

**Become an adopter today!**

Visit us at [www.herbalgram.org/adopt](http://www.herbalgram.org/adopt)

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

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

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Since the beginning of 2014, Ebola virus disease has claimed more than 4,500 lives, making it the largest epidemic of the virus in history. The United States Centers for Disease Control and Prevention (CDC) report that more than 9,000 total individuals in Guinea, Liberia, Sierra Leone, and other West African countries have been infected with Ebola, which kills roughly half of its victims. The first two recorded outbreaks of the disease occurred simultaneously in 1976 in Sudan and in a village in the Democratic Republic of Congo near the Ebola River, after which the virus is named.2

Biopharmaceutical Drug Produced Using Tobacco Plants May Offer Hope for Ebola Victims

**FDA and Industry Organizations Warn Companies, Consumers about Herbal “Cures” for Ebola**

On September 30, 2014, the CDC reported the first case of Ebola in the United States. The patient, Thomas Eric Duncan, traveled from Liberia to Dallas on September 20 and began exhibiting symptoms four days later. He was quarantined and treated with the experimental pharmaceutical drug brincidofovir at Texas Health Presbyterian Hospital, but later died on October 8, 2014.3,4 Since that time, two healthcare workers who had contact with Duncan have tested positive for Ebola, and the CDC currently is monitoring hospital employees for symptoms.5

Prior to the recent cases in Dallas, two American aid workers volunteering in impacted regions in West Africa contracted Ebola.6 The infected Americans were among the first humans to receive an experimental drug known as ZMapp™, a biosynthetic drug produced in a species of low-nicotine tobacco (Nicotiana benthamiana, Solanaceae) leaves through a process generally known as “biopharming” — the process of using plants to produce genetically engineered disease-fighting agents. (Nicotiana benthamiana, or “native tobacco,” is endemic to northern Australia.)7 Both individuals have recovered from the virus, although the extent to which ZMapp contributed to their recovery is unknown.6 Due to the severely limited supply of the drug, ZMapp has been given only to seven individuals, two of whom have died.8

In a region of the world that was largely unprepared for an Ebola outbreak of this magnitude, confusion and fear-mongering abound. There are currently no drugs — pharmaceutical or otherwise — shown to be effective for curing Ebola, and treatment often consists of “supportive therapy,” which includes maintaining patients’ fluids, oxygen levels, and blood pressure, among other measures.1 Amid widespread media coverage of the outbreak and fear bordering on panic, some companies and individuals have recommended unproven plant-based and non-herbal “cures” for the virus. In mid-August, the US Food and Drug Administration (FDA) and the World Health Organization (WHO) issued statements alerting consumers to such deceitful — and potentially harmful — product claims, and, in late September, the FDA sent warning letters to three American companies advertising herbal products as being effective for treating and preventing Ebola.9

“Unfortunately, during outbreak situations, fraudulent products that claim to prevent, treat, or cure a disease all too often appear on the market,” the FDA noted in its August statement.9 “Although there are experimental Ebola vaccines and treatments under development, these investigational products are in the early stages of product development, have not yet been fully tested for safety or effectiveness, and the supply is very limited.”

**ZMapp and the Promise of Biopharming**

In January 2014, the San Diego, California-based companies Mapp Biopharmaceutical and LeafBio, working in conjunction with Defyrus, Inc. in Toronto, Canada, identified a promising new experimental treatment for Ebola.10 The drug, ZMapp, is not a single compound; rather, it is a combination of plant-produced antibodies. “It is an optimized cocktail combining the best components
of MB-003 (Mapp) and ZMAb (Defyrus/[[Public Health Agency of Canada]],” Mapp Biopharmaceutical explains.11

The final stages of the multi-step process used to produce ZMapp require the use of tobacco plants, which act as miniature factories that produce genetically modified Ebola-fighting agents. The overall process consists of three main components10:

First, Ebola antigens (i.e., substances that elicit an immune response in the body) are injected into mice, which then begin to produce Ebola antibodies (i.e., proteins used by the immune system to recognize and attack antigens).

The Ebola antibodies are combined with B-cells (i.e., white blood cells that produce antibodies) and certain cancer cell lines, which form what are known as “hybridomas” — specialized cells designed to produce the Ebola antibodies.

Finally, tobacco plants are infected with the hybridomas, which replicate and produce Ebola antibodies in the plants’ leaves. The process eventually kills the plant, and the antibodies are extracted and purified from the leaves.10

Although ZMapp has not yet been studied in humans, animal studies suggest that an earlier version of the drug known as ZMAb may provide some benefit for Ebola-infected primates.

According to a November 2013 article in the journal Scientific Reports, researchers treated six Ebola-infected monkeys with ZMAb, all of which survived.12 In a separate experiment conducted by the same research team, the animals were infected with the virus again after 13 weeks, and four of the six monkeys survived.12

Currently, there are 30 antibody-based drugs approved for use in the United States, many of which are used as cancer treatments. Each of these drugs is produced using animals — most often hamsters — as antibody factories.13 However, the use of plants to produce antibody-based drugs may offer some unique manufacturing benefits — and challenges.

These so-called “plantibody” drugs “may prove to be faster, higher yielding and cheaper than current methods using mammalian cells.”13 According to Victor Klumyuk, COO of drugmaker Icon Genetics, plant-based biopharming “may work best when speed is required or when flexibility is required … to manufacture vaccines for an epidemic or for fast, reliable production.”13 For example, creating a flu vaccine using chicken eggs takes approximately six months; using plant-based methods, flu vaccines can be produced in as little as one week.14

The particular type of tobacco used in the production of ZMapp — which is related to, but not the same as, smoking tobacco — was chosen carefully by the drug’s manufacturer. “In selecting an appropriate production platform, we needed a system that was rapid and scalable,” notes Mapp Biopharmaceutical on its website.10 “The low nicotine tobacco plant, Nicotiana benthamiana, is capable of expressing foreign (non-tobacco) proteins using indoor cultivation under tightly controlled conditions.”

However, the FDA has raised numerous concerns about the process of biopharming. The Agency lists such potential issues in its 2002 draft guidance document on “Drugs, Biologics, and Medical Devices Derived from Bioengineered Plants for Use in Humans and Animals.”15 Specifically, the FDA cites the following concerns in the document: the consistency of the final product; “the potential for the plant to express an allergenic or toxic compound; the method of plant propagation and the measures to ensure confinement; and, if it is a food crop species engineered to produce non-food material, the measures to ensure that non-food (or non-feed) material will not get into food or feed.”

“The ostensible objective of the regulation is to avoid biopharmed drugs winding up in food,” explained the author of a recent Wall Street Journal article.16 “But the fear is overblown, and contamination can be avoided in several ways. Production involving a non-food crop like tobacco is an obvious one.”

Herbal “Cures”: FDA Warning Letters and Industry Response

With no available cure or scientifically proven treatment for Ebola, some traditional healers and officials in Africa have claimed that various herbal concoctions such as those made with bitter kola (Garcinia kola, Clusiaceae),17 ashwagandha (Withania somnifera, Solanaceae),18 and jute (Corchorus capsularis, Malvaceae)19 can offer protection against the virus or cure those infected. In late September, the FDA issued warning letters to three American
companies that promoted their products for the treatment of Ebola.20-22 In perhaps the most egregious violation, Natural Solutions Foundation was warned for advertising its non-herbal colloidal Nano Silver Solution23 as “the definitive prevention and therapy for Ebola virus.”20

Similarly, the FDA sent warning letters to Utah-based companies Young Living and doTERRA International, LLC for their essential oil products. “Ebola Virus can not live in the presence of cinnamon bark ... nor Oregano,” Young Living claimed on its website.21 “Viruses (including Ebola) are no match for Young Living Essential Oils.” Certain doTERRA essential oil products, according to the FDA warning letter, also violate federal law due to unsubstantiated, drug-like claims. Consultants for the company claimed online that doTERRA’s products are helpful for “conditions including, but not limited to, viral infections (including ebola [sic]),” and a primary use of the company’s oregano oil product is listed as “Ebola virus.”22

Each of the three companies was warned for promoting products for “conditions that cause them to be drugs under section 201(g)(1)(B) of the Federal Food, Drug, and Cosmetic Act,” therefore rendering the products adulterated. The companies were given 15 business days to rectify the violations.20-22

Roughly two weeks after FDA sent the warning letters, a coalition of five natural products industry organizations issued its own statement on October 7, 2014, regarding supplements claiming to treat or cure Ebola.24 “We are unaware of any scientific data supporting the use of dietary supplements to prevent Ebola virus infection or treat Ebola virus disease,” noted the American Herbal Products Association, Consumer Healthcare Products Association, Council for Responsible Nutrition, Natural Products Association, and United Natural Products Alliance.

In addition to urging that anyone who may have come into contact with the virus seek immediate professional medical help, the joint statement included two main recommendations: (1) “Marketers and retailers of dietary supplements are urged to refuse to stock or sell any supplements that are presented as treating or curing Ebola virus disease, or preventing Ebola virus infection;” and (2) “Marketers and retailers should refrain from promoting any dietary supplement as a cure or treatment for Ebola virus disease.”24

The Future of Ebola Treatments

On August 13, 2014, Mapp Biopharmaceutical announced that its supply of the plantibody drug ZMapp had been exhausted.19 At present, the company is collaborating with other companies — including Caliber Biotherapeutics in Texas8 and Kentucky Bioprocessing, a division of the cigarette manufacturer Reynolds American — to ramp up production of the drug.13 However, progress has been slow. Mapp Biopharmaceutical expects it will be a number of months before additional supplies of ZMapp are available, and the company is currently in the process of initiating Phase 1 clinical trials for the drug.6

A number of US government agencies — including the National Institute of Allergy and Infectious Diseases, the Defense Threat Reduction Agency, and Biomedical Advanced Research and Development — are working on experimental treatments and vaccines for Ebola in conjunction with Mapp Biopharmaceutical and other companies.4 Additionally, an influenza drug known as fabirpiravir developed by a division of the Japanese company Fujifilm is being considered as a treatment option; the drug was given to French nurse infected with Ebola while working in Africa, who has since recovered.25 Most recently, on October 13, 2014, the Public Health Agency of Canada began testing an Ebola vaccine made from a modified rabies virus at the Walter Reed Army Institute of Research in Silver Spring, Maryland.25

Approximately one month after Mapp Biopharmaceutical’s announcement, the CDC released updated statistics on projected Ebola cases in West Africa. The figures were grim; the CDC estimated as a worst-case scenario that Liberia and Sierra Leone could have a combined 1.4 million cases of Ebola infection by January 20, 2015, if additional measures are not taken to control the spread of the virus.26

In the meantime, the CDC and WHO recommend
against taking unproven herbal or alternative therapies for the prevention, treatment, or cure of Ebola, as such remedies, they state, could lead to more harm than good. In Nigeria, for example, the claim that drinking saltwater could protect against Ebola has led to the deaths of two individuals. Such bogus claims are “predictable, but hugely worrying,” noted bioethicist Arthus L. Caplan of New York University’s Langone School of Medicine in an August 15 New York Times article. “Whenever there is fear, misery and death, there are people who will take your money promising you a cure.”

—Tyler Smith

References
Remifemin® Black Cohosh Extract Reduces the Size of Uterine Fibroids in Menopausal Women


Uterine fibroids (also called myomas) are the most common benign tumors in women. The use of hormone replacement therapy (HRT) to ameliorate menopausal symptoms in women with uterine fibroids is controversial because there is some evidence that estrogens can increase the growth of uterine fibroids. The drug tibolone (a hormone-like medication) and isopropanolic black cohosh (Actaea racemosa syn. Cimicifuga racemosa, Ranunculaceae) root and rhizome extract (iCR) are used to treat menopausal symptoms. The purpose of this randomized, double-blind, parallel-controlled study was to compare the effect of tibolone and iCR treatment on uterine fibroid size in women treated for menopausal complaints.

This study constitutes a subgroup analysis of a previously published report on 244 patients. The present study included only the women in the original trial who had uterine fibroids (n=62, aged 41 to 60 years). Study participants were recruited from five hospitals in China. The patients were treated with 40 mg/day iCR (n=34, Remifemin®; Schaper & Brüunner GmbH; Salzgitter-Ringelheim, Germany) or 2.5 mg/day tibolone (n=28, Zizhu Pharmaceutical Co., Ltd.; Beijing, China) for 12 weeks. At baseline, four weeks, and 12 weeks of treatment, the patients underwent transvaginal ultrasonography to measure myoma volume and diameter. If the patient had multiple myomas, the largest one was used for the analysis.

At baseline, there was no significant difference between groups. The median volume of the largest myoma at the end of the study was...
decreased in the iCR group (P=0.085). The volume was decreased in 24 (70.1%) women in the iCR group with a volume reduction of 30.3%. In comparison, a decrease was observed in only 10 (35.7%) women in the tibolone group; the difference between groups was significant (P=0.016). Similarly, the mean diameter and the geometric mean diameter of the myomas significantly decreased with iCR treatment (P=0.006 and P=0.006, respectively), but not with tibolone treatment (P=0.819 and P=0.778, respectively); again, the difference between the groups was significant (P=0.021 and P=0.016, respectively). For the tibolone group, no statistical difference from baseline was observed for these parameters.

In over one-half (53.6%) of the women treated with tibolone, fibroid volume increased by an average of 4.7% (equivalent to 21% per year). However, these findings are in agreement with two other studies assessing the natural change in fibroid volume over time. The authors conclude that 2.5 mg/day tibolone for 12 weeks does not interfere with the natural course of uterine fibroids but caution that regular reexaminations should be conducted.

The authors also conclude that while both groups had a significant improvement in menopause symptoms, iCR decreased uterine fibroid size and tibolone did not. They state, “iCR seems to be the better choice in alleviating menopausal symptoms in women with uterine fibroids … as it provides adequate relief from menopausal symptoms and avoids increase in uterine fibroid size, which is usually a cause of concern for the patient.” The study is limited by its small population size and short duration. Women using therapeutics to ameliorate complaints associated with menopause typically are treated for more than 12 weeks. Therefore, the effect of iCR on uterine fibroids needs to be evaluated in trials of longer duration. With respect to the known non-hormone-like/non-estrogenic effects of this herbal extract, similar results also are expected.2

References

—Heather S. Oliff, PhD

Black Cohosh Actaea racemosa. Photo ©2014 Steven Foster
Episiotomy, a common obstetric intervention during which an incision is made to enlarge the vaginal opening during childbirth, is often accompanied by perineal pain in the immediate postpartum period that can affect child care and other responsibilities. Episiotomy treatments include nonsteroidal anti-inflammatory drugs for pain and Betadine® (Purdue Pharma L.P.; Stamford, Connecticut) for wound healing (although Betadine is no longer used frequently in the United States for postnatal perineal care). For some women, these therapies are unsatisfactory; instead, they seek more effective, safer options. Cinnamon (Cinnamomum spp., Lauraceae) bark’s essential oil and ethanolic extract preparations exhibit numerous beneficial properties, including anti-inflammatory, antioxidant, and antimicrobial activities; however, no human studies have been conducted on its analgesic and healing effects. These authors conducted a randomized, double-blind, placebo-controlled trial to determine the effects of a cinnamon extract ointment on episiotomy wounds.

Women aged 18 to 40 years who had given birth vaginally with episiotomy were recruited in Tabriz, Iran, at two hospitals affiliated with Tabriz University of Medical Sciences (Alzahra and Taleghani Hospitals) and at one hospital affiliated with the Iranian Social Security Organization. In these hospitals, 90% of women undergo episiotomies during their first vaginal delivery and 70% during their second and third deliveries. (One reviewer of this article noted that such high percentages of women undergoing episiotomies in these hospitals represents “irresponsible and outdated medical care.” In 2005, episiotomies for vaginal births were performed on only 30 to 35% of women in the United States.) The authors recruited 144 patients (mean age: 26.4 ± 4.9 years) from February 20, 2013 to October 31, 2013; follow-up ended on November 11, 2013. While in the hospital, the patients completed a questionnaire on socio-demographic and reproductive characteristics. Each patient’s episiotomy incision was measured, and a baseline of perineal pain and wound healing was assessed.

The authors randomly assigned 72 patients to the cinnamon ointment group or the placebo group, both of which were similar in terms of socio-demographic and reproductive characteristics. For more than half of the women in each group, the delivery was their first. The patients were instructed on how to apply the ointment to the episiotomy wound twice daily every 12 hours for 10 days.

The hydroalcoholic cinnamon bark extract ointment (2% by weight; prepared at the Industrial Pharmacy Laboratory at the Tabriz University of Medical Sciences) contained cinnamon, methyl paraben, propyl paraben, and Eucerin® (a dermatological cream for dryness, itching, etc.; Beiersdorf AG; Hamburg, Germany). Prepared at the same laboratory and placed in tubes identical in color, shape, and size, the placebo ointment contained the same ingredients except for the cinnamon extract.

For pain relief, 10 mefenamic acid capsules (400 mg) were administered to each patient. The patients were given a diary to record ointment use, analgesics taken, and any adverse side effects, and they were instructed to return to the hospital with their empty ointment tubes after 10 to 11 days for reassessment.

Primary outcomes were assessed as follows: Perineal pain was measured by visual analogue scale (VAS) and recorded at baseline (one hour after
episiotomy repair), four (±1), and eight (±1) hours after the first treatment with the ointment, and at 10 to 11 days after delivery. Wound healing was assessed at baseline, eight (±1) hours after first applying the ointment, and at 10 to 11 days after delivery by using the Redness, Edema, Ecchymosis, Discharge, Approximation (REEDA) scale. Secondary outcomes included components of REEDA, the number of analgesics taken during the trial, the resumption of normal daily activities within five days postpartum, and adverse side effects. At 10 to 11 days postpartum, 62 patients in the cinnamon group and 61 in the placebo group remained in the trial for final analysis.

At baseline, the mean pain intensity was 5.0 ± 1.8 in the cinnamon group and 4.6 ± 2.0 in the placebo group. Pain intensity in the cinnamon group was significantly lower than in the placebo group after four hours (mean difference [MD]: -0.6; 95% confidence interval [Cl]: -1.0 to -0.2); after eight hours (MD: -0.9; CI: -1.4 to -0.3); and after 10 to 11 days (MD: -1.4; CI: -2.0 to -0.7). Compared with baseline values, pain intensity reduced by 16% at four hours, by 26% at eight hours, and by 76% at days 10-11 in the cinnamon group; the placebo group had pain intensity reductions of 2% at four hours, 4% at eight hours, and 43% at days 10-11. REEDA healing scores were significantly lower in the cinnamon group than in the control group at eight hours (MD: -0.2; CI: -0.4 to -0.04) and at days 10-11 after delivery (MD: -1.6; CI: -2.0 to -1.1). Compared with baseline, REEDA scores were 53% lower in the cinnamon group and 6% lower in the placebo group at days 10-11. Overall, both pain intensity and healing scores were significantly lower after cinnamon ointment intervention compared with placebo ointment intervention (P<0.01).

Evaluation of secondary outcomes revealed no significant between-group differences in the REEDA components at baseline and after eight hours, except for improved scores for wound approximation in the cinnamon group (P=0.02). Compared with baseline scores, wound healing scores in the cinnamon group improved significantly more than in the placebo group in four of five components (P<0.01 for redness and edema, P=0.021 for ecchymosis, and P=0.003 for approximation). At days 10-11 postpartum, no significant between-group differences were noted in the number of mefenamic acid capsules or other analgesics taken.

The number of patients resuming their normal daily activities within five days postpartum was significantly higher (P=0.003) in the cinnamon group (46 women; 74%) than in the placebo group (29 women; 48%). No adverse side effects were reported in either group.

Cinnamon bark’s three main compounds are eugenol, cinnamaldehyde, and linalool. According to the authors, eugenol, which has a topical numbing effect, may affect inflammation by reducing prostaglandin biosynthesis. Cinnamaldehyde also has anti-inflammatory properties, and linalool possesses analgesic and anti-inflammatory properties that work by reducing nitric oxide and activating analgesic paths of cholinergic and glutamatergic compounds. The cinnamon polyphenols may also reduce inflammation.

