

HerbalGram 130 • May – July 2021 Redouté Botanical Illustrations • Indena Celebrates 100 Years • Elder Berry Adulteration
Artichoke Herb Profile • Colchicine & COVID-19 • CBD Dosage & Efficacy Review

HERBALGRAM

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Ruby walks amid towering Mullein stalks during the harvest on our Certified Organic farms in southern Oregon.



dear reader

Our cover story by *HerbalGram* Assistant Editor Connor Yearsley focuses on the life and beautiful artistry of Pierre-Joseph Redouté (1759–1840), who was born in present-day Belgium and is widely considered one of the greatest botanical artists of all time. In the first half of the 19th century, his paintings and copper stipple engravings were commissioned by royalty and the social and political elites of France. This article is part of ABC's ongoing commitment to share the beauty, morphology, color, and diversity of edible, medicinal, and aromatic plants — in this case, through botanical artwork, which historically was meant to advance science as well as exude beauty. *HerbalGram* thanks Cologne, Germany-based art book publisher Taschen for providing the beautiful engravings featured in this issue.

The popular cold and flu herb elder berry (often written as “elderberry”) has been one of the five top-selling botanical dietary supplements in mainstream US retail outlets since 2018. During the COVID-19 pandemic, consumers purchased elder berry supplements at significantly increased levels. In April 2020, we predicted that increased demand for immunomodulating botanicals would create shortages of elder berry raw material, thereby increasing the possibility of adulterated “elder berry” entering the market. As part of the ABC-AHP-NCNPR Botanical Adulterants Prevention Program, we initiated a literature search for evidence of elder berry adulteration. Curiously, we found none in the peer-reviewed scientific literature.

In this issue, ABC Chief Science Officer Stefan Gafner, PhD, and 14 co-authors present an overview of elder berry science and compile the results of analyses at four industry in-house labs and four third-party analytical labs on a total of 532 raw materials, extracts, and finished products labeled as containing elder berry. Of these samples, 11% failed identity tests and were determined to be adulterated. This report, first published in March 2021 in ABC's digital newsletter *HerbalEGram*, is the first known peer-reviewed publication in the global scientific literature that documents the intentional adulteration of elder berry.

Indena, the Milan, Italy-based producer of chemically standardized medicinal plant extracts, founded in 1921, is the subject of an extensive article by frequent contributor Karen Raterman as part of our occasional Legacy Herb Companies series. Our heartfelt congratulations to the Della Beffa family and their entire staff on Indena's 100th anniversary! (Previous articles in the Legacy Herb Companies series have profiled Indiana Botanic Gardens, Eu Yan Sang, Dr. Willmar Schwabe, and Thayers Natural Remedies.)

Our herb profile in this issue explores a popular food, artichoke, and is another excellent example of “food as medicine,” as is frequently documented in our *HerbalEGram* series. Profound gratitude goes to longtime contributor Josef Brinckmann and co-author Marisa Williams, ND, at Traditional Medicinals.

On April 21, the eve of the 51st Earth Day, ABC announced that it has contracted with an international executive search firm to seek talented and qualified candidates for the position of ABC Executive Director. I am deeply grateful for the many comments we have received since then supporting this strategic move, which intends to help strengthen ABC for future growth and continued delivery of our unique nonprofit research and educational mission, publications, and programs. We are looking forward to working with a dynamic new leader.

And, to be clear, I intend to stay with ABC for many years, working with the new executive director, ABC staff, the ABC Board of Trustees, Advisory Board members, and others, to continue the compelling work we started here more than 33 years ago. The ABC Trustees and leadership team have long recognized that sooner or later, ABC would need a Success(ion) Plan to be able to continue to flourish as a nonprofit organization. As I approach the age of 75 this year, we are preparing for ABC's next chapter. Working with the new leader, I will continue to be actively involved in research, education, editorial content, development, community relations, collaborations, and planning for ABC's bright future. HG

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American Botanical Council

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50 Radiant Redouté: Botanical Artwork of ‘the Raphael of Flowers’

By Connor Yearsley

Born in present-day Belgium, Pierre-Joseph Redouté (1759–1840) is widely considered one of the greatest botanical artists ever. He produced more than 2,000 paintings of more than 1,800 plant species, many of which were published in volumes as copper stipple engravings. In 1782, Redouté arrived in Paris, where he began designing stage scenery and depicting plants at the *Jardin du Roi*. Eventually, due to his skill and personality, he gained influential patrons, including Queen Marie Antoinette and Empress Joséphine Bonaparte. Napoleon even used some of Redouté’s work as official diplomatic gifts. In 2019, art book publisher Taschen published *Pierre-Joseph Redouté: The Book of Flowers*, which includes a large sample of engravings of Redouté’s paintings and provides a glimpse into a bygone Paris. This feature article includes 11 engravings from Taschen’s beautiful 608-page book. *HerbalGram* is grateful to Taschen for generously providing these historical botanical prints.



Dentelure bleu-ciel.
P. J. Redouté

Plumbago auriculata
Choix

Leadwort (*Plumbago auriculata*) engraving from Redouté’s *Choix* (1827–1833). Courtesy of Taschen, Cologne.