The authors conclude: “Our study results showed that use of cinnamon ointment on episiotomy incision for 10 d[ays] reduced intensity of perineal pain and improved healing of the incision with no significant side effects.” RH

References

—Shari Henson
One of the primary precursors to type 2 diabetes (T2DM) is impaired glucose tolerance (IGT). People with IGT also may be at greater risk for cardiovascular disease. Restoring glucose tolerance could reduce this risk and improve health in general. The mixture of traditional Chinese medicinal herbs known as Tianqi (consisting of Astragalus spp., Fabaceae; Coptis spp., Ranunculaceae; Trichosanthes spp., Cucurbitaceae; Lonicera spp., Oleaceae; Dendrobium spp., Orchidaceae; Panax spp., Araliaceae; Lycium spp., Solanaceae; Eclipta spp., Asteraceae; Rhizoma spp., Anacardiaceae; and Cornus spp., Cornaceae) includes several botanicals shown to have anti-hyperglycemic activity. This 11-center, double-blind, randomized, placebo-controlled trial investigated the effects of Tianqi in patients with IGT.

Included patients were between 25 and 70 years of age diagnosed with IGT (not controlled with pharmaceuticals) who had not participated in a clinical trial for three months prior to the study. Patients were excluded if they had cardiovascular disease; experienced a heart attack in the six months preceding the study; had “severe” stress or hyperglycemia; deviated from the study protocol; had mental health disorders; were pregnant, lactating, intending to become pregnant, or not using contraception; or were allergic to Tianqi. Other exclusion criteria were systolic blood pressure (SBP) ≥ 160 mmHg, diastolic blood pressure (DBP) ≥ 100 mmHg, total cholesterol ≥ 6.22 mmol/L, or low-density lipoprotein (LDL) cholesterol ≥ 4.14 mmol/L.

From the 804 patients who were screened, 480 were enrolled in the study, and 420 patients met the inclusion criteria and were randomized to the Tianqi group (n=210) or the placebo group (n=210). All patients received lifestyle counseling consisting of diet information provided by a nutritionist and were requested to maintain their routine physical activity. Counseling occurred at baseline and at three, six, and nine months. Three times per day prior to meals, patients took five capsules (total 4.8 g/day) of Tianqi or placebo (sugarless starch and iron oxide) for 12 months. Both the Tianqi and placebo were provided by Heilongjiang Baoquan Pharmaceutical Co. (Heilongjiang, China). The Tianqi was characterized by ultra-performance liquid chromatography-tandem mass spectrometry. Levels of magnoflorine, berberine, gallic acid, astragaloside IV, palmitic...
acid, and ginsenosides were used as quality control markers. The contents of the eight compounds in the capsules were determined using standard curves of corresponding standards.

The oral glucose tolerance test (OGTT) was employed to measure IGT at baseline and every three months throughout the trial. The primary outcome was the diagnosis of progression to T2DM. Additionally, weight, body mass index (BMI), metabolic parameters, and liver and kidney function also were determined. The occurrence of adverse effects (AEs), their severity, and progression were recorded.

Of the 420 randomized subjects, 198 in the Tianqi group and 191 in the placebo group finished the study. Reasons for patient dropouts included loss to follow-up (28), AEs (2), and deviation from inclusion criteria (1). Although there were no significant differences in patient metabolic parameters between the two groups at baseline, the majority of the patients had high concentrations of triglycerides, total cholesterol, and LDL.

At the trial’s completion, a significantly greater number of patients in the placebo group had progressed to T2DM as compared to the Tianqi group (56 vs. 36, respectively; P=0.01). Also, a significantly greater number of patients in the Tianqi group had normal glucose tolerance (NGT) in comparison to the placebo group (125 vs. 89, respectively; P=0.001). The risk of developing T2DM in those consuming Tianqi was reduced by 32.1% as compared to placebo. The progression to T2DM was 13.79-25% in the Tianqi group and 26.67-35.71% in the placebo group at the end of the study. Alternately, those with NGT ranged from 56.25-68.97% in the Tianqi group and 42.8-50% in the placebo group. After the final patient finished the study, 50 patients in the Tianqi group had T2DM, and 67 patients in the placebo group had T2DM. Additionally, 71 patients in each group still had IGT.

Of all patients, 15 in the Tianqi group and 11 in the placebo group reported AEs. All of the AEs were considered mild and consisted of gastrointestinal complaints, rash, tinnitus, genital swelling, and high concentrations of urinary protein.

In summary, the calculated risk reduction experienced by those in the Tianqi group was similar to that offered by standard pharmaceutical treatments for T2DM. The authors conclude that Tianqi might be a useful treatment to prevent the progression from IGT to T2DM, especially in regions of the world accustomed to the use of botanical medicines. According to the authors, limitations of this trial include the length of the study, relatively small sample size, and the lack of assessment of insulin or glycated hemoglobin concentrations. Overall, this study suggests that Tianqi is well tolerated and efficacious in reducing the risk of T2DM in high-risk populations. hG

—Amy C. Keller, PhD

“I look forward to serving our community with other professionals to provide an integrative healing approach for our patients.”
Carol Micek, MSAOM (2014)
Xanitrol™ Herbal Blend Reduces Body Weight Compared to Placebo


Successful weight loss is accomplished by decreasing energy intake and increasing energy expenditure. Pharmaceutical drug treatments for obesity focus on reducing caloric intake. This study evaluates IQP-GC-101 (Xanitrol™; InQpharm Europe Ltd.; Berlin, Germany), which is hypothesized to reduce body weight by inhibiting fatty acid synthesis and increasing thermogenesis and metabolism. IQP-GC-101 is a patented herbal blend that contains 650 mg garcinia (Garcinia cambogia, Clusiaceae) fruit extract standardized to 60% hydroxycitric acid (HCA), 100 mg green tea (Camellia sinensis, Theaceae) leaf extract (15% epigallocatechin-3-gallate and 11% caffeine), 75 mg green coffee (unroasted Coffea arabica, Rubiaceae) seed extract (25% chlorogenic acid and 5% caffeine), and 25 mg banaba (Lagerstroemia speciosa, Lythraceae) leaf extract (5% corosolic acid). All four of these ingredients have been shown in vivo to have a role in weight loss.

The purpose of this randomized, double-blind, placebo-controlled study was to evaluate the effect of IQP-GC-101 on body weight and body fat reduction in overweight Caucasians. The study design followed the guidance of the European Food Safety Authority that requires evidence of weight loss over a minimum of 12 weeks.

Subjects (n=92, aged 18 to 60 years) were recruited via newspaper advertisement to participate in the study, which was conducted at two centers in Berlin, Germany. Included subjects met the following criteria: Caucasian, body mass index (BMI) between 25 and 32 kg/m², stable body weight for three months before study enrollment, accustomed to eating three meals per day, committed to adhering to the diet plan, agreed not to use other weight-loss products during the study period, and consented to birth control use. The exclusion criteria were as follows: known hypersensitivity to the study ingredients; current or history of systemic or gastrointestinal
The study began with a two-week run-in phase during which subjects were assessed for compliance with the diet and treatment (placebo). Those who could comply were randomized into the study. All subjects received diet counseling and a diet plan that provided them with a 500 kcal deficit diet (calculated on the basis of each participant's body weight, height, age, gender, and activity level). The diet provided 30% of the ingested energy as fat. A food diary was kept so that diet compliance could be monitored. Subjects took placebo or IQP-GC-101 three times per day for 12 weeks. The primary outcome measures were mean loss of body weight and body fat mass after 12 weeks of treatment. Secondary outcome measures were the change in fat free mass, waist circumference, and hip circumference measured at baseline and weeks four, eight, and 12. The Control of Eating Questionnaire (COEQ) was used to measure hunger, fullness, the desire to eat different types of food, food cravings, mood, and alertness. Blood was drawn at baseline and at week 12 to assess full blood count, electrolyte levels, liver function, renal function, lipid metabolism, and carbohydrate metabolism.

At baseline, both groups were similar in terms of mean age, height, body weight, and body fat mass. At week 12, the IQP-GC-101 group had significantly greater weight loss than the placebo group (mean 4.98 lbs vs. 1.23 lbs, respectively; P=0.001). At week 12, the IQP-GC-101 group had significantly greater body fat loss than the placebo group (mean 2.47 lb loss vs. 0.81 lb gain, respectively; P=0.001). Accordingly, at week 12, the IQP-GC-101 group also had a significantly greater decrease in BMI than the placebo group (mean 0.78 kg/m² loss vs. 0.22 kg/m² loss, respectively; P=0.002). Also, the IQP-GC-101 group had a significantly greater decrease compared to placebo in waist circumference (mean 2 cm loss vs. 0.69 cm loss, respectively; P=0.006) and hip circumference (mean 1.54 cm loss vs. 0.64 cm loss, respectively; P=0.019).

There was no significant difference between groups on the COEQ or in laboratory parameters. All adverse events (AEs) were considered to be unrelated to treatment, and both groups had a similar frequency of AEs. Although adverse reaction reports have associated HCA with hepatotoxicity, there were no clinically relevant or statistically significant changes in liver enzyme or bilirubin levels observed in this study.

The authors conclude that IQP-GC-101 plus a slightly hypocaloric diet safely and significantly reduced body weight and body fat mass. They state that the degree of effectiveness in this study was on par with studies of other pharmaceuticals approved by the US Food and Drug Administration for weight loss. All subjects lost weight initially; however, those in the placebo group stopped losing weight after four weeks and had gained fat mass by week 12. The authors hypothesize that after four weeks of weight loss, the body started to store fat as a form of homeostasis, and they infer that IQP-GC-101 reduced lipogenesis (fat production), thereby promoting fat oxidation and thermogenesis. A limitation of this study was that there was no control or monitoring of energy expenditure (e.g., exercise), diet compliance, or coffee/tea/caffeine intake. Longer duration studies with larger sample sizes and more rigorous controls are needed to determine if the reported rate of weight loss is sustained and to better assess safety. Subjects also should be followed after treatment cessation to evaluate potential rebound effects.

—Heather S. Oliff, PhD
Cochrane Review of Safety and Efficacy of Echinacea Preparations Shows Trend of Small Preventive Effect for Common Cold Symptoms


Preparations of the echinacea plant of the daisy family (Asteraceae) are used widely to treat or prevent the common cold. Three different species of the genus Echinacea — E. purpurea, E. pallida, and E. angustifolia — are used medicinally. Echinacea preparations vary greatly, utilizing different parts of the plant (fresh or dried root, aerial parts [leaf and/or flower], fresh-pressed juice from aerial parts, and combinations thereof), various manufacturing methods, and other herbs or homeopathic components are sometimes added. The authors of this paper conducted a systematic review to assess whether or not evidence from randomized controlled clinical trials exists to support the efficacy and safety of echinacea preparations compared with placebo in preventing and/or treating the common cold. (Multiple authors have written about the challenge of conducting a meaningful meta-analysis of trials involving echinacea preparations, insofar as the clinical literature is based on so many different types of preparations.1,2)

This review is the third in a series of systematic reviews of clinical trials on echinacea preparations by these authors, the last one of which was published in 2006.3 Since then, “several new trials have been published and evidence may have changed. Therefore, a major update of this review was necessary,” wrote the authors.

Included Trials, Participants, and Preparations

The authors searched numerous databases — including CENTRAL, MEDLINE, Embase, CINAHL, AMED, LILACS, Web of Science, CAMBASE, the Centre for Complementary Medicine Research, WHO ICTRP, and clinicaltrials.gov — screened references, and questioned experts in the field about published and unpublished studies.

The review included placebo-controlled trials of oral echinacea monopreparations with clinical outcome measures related to occurrence, severity and duration of infections, and safety. Both prevention and treatment studies were included. The authors identified 82 papers describing clinical trials that tested echinacea preparations alone or in combination with other plant extracts. Of those, 24 double-blind trials (in 29 publications) with 4,631 participants in total met the inclusion criteria. Those trials comprised 33 comparisons of various echinacea preparations and placebo. (Some clinical trials may use more than one variation of an experimental treatment, which results in multiple “comparisons” in a single study.) Of the 24 trials, 10 (with 13 comparisons) were prevention studies, and 15 (with 20 comparisons) were treatment studies (one trial evaluated both prevention and treatment).

All studies enrolled adults, except for one conducted with child participants. The trials were conducted in the following countries: 12 in the United States, five in Germany, three in Canada, two in Sweden, one in the United Kingdom, and one in Australia. Two trials from the United States and one from Canada were available only as unpublished manuscripts. Rated using the Cochrane “risk of bias” tool, 10 trials were considered to have a low risk of bias, six to have an unclear risk, and eight to have a high risk.

Most of the echinacea preparations used in the trials were of the following compositions: pressed juices stabilized with alcohol (12 trials; made from fresh aerial parts of the plant), alcohol (ethanol) tinctures made from root and/or aerial parts (five trials), or tablets/capsules made from dried extracts of root and/or aerial parts (12 trials).

Analyses and Results

Occurrence of the common cold was investigated in all 10 prevention trials; other outcomes such as the number of
participants with more than one cold episode and duration/severity of cold episodes were measured in some of those trials as well.

Subjects with at least one cold episode

Nine prevention trials with 12 comparisons reported the number of participants with at least one cold episode, and three trials with four comparisons reported the number of participants with more than one cold episode. Differences were observed between echinacea and placebo groups in individual trials, while pooling all trials (1,167 total participants) yielded a significant risk reduction (RR=0.83; 95% CI: 0.75-0.92; P<0.001). Results were highly consistent across the studies despite certain asymmetry in the funnel plot (Eggers test; P=0.03). The largest clinical study by Jawad et al4 (n=755; 673 completed) reported total experienced cold episodes under echinacea and placebo prevention rather than patient-related data and came to a similar effect size of 26% with regard to cumulated episodes and total episode days (P<0.05).

Severity and duration

Four prevention trials with five comparisons reported duration of cold episodes. One small four-week trial5 with 32 participants found a significant effect of standardized E. purpurea (plant parts not reported) supplementation over placebo (cold duration of was an average of 5.2 days longer in the placebo group). Effect sizes between all included studies, however, varied considerably.

Data in five prevention trials with seven comparisons were used to calculate the effect of the treatments on severity of cold episodes. A pooled analysis indicated a small beneficial effect of echinacea over placebo.

Of the nine treatment trials with nine comparisons assessing both severity and duration, two trials using E. purpurea preparations of juice from above-ground plant parts (487 total participants) and two trials (184 total participants) using a standardized extract of E. purpurea flower, stem, and root (Echinilin®; Inovobiologic, Inc.; Calgary, Alberta; same as Echinamide®; Natural Factors; Coquitlam, British Columbia) reported conflicting results; only one of these trials found a significantly shorter cold duration in the echinacea group. No significant differences were reported among the other trials (using E. purpurea and/or E. angustifolia).

Adverse side effects

Eight prevention trials (with nine comparisons) included information on subjects’ reported adverse side effects. There were no significant differences recorded except in one study6 (with 111 total participants in the final analysis) that found significantly fewer reported adverse effects in the placebo group. A trend toward fewer adverse effects in the placebo groups compared with the echinacea groups was seen in most of the other prevention trials. In the treatment studies, the number of participants reporting adverse effects did not differ significantly between echinacea and control groups.

Dropout rates

The authors also examined the number of participants who dropped out of studies. Of the prevention trials, seven studies with eight comparisons reported the number of participants who dropped out because of adverse effects (the main outcome measure for safety and acceptability). Two prevention studies4,7 (1,072 total participants) reported a significantly higher dropout rate in the echinacea groups than in the placebo groups. The other trials reported no significant differences in the dropout rates. In a pooled analysis, the authors report that 12.7% of participants in the echinacea groups and 9.0% in the placebo groups dropped out of the prevention studies, which was an insignificant difference (P=0.06).
For the treatment trials, the dropout rates tended to be similar in the echinacea and placebo groups. In 11 trials with 14 comparisons, only three of 1,088 participants who received an echinacea product and none of the 930 participants who received placebo dropped out because of adverse effects.

Conclusions and Recommendations

This review included more treatment trials — investigating whether taking echinacea preparations after the onset of cold symptoms shortened the duration compared with placebo — than prevention trials. While “the overall evidence for clinically relevant treatment effects over placebo is weak,” wrote the authors, some echinacea products may be more effective than placebo for treating colds. The prevention trials showed a trend toward preventive effects of the echinacea interventions, with a “relative risk reduction of 10% to 20%.” The number of participants who dropped out or reported adverse effects did not differ significantly between treatment and control groups in all trials combined.

The current Cochrane analysis by Karsch-Völk et al reviewed a total of 24 prevention and acute treatment studies on a large variety of echinacea monopreparations (i.e., no other botanicals or active ingredients were present). Various products prepared from different echinacea species, with different plant parts, and in different forms have been compared with placebo in randomized trials, as reported in this review. “The great heterogeneity of preparations tested makes conclusions difficult,” stated the authors of this review. “The most important recommendation for consumers and clinicians is to be aware that the available Echinacea products differ greatly.”

Acknowledging that further research is needed, the authors cautioned that with the many diverse products on the market, applying the knowledge gained from research is challenging. The use of chemically well-defined preparations is important and will improve researchers’ ability to compare results of future studies. “Echinacea products have not here been shown to provide benefits for treating colds, although, it is possible there is a weak benefit from some Echinacea products,” the authors concluded. “[T]he results of individual prophylaxis trials consistently show positive (if nonsignificant) trends, although potential effects are of questionable clinical relevance.”

Principally, the new Cochrane analysis acknowledges echinacea as having a possible “weak benefit” for cold and flu management. At the same time, it highlights the necessity for chemically characterized, properly manufactured, and clinically researched extracts, since commercially available echinacea products vary considerably.

“The most important recommendation for consumers and clinicians is to be aware that the available Echinacea products differ greatly.”

References

Study Shows Ginger May Be Effective in Preventing Antiretroviral-Induced Nausea and Vomiting


Antiretroviral therapy used to treat human immunodeficiency virus (HIV) infection produces nausea in 42% to 57% of patients and vomiting in 28% to 32% of patients. Although the nausea and vomiting disappear over time, they adversely affect treatment adherence. Pharmaceutical treatments are available to decrease these reactions; however, these treatments have their own adverse side effects, can produce drug-drug interactions, and may be cost prohibitive.

Clinical studies have demonstrated that ginger (Zingiber officinale, Zingiberaceae) rhizome can alleviate certain gastrointestinal symptoms associated with pregnancy, recovery from surgery, and chemotherapy. The purpose of this randomized, double-blind, placebo-controlled study was to evaluate the efficacy of ginger for the prevention of antiretroviral-induced nausea and vomiting.

Patients (n=115, aged 18 to 65 years) with HIV participated in this study conducted at the HIV clinic of Imam Khomeini Hospital in Tehran, Iran. Excluded patients had current presentation or a history of peptic ulcers, dyspepsia, or nausea and vomiting; were using antiemetic or antacid products; had a history of ginger hypersensitivity; or were taking concomitant anticoagulant therapy. All patients were treated with antiretroviral drug combinations — either efavirenz plus lamivudine and zidovudine, or lopinavir/ritonavir and didanosine.

Patients received placebo or 500 mg powdered ginger rhizome (Goldaroo Pharmaceutical Company; Isfahan, Iran) twice per day, 30 minutes before each dose of antiretroviral drugs for 14 days. (According to the article, Goldaroo’s products undergo “periodical analysis and quality control” under the supervision of the Iran Ministry for Health’s Drug and Food Control Laboratory, although no additional analytical details were provided.) Patients were instructed not to take any additional treatment for gastrointestinal (GI) problems such as nausea and vomiting. Any patient requiring pharmaceutical treatment for GI problems was withdrawn from the study. Patients also were instructed not to change their meal regimens. Severity of nausea was assessed with a visual analog scale, and patients were monitored daily by telephone.

At baseline, both groups had similar characteristics and laboratory data. Significantly more patients in the placebo group (90.2%) than in the ginger group (56.9%) had some degree of nausea (P=0.001). Also, the ginger group had a significantly lower frequency of mild, moderate, and severe nausea than the placebo group (P=0.02, P=0.04, and P=0.001, respectively). Placebo-treated patients reported an occurrence of at least one episode of vomiting significantly more often (47.1%) than the ginger-treated patients (9.8%) (P=0.01). Ginger was well tolerated. The authors conclude that ginger was effective at decreasing nausea and vomiting associated with antiretroviral therapy, but it was more effective in the prevention of vomiting.

A peer reviewer of this Research Review noted that there are several key limitations of this study: First, there was poor characterization and study design to assure the placebo comparison was meaningful, particularly the description of allocation concealment, masking of the ginger and placebo (it is easy to both smell and taste ginger root), and the evaluation of the success of masking, which is usually accomplished by asking participants to guess which treatment they received at the end of the study. Without these elements, the placebo comparison may not be valid, and study results might be biased in favor of the ginger intervention. The second limitation was the researchers’ decision to withdraw patients requiring further anti-emetics and not including those “treatment failures” in an intention-to-treat analysis.

It also should be noted that ginger can inhibit cytochrome CYP enzymes and may alter the efficacy and safety of protease inhibitors used to treat HIV. Future studies need to evaluate other doses of ginger, whether starting ginger therapy prior to starting antiretroviral therapy would increase efficacy, and whether there is an optimal time in the day to take the ginger therapy. HG

—Heather S. Oliff, PhD

“It took 13 years for the United States to come to its senses and end Prohibition, 13 years in which people kept drinking, otherwise law-abiding citizens became criminals and crime syndicates arose and flourished. It has been more than 40 years since Congress passed the current ban on marijuana, inflicting great harm on society just to prohibit a substance far less dangerous than alcohol. The federal government should repeal the ban on marijuana.”¹

So wrote The New York Times (NYT) editorial board early this summer, in a seminal article advocating the legalization of cannabis (Cannabis sativa, Cannabaceae) titled “Repeal Prohibition, Again.” In it, the editorial board proposed change to the federal laws concerning cannabis — so citizens and states will not be subject to changing presidential administrations’ views on the matter — as well as the establishment of cannabis regulations similar to those pertaining to alcohol and tobacco.

The NYT board cited a US Federal Bureau of Investigation figure of 658,000 cannabis arrests for 2012 in the initial editorial article, contrasting that number with only 256,000 arrests made for heroin, cocaine, and their derivatives for the same year. “Even worse, the result is racist,” the NYT editorial board wrote, “falling disproportionately on young black men, ruining their lives and creating new generations of career criminals.” According to the article, the editorial board of the NYT believes that the health risks of cannabis absolutely do not outweigh those of legal alcohol and tobacco use; however, they do propose a legal age of 21 be enacted due to potential adverse effects of cannabis on the adolescent brain.

Additionally, in “Repeal Prohibition, Again,” the NYT editorial board announced the commencement of a series of editorials on cannabis issues — titled “High Time: An Editorial Series on Marijuana Legalization” — which was published over the summer of 2014 and is summarized herein.

Part 1: Let States Decide on Marijuana
by David Firestone, July 26, 2014²

This article begins by setting the scene in 1970, with President Nixon “at the height of his white-hot war on crime.” It was in that year that he appealed for the passage of the Controlled Substances Act by Congress; Firestone wrote that the Senate voted unanimously to pass it after Senator Thomas Dodd (D-Connecticut) claimed that cannabis caused “dreadful hallucinations” to the point that it led an Army sergeant to command an attack on his own troops in Vietnam.

Firestone describes the Controlled Substances Act as “antique,” superficially illustrating this view by pointing out the law’s spelling of “marihuana.” Interestingly, he notes that changing the law needn’t involve Congress: both the US Attorney General and the Secretary of Health and Human Services have the power to do so.

With cannabis already legalized either medicinally, recreationally, or both in 35 states in the US and the District of Columbia, “[r]epealing the [Controlled Substances Act] would allow the states to decide whether to permit marijuana use and under what conditions.” Firestone goes on to call the position of the federal government at the time of the Act’s passing absurd and archaic, specifically because of its categorization of cannabis as a Schedule I drug with no medical value “alongside some of the most dangerous and mind-altering drugs on earth, ranked as high as heroin, LSD and bufotenine, a highly toxic and hallucinogenic toad venom that can cause cardiac arrest.” Cocaine and methamphetamine, meanwhile, are Schedule II drugs with recognized “legitimate medical use.”

“It’s hard for the public to take seriously a law that says marijuana and heroin have exactly the same “high potential for abuse,” wrote Firestone, “since that ignores the vastly more addictive power of narcotics, which have destroyed the lives of millions of people around the world.” No wonder, after more than 40 years of congressional and presidential refusal to reschedule cannabis — which has caused zero deaths from overdose — states are now defying federal law, he asserts. In 18 states and the District of Columbia, Firestone adds, marijuana has been “decriminalized” — “generally meaning that possession of small amounts is treated like a traffic ticket or ignored.” This year, voters in Oregon and Alaska will determine whether to join Washington and Colorado as states in which recreational cannabis use is legal. “The states… are weary of locking up thousands of their own citizens for possessing a substance that has less potential for abuse and destructive power than alcohol,” wrote Firestone.

The article explains that unlike reproductive rights and marriage equality, the ability to use marijuana is not a “fundamental right” and therefore belongs in the states’ purview; the fact that marijuana is illegal on a federal level and carries heavy penalties, however, has discouraged some states from legalizing it.

According to Firestone’s article, the Justice Department
stated in August 2013 that it wouldn’t meddle in Colorado and Washington, so long as the following criteria were met:

1. Marijuana must not be accessible by minors or criminal gangs;
2. Transport out of state must be prohibited, and;
3. Prohibition against drugged driving, violence, and illegal drugs must be enforced.

Of course, this guidance “applies only to this moment in this presidential administration” — a reference to the fact that a future president may or may not agree with the current administration’s position and might even propose policies that revert to the previous status quo.

Firestone proposes that the sensible thing is for the federal government to let states make their own choices about marijuana, the same way they’ve made their own choices about alcohol since Prohibition ended in 1933. Some longshot legislation has been proposed that aligns with this view, including the “Ending Federal Marijuana Prohibition Act,” which, if passed, would result in the following:

1. Marijuana would be eliminated from the Controlled Substances Act;
2. A federal permit would be required to grow or distribute cannabis;
3. It would be regulated like alcohol is currently regulated by the Food and Drug Administration and the Bureau of Alcohol, Tobacco, Firearms, and Explosives.

Another relevant bill — “which would not be as effective” — called the “Respect State Marijuana Laws Act” has been introduced. If it became law, Firestone explained, cannabis would remain classified as a Schedule I substance, but the Controlled Substances Act would not be enforced “against anyone acting in compliance with a state marijuana law.”

Libertarian Republicans and liberal Democrats, Firestone notes, have a more harmonious perspective on the matter than some may think. “In a surprise move in May, the House [of Representatives] voted 219 to 189 to prohibit the Drug Enforcement Agency from prosecuting people who use medical marijuana, if a state had made it legal,” wrote Firestone. “The measure’s fate is uncertain in the Senate.”

In the meantime, Firestone put forward a suggestion for President Obama, who has been quoted as being in favor of Colorado and Washington’s measures but has punted the matter of cannabis rescheduling to Congress: “[O]rder the attorney general to conduct the study necessary to support removal of marijuana from Schedule I.”

Firestone describes the Controlled Substance Act as “antique,” superficially illustrating this view by pointing out the law’s spelling of “marihuana.” Interestingly, he notes that changing the law needn’t involve Congress: both the US Attorney General and the Secretary of Health and Human Services have the power to do so.
“For too long, politicians have seen the high cost — in dollars and lives locked behind bars — of their pointless war on marijuana and chosen to do nothing. But many states have had enough, and it’s time for Washington to get out of their way,” wrote Firestone in closing.

Part 2: The Injustice of Marijuana Arrests
by Jesse Wegman, July 28, 2014

This article addresses the trends in and consequences of marijuana arrests. “The toll,” writes Wegman, “can be measured in dollars — billions of which are thrown away each year in the aggressive enforcement of pointless laws. It can be measured in years — whether wasted behind bars or stolen from a child who grows up fatherless. And it can be measured in lives — those damaged if not destroyed by the shockingly harsh consequences that can follow even the most minor offenses.”

To illustrate, Wegman turns to the 2010 case of Bernard Noble, who was sentenced to 13 years in prison for possessing a “small amount of marijuana in his pocket.” He had only two nonviolent offenses on his record. Next, Wegman tells the story of Jeff Mizanskey, who received a sentence of life in prison without parole in 1993 “for participating (unknowingly, he said) in the purchase of a five pound brick of marijuana” after two previous nonviolent marijuana convictions.

Prison sentences aren’t the only deeply damaging punishments for marijuana arrests, which affect opportunities for employment and home ownership, among other things, because such arrests remain on an individual’s record for years, according to the article. “[P]olice departments that presumably have far more important things to do waste an enormous amount of time and taxpayer money chasing a drug that two states have already legalized and that a majority of Americans believe should be legal everywhere,” wrote Wegman.

The article claims that 8.2 million marijuana arrests were carried out by police from 2001 to 2010 in the United States, with approximately nine of 10 charged for mere possession; startlingly, according to Wegman, in 2011 “there were more arrests for marijuana possession than for all violent crimes put together.”

Citing the American Civil Liberties Union (ACLU), the Times editorial states that $3.6 billion are spent annually just to enforce existing cannabis possession laws. And still, every year, around 30 million Americans consume cannabis undeterred.

Again crediting the ACLU as a source, Wegman states that while the use of cannabis is comparable between blacks and whites, black individuals are nearly four times as likely to be arrested as white people for possession. “In the worst-offending counties in the country,” wrote Wegman, “[black people] are up to thirty times more likely to be arrested.” Even when charges are dropped, records for arrests are not expunged, to the detriment of people of color in impoverished communities. These “criminal histories,” according to Wegman, can and do result in harsher consequences for minor subsequent offenses.

Of the United States’ 2.4 million inmates, very few — about 1% — are serving sentences for distributing or possessing cannabis, according to the article. Still, many of those sentences are bloated as a result of records tarnished by insignificant offenses. Wegman wrote, adding that approximately nine in 10 have no history of violence and “blacks are 10 times as likely as whites to go to prison for drug offenses.”

On the outside, growers and dispensary proprietors in more than 25 states — particularly those where it is legal recreationally — profit from selling cannabis. Wegman poignantly quotes Ohio State University law professor Michelle Alexander: “40 years of impoverished black kids getting prison time for selling weed, and their families and futures destroyed. Now, white men are planning to get rich by doing exactly the same thing?”

Part 3: The Federal Marijuana Ban is Rooted in Myth and Xenophobia
by Brent Staples, July 29, 2014

Staples chronicles the historical origins of the criminalization of cannabis in the United States, which had less to do with public health concerns than with the stigmatization of minority communities associated with cannabis use in the 1930s — specifically, African Americans and Mexican immigrants.

According to the article, in the mid-1800s, cannabis cultivation was common in the United States for textile purposes. “The practice of smoking it appeared in the Texas border towns around 1900,” wrote Staples, “brought by Mexican immigrants who cultivated cannabis as an intoxicant and for medicinal purposes as they had done at home.” Soon it was prevalent in the region and available in drug and grocery stores. Nevertheless, local law enforcement attacked the substance because of its popularity among “immoral” poor minority groups, which ultimately led to marijuana’s confounding classification as a “narcotic,” along with opium-derived drugs, and, later, the prohibition of

* At this time, cannabis appeared in the United States Pharmacopeia for rheumatism, nausea, and pain, among other indications.
non-medically recognized cannabis* in more than 30 states by the early 1930s.

Staples describes the incitement of the federal government’s prohibition of cannabis, beginning with a “prominent doctor[s]” claim that cannabis smokers were responsible for a surge in theft. “Sensationalistic newspaper articles” abounded, perpetuating exaggerated stereotypes, false facts, and rousing fear among the general population, according to Staples.

Harry Jacob Anslinger, the commissioner of the Federal Bureau of Narcotics and the “architect of national prohibition,” loudly proclaimed that cannabis spurred insanity and harrowing crimes. His propaganda worked — passage of The Marihuana Tax Act of 1937 established a prohibitively high tax on cannabis,† according to the Times article.

In 1951, the Public Health Service Hospital’s director of research, Harris Isbell, testified before Congress that “smoking marijuana has no unpleasant after-effects, no dependence is developed on the drug, and the practice can easily be stopped at any time.” But the damage, it seemed, had been done, according to Staples. The consequences for using cannabis became more severe on federal and state levels, even as arguments concerning marijuana’s addictive qualities receded. A trope was born: Cannabis as the “gateway drug.”

It wasn’t until the 1960s, Staples highlights, that the American public began to revisit its stance on cannabis due to the appropriation of the substance by white, well-off young people; the reality of the devastating toll of a marijuana conviction finally was reverberating across the country. The 1972 National Commission on Marihuana and Drug Abuse determined that “criminalization was ‘too harsh a tool to apply to personal possession even in the effort to discourage use,’ and that ‘the actual potential harm of use of the drug is not great enough to justify intrusion by the criminal law into private behavior, a step which our society takes only with the greatest reluctance.’” President Nixon was unmoved by these conclusions, but within a decade, most states began a steady mellowing of possession penalties, according to Staples. Today our federal and state cannabis laws remain out of harmony.

“The federal government] clings to a policy that has its origins in racism and xenophobia and whose principle effect,” Staples asserts in closing, “has been to ruin the lives of generations of people.”

Part 4: What Science Says About Marijuana
by Philip M. Boffey, July 31, 2014

Boffey begins his health-focused editorial with a 2012 quote to Congress from Michele Leonhart, administra-

† Up to $24 annually; taking inflation into account, this would be nearly $400 today.
tor of the Drug Enforcement Agency (DEA): “All illegal drugs are bad for people.” According to the article, Leonhart “refus[ed] to say whether crack [coca], methamphetamines or prescription painkillers are more addictive or physically harmful than marijuana.” Boffey uses her testimony to illustrate the chasm between the federal position on cannabis and the scientific facts.

Of all of the editorials in the series, this is perhaps the most dense — and for good reason. Before diving into the deep end, Boffey reiterates that more dangerous and addictive drugs, tobacco and alcohol, are legal; that there is no documentation of a fatal cannabis overdose; and that the research thus far on cannabis does not indicate that it causes cancer. Having made those statements, Boffey then clarifies that cannabis is not altogether innocuous. “[T]he potency of current strains may shock those who haven’t tried it for decades,” wrote Boffey, “particularly when ingested as food. It can produce serious dependency, and constant use would interfere with job and school performance.”

For healthy adults, the article claims, “casual” use of cannabis carries few risks, if any. According to Boffey, in 2010, a British independent scientific committee analyzed the personal and societal damage caused by 20 drugs (including cannabis, heroin, crack cocaine, and alcohol, among others) and attempted to rank them by harmfulness. Alcohol was determined to be the most harmful; cannabis placed eighth. Also cited is a nearly 20-year-old World Health Organization study that determined that the detrimental health effects of tobacco and alcohol would be greater than those of cannabis in the West, even if cannabis were to be used as much as the aforementioned legal substances.

A 2012 study, Boffey wrote, concluded that no adverse effects on pulmonary function were associated with smoking one cannabis cigarette (or “joint”) each day over the course of seven years.

A 2012 study, Boffey wrote, concluded that no adverse effects on pulmonary function were associated with smoking one cannabis cigarette (or “joint”) each day over the course of seven years. Experts say that marijuana increases the heart rate and the volume of blood pumped by the heart, added Boffey, “but that poses a risk mostly to older users who already have cardiac or other health problems.”

As for the supposed addictive qualities of marijuana, Boffey clarifies that unlike heroin, which is a physically addictive drug, cannabis use can result in a “psychological dependence.” Tolerance can develop in heavy users, necessitating larger doses, and withdrawal can be accompanied by typically mild discomfort. Still, a 2012 American Society of Addiction Medicine white paper stressed that cannabis addiction “is a significant health problem,” according to the Times article.

Comparatively, though, cannabis addiction or dependence (or the potential for either to develop) is not the scourge to society that other drugs are. Citing a 1999 study from the National Academy of Science’s Institute of Medicine, Boffey claims that a mere nine percent of cannabis users become dependent, as opposed to 32 percent of tobacco users, 23 percent of heroin users, 17 percent of cocaine users, and 15 percent of alcohol users.

One of the longest-running theories posited in the discussion of cannabis’s potential detrimental health effects on minors is that it serves as a “gateway” to use of more harmful substances. “People who try marijuana are more likely than the general population to try other drugs, but that doesn’t mean marijuana prompted them to do so,” wrote Boffey. “The real gateway drugs are tobacco and alcohol, which young people turn to first before trying marijuana.”

Boffey upholds the NYT editorial board’s earlier suggestion that cannabis remain illegal for minors. To support the reasoning of this proposal, he refers to a long-term 2012 study claiming heavy cannabis smoking beginning in one’s teen years and sustained into adulthood results in the loss of eight IQ points by age 38. A 2002 study, Boffey wrote, “also found an IQ loss among heavy school-age users who smoked at least 5 joints a week.” (There is some speculation regarding causality and correlation, among other concerns.)

The prevailing science does not support cannabis’s current status as an illegal drug; rather, it supports conscientious legalization and regulation. Unfortunately, Boffey does not address in this article the significant, absurd restrictions on medical and scientific research on cannabis due to its Schedule I classification.

Part 5: The Great Colorado Weed Experiment

by Lawrence Downes, August 2, 2014

Since January of 2014, Downes opens, Coloradans have

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1 The original NYT editorial did not cite a specific study or studies in support of this statement. A peer reviewer of this article suggested the following study should be referenced: Hashibe M, Morgenstern H, Cui Y, et al. Marijuana use and the risk of lung and upper aerodigestive tract cancers: results of a population-based case-control study. Cancer Epidemiol Biomarkers Prev. 2006;15(10):1829-1834.

2 A peer reviewer of this article characterized this as a very poor quality study, stating that it did not control for binge drinking and alcohol abuse. Further, according to the reviewer, the study employed only one brain scan, and the researchers’ negative conclusions regarding density of the hippocampus contradict the preponderance of scientific literature.

The reviewer added that “All effects on cognition and brain function are reversible after 30 days of abstinence [from cannabis],” citing the following study: Pope HG Jr, Gruber AJ, Hudson JJ, Huestis MA, Yurgelun-Todd D. Neuropsychological performance in long-term cannabis users. Arch Gen Psychiatry. 2001;58(10):909-915.
been consuming a variety of (state-) legal cannabis products and cultivating their own plants for recreational purposes. (Medicinal cannabis has been legal in Colorado since 2000.)

“Cannabis sales from January through May brought the state about $23.6 million in revenue from taxes, licenses and fees,” reported Downes. “This is not a huge amount in a $24 billion budget, but it’s a lot more than zero, and it’s money that was not pocketed by the black market.”

Citing the Denver Post, Downes notes that cannabis prosecutions decreased by 77 percent compared with the previous year. Other crime, specifically theft, also has decreased. Economic and employment opportunities, on the other hand, have increased since the state enacted Amendment 64 to “regulate marijuana like alcohol,” according to the article. The amendment should direct significant tax revenue to education and medical research.

Downes highlights that despite the fact that Colorado Governor John Hickenlooper was averse to Amendment 64, “his administration is trying to make legalization work.” Cannabis regulations pertaining to public consumption and age restrictions are being established and enforced; cannabis plants are digitally tracked “from seed to sale.” According to the article, 100% compliance to the law restricting sales to minors was determined for cannabis businesses in Denver and Pueblo under surveillance by Colorado regulators.

The state is also in the process of developing and refining tools to deter drugged driving, which, in the case of cannabis, is more difficult to determine than drunk driving because THC can linger in the body long after use. Downes reports that, according to the Colorado State Patrol, fatal vehicle collisions decreased by about 25% in the first quarter of this year compared to the first quarter of 2013.

As the first state to legalize recreational cannabis, Colorado is on the frontline of identifying and, subsequently, taking responsible measures to counter unforeseen issues such as clear labeling for edibles, the lack of which previously caused concern after a small number of non-fatal overdoses was highly publicized. The state also is leading the way in the areas of educating children and marketing to minors to discourage underage use of cannabis. According to Downes, Colorado is devoting $17 million to these priorities.

In short, by virtue of its early adoption of legalized medicinal and non-medicinal cannabis, Colorado is likely to serve as a national model — encountering unexpected issues and discovering what works and what does not as the proverbial eyes of the United States look on. Its experiment with fully legalized marijuana will be instructive.
for all. Though Washington state, too, has legalized both medicinal and recreational cannabis, according to Downes, it has implemented “far stricter controls on advertising and public displays, and a tight licensing process that, so far, has allowed relatively few marijuana stores to open, with limited supplies at very high prices.” Consequently, Downes posits, legalized recreational cannabis may not overcome less-expensive black market product — at least among Washington state residents.