66 Indena Centennial: Finding Quality in Nature and Science

By Karen Raterman

As part of ABC’s “Legacy Herb Companies” series, guest contributor Karen Raterman reports on the 100th anniversary of Milan, Italy-based Indena SpA. The company credits its longevity to its family-owned model, a deep respect for the link between nature and science, and its forward-thinking strategies. Since 1921, Indena has weathered war, economic crises, and leaps in technological advances and remains a thriving manufacturer of natural products. The company’s product catalog emphasizes scientific rigor, safety, and efficacy, which includes control over the supply chain from seed to shelf. Indena representatives say that their focus on sustainability is beneficial for both the company and the health of the planet.

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Perilla (*Perilla frutescens* var. *crispa*, Lamiaceae)



On the Cover
Autumn crocus (*Colchicum autumnale*)
engraving from Redouté's *Les Liliacées*
(1802–1815). Courtesy of Taschen, Cologne.

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Artichoke *Cynara cardunculus*
Photo ©2021 Matthew Magruder

Artichoke

Cynara cardunculus (syn. *C. scolymus*)

Family: Asteraceae

By Josef Brinckmann and Marisa Williams, ND

INTRODUCTION

A member of the daisy family (Asteraceae), the genus *Cynara* is small, and the classification of species in this genus continues to evolve. In the 18th and 19th centuries, it was believed that there were three *Cynara* species.¹ In a 1992 study, a taxonomic revision of the genus proposed the recognition of eight *Cynara* species and four subspecies.² Presently, the *Plants of the World Online* (POWO) database of the Royal Botanic Gardens, Kew, includes 10 accepted *Cynara* species.³ Although much of the literature has treated *C. cardunculus* and *C. scolymus* as separate species, the latter is now considered a synonym of *C. cardunculus*.³ *Cynara cardunculus* is a species complex that contains three taxa: globe artichoke (var. *scolymus*), cultivated or leafy cardoon (var. *altilis*), and wild perennial cardoon (var. *sylvestris*),⁴ the latter believed to be the wild progenitor of both varieties *altilis* and *scolymus*.^{5,6}

There are also two accepted subspecies, *C. cardunculus* subsp. *flavescens* and *C. cardunculus* subsp. *zingaroensis*.³ The Jerusalem artichoke (*Helianthus tuberosus*, Asteraceae), native to parts of Canada and the United States, should not be confused with artichoke or cardoon and is outside the scope of this article.

Cynara cardunculus is a perennial plant with a rosette of large pinnate leaves that are green above, white below, and strongly veined. From the second year of growth, large flowerheads of tubular purple flowers bloom on branched stalks. The fleshy floral receptacle at the base of the inflorescence bracts is edible and constitutes the popular food item known as artichoke heart.⁷ This article focuses mainly on the medicinally used substances from this plant, including “*Cynarae folium*,” described in the *European Pharmacopoeia* as the whole or cut dried leaf of *Cynara cardunculus* (syn. *C. scolymus*), containing minimum 0.7% chlorogenic acid,⁸ and

“Cynarae flos,” defined in the *Pharmacopée Africaine* as the fresh lower part of the capitula (involucral bracts [leaf-like bracts that surround the base of a capitulum] and receptacle), containing minimum 0.1% cynarin.⁹

The native range of *C. cardunculus* lies within Mediterranean southern Europe (Portugal, Spain, France, Italy, and the Western Balkans), the Balearic Islands of Spain, parts of Macaronesia (i.e., Canary Islands of Spain and Madeira archipelago of Portugal), and northern Africa (Morocco, Algeria, Tunisia, and Libya).³ The subspecies *flavescens* is native to much of the same range, while the subspecies *zingaroensis* is native to Sicily.³ Recent research suggests that the center of origin of *C. cardunculus* is likely southern Italy and probably the island of Sicily.⁶ Evidence also suggests that the globe artichoke (var. *scolymus*) was domesticated in Sicily about 2,000 years ago,¹⁰ although the first known attempts at selective breeding reportedly took place in Italian monastery gardens in the 15th century.¹¹

Recently, several European regulations have been enacted for market promotion of distinct artichoke ecotypes (genetically distinct subpopulations that are especially adapted to particular environmental conditions) with protected geographical indication (PGI) or protected designation of origin (PDO) specifications. For example, in Italy, *Carciofo Spinoso di Sardegna*, of the local *Spinoso Sardo* ecotype, is a PDO with specifications for its physical and chemical characteristics, organoleptic properties, and specific production steps that must occur in a defined geographical area, among other requirements.¹² In Spain, *Alcachofa de Benicarló* of the globe artichoke variety *Blanca de Tudela* has a PGI designation and is grown in specified municipalities near the coastal region of Baix Maestrat, Castellón province, Comunidad Valenciana.¹³ Outside of its native range, *C. cardunculus* is an invasive species (e.g., in South America, Oceania, and the western United States), releasing allelochemicals into the environment that inhibit germination or growth of potentially competitive native plants in the invaded range.¹⁴