Given the remarkable ease with which a medical cannabis ID card is obtained in the state of California — where it is not technically legal for recreational purposes — Downes suggests that perhaps readers yet ought to consider cannabis, for all intents and purposes, unofficially across-the-board state-legal there. Certainly there have been some growing pains since California legalized medicinal cannabis in 1996; however, exceptionally accessible cannabis hardly has transformed the state into an apocalyptically crime-ridden dystopia over the last two decades.

Part 6: Rules for the Marijuana Market
by Vikas Bajaj, August 4, 2014

“How should governments regulate the production and sale of [cannabis]?” asks Bajaj. An effective regulatory system, the author asserts, should ensure that cannabis abuse does not increase even as the substance becomes more widely accessible. Further, it should “protect consumers from both dangerous and counterfeit products” and should “undermine and eventually eliminate the black market for marijuana, which has done great damage to society.”

After a state legalizes, the cost of cannabis could decrease as much as 90 percent, according to a Times-cited figure from Stanford law professor Robert MacCoun and colleagues; thusly, cannabis retailers will be motivated to encourage cannabis use for economic gain. According to Bajaj, the Colorado Department of Revenue claims that “nearly 90 percent of the demand for marijuana in the state this year would come from only 30 percent of users, those who use the drug 21 to 31 days a month.”

In light of that knowledge, Bajaj proposes that licensed cannabis retailers decrease prices only to the extent that they push out black-market distributors — adding that anything more may encourage more widespread use and/or dependence. High taxation based on factors other than price (as is the present custom in both Colorado and Washington state) — potentially on potency, inflation, and medicinal vs. recreational — Bajaj offers, may present a solution that will allow the market to circumvent the consequences wrought by insignificant taxation of alcohol.

Further, Bajaj wrote, regulations must be established for marketing to discourage underage use, in the same way regulations ban “outdoor advertising and product placements that the tobacco industry accepted as part of its settlements with state attorneys general in 1998.” Minors also will be protected via labelling regulations and the even distribution of psychoactive ingredients, according to the article. Regulation should address adulteration, as well.

To avoid vertical integration, Bajaj suggests that the cultivation and retail aspects of the cannabis industry be kept apart in the long-run. “Colorado initially required growers to also be retailers in the interest of getting the legal market going quickly but has since allowed them to specialize,” wrote Bajaj, adding that ideally production and sales ought to be separated — as Washington state already has required.

Overall, Bajaj presents what is, in his view, an optimal system of regulation meant to ensure that the cannabis industry does not repeat the mistakes of the alcohol and tobacco industries, both of which are dominated by a very few, and, in the case of the former, has resulted in the imposition of unfair regulations on small artisanal producers. In the case of the latter, scientific inquiry was, for a time, suffocated.

“Whatever states decide to do, it is important that they stand ready to modify policies as legal marijuana markets evolve,” wrote Bajaj. “Policy makers have little experience regulating a fully commercial market in this drug. It makes sense for states to proceed with caution and reserve the right to change as they learn more,” he concluded.

Conclusion

In addition to its longstanding tradition of endorsing presidential candidates throughout the years, the New York Times editorial board has expressed its position on a number of important issues — including marriage equality, the Affordable Care Act, and Guantanamo Bay Detention Camp, to name just a few — in the pages of the “Old Gray Lady,” as the 163-year-old newspaper is sometimes called. The dedication of an entire series of articles to cannabis is apt as the majority of Americans have now shifted in favor of legalization, and because there are plentiful, significant angles from which cannabis’s past and future impacts should be addressed in conjunction with the NYT editorial board’s proposal for federal legalization. So abundant is the relevant information, and so dynamic is the discussion, that it would be virtually impossible to cover every aspect of these changing social, economic, medical, political, and legal trends — but the Times series has succeeded in making accessible some of the more esoteric components of the cannabis conversation, encouraging supplementary edification. In time, readers and activists may come to call this the summer of the “Old Green Lady.”

—Ash Lindstrom

References


Supplement Company Tied to Former Virginia Governor’s Corruption Trial Halts Sales of Tobacco Alkaloid-Based Products; Governor and Wife Convicted on Federal Charges

By Tyler Smith

In the past year, much has changed for Jonnie R. Williams Sr. and his dietary supplement company, Star Scientific, Inc. In December 2013, the US Food and Drug Administration (FDA) sent a warning letter to Williams notifying him that two of his company’s products — Anatabloc® and CigRx® — did not meet the legal definition of a dietary supplement and were therefore adulterated under the Federal Food, Drug, and Cosmetic Act.1 Both products contain anatabine, a minor alkaloid present in small quantities in tobacco (Nicotiana tabacum, Solanaceae) and certain other plants (see Table 1), which the company promotes for its anti-inflammatory properties and smoking cessation benefits.2 Shortly thereafter, Williams stepped down as the CEO of Star Scientific, and by mid-2014 the company had rebranded itself as Rock Creek Pharmaceuticals, Inc. and moved its headquarters from Glen Allen, Virginia to Sarasota, Florida.3
Tobacco for Health: A Brief History of Star Scientific

Williams, an entrepreneur and businessman, dabbled in a number of different ventures in the 1980s including car sales and optometry startups. In 1990, Williams founded Star Tobacco with the goal of making "safer" tobacco.8 “I don’t like tobacco,” Williams said in a Richmond Times-Dispatch article from 1988. “I am more interested in health care.”

Star Scientific introduced smokeless tobacco products in the 1990s, and Williams eventually patented a tobacco-curing process using microwave radiation, which greatly reduced the amount of tobacco-specific nitrosamines, a group of potent carcinogens, in the dried plant material. In the late ’90s, the company significantly reduced the scope of its cigarette manufacturing operations, and Williams was appointed CEO of the newly renamed Star Scientific in 1999.9,10 “For most of its history as a maker of cigarettes, then smokeless tobacco, Star Scientific has presented itself as an innovator, seeking to bring change to an industry that for decades resisted it,” commented the author of a recent article in Richmond Times-Dispatch.10

In a span of roughly two decades, Star Scientific transformed from a cigarette manufacturer to a “technology-oriented company” concentrating on the nicotine-like chemical anatabine. The company’s new health-focused goal, according to Star Scientific, is “to develop a range of non-nicotine dietary supplements and related pharmaceutical products that could be beneficial in maintaining a healthy metabolism and in supporting good nutrition.”11

Table 1. Reported Natural Sources of Anatabine*

<table>
<thead>
<tr>
<th>Source</th>
<th>Reference</th>
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<tr>
<td>Anatabine exists in tobacco and certain foods [in the nightshade family, Solanaceae], including <strong>green tomatoes</strong> [Solanum lycopersicum], <strong>green potatoes</strong> [Solanum tuberosum], <strong>ripe red peppers</strong> [Capsicum annuum], <strong>tomatillos</strong> [Physalis philadelphica], and <strong>sundried tomatoes</strong> [Solanum lycopersicum].</td>
<td>12</td>
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<tr>
<td>As an alternative to preparing anatabine synthetically, anatabine can be obtained by extraction from <strong>tobacco</strong> or other plants, such as members of [Solanaceae], e.g., <strong>jimson weed</strong> [Datura spp.], <strong>mandrake</strong> [Mandragora officinarum], <strong>belladonna</strong> [Atropa belladonna], <strong>chili peppers</strong> [Capsicum spp.], <strong>potato</strong>, … <strong>eggplant</strong> [Solanum melongena], and petunia [Petunia spp.].</td>
<td>12</td>
</tr>
<tr>
<td>Although anatabine is present as an inherent constituent of foods such as <strong>cauliflower</strong> [Brassica oleracea], <strong>eggplant</strong>, <strong>potatoes</strong>, and <strong>tomatoes</strong>, FDA is not aware of any information indicating that anatabine itself is an article used for food.</td>
<td>1</td>
</tr>
<tr>
<td><strong>Corkwood</strong> (Duboisia myoporoides) <strong>Tobacco</strong></td>
<td>13</td>
</tr>
</tbody>
</table>

*References 1 and 12 do not include primary scientific data supporting anatabine’s presence in the plants listed.
On August 5, 2010, Star Scientific launched CigRx, a dissolvable smoking cessation lozenge that contains anatabine and yerba maté (Ilex paraguariensis, Aquifoliaceae) as its active ingredients.14 One year later, the company introduced the dietary supplement Anatabloc, which retailed for $99.99 for a 30-day supply.2 According to its online description, “Anatabloc” leverages the body’s natural process for regulating its own inflammation using anatabine, a naturally-occurring compound found in some plants, combined with Vitamin A and D3.2 In 2012, a $300 facial cream was added to the product line, promoted as being “infused with anatabine citrate, a rare ingredient that is exclusive to Anatabloc.”15

Star Scientific announced in December 2012 that it would focus on dietary supplements, officially severing ties with the tobacco industry. Despite Star Scientific’s revamped mission and new products, the company has reported 11 consecutive years of financial losses through 2013, according to the most recent SEC report available.6

“Our future prospects,” Star Scientific notes in the report, “therefore are dependent on the expanded distribution and consumer acceptance of our dietary supplement products and cosmetic product.”6

McDonnells Indicted and Convicted of Corruption

Williams allegedly first became acquainted with Bob McDonnell during his 2009 gubernatorial race, when McDonnell’s staff requested the use of Williams’ private jet for campaigning purposes. Shortly after McDonnell was elected governor of Virginia, Williams asked to meet with the McDonnells at a political event in New York City, and they remained in varying degrees of contact through March 2013.4

The federal indictment charges that over a period of roughly two years, the McDonnells schemed to provide “official actions . . . to legitimize, promote, and obtain research studies for Star Scientific’s products, including Anatabloc” in exchange for loans and gifts from Williams, reportedly totaling more than $177,000.4,5

McDonnell — whose campaign slogan was “Bob’s for Jobs” — has maintained that any actions he took to support Williams or Star Scientific were consistent with his goal to promote Virginia businesses.16

The 43-page indictment provides numerous examples of such “official actions” performed by McDonnell, including the following:

1. “Arranging meetings for [Williams] with Virginia government officials, who were subordinates of the Governor, to discuss and promote Anatabloc;”
2. “Hosting, and the defendants attending, events at the Governor’s Mansion designed to encourage Virginia university researchers to initiate studies of anatabine and to promote Star Scientific’s products to [medical] doctors for referral to their patients;
3. “Contacting other government officials in the OGV [Office of the Governor of Virginia] as part of an effort to encourage Virginia state research universities to initiate studies of anatabine;
4. “Promoting Star Scientific’s products and facilitating its relationships with Virginia government officials by allowing [Williams] to invite individuals important to Star Scientific’s business to exclusive events at the Governor’s Mansion; and
5. “Recommending that senior government officials in the OGV meet with Star Scientific executives to discuss ways that the company’s products could lower healthcare costs.”74

Maureen McDonnell, who, according to her daughter’s court testimony, had a “mild obsession” with Williams, also was allegedly involved in promoting Anatabloc in return for luxury gifts, including designer clothes, shoes, and a $6,500 Rolex for her husband.4 At a campaign event for Mitt Romney in 2012, Maureen — who was “particularly enthusiastic” about Anatabloc — reportedly suggested to Ann Romney that the supplement “could potentially cure [her] multiple sclerosis.”18

Legal and Regulatory Concerns

On December 20, 2013, anatabine became the latest dietary supplement ingredient with claimed botanical origins to receive a warning letter from the FDA. However, in contrast with recent FDA actions against supplements with controversial “botanical” ingredients — e.g., DMAA (1,3-dimethylamylamine) and dendrobium (Dendrobium nobile, Orchidaceae) extract — the FDA did not comment on the natural or synthetic source of anatabine in Star Scientific’s products. Instead, the agency focused on the product’s therapeutic claims and anatabine’s new dietary ingredient (NDI) and investigational new drug (IND) status.1

Therapeutic/Drug Claims

According to the FDA’s warning letter, Star Scientific’s website “promotes the product Anatabloc for conditions that cause the product to be a drug under section 201(g)(1)(B) of the Federal Food, Drug, and Cosmetic Act.”1

In the “Health Research” section of its website — which has since been taken down — Star Scientific cited studies that suggested anatabine may be helpful in treating multiple sclerosis, mitigating “neuro-inflammatory conditions,” preventing ulcerative colitis, treating Alzheimer’s disease, and “alleviat[ing] the negative consequences of traumatic brain injury.”1

At the time of this writing (October 2014), only two...
randomized, controlled human clinical trials have been published on anatabine. The first study, published in July 2013, found no benefit of anatabine over placebo in muscle damage indicators or strength recovery in 18 men following strenuous workouts. The second study, published a few months later, examined the effects of anatabine in 146 participants with Hashimoto’s disease, a condition otherwise known as chronic lymphocytic thyroiditis. The authors found that anatabine had an impact on the levels of one thyroid antibody and recommended further study. (Both studies were funded by Rock Creek Pharmaceuticals and included company employees as authors.)

Star Scientific noted in its most recent annual SEC filing that it was taking steps to address some of the concerns in the warning letter. “In light of our receipt of the FDA letter, we have substantially limited the marketing and advertising of our dietary supplements,” the company wrote.

**INDs & NDIs**

According to the FDA’s warning letter, anatabine was authorized as an IND on June 8, 2012. On August 11, 2014, however, the FDA notified Rock Creek Pharmaceuticals that its IND application had been put on a clinical hold pending clarification of previously submitted data.

As the FDA explains online, an IND application is designed “to determine if the product is reasonably safe for initial use in humans.” Importantly, the FDA continues, an “IND is not an application for marketing approval. Rather, it is a request for an exemption from the Federal [statute] that prohibits an unapproved drug from being shipped in interstate commerce.”

“Under section 201(ff)(3)(B) of the [Food, Drug and Cosmetic] Act,” the FDA notes, “a dietary supplement may not include an article authorized for investigation as a new drug for which substantial clinical investigations have been instituted and made public, unless the article was marketed as a dietary supplement or food before its investigation was authorized.”

Anatabine’s IND authorization, as detailed in the December 20 warning letter, thus complicates Anatabloc’s classification as a dietary supplement. Star Scientific began marketing Anatabloc one year before and CigRx two years before anatabine’s June 2012 authorization as an IN. According to FDA’s warning letter, however, because anatabine is considered an NDI, and Star Scientific has failed to comply with legal requirements to provide the FDA notice within 75 days prior to introducing Anatabloc into the US market as an NDI, the marketing of anatabine prior to the IND authorization was not lawful.

Therefore, anatabine was not “marketed” as a dietary supplement before it obtained status as a “drug” under the relevant provision of federal law (i.e., 21 USC § 321(ff)(3)(B)(ii)). And, according to the FDA, the company’s failure to file an NDI notification (NDIN) for the compound — before it sought to study anatabine as a new drug — disqualifies it from the definition of dietary supplement and precludes its marketing as a dietary supplement.

In June 2014, Star Scientific submitted an NDIN notification for anatabine in an attempt to address this issue, qualifying its decision in the August SEC report: “Although the company does not believe that an NDIN is a prerequisite to the lawful marketing of the nutritional supplement,” the company explains, “the NDIN was voluntarily submitted to provide the FDA with preclinical and clinical data concerning the supplement.”

On September 12, 2014, the newly renamed Rock Creek Pharmaceuticals — formerly the name of a Star Scientific subsidiary, and, as of June 2, the company’s official new name — announced that it had received a response from the FDA regarding their NDIN. The FDA, reiterating certain points from the 2013 warning letter, responded in opposition to the request, telling the company that they consider anatabine citrate to be a drug that is “the subject of a previously filed Investigational New Drug Application.”

**Presence in Food & Origin of Anatabine**

Unlike the previously mentioned example of DMAA — which has yet to be definitively proven to exist naturally in botanicals — anatabine is known to be present in small quantities in certain plants such as tobacco, tomatoes, potatoes, and eggplant (see Table 1). However, this does not automatically qualify anatabine as a so-called old dietary ingredient (i.e., the term frequently used to refer to an ingredient marketed prior to October 15, 1994, when Congress passed the Dietary Supplement Health and Education Act of 1994).

“[T]he mere presence of anatabine in such foods, without any evidence the foods were promoted for their anatabine content,” the FDA states in the warning letter, “does not constitute ‘marketing’ of anatabine as a food under section 201(ff)(3)(B).”

Although the FDA did not go into detail about the natural or synthetic derivation of anatabine in Star Scientific’s supplements, several publicly available documents suggest a possible synthetic origin. In an archived version of Anatabloc’s website under the question heading “Does Anatabloc contain Tobacco?” the company states: “Although we first looked at the anatabine alkaloid in tobacco plants, the anatabine in Anatabloc is not derived from tobacco.”
On March 23, 2010, Rock Creek Pharmaceuticals filed a patent titled “Methods of synthesizing anatabine.” According to the document, “The present invention relates to improved methods of synthesizing anatabine, especially methods that are useful in larger scale syntheses.”

McDonnell, who has claimed that his support of Anatabloc was part of his job as governor to promote Virginia businesses, originally was not aware of the compound’s synthetic origin. “It was only later that McDonnell learned, he said [in his court testimony on August 22, 2014], that Star synthesized anatabine out of state instead of drawing it from tobacco leaves.”

Tobacco Exclusion

Perhaps the most straightforward reason why the FDA claims Anatabloc is not a legal dietary supplement is because anatabine is found in — and can be derived from — the tobacco plant. “[I]t appears that anatabine can be manufactured from tobacco,” the FDA observes in its warning letter. “It is important to note that tobacco, including its constituents, is excluded from the definition of ‘dietary supplement’ under section 201(ff)(1) of the Act” (see Table 2).

Conclusion

After the McDonnells’ roughly six-week federal trial — “the biggest trial in Virginia political history” — it took the jurors less than two days to render a verdict. Pending an appeal, Bob McDonnell could face up to 10 years in prison for his corrupt dealings with Williams.

In his 23 years as the head of Star Scientific, Williams oversaw the company’s transition from a cigarette manufacturer to an innovative dietary supplement business. However, in just the past year, new legal, regulatory, and financial issues have put the company in a state of flux once again.

The tone of Rock Creek Pharmaceutical’s most recent SEC quarterly report is, at times, decidedly somber. “Since the introduction of Anatabloc®, the Company’s revenues have been derived almost exclusively from the sale of this product. Future sales of the Company’s dietary supplements will be dependent on it resolving issues with the [FDA] relating to the status of its Anatabloc® and CigRx® products,” the report states. “In the long term, the Company expects that its revenues will shift to be more dependent on the ability to successfully implement its drug development program, but it has no drug products in advance development as of this date.”

Bob McDonnell’s future remains uncertain as well. Less than two weeks after his conviction, McDonnell asked a federal judge to be acquitted of his charges, claiming that there was “insufficient evidence” and that the term “official acts” was improperly defined during his trial. McDonnell’s lawyers will appeal the verdict after his sentencing on January 6, 2015. It remains to be seen what impact this ongoing case will have on the future of Rock Creek Pharmaceuticals and Anatabloc.

Table 2. Relevant Sections of the US Federal Food, Drug, and Cosmetic Act

<table>
<thead>
<tr>
<th>Section</th>
<th>Topic</th>
<th>Language</th>
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<tr>
<td>201(g)(1)(B)</td>
<td>Definition of a drug</td>
<td>The term “drug” means … articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals.</td>
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<tr>
<td>201(ff)(1)</td>
<td>Definition of a dietary supplement</td>
<td>The term “dietary supplement” … means a product (other than tobacco (emphasis added)) intended to supplement the diet that bears or contains one or more of the following dietary ingredients: (A) a vitamin; (B) a mineral; (C) an herb or other botanical; (D) an amino acid; (E) a dietary substance for use by man to supplement the diet by increasing the total dietary intake; or (F) a concentrate, metabolite, constituent, extract, or combination of any ingredient described in clause (A), (B), (C), (D), or (E).</td>
</tr>
<tr>
<td>201(ff)(3)(B)(iii)</td>
<td>Dietary supplements and INDs</td>
<td>The term “dietary supplement” … does … not include … an article authorized for investigation as a new drug, antibiotic, or biological for which substantial clinical investigations have been instituted and for which the existence of such investigations has been made public, which was not before such approval, certification, licensing, or authorization marketed as a dietary supplement or as a food unless the Secretary, in the Secretary’s discretion, has issued a regulation, after notice and comment, finding that the article would be lawful under this chapter.</td>
</tr>
<tr>
<td>350(b)(d)</td>
<td>Definition of a new dietary ingredient</td>
<td>For purposes of this section, the term “new dietary ingredient” means a dietary ingredient that was not marketed in the United States before October 15, 1994 and does not include any dietary ingredient which was marketed in the United States before October 15, 1994.</td>
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<tr>
<td>413(a)(1) and (2)</td>
<td>Dietary supplement adulteration</td>
<td>A dietary supplement which contains a new dietary ingredient shall be deemed adulterated under section 402(f) unless it meets one of the following requirements: (1) The dietary supplement contains only dietary ingredients which have been present in the food supply as an article used for food in a form in which the food has not been chemically altered. (2) There is a history of use or other evidence of safety establishing that the dietary ingredient when used under the conditions recommended or suggested in the labeling of the dietary supplement will reasonably be expected to be safe and, at least 75 days before being introduced or delivered for introduction into interstate commerce, the manufacturer or distributor of the dietary ingredient or dietary supplement provides the Secretary with information, including any citation to published articles, which is the basis on which the manufacturer or distributor has concluded that a dietary supplement containing such dietary ingredient will reasonably be expected to be safe.</td>
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</table>

*As amended by the Dietary Supplement Health and Education Act (DSHEA) of 1994.
The Science of Anatabine
By Jay Pierotti, PhD

What exactly is anatabine? Are there scientific data to support its claimed health benefits? The answers to these questions and more are available in an online companion article—“Anatabine: A Tobacco Alkaloid Sold in a Dietary Supplement.” In the article, HerbalGram guest author Jay Pierotti, PhD, a chemist with previous professional experience in tobacco analysis, discusses various scientific aspects of anatabine and related compounds. Featuring numerous graphics and tables, Dr. Pierotti’s in-depth review explores the chemistry, toxicology, and animal and human clinical pharmacology of this once-obscure, nicotine-like chemical.


References

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On December 21, 2013, The New York Times published an article by reporter Anahad O’Connor titled “Spike in Harm to Liver Is Tied to Dietary Aids,” based on a presentation by Victor Navarro, MD, chair of hepatology at the Einstein Healthcare Network in Philadelphia, Pennsylvania, given at the American Association for the Study of Liver Diseases’ “Liver Meeting” conference in early November 2013. In his lecture, Dr. Navarro pointed out that “the percentage of liver injuries related to herbal dietary supplements (HDS) products in a research cohort of patients referred to the Drug-Induced Liver Injury (DILI) Network* increased from 7% of cases between 2004 and 2005 to 20% between 2010 and 2012 (P<0.001). This trend was significant both for cases attributable to bodybuilding products (P=0.01) and for all other HDS products (P=0.05).” Based on the reported statistics, the data from Dr. Navarro would amount to an average of four cases of liver injury that are connected to HDS per year between 2004 and 2005, and 20 cases per year between 2010 and 2012. These data and their percentages are based on 130 hepatotoxicity cases linked to dietary supplements from a total of 839 people for which reports were entered into the final analysis for the 10-year period between 2004 and 2013. Besides addressing bodybuilding and weight-loss supplements, the piece by O’Connor mentioned green tea (Camellia sinensis, Theaceae) extract as frequently implicated in dietary supplement-associated liver toxicity, and the author provided details from a case report published earlier by Patel et al.3

More details about HDS-related liver injuries reported to the DILI Network subsequently have been published in the scientific journal Hepatology.4 The publication received considerable attention from the media, and led — in some instances — to the dissemination of inaccurate information to the public with headlines such as “Liver injuries from dietary supplements rose in one population over the last decade. They caused more deaths than traditional [i.e., conventional] medications, too,” and “Supplements now more likely than medications to cause death.”5 6

* The Drug-Induced Liver Injury Network was established in 2003 by the National Institutes of Health’s National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) to collect and analyze cases of severe liver injury caused by prescription drugs, over-the-counter drugs, and alternative medicines such as herbal products and supplements.
Incidence of Herbal Dietary Supplement-Induced Liver Injury

There are no reliable population-based statistics for the incidence of liver toxicity attributable to HDS in the United States. In order to put the numbers for HDS-induced liver injury in perspective, it is important to consider the widespread use of HDS. Herb usage by the adult population in the United States has remained fairly popular for the past 15 years or more, with retail sales climbing almost every year, but actual statistics on the use of dietary supplements in the US vary depending on the source. For example, a 2003 survey showed that about 34% of the US adult population used herbal dietary supplements, while a 2010 survey suggested that perhaps up to 47% of American consumers had used an HDS in the previous year (although the difference may simply reflect the growth in use in the seven-year period). The LiverTox database estimates 40% of the US population uses alternative therapies, most often HDS. On the other hand, according to the 2013 CRN Consumer Survey on Dietary Supplements from the Council for Responsible Nutrition, an industry trade organization, only 19% of Americans take herbal and botanical dietary supplements on a regular basis. Based on an estimated US population of 318 million in June 2014, with approximately 77% of people over the age of 18, this would indicate that between 47 and 115 million adults use HDS. So even if the number of cases reported to the DILI Network comprises only a small fraction of all dietary supplement-related incidences of hepatotoxicity, the risk of hepatotoxicity due to botanicals would still be relatively low and, most probably, not as significant as some of the media reports have suggested.

In the Drug-Induced Liver Injury Network, HDS generally were implicated in approximately 10% of reported cases (the remaining 90% were due to pharmaceutical drugs), but this rate appears to be increasing and most recently accounted for more than 20% of cases. The newly released American College of Gastroenterology (ACG) clinical guideline on the diagnosis and management of idiosyncratic DILI even suggests that “herbal and dietary supplements are among the most common therapeutic classes to cause DILI in the Western world.”

On the other hand, according to the LiverTox database, the incidence of liver toxicity caused by HDS is likely to be very low. A retrospective cohort study from 2009 reported that the main substances involved in acute liver failure were

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† The LiverTox database is a website with information on liver injuries caused by prescription drugs, nonprescription drugs, and dietary supplements, produced by the NIDDK and the National Library of Medicine (NLM).
designed and manufactured HDS products and adulterated products or illegal drugs (e.g., the erectile dysfunction drug sildenafil and analogues) sold as dietary supplements before they implicate a product that purports to be an HDS in a case of liver toxicity.

**The Safety of Green Tea Extract**

Liver toxicity is a serious health concern, and the data potentially associating GTE with hepatotoxicity have to be carefully evaluated. In the toxicological evaluation of a hydroalcoholic GTE by the National Toxicology Program (NTP), rats and mice were administered between 0 (vehicle control) and 1,000 mg GTE/kg body weight in deionized water by gavage five days per week for three months. In the three-month study in mice, six males and four females administered 1,000 mg/kg died before the end of the study; early deaths were due to liver necrosis.

In the two-year NTP study, rats received between 0 and 1,000 mg green tea extract/kg body weight in deionized water by gavage, while mice were fed between 0 and 300 mg GTE/kg. The study showed a statistically significant increase in liver necrosis in rats receiving the highest dosage of GTE (1000 mg/kg), but not at 300 mg/kg or below. On the other hand, the study indicated a lower incidence of primary liver neoplasms in female and male mice at higher GTE dosages. For example, in the two-year study in male mice, hepatocellular adenomas, hepatocellular carcinomas, and hepatoblastomas occurred in 40 out of 50 mice (80%) receiving the vehicle control, and in 39 (78%), 35 (70%), and 22 (44%) out of 50 mice receiving 30 mg/kg, 100 mg/kg, and 300 mg/kg GTE, respectively. When the numbers were adjusted for survival, the incidence rates were 83%, 80%, 71%, and 47%, respectively. This reduction in occurrence of liver neoplasms would suggest a chemopreventive effect of GTE.

The safety of green tea extract in humans has been evaluated extensively by the United States Pharmacopeia (USP) Dietary Supplements Information Expert Committee (DSI EC). Based on a review of all 34 case studies available through 2007, the committee ranked GTE as a class 2 supplement. Class 2 indicates “articles for which the DSI EC is unaware of significant safety issues ... when that article is used and formulated appropriately provided there is a warning statement in the labeling section.” The DSI EC later changed its position and re-classified GTE as a class A supplement (supplements for which the available evidence does not indicate a serious risk to health or other public health concern that precludes inclusion of a quality monograph into the compendia), for which a warning label is not required.

Most of the cases involving GTE-containing products present other possible confounding factors (e.g., concomitant use of over-the-counter or prescription drugs, use of polyherbal formulations, or incomplete patient data). A majority of the green tea case reports listed by Navarro et al indicate that the putatively hepatotoxic products reported to the DILI Network contained GTE with other ingredients, or were cases in which GTE was used in combination with other HDS. The USP DSI EC emphasized that the individual case reports were not strong, and that the most frequently implicated product contained a hydroalcoholic GTE, which, on the surface, should not pose any unusual hepatotoxic risk. (That GTE-containing product was Exolise®, a weight-loss formulation made by Arkopharma [Carros, France], which was later recalled). However, the DSI EC also noted that plasma concentrations of the purported hepatotoxin epigallocatechin gallate (EGCG), one of the key catechins in green tea and GTE, are considerably higher when concentrated GTEs are consumed when fasting, as may often be the case with a weight-loss product like Exolise. The purported hepatotoxic GTE products listed in the USP report were analyzed in only one of the reported adverse events, so it remains unclear if the actual composition of the products

‡ In general this paper refers to green tea extract with the acronym GTE. However, there is no singular standard for what constitutes GTE; there are numerous extracts available with various chemical profiles standardized to varying levels of catechins (e.g., 60%, 90%, etc.).
corresponded to the label claims or if potentially toxic contaminants (e.g., certain residual solvents that may have been used in the extraction process) also were present.19 (According to records at the American Botanical Council, the manufacturer of Exolise claimed that no other solvents other than ethanol and water were used in the preparation of the GTE used in Exolise.)

More recently, Navarro et al analyzed 97 HDS products implicated in hepatotoxicity cases for catechins but found no statistically significant correlation between the amount of catechins consumed and the severity or pattern of liver injury.22 Additionally, there are very few reports of liver injury after drinking green tea, so the traditional use of green tea as a beverage should not be considered a safety concern. The second edition of the American Herbal Products Association’s Botanical Safety Handbook (BSH2) lists green tea as class 1 safety ingredient, meaning that history of widespread safe use and other evidence strongly support the proposition that green tea can be consumed safely when used appropriately. As a precautionary statement, the BSH2 indicates that “ethanol extracts of green tea should be taken with a meal.”23

**Other Herbal Ingredients**

In the LiverTox database, a number of single herbs have been implicated in liver toxicity.10 Examples of herbs and herbal products that have a well-established potential to cause liver injury include those containing certain types of pyrrolizidine alkaloids — i.e., pyrrolizidines with a chemical structure characterized by an unsaturated necine ring (saturated pyrrolizidines are not considered hepatotoxic)24 — found in comfrey (Symphytum x uplandicum, Boraginaceae) leaf and root, coltsfoot (Tussilago farfara, Asteraceae) herb, butterbur (Petasites hybridus, Asteraceae) leaf and root, and others. In addition, other plants with reports of hepatotoxicity include herbs such as chaparral (Larrea tridentata, Zygophyllaceae) leaf, germanium (Teucrium spp., Lamiaceae) herb, celandine (Chelidonium majus, Papaveraceae) herb, pennyroyal (Mentha pulegium, Lamiaceae) essential oil, mistletoe (Viscum album, Viscaceae), kava (Piper methysticum, Piperaceae), and weight-loss preparations containing usnic acid (a compound that can be obtained from several lichen species).

In the ACG clinical guideline, the authors specifically mention the following items under the header “herbals and dietary supplements”: GTE, anabolic steroids§, pyrrolizidine alkaloids, and flavocoxid™ — a proprietary mixture of flavonoids extracted from Chinese skullcap (Scutellaria baicalensis, Lamiaceae), catechins from betelnut palm (Areca catechu, Arecaceae), and zinc bisglycinate sold under the brand name Limbrel™ (Primus Pharmaceuticals; Phoenix, Arizona), a medical foodǁ that is available by prescription only.12 With regard to Limbrel, Robert Levy, MD, the director of clinical development at Primus, explained that “liver toxicity is seen with many drugs, herbal supplements, chemicals and other environmental agents either due to direct cellular toxic effects or, more commonly, due to hypersensitivity reactions. In clinical trials against [the NSAID] naproxen, Limbrel and naproxen had similar levels of liver toxicity although Limbrel had a better overall safety profile.” Dr Levy added, “The Limbrel package insert outlines this toxicity and, in fact, uses language almost identical to that which appears in the package insert of every non-steroidal anti-inflammatory drug. Overall, we have seen a small number of liver function test abnor-

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§ Anabolic steroids are listed as controlled substances in the United States and are available by prescription only. By law, anabolic steroids legally cannot be sold as dietary supplements.

ǁ A medical food is defined in the United States Code, Title 21, section 360ee (b)(3) as “a food which is formulated to be consumed or administered enterally under the supervision of a physician and which is intended for the specific management of a disease or condition for which distinctive nutritional requirements based on scientific principles are established by medical evaluation.”
malities, about 5% in clinical trials, with occasional reports to us in our detailed post-marketing surveillance” [R. Levy email to M. Blumenthal, September 5, 2014].

A recent publication by Teschke et al highlights the hepatotoxic potential of herbal ingredients used in Traditional Chinese Medicine (TCM).25 The compilation lists 39 potentially hepatotoxic individual herbs. In hepatotoxicity case reports of single herbs used in TCM published since 2011 where the Council for International Organizations of Medical Sciences (CIOMS) scale was applied, probable and highly probable causality gradings were found for du huo (Angelica archangelica, Apiaceae) root, he shou wu or fo-ti (Polygonum multiflorum, Polygonaceae, syn. Reynoutria multiflora) root, and the liver-toxic unsaturated pyrrolizidine alkaloid-containing herb shan chi (Gynura japonica, Asteraceae, syn. G. segetum, G. pinnatifida). Chinese and other Asian herbal medicines also are listed as potentially hepatotoxic in the LiverTox database.10 The most frequently implicated single herbs or mixtures are ba jiao lian (Dysosma pleianthus, Berberidaceae), chi ryan (Brenynia vitis-idaea, Phyllanthaceae, syn. B. officinalis), jin bu huan — an herbal mixture of variable composition¶ that can include Aristolochia yunnanensis, Aristolochiaceae; Huperzia serrata, Lycopodiaceae; Panax pseudoginseng, Araliaceae; Polygala chinensis, Polygalaceae; Rumex madaio, Polygonaceae; R. patientia, Polygonaceae; Selaginella tamariscina, Selaginellaceae, syn. S. involvens; and/or Stephania spp., Menispermaceae — ma huang (Ephedra sinica, Ephedraceae and other Ephedra spp.), and shou wu pian (containing he shou wu).

The Assessment of Herbal Dietary Supplement-Induced Liver Injury

In general, the establishment of HDS-associated liver injury needs to be based on the principles of causality assessment, including a chronology establishing that the HDS was taken before the onset of the liver injury, the exclusion of other causes of liver disease, and symptom improvement after product use is ceased. Appearance of the symptoms after re-administration of the HDS (positive re-challenge) is another strong indicator that may link a product to liver injury, but is not advised due to ethical reasons. Some case reports involving a particular HDS turn out to be with patients who had other risk factors like pre-existing liver conditions, co-medication with pharmaceutical drugs with potential liver liabilities, and/or alcohol consumption.26-28 One analysis of 573 cases with assumed herbal-induced liver injury found alternative causes unrelated to the initially alleged herb in 48.5% of these cases, and an additional 29% of cases were barely assessable.26 The authors of a review in 2011 of all published case reports of hepatotoxicity related to consumption of black cohosh (Actaea racemosa, Ranunculaceae, syn. Cimicifuga racemosa) products concluded that black cohosh did not pose an apparent risk for liver injury.29 However, even if there are other factors that may have led to the liver injury, the associa-

One analysis of 573 cases with assumed herbal-induced liver injury found alternative causes unrelated to the initially alleged herb in 48.5% of these cases, and an additional 29% of cases were barely assessable.

¶ Products called “jin bu huan” appear to be sold with a variety of different ingredients depending on the manufacturer. In the case of the commercial jin bu huan preparation anodyne, the product was supposed to contain Polygonum multiflorum without some of the other ingredients that may be otherwise found in jin bu huan.
tion between HDS consumption and liver injury still may be possible since the HDS may impact or enhance the toxicity of co-medication with a pharmaceutical drug or co-consumption of alcohol.

The question of which objective methods should be used to assess the causality of drug-induced hepatotoxicity is still a matter of debate, since the different methods tend to suffer from low concordance. According to Neil Kaplowitz, MD, professor of medicine and chief of the division of gastro-intestinal and liver disease at the University of Southern California Liver Transplant Program and Center for Liver Disease, attribution of causality is a major challenge, and “in the absence of a convenient gold standard, the diagnosis is subjective and is made with a varying level of confidence.”

A review of case reports of herbal hepatotoxicity linked to Traditional Chinese Medicine listed 18 defined TCM mixtures, a group of unclassifiable TCM mixtures, and 39 individual herbs as posing a risk of liver injury; however, the authors noted that “firmly determining individual causality with exclusion of possible alternative causes was rarely done in these reports.” Teschke et al have examined the many scoring systems used to determine DILI and are particularly critical of the use of the Naranjo scale employed by the USP, since it is not validated specifically for hepatotoxicity. They recommend the CIOMS scale since it has been validated for liver toxicity, is considered to be quantitative, and is more widely used for the determination of DILI. On the other hand, the authors of the systematic review of green tea liver toxicity specifically used the Naranjo scale because it allowed a scoring of the probability of case reports’ association with GTEs despite the lack of important information in many of those case reports.

Finally, the authors of the new ACG clinical guideline argue that an approach based on expert opinions is the current “gold standard” in attributing causality of herbal-induced liver injury. From a practical point of view, it seems doubtful that clinicians will use any of the proposed scoring systems, which will most likely lead to a continuation of the already ongoing discussions and debate regarding the safety of botanical extracts.

In many cases of putative HDS-induced liver injury, it is not known if the consumer followed the dosage regimen indicated on the product label. For a number of HDS ingredients, the potential for liver injury after prolonged use is not well known. Ingesting excessive amounts of HDS to achieve faster results (e.g., in the weight-loss category) possibly will increase the risk of adverse events, including the potential for liver injury. More data on compliance with the dosage recommendations are needed to have a better idea of the hepatotoxic potential of certain herbal ingredients. However, most cases of presumed or ostensible HDS-induced liver injury are idiosyncratic: that is, the toxicity is not directly related to the chemistry of the product and/or its dosage, but stems from complex interactions among non-genetic (e.g., age, sex, drug interactions, and conditions such as human immunodeficiency virus [HIV] infection) and genetic factors. The low frequency and unpredictability of DILI suggest that genetic mutations in drug-metabolizing enzymes or drug receptors can make a consumer overly sensitive to certain ingredients. For example, polymorphisms in the liver enzyme (i.e., different forms of the enzyme depending on the individual’s genetic composition) cytochrome P450 2D6 — which is involved in the metabo-
lism of many xenobiotics (e.g., pharmaceutical drugs, artificial preservatives, or plasticizers to which the body is not exposed as part of the normal metabolism) — have been implicated in the hepatotoxicity of senna (Senna alexandrina, Fabaceae).35

In addition, according to Dr. Kingston, little is known about the relative risk of liver injury occurring from the use of an herbal ingredient. Contrary to pharmaceutical drugs, data on the number of liver injury cases in relation to the frequency of use of HDS are not available in many cases, and, combined with the variability of the composition (e.g., due to different manufacturing processes) and dosage regimens, a risk assessment is very difficult. Some herbal ingredients inevitably will lead to liver injury at a certain dosage (e.g., herbs containing certain pyrrolizidine alkaloids), while others may cause liver toxicity only in a few sensitive individuals. In the latter case, reports on liver injury from very widely used botanicals like GTE or licorice (Glycyrrhiza glabra, Fabaceae) root will more likely be found than from those that have only a marginal use. This could lead to a situation in which a widely used and comparatively safe herb may be considered hepatotoxic, or that a potentially hepatotoxic herb is considered safe.

A good example of this problem is the recent ruling by a German administrative court in Cologne to overturn the ban of kava sales, which was implemented by the BfArM (Bundesamt für Arzneimittel und Medizinprodukte; German Federal Institute for Drugs and Medical Devices) after the appearance of case reports of liver toxicity due to kava product consumption.36 The court stated that the authorities must demonstrate risk in a reproducible manner. If the risk cannot be clearly corroborated, the government’s withdrawal of marketing authorizations for kava medicinal products is unlawful, and, in view of the exposure data, the risk does not seem unusually high. Based on the relatively widespread use of kava, the incidence of liver toxicity has to be rated as “rare” or “very rare.” Furthermore, the court concluded that BfArM used duplicate case reports in support of the ban, and, therefore, the quantity of case reports alone is of little significance.

**Need for Appropriate Authentication of Herbal Materials Implicated in Liver Injury Cases**

Although the FDA mandates that dietary supplement labels accurately reflect the products’ contents, there is evidence for cases of contamination and presence of adulterants in various HDS products. Adulterants can be either undeclared botanical materials or sometimes even prescription drugs.** Contaminants also can include herbicides and pesticides, heavy metals, microbes, and/or residual solvents used in the preparation of extracts. A number of prescription drugs, solvents, and pesticides are known liver-toxicants.37 The individual levels of any of these contaminants would likely be too low to cause liver effects alone. However, the aggregate exposure of multiple contaminants with liver liabilities may exacerbate hepatotoxicity.

Authentication of the implicated product by appropriate means (e.g., chemical analysis) is crucial in assigning causality to a listed ingredient and/or product, but such analyses were not performed in a majority of the published reports. Analytical phytochemistry of HDS products associated with liver injury often reveals adulteration or contamination of one or more of the ingredients in the product, and it sometimes exposes mislabeling or absence of the botanical listed on the label and/or presence of a related or unrelated herb that may be the hepatotoxic agent. Examples of adulterants found in herbal preparations include germander in products labeled as skullcap38 and various Asian Actaea species in products labeled as black cohosh.39,40 Furthermore, some of the liver toxicity cases associated with Chinese medicinal herbs were later found to be the result of the presence of adulterants, such as the purported liver toxicity of jing tian san qi (Sedum aizoon, Crassulaceae) that was due to substitution with the pyrrolizidine alkaloid-containing plant shan chi, or cases of jin bu huan (anodyne*, manufactured by Kwangsi Pai Se Pharmaceutical/Bose Drug Manufactory; Kwangsi, China) tablets supposedly containing Polygala chinensis (Polygalaceae) that were found to be a mixture of synthetic l-tetrahydropalmatine and starch.41,42

**Conclusion**

Owing to the popularity and increased use of HDS and the FDA mandate for manufacturers to report serious adverse events involving HDS, the amount of available data on hepatotoxicity and HDS has continued to grow. Future adverse event reports may identify indicators requiring investigation of other herbs for a possible link to liver injury when used by themselves or in combination with other herbs, similar to the case of coltsfoot in the 1990s. Accumulating more data on the safety of HDS products can be beneficial for everyone interested in herbal products. However, the sensational nature of recent media coverage may lead to increasing concerns about the safety of HDS by the consumer and by health professionals, even if the appropriate use of most ingredients found in herbal dietary supplements should be considered relatively safe with little risk of causing harm to the liver.16

**References**


5. Engel M. Supplements cause more liver damage, decade-long


Residual Methanol in Botanical Dietary Ingredients: Perspectives of a Manufacturer

By Deepak Mundkinajeddu, PhD, and Amit Agarwal, PhD

Organic solvents such as methanol, ethanol, ethyl acetate, and acetone are employed during the extraction and downstream processing of medicinal herbs to manufacture standardized herbal extracts (SHEs). The SHEs from medicinal plants increasingly are used as ingredients in herbal dietary supplements (also known as food supplements in some countries), complementary medicines, licensed nonprescription drug preparations, functional foods, and natural cosmetics all over the world. It is almost impossible to remove the residual solvents completely from liquid and dried herbal extracts. Since many organic solvents can be toxic to humans — i.e., depending on the level of exposure — maximum residue limits (MRLs) are necessary for SHEs. The intention of this brief article is to provide an overview of various issues associated with methanol as a residual solvent in SHEs used in botanical dietary ingredients and supplements.

Manufacturers of SHEs often favor the use of methanol for extraction of medicinal plants due to its lower boiling point, higher volatility, and higher extraction efficiency compared to ethanol (depending on the desired secondary metabolite composition). Methanol also is used as a co-solvent to enhance extraction efficiency in supercritical fluid extractions. As a means to minimize the abuse of ethanol, most government-sanctioned licensing systems normally require producers, distributors, and sellers of ethanol to obtain licenses, the availability of which may be restricted, particularly in the retail sector. Overall, licensing requirements (in which any license is required) exist in 142 countries worldwide.

In the United States, dietary supplements are governed under food laws and are frequently available in solid dosage forms, e.g., tablets or capsules. Doses of botanical dietary supplements typically range from 250 mg up to 2.5 g per person per day. Based on our experience, properly dried SHEs processed with methanol tend to contain 50 ppm to 1,000 ppm (parts per million) of methanol, which is well within the guidelines established by the International Conference on Harmonization (ICH) for residual solvents for pharmaceutical products. (These guidelines have been adopted as legally binding for SHEs in several countries.) The MRLs of residual methanol, as per the regulations of different selected countries, are shown in Table 1.

Although the toxicity of methanol at high doses is well established, less is known about potential adverse effects from lower levels of exposure over a long period of time, which often is the case with methanol-containing SHEs. To our knowledge, no studies seem to have been performed, so far, specifically to evaluate the toxicity of SHEs due to the presence of residual methanol. Under these circumstances, regulatory bodies typically apply the same limits for residual

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† Values are specific to the ingredients listed in the respective food additives regulation. In general, most food additives have been given the limit in the range specified in Table 1 with the exception of pectin, which has a MRL of 10,000 ppm.
‡ If the use of a solvent remains inevitable in the course of manufacturing, the residue levels shall be kept at the minimum quantity achievable in the manufacturing process.
methanol that are applicable to conventional foods, though the intake of dietary supplements is far less than conventional food.

Sources of Exposure to Methanol

Methanol is normally present in the human body as a naturally occurring byproduct of protein formation. According to the International Programme on Chemical Safety Poisons Information Monograph, the normal blood methanol concentration in humans is approximately 15 mg/L (range 2-30 mg/L).23

Naturally occurring methanol in food and beverages

Methanol has been found in food, particularly fresh fruit and vegetables, which is absorbed during digestion.19 It occurs as free methanol or can be converted to methanol in the gastrointestinal tract after hydrolysis of methyl esters of fatty acids or methoxy groups on polysaccharides (e.g., pectin).17 Concentrations of methanol in fresh orange (Citrus sinensis, Rutaceae) and grapefruit (Citrus x paradisi, Rutaceae) juices are in the range of 11-80 mg/L and 12-60 mg/L, respectively. In human volunteers, consumption of 10-15 g isolated pectin or of one kg apples (Malus spp., Rosaceae) containing approximately 10 g natural pectin induced a significant increase in methanol in the breath and, by inference, in the blood. Consumption of one kg apples was estimated to release 500 mg methanol. It has been estimated that humans may be exposed to approximately 1,000 mg methanol per day from fruits and vegetables. Ripe fruit was found to release more methanol than unripe fruit.17,20,21

Methanol also occurs at low concentrations in alcoholic drinks. Concentrations of 6-27 mg/L have been measured in beer, 96-321 mg/L in wine, and 10-220 mg/L in distilled spirits.22 The European Union regulatory limit on methanol in vodka is set at 10 g per hectoliter of 100% vol. alcohol (i.e., 100 mg methanol per liter of alcohol, equivalent to 37 mg/L if the vodka contains 37% alcohol).23

Naturally occurring methanol in plants and SHEs

The methanol content of plant leaves and the potential methanol released from leaves into the atmosphere have been investigated by several researchers. Free methanol has been found in common bean (Phaseolus vulgaris, Fabaceae) leaves at levels ranging from 10-27 µg/g fresh weight. Pectin demethylation, mediated by pectin methyl-esterase, in the cell walls is considered the likely source of methanol in leaves,24,25 as well as in fruits like tomato (Lycopersicon esculentum, Solanaceae).26 Methanol is known to be produced in plants during the early stages of leaf expansion.27 As such, it can be inferred that methanol is naturally present in plants, and its level may differ depend-

§ A panel of the European Food Safety Authority (EFSA) recently released a scientific opinion in which it concluded that methanol released in the human body by the metabolism of the artificial sweetener aspartame is not expected to pose a safety risk. The panel noted that aspartame-derived methanol contributed to less than 10% of the total mean anticipated exposure to methanol from all sources.19
of compounds in raw materials, or during chemical analysis by hydrolysis of compounds at high temperatures. The formation of methanol by the latter process, according to the authors, would lead to an overestimation and should be minimized.\textsuperscript{31}

Based on our in-house analyses of residual solvents (unpublished results), some crude powders of Indian medicinal plants and dried aqueous extracts show methanol residues in the range of 10-100 ppm when analyzed by headspace gas chromatography. These results need to be further investigated, confirmed, and published.

**Observations and Recommendations**

The ICH guidelines\textsuperscript{7}— which apply to the manufacture or purification of drug substances, their excipients, or drug products — list methanol as a class 2 solvent, which means that it should be limited in pharmaceutical products to a permitted daily exposure of 30 mg per day and a concentration limit of 3,000 ppm in finished consumer products. The SHEs intended as dietary ingredients in dietary supplements (typically in the form of tablets or capsules) in most cases have an average daily dose of less than 2.5 g per day.\textsuperscript{6} Assuming the maximum limit for methanol given in the ICH guidelines (3,000 ppm) is present in SHEs with a dose of, for example, 10 g per day (given a combination of five extracts at two g each), the maximum daily consumption of methanol would be about 30 mg per day. Compared to a potential exposure of 1,000 mg of methanol per day from fruits and vegetables,\textsuperscript{17} the maximum exposure of methanol (30 mg per day) from dietary supplements appears relatively low and is highly unlikely to pose a toxicity concern. It may also be noted that US Environmental Protection Agency’s Integrated Risk Information System revised the Reference Dose for Chronic Oral Exposure of methanol to two mg/kg per day.\textsuperscript{5} The revised RfD of methanol is in addition to the background levels of methanol derived from a diet that includes fruits and vegetables.\textsuperscript{32}

In this context, we believe that the limit of 3,000 ppm in the ICH guidelines adequately addresses the safety concerns that could arise from methanol residues in SHEs. We propose that the ICH guidelines should be adopted by all regulatory agencies across the world for residual methanol concentrations in botanical extracts that are meant to be used as ingredients in dietary supplements. HG

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**References**

Crafting Dietary Supplement Warnings: Recent Developments and Guidelines for Mitigating Risk Associated with Product Liability “Failure to Warn” Claims

By Paul D. Rubin, Lee S. Gayer, and Jessica M. Band

This article addresses some of the fundamental issues impacting the development of dietary supplement warning labels based, in part, upon potential product liability exposure resulting from a “failure to warn” of applicable risks. As explained herein, determining whether to include a warning on dietary supplement labeling is a complex undertaking and requires careful assessment of multiple factors. This article addresses some of the factors companies should consider in making this determination, and provides guidance and suggested strategies for companies to mitigate product liability exposure. Furthermore, this article also reflects and revises an article previously published in HerbalGram #56 on this subject by the primary author of this article.1

Proliferation of Product Liability Litigation (and Related Class Action Litigation) Directed against Dietary Supplements

The growth of the dietary supplement industry, and risks presented by a small subset of dietary supplements, has led to a proliferation of product liability-related litigation directed against companies marketing dietary supplements.

The success experienced by the supplement industry in the United States in recent years, which is projected to continue, raises the likelihood of increased product liability claims and lawsuits, which are often closely associated with expanding markets. Indeed, in 2012, dietary supplement companies generated approximately $32 billion in revenue; that figure is projected to nearly double to $60 billion by 2021.2 Industry analysts estimate that one third of all Americans use herbal remedies such as echinacea (Echinacea spp., Asteraceae), ginseng (Panax spp., Araliaceae), or St. John’s wort (Hypericum perforatum, Clusiaceae), and that 123.5 million Americans use some kind of supplement (whether categorized as herbs, vitamins, minerals, enzymes, or amino acids).3 In step with the rise in consumer demand, dietary supplement companies increasingly are confronted with myriad legal issues, including product liability exposure (and potential exposure in class-action lawsuits).

Despite the strong safety profile of the dietary supplement category, some scientists, health professionals, and regulators claim that a small subset of dietary supplements may be capable of injuring consumers. For example, scientists have posited that certain dietary supplements, which constitute a small percentage of the industry’s total sales, may damage the liver — typically as a result of misuse.4 According to one report, products promoted as alleged dietary supplements may account for 20% of liver injuries diagnosed in hospitals, up from 7% a decade ago.4 Regardless of whether these reports are accurate*, they reflect a growing interest in this issue by concerned health professionals, public health officials, industry critics, and plaintiffs’ lawyers.

Not surprisingly, therefore, over the past ten years, sizable class-action lawsuits have been brought against dietary supplement companies with significant product liability dimensions. In the case of ephedra (Ephedra sinica, Ephedraceae), for example, the United States Food and Drug Administration (FDA) began receiving adverse event reports (AERs) concerning dietary supplements containing ephedrine alkaloids in the 1990s; these AERs included alleged health problems ranging from insomnia and arrhythmia to heart attack, stroke, and, in a few cases, death.5 In April 2004, more than 300 ephedra product liability cases were consolidated in the US District Court for the Southern District of New York.6,7 As of 2007, plaintiffs had recovered at least $100 million in settlement payments.8 The litigation wound down by 2008.9

More recently, in April 2012, the FDA sent warning letters to 10 manufacturers and distributors of dietary supplements containing a synthetic chemical compound commonly known as DMAA (1,3-dimethylamylamine HCl),10 asserting that the supplements were “adulterated” based upon the presence of a “new dietary ingredient” that was not subject to a 75-day notification to the FDA as required by Section 8 of the Dietary Supplement Health and Education Act of 1994 (DSHEA).11 Furthermore, the warning letters stated that “[e]ven if the required notification had been submitted,” the products would still be adulterated because “there is inadequate information to provide reasonable assurance that [the new dietary ingredient] does not present a significant or unreasonable risk of illness or injury.”11 The FDA issued a press release,10 and plaintiffs began filing product liability-related class action complaints within a few days.12 Claims include negligence, strict liability, breach of warranty, and false advertising.13,14 This litigation is still ongoing.

As demonstrated by the DMAA example, in addition to product liability lawsuits, dietary supplement companies are increasingly being targeted in class-action lawsuits filed under state consumer protection laws, alleging the dissemination of false or deceptive claims. Unlike product liability cases, these types of class-action lawsuits may be successful even if consumers are not physically harmed. Although beyond the scope of this article, dietary supplement manufacturing and marketing companies should consider potential exposure to consumer protection class-action lawsuits as

*See “Perspectives about the Potential Hepatotoxicity of Various Herbs, Including Green Tea Extract” on page 52 of this issue.
a potential factor in the product liability exposure assessment described herein.

**FDA Mandates Very Few Dietary Supplement Warnings, but Frequently Issues Safety-Related Statements Applicable to the Dietary Supplement Industry**

Although FDA regulation of dietary supplements pursuant to DSHEA is beyond the scope of this article (it has been adequately elaborated elsewhere), it is worth noting that the FDA mandates very few dietary supplement warnings. Although, for example, the FDA may require warnings for certain dietary supplements that contain iron, protein, or psyllium, the vast majority of dietary supplements are not subject to mandatory FDA warnings.†

Rather, pursuant to the Federal Food, Drug, and Cosmetic Act (FFDCA), dietary supplement companies are obligated — consistent with requirements applicable to other FDA-regulated entities — to reveal material facts relevant to the consequences of using a dietary supplement. In addition, according to DSHEA, the FDA must determine if a dietary supplement is “adulterated” based upon whether the dietary supplement presents a significant or unreasonable risk of illness or injury under “conditions of use recommended or suggested in labeling.” Accordingly, the FDA permits companies to add voluntary dietary supplement warnings, and the addition of such warnings may mitigate FDA regulatory liability in addition to potential product liability exposure.

Despite the relative absence of mandatory dietary supplement warnings, the FDA occasionally disseminates safety-related information that may impact the voluntary determination to add warnings to dietary supplement labeling. For example, according to an article recently published in HerbalGram, FDA has issued an extensive number of alerts and letters to healthcare professionals regarding the safety of specific dietary ingredients in recent years. In addition, FDA’s Dietary Supplement Compliance Program Guidance Manual identifies a number of botanical ingredients subject to higher-priority FDA inspectional review based upon potential safety concerns. The FDA also recently issued an import alert for the botanical ingredient kratom (Mitragyna speciosa, Rubiaceae) based upon alleged safety concerns and instituted a seizure action against 25,000 pounds of the herb held by a California company.

**Product Liability Overview – Elements of a Failure to Warn Claim**

Product liability actions in the United States are generally based upon three potential common-law causes of action: (1) negligence, (2) strict liability, and (3) breach of warranty (express or implied). Each cause of action generally can address various types of product defects, such as manufacturing defects (defects in the production process for a specific batch of products), design defects (defects in intended product formulation), and marketing defects (including a failure to warn claim).

While claims against dietary supplement companies span the spectrum of potential product liability claims, it is the failure to warn claim that most frequently results in product liability exposure for dietary supplement companies. Thus, while there have been cases against dietary supplement companies involving manufacturing defects, those are normally “one-off” events that involve adulteration or contamination; examples include pesticides found in tablets containing Asian ginseng (Panax ginseng, Araliaceae) or prescription drugs found in certain supplements (which generally are described as illegal pharmaceutical drugs masquerading as “dietary supplements”).

Claims related to the marketing of dietary supplement products, and specifically failure to warn claims, are the most common and also have received the most attention in the industry. They also present an opportunity for risk mitigation by addressing potential warning issues in a proactive way, as discussed in the section titled “Assessment of Potential Voluntary Warnings,” to follow.

The common elements of a product liability action based upon a failure to warn claim generally include a determination of the following: (1) whether the supplement company knew or should have known of the risk of harm, and (2) whether the company through labeling could have prevented or reduced the risk. When both of these elements are met, the company may be held to have a “duty to warn” consisting of two responsibilities: to provide adequate instructions for safe use and to provide a warning regarding potential dangers.

Courts generally have held that companies have a duty to warn of a particular risk if it is known or knowable at the time of manufacture and distribution. However, some courts have held that manufacturers should warn of risks discovered after the product is initially sold (i.e., that there is a continuing duty to warn). In a 2012 Ninth Circuit decision, *Rosa v. Taser International, Inc.*, the court noted that “a manufacturer may be liable … for failure to warn of a risk that was subsequently discovered.” Although complaints filed by plaintiffs often assert that a duty to test or conduct post-market research exists, the applicability and scope of this duty for dietary supplement companies remains largely untested given the limited case law.

Manufacturers generally cannot, however, be held liable for failing to warn of unknowable or unforeseeable risks.

† Although beyond the scope of this article, certain states may require warnings for dietary supplements, as demonstrated by the number of states (including California and Texas) that required warnings for dietary supplements that contain ephedra.

The vast majority of dietary supplements are not subject to mandatory FDA warnings.
associated with the product. Additionally, companies typically are not expected to warn against risks that a reasonable, informed person would have been aware of at the time of the sale.25

Importantly, courts generally have recognized that warnings must be selective in order to be effective. Indeed, dietary supplement label space is extremely limited, and too many warnings (i.e., “overwarning”) may detract attention from the most important warnings. Courts therefore have been reluctant to require warnings about relatively minor risks, risks that are not scientifically established, or risks that are extremely rare.26

In light of the applicable legal standards, the two critical issues for dietary supplement companies are (1) whether a potential risk is known, knowable, or foreseeable, and (2) whether a reasonable, informed person would be aware of potential risks, such as herb-drug interactions, in the absence of label warnings.

Failure to Warn Cases – Difficulty in Establishing Causality

As a general rule, under the Daubert doctrine,27 trial courts can admit expert testimony for scientific questions such as causality only if the expert employs reliable methodologies based upon valid scientific data. While guiding precedent in many US courts of appeals on the admissibility of expert testimony remains sparse and inconsistent,28 the ephedra litigation is instructive for the dietary supplement industry; in McClain v. Metabolife International, Inc., the Eleventh Circuit took a restrictive approach regarding the admissibility of the plaintiffs’ expert evidence.

Specifically, in McClain, the plaintiffs claimed that they sustained significant injuries (strokes and one heart attack) because they ingested ephedra in a Metabolife product and alleged that Metabolife sold the product without adequate warnings.29 Although a jury had found Metabolife liable for $15 million in damages,30 the Eleventh Circuit reversed the verdict in full based on the trial court’s error in admitting the plaintiffs’ expert testimony.29

Under the McClain precedent, courts would be required to conduct a rigorous analysis of expert testimony in support of both general and individual causation.5 According to the McClain ruling, reliable expert testimony should include testimony on the dose-response relationship31 (i.e., the relationship between the dose of a product and the body’s reaction to it) and account for background risk.32 Furthermore, expert testimony that relies solely on unsubstantiated comparisons of the supplement with similar substances,33 adverse event reports,34 or actions by the FDA35 may not be deemed sufficiently reliable.

While McClain may appear to pose a significant barrier to plaintiffs in dietary supplement cases, a few important caveats should be noted. First, in McClain, the expert testimony was markedly deficient. The plaintiffs’ key expert based his testimony primarily on traits associated with a broad category of substances that imitate the effects of ephedra, but offered no data on ephedra’s dose-response relationship, no epidemiological or animal studies, and no direct biological evidence of ephedra’s harmful effects.36 Accordingly, even after McClain, the minimal threshold of evidence required for admissibility remains unclear. Secondly, although other Eleventh Circuit cases have applied the McClain standard,28 other jurisdictions do not apply a uniform approach. Thus, this area of the law remains unsettled and should be monitored carefully.

Assessment of Potential Voluntary Warnings

As explained above, if and when a voluntary dietary supplement warning is issued depends on the specific product in question and the specific risk of harm. That said, dietary supplement companies may seek to mitigate exposure to failure to warn claims by monitoring developments that may give rise to a duty to warn.

More than 10 years ago, the Office of the Inspector General of the Department of Health and Human Services issued a report criticizing the dietary supplement industry for, among other things, not including a sufficient number of dietary supplement warnings on product labels.37 Although it is reasonable to assume that the dietary supplement industry has become more proactive in recent years in adding voluntary dietary supplement warnings, we nonetheless provide below a number of recommendations to help dietary supplement companies establish procedures for monitoring safety issues and assessing the need for additional voluntary warnings. However, we caution that due to the complexity of these issues, manufacturers and marketers of dietary supplements should consult with legal counsel to address potential issues associated with product liability exposure, including the potential addition of voluntary warnings.

Monitor FDA Statements, Scientific Developments, and Literature that May Be Relevant to the Product

According to failure to warn product liability case law, the critical issue in determining liability is whether a company knew or should have known about the potential for harm. Thus, at a fundamental level, the law charges supplement
manufacturers, like the manufacturers of all products introduced into the stream of commerce, with knowledge of what they reasonably should know about a product. By way of example, once the FDA issues a safety-related communication regarding a specific dietary ingredient or product, manufacturers may be deemed to be "on notice," and the potential harm may be considered "known" or "knowable," thus giving rise to a duty to warn.

While the obligation to be aware of developments may be self-evident, the vast amount of information available through electronic media presents a challenging environment for companies seeking to keep abreast of developments relevant to their products. Although general familiarity with the industry may result in anecdotal information coming to the attention of management, it is typically prudent for companies to periodically check relevant databases and other sources to keep up to date on safety-related developments. Obvious sources of information include the FDA website as well as industry publications, trade association updates and policies (if the company is a member of the association), peer-reviewed scientific journals, newsletters, etc. With respect to the sale of herbs and other botanical-based dietary supplements, companies should review the relevant sections of the American Herbal Product Association’s Botanical Safety Handbook, 2nd edition (CRC Press, 2013), since this expanded edition has been compiled by herbal experts and has been extensively peer reviewed, constituting an authoritative and reliable source on the relative safety of more than 550 herbs sold in commerce in the United States.38 Further, companies also periodically could review sources of information concerning claims and lawsuits, scientific publications, news reports, and other web-based sources of data.

Monitoring of these various sources can be conducted in-house or through outside counsel or other outside contract services, but companies may want to develop a process that reasonably ensures that they are aware of relevant information.

Review Warnings Used for Other Products

Because very few dietary supplement warnings are mandated by the FDA, a court’s determination of whether a label warning should have been issued may often depend, at least in part, on what is reasonable in the industry (i.e., "industry custom"). Management should therefore assess whether other companies distributing similar products have disseminated warnings. Accordingly, as a corollary to the monitoring procedure discussed above, it may be prudent — in certain situations — for companies to periodically review warnings issued by other companies for similar products.

Courts therefore have been reluctant to require warnings about relatively minor risks, risks that are not scientifically established, or risks that are extremely rare.

Causation Analysis and Harm Potential

In the event management becomes concerned that a potential harm may exist, the next step in the process is much more challenging — determining if the science supports the notion that ingestion of the product can actually cause harm. As noted, this is an extremely complex issue. Courts have acknowledged that the scientific link between ingestion of a dietary supplement product and the harm being alleged often is tenuous, and plaintiffs’ claims against a supplement manufacturer or distributor often may be defeated on that basis. Thus, when a company is confronted with anecdotal information that a product may be causing harm (e.g., complaints or reports by consumers) but the scientific data are inconclusive, the question arises as to whether warnings should be issued. In this scenario, warnings based on partial or unsubstantiated data actually could be counterproductive, as consumers would, among other things, be provided inaccurate information.

Again, in the absence of regulatory guidance, management may want to consider — in appropriate situations — engaging an independent scientific expert to analyze and determine if there is a basis to believe the product causes the alleged harm. Such analyses may be useful in defending against product liability lawsuits and also in providing consumers with information concerning the safety of the product. If, on the other hand, the results of the analysis provide data that may support the existence of a risk of harm, management can make an informed decision regarding the addition of a voluntary product warning.

Development of Warning Verbiage

If a company decides to add a label warning, it must consider carefully the content of the warning. As a general matter, language should be as clear and concise as possible and should avoid technical jargon. Depending on the situation, it may be necessary to advise consumers of the likelihood and severity of the risk. Placement of the warning also can be crucial, as a warning can be deemed insufficient if not positioned appropriately on the label.

Based on the above criteria, it is often helpful to review FDA-required warnings (regardless of their applicability to food/dietary supplement companies, drug companies, or device companies) as templates for the development of appropriate warning verbiage and placement. The FDA has substantial expertise developing product warnings, and courts may be deferential to warning verbiage — and placement — that mimics the language mandated by the FDA in similar situations. Ulti-
mately, though, the development of appropriate warning language requires an individualized assessment by appropriate experts.

**Bring Along the Industry**

In cases where management determines that a warning should be added to product labeling based upon an issue that may relate to other products as well (e.g., an ingredient-related warning potentially applicable to an entire class of products), it may be advisable to notify competitors, trade associations, and/or the FDA in order to ensure that potential risks are publicized appropriately. This also will help to ensure that the warning is used throughout the industry and is not viewed by consumers as being product-specific. For example, a dietary supplement company could work with a trade association to develop a model ingredient warning for wider dissemination throughout the industry. This would avoid the competitive disadvantage that may arise from being the “first adopter” of a warning.

**Transactional Issues**

Increasingly, dietary supplement companies have become attractive targets for acquisitions and other merger and acquisition-related activity. Both financial and strategic buyers need to be aware of the potential risk of product liability claims and lawsuits and should engage experienced counsel during the diligence process to assess the risk associated with the target’s operations both from a regulatory and litigation standpoint.

In this regard, it is important to understand historical claims data as well as the company’s quality assurance processes. It is often well worth the time and expense to exercise diligence on behalf of the company’s manufacturing processes and historical labeling/warning practices in order to identify potential risks.

**Insurance Coverage**

As the dietary supplement industry grows and matures, companies may see advantages in exploring different levels of insurance coverage for product liability claims. As in the pharmaceutical industry, traditional coverage may be difficult to obtain or be overly expensive. Accordingly, companies should consider exploring self-insured programs, captive arrangements, and other alternatives for mitigating risk and controlling costs.

**Conclusion**

The dietary supplement industry represents an important and growing component of the US economy, as consumer demand for dietary supplements continues to increase. As with any successful industry, market penetration and growth often comes with a price: greater exposure to product liability risk. Although the dietary supplement industry can claim a strong safety record to date, dietary supplement companies nonetheless should adopt a proactive approach to mitigating product liability risk by considering the addition of product warnings — where appropriate — based upon the recommendations outlined herein.

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**Advances in Natural Medicines, Nutraceuticals and Neurocognition**


The editors of this book have been doing research in this field throughout their careers and have co-authored two of the 16 chapters. Andrew Scholey, PhD, is a professor of behavioral and brain sciences and Con Stough, PhD, is a professor of cognitive neuroscience. Together they direct the Centre for Human Psychopharmacology at Swinburne University in Melbourne, Australia.

This book is divided into four parts: (1) Methodologies to Measure Cognition in Natural Medicine Trials; (2) Vitamins and Nutrients; (3) Essential Fatty Acids and Neurocognition; and (4) Herbal Medicines, Nutraceuticals and Neurocognition.

“Methodologies to Measure Cognition” (Part 1; two chapters) is not without controversy; this is apparent when reading the section. The parameters of memory that are measured most often are ideally those associated with mild cognitive impairment, which may be a prodrome to states of dementia (from which there is currently no return) such as Alzheimer’s disease. Most studies, however, use normal or normal elderly adults. Significant effects are hard to come by, perhaps because enhancing memory above “normal” is difficult and may not be relevant to delaying memory loss in elderly patients. Delaying memory loss is really the goal of therapeutic intervention, and so far no treatments (including pharmaceuticals) have been shown to be effective.

Part 2 has five chapters that examine various isolated compounds, including B vitamins and antioxidant vitamins, N-acetyl-cysteine, zinc, and lipoic acid. The rationale for using these agents is based mostly on the notion that senility and dementia are caused by increased oxidative stress during aging. These nutrients are thought to intervene somewhere in the cascade of events involving oxidation and inflammation, which first leads to neuronal dysfunction (which may be reversible) and ultimately to neuronal degeneration (which is probably not reversible). While there is some evidence in animal models that it may be possible to enhance the formation of new neuronal cells, this is controversial, and it is unclear if the cells are really functional. Most of the information presented in these chapters is used to explain the theoretical basis for why these agents might interact with pathological processes. Clinical evidence is rare, and evidence based on epidemiology studies can demonstrate only correlation, not causality. Data based on food frequency questionnaires are not really useful and often lead to incorrect conclusions. Failure to find evidence in favor of something is not equivalent to finding evidence against it. This is especially true for epidemiology studies. Meta-analyses that include poor-quality studies using ineffective doses don’t improve the science. I also was disappointed at the lack of discussion regarding the relative physiologic and neuroprotective roles of different vitamin isomers and of optimal doses in various populations and how this can affect results. An annoyance of this and other sections is that much of the information is rather old. There are almost no references published after 2009.

Part 3 consists of two chapters that describe the roles of essential fatty acids (EFAs) in neurocognition. These chapters were particularly well written and noticeably more positive in relation to the potential for prevention and treatment of cognitive decline. Unlike the antioxidants or even the anti-inflammatory drugs, which largely rely on this single mechanism, EFAs (especially the long-chain omega-3s) affect multiple systems and pathways that are known to be involved with pathologic neurodegenerative processes. In addition, they are one of the major structural components of brain phospholipid membranes. While deriving conclusions from the literature can be problematic since faulty data derived from food questionnaires and treatment studies with ineffective doses have been included, there remains a core of compelling evidence suggesting that omega-3 is central to cognition. The large literature on the positive role of omega-3 in mood disorders and other psychiatric conditions is consistent with positive effects on cognition. Supporting evidence includes the critical role in neurodevelopment and of neuroprotection in animals and humans.

Part 4 comprises seven chapters dealing with the possible effects of herbal medicines and various nutraceuticals on neurocognition. Chinese medicine, a green tea (Camellia sinensis, Theaceae) extract (epigallocatechin), huperzine (from Huperzia serrata, Lycopodiaceae), and wine-derived phenolics each have their own chapter. Two chapters are devoted to Bacopa monnieri (Plantaginaceae); the first by the editors on human clinical effects is rather encouraging. In addition to a long history of traditional use in Ayurveda, there is considerable modern evidence supporting beneficial effects of bacopa. (The government of Australia is supporting a large intervention study that will look at mechanisms.) The second bacopa chapter is mostly on animal studies performed at the Central Drug Research Institute in Lucknow, India.
While *H. serrata* is a Chinese medicine, huperzine has its own chapter due to the relatively large amount of modern data. Huperzine is of interest in Western medicine perhaps because its pharmacology is similar in some ways to drugs approved for the treatment of Alzheimer’s (cholinesterase inhibitors).

In summary, the chapters of this book have been assembled by the editors around the topic of natural treatments for neurocognition, though each chapter really stands alone. Some chapters are better than others but all contain rather old references, suggesting that the book started its life some years ago but only recently was published. I agreed to review this book because I wanted my own copy to serve as a future reference. As a psychopharmacologist, I read and enjoyed every page, and I think others will too.

—Jerry Cott, PhD
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Sweeteners derived from *Stevia rebaudiana* (Asteraceae) have been of much interest due to several widespread approvals in the last decade. According to the preface, the book *Stevioside: Technology, Applications and Health* “covers the state of the art of stevioside extraction with an emphasis on membrane technology....”3 The book also presents an account of the history, medicinal values, and other applications in some detail.” The authors are a chemical engineering professor, Sirshendu De, PhD, who has considerable experience in membrane filtration technology, and two graduate students, Sourav Mondal and Survrajit Banerjee.

As one may expect based on the experience of the authors, the book focuses on membrane filtration of stevia extracts; in fact, six of the 10 chapters are dedicated to this topic. The other chapters include an overview on stevia, a review of biological effects, applications, and extraction processes other than those using filtration. As a text on lab-scale filtration of stevia, this book does provide a detailed review. At times, *Stevioside* reads more as a journal article in this regard, giving details such as which company provided the membranes used. Due to the sparse citations in these sections, it would seem that great swaths of the filtration chapters are excised from a few manuscripts.

While the text shows evidence of scientific authority on membrane filtration technology, the background on stevia is a bit outdated. For example, in the “list of all the chemical constituents of *S. rebaudiana*” provided in this book, except for the pigments mentioned, the most recent reference given is from 1988. Consequently, the aforementioned table names only eight ent-kaurane diterpenoids from *S. rebaudiana*, while a recent review by Ceunen and Geuns lists 35.1

A continual issue with the text is the stated focus on stevioside. In truth, the text alternates focus among stevia extract, steviol glycosides in general, and stevioside specifically. On occasion, it seems that these terms are used interchangeably or that stevioside is forced into the text. For example, the statement is made that “stevioside and *Stevia* extract can be used for the treatment of diabetic patients,” referencing an article by Renwick and Molinary from 2010.2 The cited review article does not mention any studies involving purified stevioside; however, a human study with rebavidoide A and a rat study with stevia extract are discussed briefly. This is a common theme in the chapter covering health benefits of steviol glycosides, where claimed biological effects are overstated relative to the cited work — most frequently manifested by representing in vitro or animal studies as activity in humans.

Unfortunately, there are several instances of this text making bold claims in the absence of any references. The text sometimes reads as a polemic against the use of organic solvents in stevia refining. Water-based extraction techniques are touted as “health friendly” and using “no chemicals,” while solvents are called “toxic chemicals which may be deleterious to health.” Perhaps the most egregious example is that calcium chloride is called a “toxic chemical.” According to the US Food and Drug Administration’s Select Committee on GRAS Substances, there is “no evidence in the available information on calcium acetate, calcium chloride, calcium gluconate, and calcium phytate that demonstrates, or suggests reasonable grounds to suspect, a hazard to the public when they are used at levels that are now current or that might reasonably be expected in the future.”3 Additionally, stevia is touted as “the world’s only natural [no calorie] sweetener,” a statement inconsistent with the substantial literature on natural high potency sweeteners in general; and the growing use of monk fruit (*Siraitia grosvenorii*, Cucurbitaceae, syn. *Momordica grosvenorii*)-based sweeteners in particular.
Overall, as a source of information on membrane filtration techniques possible for the preparation of refined stevia extracts, this text is satisfactory. However, given the bias against other extraction techniques and the reliance on laboratory scale equipment, the “state of the art of stevioside extraction” is not fully covered. This book could be used as a reference for those wishing to learn more about membrane filtration of stevia extract, and functions quite well as a collection of membrane filtration experiments on stevia extract with theoretical background. However, those wishing to learn about stevia-based sweeteners or stevioside should look elsewhere.

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References


This second edition is a revised and expanded iteration of Edible & Medicinal Wild Plants of Minnesota & Wisconsin (2001). The author decided to change the title “[b]ecause the majority of the plants discussed herein flourish in a larger range than simply that encompassing Minnesota and Wisconsin — occurring also in Iowa, Michigan, the Dakotas, and other Midwestern states.” Other additions to the newer edition include a section titled “Personal & Professional Use,” in which the author has added his personal and/or clinical experience to each monograph; a history of herbalism in the United States; and a “Comparison Chart of Wild vs. Domestic Veggies.”

The book showcases 100 plants with 171 color photographs. There is an appendix listing “Physiological Actions of the Plants” with “superior ones in their categories” italicized, a “Measurements & Equivalents” page, and a brief two-page primer on “How to Make Herbal Preparations at Home.” The glossary includes definitions for physiological action terms, different formula names, symptoms, and botanical terms. There are more than 1,000 references, and the index differentiates by font diseases/conditions, physiological functions, Latin genera, book titles, and plant chemicals.

The General Introduction, “The Art of Wild-Plant Foraging,” has multiple helpful tips on how to forage safely, where to forage, foraging ethics, and how to preserve and prepare the harvest. The Auxiliary Introduction, “Health, Medicine, and Weeds,” includes a section on wild-plant nutrients (with the comparison chart noted above) and explanations of phytochemicals.

The majority of the book is the “Field Guide & Description of Plant Uses: Individual Plant Monographs Alphabetized by Common English Name.” The author used the common name he believed to be most well known; the scientific names are listed in the index. The entries include other common names, the scientific name, a description of plant morphology, range and habitat, seasonal availability, major nutrient constituents, food and health/medicinal uses (including harvesting and preparation techniques), the author’s experience, and cautions. Each information-rich entry spans roughly two to five pages.

Edible & Medicinal Wild Plants of the Midwest is unique in its genre; similar books usually focus on either edible or medicinal plants. Though there has been demand for books that do both, it seems few authors have dared to attempt it. Matthew Alfs, a nature teacher, forager, environmentalist, and practicing herbalist, seems well qualified to take on this large project.

Of the 100 included plants, many are less common species or at least less frequently written about — another reason the book is a valuable resource, besides the plethora
of information it offers. The traditional Native American uses, along with modern uses, and the author’s experience with the plants are helpful, too. This book accomplishes its purpose and more. It is not just a reference to sit on the shelf; it belongs on the table for frequent use and consultation where other references are lacking. It can be utilized by the novice or the more expert forager. Though calling it a field guide might be a little out of the question — its 400-plus pages and 8-by-10 inch size make it rather bulky to take out to the field — it is definitely one to consult on the way to or from the field.

More than a foraging manual, a field guide, or a materia medica, *Edible & Medicinal Wild Plants of the Midwest* is a multipurpose book accomplishing these functions in addition to covering scientific studies, ethnobotany, nutrition, and more. It highlights the plants of a biodiverse region not often written about, though many of these plants may be found in an even broader region than just the Midwestern United States. With such a large number and variety of references employed, this is a versatile plant guide not to be missed.

—Abby Artemisia
Botanist, Herbalist, Professional Forager
Burnsville, North Carolina

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*Essential Chinese Formulas* by Jake Paul Fratkin, OMD, LAc, provides the Traditional Chinese Medicine (TCM) practitioner a manual for 225 commonly used formulas based on Fratkin’s extensive clinical experience. The book features 133 classical formulas, 83 modern formulas, and nine single herbs, organized under clinical chapter headings unique to Fratkin’s organization system. Each formula lists ingredient percentages, TCM indications, applications, contraindications, and cautions, as well as the unique clinical experiences of the author.

Fratkin showcases commonly used classic and modern formulas available in the current marketplace, often comparing various versions of formulas that have the same name. This is an important bridge that Fratkin builds for the modern clinic: He points out modern applications of classical formulas, while also introducing important modern formulas of which practitioners may be less aware. As more and more companies are restricted in describing their formulas’ health benefits — due to increased regulatory activity in the United States and elsewhere — there has been a decrease in product literature from various companies. Fratkin’s descriptions in *Essential Chinese Formulas* enlighten and inform readers of the modern applications and availability of these products.

This comes as a welcome resource for the many practitioners of TCM who are hesitant to explore the clinical practicality of Chinese herbal medicine despite their extensive training. Fratkin connects the dots and gets the practitioner to re-think applications and uses of Chinese herbal medicine for the many clients who walk into the clinic.

On the inside back cover of *Essential Chinese Formulas*, there are specific codes for the therapeutic herbal categories as well as a concise list of all of the herbal companies (and their individual formulas) that are represented throughout the text. This affords the practitioner a device for understanding how herbs are placed in a formula. Once one gets accustomed to this organization, it makes the book a quick and easy reference in a clinical situation. It also is convenient that each formula opens to two full pages of description and application.

This book is quite similar in tone to Fratkin’s previously published *Chinese Herbal Patent Medicines: The Clinical Desk Reference* (Shya Publications, 2001). That book was very popular with students and practitioners 14 years ago, and many people may wonder: “Why should I get the new one?” Whereas the previous books details 900 patent medicine formulas, many of which are available only in specialty herb stores, this work fills the need of current practitioners and students wishing to concentrate on the most important and available 225 formulas. It also collects information from and focuses on the author’s continued clinical experience, as well as his integration of material from newer texts from China and the United States. I recommend this book for students and teachers of traditional Chinese herbal medicine, as well as for the dedicated practitioner.

—Shellie L. Rosen, DOM
Practitioner and Consultant
Albuquerque, New Mexico

This book claims to fill a much-needed void. It was written to assist healthcare professionals (e.g., clinicians, pharmacists, dietitians, nurses, and health coaches) with evidence-based science and practical information about recommending dietary supplements to patients.

On the positive side, Dr. Guilliams has written an easy-to-read, factual book about some, but not all, dietary supplements. The information is current, and key references are cited. The chapters on probiotics and how to choose a marine-derived omega-3 product were superb and worth the price of the book. In the section where clinicians can readily find information about supplements — the meat of the book — most pages (about 60 to 80) are devoted to vitamins and minerals. Healthcare providers usually know about these.

Instead, I wish the author had included less well-known nutrients. He reviewed only a few (e.g., choline, coenzyme Q10, and probiotics), and these were covered briefly (20 pages). In addition, the section on herbs dealt with how they are prepared and contamination issues — both of which are important, but clinicians really want to know how much of which herbs should be used for a specific condition.

What concerned me was that I am not sure that the book delivered on its promise. This was supposed to be a primer for a healthcare professional, but Dr. Guilliams does not seem to have experience in a clinical setting (His PhD is in molecular immunology, and he is currently the vice president of science and regulatory affairs for Ortho Molecular Products, a manufacturer of dietary supplements sold through health professionals). At times, he writes statements that, to me, are not in the best interest of the patient. For example, Dr. Guilliams presents a table of “dirty” and “clean” fruits and vegetables. On some level, this may be important, but in my experience providing nutritional counseling to patients for more than 20 years at urban teaching hospitals, most patients do not consume enough fruits and vegetables. Suggesting some over others simply reduces the likelihood patients will eat more of them, which they should. In addition, the chapter on protein has information on vegetarian and non-vegetarian sources, which is desirable; however, he never acknowledged the importance of protein quality (e.g., as rated by the Protein Digestibility Corrected Amino Acid Score [PDCAAS]). During convalescence, it is imperative to recommend a high-protein diet and one with a high PDCAAS to optimize protein synthesis. He recommended hemp, rice, and potato proteins, which have low PDCAAS compared to whey protein, which he also recommended.

However, as I continued reading the book, the proverbial light bulb finally lit up. All along, I thought the book was for healthcare professionals who work in conventional institutional settings. I went back to re-read the preface and realized that the book really is geared toward functional and integrative medicine practitioners, with whom Dr. Guilliams spent a lifetime teaching and interacting. In fact, he founded the Point Institute, the publisher of this book, as “an independent research organization focused on examining and disseminating information about the use of natural therapeutic options for treating and preventing chronic disease.” For clinicians who practice functional and integrative medicine, the book is a home run; anyone who practices in this sector should own this book. Besides containing information on dietary supplements, the book also has excellent materials on defining what dietary supplements are and how they are regulated, dietary patterns that promote health, and an overview of macronutrients (i.e., protein, carbohydrate, and fat). At the end, Dr. Guilliams presents a diet plan for implementing a low-glycemic load “Mediterranean” diet. Readers should know that the book includes more than just dietary supplement information, as the title suggests.

For those who work in more conventional practices (e.g., hospitals, nursing homes), the book is full of excellent information, but it does not deliver on its promise of being a quick-reference guide to help with dietary supplement recommendations. I hope Dr. Guilliams, with his excellent knowledge about the science of dietary supplements, will consider writing a book geared toward this group of clinicians. He could skip the information on vitamins and minerals and include more content about less-conventional dietary supplements.

—Stacey J. Bell, RD, DSc
Nutritional Consultant
Belmont, Massachusetts
IN MEMORIAM

Alexander Theodore
“Sasha” Shulgin
1925-2014

The foremost chemist of the mind and of mind alteration, Alexander “Sasha” Shulgin, died of cancer at age 88 on June 2 in his home and laboratory near Oakland, California, at peace after a long series of illnesses. He was born June 17, 1925, to parents who were teachers. Exceptionally bright from a young age, he began studying organic chemistry at Harvard University at age 16, but left to join the US Navy during World War II.1

After earning his doctorate in biochemistry from the University of California at Berkeley in 1954, Dr. Shulgin began working for Dow Chemical. He had his first psychedelic experience with mescaline, the psychoactive compound found in peyote cactus (Lophophora williamsii, Cactaceae) in 1960. After creating the biodegradable insecticide Zectran in 1962, Dr. Shulgin used the considerable freedom granted by Dow to explore his own interests. In 1966, he left Dow after the company asked him to stop using its name and address on his scientific papers.

Following his departure from Dow, Dr. Shulgin formed a friendship with Bob Sager, who was head of the United States Drug Enforcement Administration’s (DEA) Western Laboratory. For more than 20 years, Dr. Shulgin held a Schedule I research license that allowed him to possess, identify, and analyze controlled substances in small amounts for research purposes. This enabled him to explore potential new psychoactive — particularly psychedelic (mind-expanding) — chemicals at his own personal lab. He tested each substance to determine activity, dosage, and safety, beginning with himself, and then with the help of his “research group” consisting of six to eight of his colleagues and his wife, Ann Shulgin (née Gotlieb, a Jungian psychoanalyst). In his work with the DEA, he served as an expert witness in drug trials and published Controlled Substances: Chemical & Legal Guide to Federal Drug Laws (Ronin Publishing), the then-definitive controlled-substances reference, for the agency in 1988. To our great loss, his Schedule I research license was revoked in 1993 after the DEA, state, and county raid on his property that stopped his original research. This infamous raid resulted in a slap on the wrist and an inconclusive environmental impact report. The deal offered by the DEA was to face charges or give up his research license. He surrendered the license and was fined $25,000.

Dr. Shulgin proceeded with research on psychedelics, but without the freedom of his Schedule I license. He published four more books, in addition to Controlled Substances, and numerous papers in scientific journals. By 2005, Dr. Shulgin estimated that he had had more than 4,000 psychedelic experiences. (His wife estimated that her own numbered above 2,000.)

As described in The New York Times Magazine in 2005 and in Dr. Shulgin’s obituary in The New York Times, by the end of his long career, he had created more than 200 novel psychoactive chemicals including: “stimulants, depressants, aphrodisiacs, ‘empathogens,’ convulsants, drugs that alter hearing, drugs that slow one’s sense of time, drugs that speed it up, drugs that trigger violent outbursts, drugs that deaden emotion — in short a veritable lexicon of tactile and emotional experience.”1

I have been privileged to be Dr. Shulgin’s friend and a recipient of his largesse for decades. The erosion of a great mind, a genius mind, an earth-moving mind, is difficult and sad, however inevitable our dissolution may be. Sasha tried his best to leave us with his encyclopedia, to download his learned treasure as a gift for posterity. In this he succeeded beyond any measure. He has given the world extraordinary gifts.

It was 1973 when Andrew Weil, MD, writing in his groundbreaking The Natural Mind,2 asserted a division between the “natural” realm of psychoactive substances and the synthetic, exalting the plants and their extracts that included pure active principles themselves as safer and less materialistic, therefore directing the user toward the natural highs that occur without chemical alteration. At that time, there were few “synthetics” in circulation. The great expansion of experience with plant active principles and substituted phenethylamines and tryptamines lay ahead. That prejudice was bolstered by others, like Terence McKenna — the truth being that many who made this argument were sophisticated users of substances that were somewhat naturally occurring as well as those that were definitively “white powders,” i.e., synthetics. But the prejudice had some taint to it, and chemists like Sasha were erroneously placed on the defensive. Sasha’s absorption in the plant world was lifelong and unchallengeable, yet his work as a psycho-chemist and his personal development of hundreds of new structures left him a bit vulnerable to this mistaken identity — unfortunate, as that prejudice arose from what seems to me to have been a polemical notion.

At the center of the investigation of the relationship of mind and botany is Sasha’s prelude to the isoquino-line encyclopedia: “One can identify a plant by what it looks like, or by what is in it. One can identify a natural
compound by its structure, or by what plant it is in. Know one, find the other.² And so it goes — reciprocally, as posited — in this case, hundreds of the varieties of isoquinolines, hundreds of plants, predominantly cacti and their known constituents.

In his masterpiece on the tryptamines, TiHKAL (“Tryptamines I Have Known and Loved”; Transform Press, 1997), Sasha wrote of his early inclination towards the plant world: “Many years ago, my dream was to put together a complete review of the snuffing/drinking/smoking world of ethnobotany into one piece and write the total story. But even then, it was too complex and interdisciplinary, and I have abandoned ship.”⁴

Perhaps that vessel was forsaken, but the project has been encompassed and addressed by him. The components of that early vision took the form that coalesced behind the most personal and focused exploration of mind and substances that has ever occurred.

Here is a statement of Sasha’s motivating passion⁴:

These tools, the psychedelic drugs and plants—offer a much faster method than most of the classic alternatives for the accomplishment of the goals we seek: conscious awareness of our interior workings and greater clarity as to our responsibilities towards our own species and all others with whom we share this planet.

Sasha’s accomplishment was to link, non-causally, mind and the impact of substances on mind and body. He did this by creating chemical substitutions in the mind-altering constituents of known and recently discovered psychedelic plants. Carefully working upwards in dosage by imbibing these substances himself, he was able to separate inactive compounds from actives and to recognize specific effects. Over time, based on his increasing experience, he became able to discern relationships and patterns between chemical structures and his mind. This has led to concepts of endogenous receptors and psychoactive substances in brain, relationships to neurotransmitters, particular chemical-sensory relationships, and sophistication with potential structurally designed molecular creations. His personal experiences — his heroic path — are the basis for much of what has come into scientific and public use. When we seek the psychedelic — the mind manifesting — we are of him.

Long ago, Sasha grasped that rats and other animals were different than humans; they had different responses to potential psychoactives, and — obviously — were unable to comment subjectively on their altered experiences in the labs of the world. To understand and to be capable of describing and sharing what would occur in humans, humans themselves would have to do the exploring. They would have to take the risks and create the benefits — and suffer the consequences as well. For Sasha, this lay at the heart of his concept of personal freedom. To paraphrase: Do unto myself as I would have myself do unto me — that is my fundamental right — the consequences are mine to reap — and I will not make others responsible for my choices.

The organizationally brilliant second step in evaluating a potential new psychoactive was to present the substance to his research group, comprising a consistent group of volunteers (a chemist and two psychologists among them) who, by experiencing the substance, would validate and add to knowledge of the substance — its safety, effects, and variability — by their “sample size” and idiosyncratic reactions.

All of this research was documented meticulously in notebooks that became the reference sources for articles that included descriptions of chemical procedures for the synthesis of new substances as well as personal and group reactions. A language for describing experiences emerged that was adopted at large by psychonauts who followed the Shulgin publications. And all was for public knowledge and dissemination — no secrets, no kowtowing to repressive interests or government pressures, no money undermining the path of research. Funds sufficient to keep the work going were contributed by friends — no strings attached, no compromises for fame or fortune. Throughout, Sasha would work in outside labs to support himself, his family, and his abiding interest.

And Sasha was far from shy. Passionate about his work and the vast expanges of the journeys that his creations offered, convinced of the positive vector of psychedelic experience for consciousness and connection, Sasha held forth. He would entertain with filthy limericks interspersed between chemistry discourses and a profound interest in the experiences of those who thronged to his side. Never deliberately seeking publicity, but accepting it carefully and with knowledge of the pitfalls and distortions of the press and its too-frequent attempts to suggest criminality and misbehavior, Sasha persevered and developed — and we with him.

There are rare role models in life. Too often, those we revere are found with clay feet and we can reduce them to our own mere mortal forms — disappointed and cynical from the effort. Sasha had his share of the derogatory; there were enemies. To remain staunch in the maw of the war on drugs is no small achievement. Search Sasha Shulgin for flaws and discover the minor ones that come with being human. Emulate Sasha Shulgin as a remarkable and dedicated explorer of mind, soul, and matter, and you will go far. ¹⁵

—Philip E. Wolfson, MD
San Francisco and San Rafael, California

With biographical information added by Hannah Bauman, and with acknowledgements to David Presti, PhD, Dennis McKenna, PhD, and Wendy Tucker.

References
IN MEMORIAM

Milton “Sandi” Cutler
1950-2014

Sandi Cutler, former board of trustees member and vice-president for institutional planning and external affairs for Bastyr University in Kenmore, Washington, passed away on July 3, 2014, at the age of 63. A community organizer with strong gifts for strategy, planning, and networking, Cutler dedicated his career to improving the life and health of those around him.

Born on November 20, 1950, in San Jose, California, Cutler’s parents first instilled in him the concept of social justice and equality as they fought to desegregate California's public schools. A natural marketer, he began his career in the 1970s applying direct marketing techniques and the use of inquiry management systems for corporate clients. In the ‘80s, Cutler worked as a political consultant for a number of campaigns for local politicians, ensuring that underrepresented communities maintained their voices in government. After relocating to the Seattle area, he served as a senior political consultant for a number of campaigns for local politicians, ensuring that underrepresented communities maintained their voices in government. After relocating to the Seattle area, he served as a senior political consultant for corporate clients. In the ’80s, Cutler worked as a political consultant for corporate clients. In the ’80s, Cutler worked as a political consultant for a number of campaigns for local politicians, ensuring that underrepresented communities maintained their voices in government.

In 1984, he began working as a volunteer fundraiser for Bastyr; he became a member of the board of trustees in 1985. In 1990, Cutler joined the management staff at Bastyr, and under his leadership and guidance, enrollment grew from approximately 150 students to more than 1,300. This association with the school would ultimately lead to a period of unprecedented growth and change for the institution. Cutler further solidified his position as a strategic leader in natural medicine and healthcare by overseeing the expansion of DeVry Education Group's medical program.

“Sandi’s impact was huge, hard to adequately describe,” wrote Joseph Pizzorno, ND, founding president of Bastyr University (email, August 21, 2014). “He was integral to Bastyr's maintaining academic accreditation when critics tried to repeal it, and he was responsible for Bastyr's becoming the first NIH [National Institutes of Health]-funded center for alternative medicine research, the purchase of the beautiful 40-acre campus outside of Seattle, licensing of NDs [naturopathic doctors] in California, the remarkable almost tripling of enrollment in the 1990s—the list of his contributions to Bastyr is long.”

“[W]e worked intensely together … with Joe [Pizzorno] in assembling a white paper for the US Congress during the Clinton health reform in 1993,” wrote John Weeks, editor of the Integrator Blog News and Reports and former vice president of Bastyr (email, September 5, 2014). “Sandi offered just the right look, feel, and content directions to make that document powerful. It was the first significant introduction to naturopathic medicine for the 45 members of the US House and the US Senate from the then 8 states that licensed naturopathic doctors. Sandi’s wisdom guided its development.”

Cutler held a number of positions at Bastyr in his 14 years with the institution, including senior counsel, director of planning and special programs, vice-president for external affairs, and vice-president for finance and administration. “Sandi was a brilliant strategic and tactical thinker who helped everyone in the University be more thoughtful and effective,” wrote Dr. Pizzorno.

Along with former Bastyr President Thomas Shepherd, DHA, Cutler was involved in the successful efforts to establish licensure for naturopathic physicians in California in 2003. He also worked with Dr. Shepherd at Ross Medical School in New Jersey following Dr. Shepherd’s resignation from Bastyr.

After Cutler left Bastyr in 2005, he maintained a professional interest in public policy concerning alternative and complementary healthcare, which was manifested by serving as board president and executive director of Citizens for Health, a consumer natural health advocacy group, and by representing Bastyr University for the Campaign for Better Health.

“A quiet person with loud influence, Sandi was an invaluable member of the Board of Directors at Citizens for Health as we navigated the challenges to DSHEA [Dietary Supplement Health and Education Act of 1994] implementation, organic regulations, and a myriad of issues around access, choice, and information in natural health,” wrote Susan Haeger, former president and CEO of Citizens for Health (email, October 11, 2014). “Sandi could always be counted on to think through knotty problems and find elegant solutions. A trusted friend, he was always ready for mischief-making and could be counted on to find humor and heart in the drama of life.”

In 2012, Cutler joined the nonprofit organization Solid Ground as its chief operations and strategy officer, a position he held until the time of his death. Solid Ground is an...
advocacy group that addresses homelessness, poverty, and inequality in Washington state’s King County. “[Cutler] was at heart a gifted community organizer who believed that it was a successful day only if he had helped make the world a better place,” wrote Mike Buchman, communications director at Solid Ground.1

“I was struck by how often ‘best friend,’ ‘trusted adviser,’ [and] ‘trustworthy’ came up,” Dr. Pizzorno wrote of the remembrances of Cutler by friends and colleagues. “He was remarkable in establishing relationships with an incredible diversity of individuals and organizations.”

“Sandi Cutler was one of the most complex persons I have ever known and the gift of that complexity was his ability to reach out and touch so many different people,” wrote Peggy Brevoort, a member of the board of directors of Bastyr University and board of trustees of the American Botanical Council. “No matter how you knew Sandi, you would always be assured that you could sit and have a wonderful personal conversation and oftentimes find that the ideas flowing from that conversation would manifest for you and him in ways neither one of you had imagined.”

Cutler is survived by his wife, Janna Rome, MS, LAc, and sons Geoff, Josh, Danny, and Abe. Bastyr University held a memorial service to celebrate his life on July 27, 2014, at the campus chapel.

—Hannah Bauman

Reference
American Herb Association Quarterly Newsletter: $20/yr. AHA, P.O. Box 1673, Nevada City, CA 95969.

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


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The hoodia plant is a spiny, cactus-like succulent that thrives in dry, desert conditions. The flower emits a strong odor reminiscent of rotting meat and as a result, it is pollinated by flies rather than bees. Native to southern Africa, hoodia has had a controversial history of use in Western medicine. Its traditional use as an appetite suppressant among the San people in the Kalahari Desert drew attention from researchers and pharmaceutical companies. Hoodia was marketed as a weight-loss supplement with few side effects, causing a large market demand and dramatic price increases. As a result, the harvest and export of plants in the genus *Hoodia* is highly regulated, and some supplements claiming to contain hoodia have been determined to be adulterated with other plant material or to contain no hoodia at all. Currently, there is little scientific evidence for the efficacy of hoodia in humans, and side effects may include possible liver damage, potentially dangerous changes in blood pressure, vomiting, and headaches. Commercial drug rights were obtained first by Pfizer and then by Unilever, which researched the herb for possible use as a dietary or food ingredient, but both companies terminated their research and development efforts and returned the rights after safety and efficacy could not be sufficiently established.

References
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