The main countries for production of the immature flowers (buds) of *C. cardunculus* for the fresh food trade in terms of hectares harvested in 2019, in order of predominance, were Italy, Egypt, Spain, China, Peru, Algeria, France, Argentina, Tunisia, Turkey, Morocco, and the United States.¹⁵ The 2019 global export trade of the fresh flower buds for food use was dominated by six countries: Spain, Egypt, France, Tunisia, Italy, and the United States.¹⁶ However, the supply of artichoke leaf for medicinal use comes mainly from cultivation in European countries, namely Italy,^{17,18} France,¹⁹ Germany,²⁰ Poland,²¹ Portugal,²² Romania,^{23,24} Serbia,²⁵ and the United Kingdom.²⁶ While there are about 300 varieties of *C. cardunculus* worldwide, mostly originating from Italy, France, and Spain,¹¹ some registered cultivars are used specifically for medicinal artichoke cultivation in Europe including *Saluschocke*®, bred by SALUS Haus (Bruckmühl, Germany), *Cynamed*™, owned by Martin Bauer GmbH (Vestenbergsgreuth, Germany), and *Green Globe* and *Imperial Star*, both marketed by N.L. Chrestensen (Erfurt, Germany) and *Pharmasaat* (Artern, Germany),²⁷ among others.

In a 2014 survey of 2,359 adult consumers from Finland, Germany, Italy, Romania, Spain, and the United Kingdom, artichoke supplements ranked as the third most frequently used herbal food supplement product overall. In Spain, artichoke ranked first, and in Germany, second.^{28,29} In the United States, for reasons that are not totally clear, artichoke herbal supplement sales are relatively low, and artichoke supplements have not been listed among the 20 top-selling herbal dietary supplements in the natural health food or mainstream retail channels since at least the early 2000s, according to annual *HerbalGram* Herb Market Reports.^{30–33}

HISTORY AND CULTURAL SIGNIFICANCE

Pictorial images of artichoke on temple walls and tombs of pharaohs demonstrate its use and importance in ancient Egypt.¹¹ Greek medical botanist Pedanius Dioscorides (ca. 40–ca. 90 CE), in his *De Materia Medica*, described the use of the root as a deodorant and also to benefit stomach, liver, bladder, and kidney health.¹ The genus name *Cynara* comes from the Greek Κύναρρα, meaning “artichoke.”³⁴ The English common name artichoke stems from the Arabic *ḥarṣuf*, which led to *alcachofa* in Spanish, *artichaut* in French, and *articiocco* in Italian, from which the name *Articoca* was first used in 1542 by German botanist Leonhart Fuchs (1501–1566), afterwards named *Artischock* by Dutch physician Gemma Frisius (1508–1555).³⁵ The Syriac word *‘akkūbā*, referring to *C. cardunculus*, can best be translated as “cardo,” comparable to the Jewish Aramaic *‘akkōbītā*, meaning “a thistle sting” and Arabic *‘akkūb*, meaning “globe-thistle.”³⁶

In his 1737 work *Genera Plantarum*, Swedish botanist Carl Linnaeus (1707–1778) assigned the genus name *Cynara*,³⁷ and in his 1753 work *Species Plantarum*, he described three species: *C. cardunculus* with habitat stated as Crete, *C. humilis* with habitat of Tingatano (present-day northern Morocco) and Baetica (present-day Andalusia, southern peninsular Spain), and *C. scolymus* with habitat of Italy (in particular Sicily) and Gallia Narbonensis (Gaul of Narbonne),³⁸ which today encompasses the regions of Languedoc and Provence in southern France. Linnaeus described three varieties of *C. scolymus* and listed *C. cardunculus* as a distinct species derived from one parent and not a hybrid.³⁹

A 2004 ethnopharmacognostic survey on remedies used in central Lucania in southern Italy reported that aerial parts of wild *C. cardunculus* are decocted together with aerial parts of dog figwort (*Scrophularia canina*, Scrophulariaceae) and creeping cinquefoil (*Potentilla reptans*, Rosaceae) as an anti-rheumatic preparation and applied as a compress.⁴⁰ In a 2000 ethnobotanical survey of medicinal plants grown in home gardens in Catalonia, Spain, 14% of respondents reported using *C. cardunculus* (plant part and mode of administration not reported) as an abortive, and 5% reported using *C. scolymus* as a hepatoprotective.⁴¹ Published in 2012, another ethnobotanical survey in Salamanca province, Spain, that looked at remedies used

against witches and the “evil eye,” described traditional cheese-making by curdling milk with artichoke flowers and lamb rennet. However, if the milk did not set properly, this was attributed to having made contact with the evil eye of a witch in the village. To remedy this, the cheese-maker would smoke the milk by burning the flowering aerial parts of mastic thyme (*Thymus mastichina*, Lamiaceae) and *Magydaris panicifolia* (Apiaceae) with a few drops of olive (*Olea europaea*, Oleaceae) fruit oil.⁴²

In Greek folk medicine, the pulverized fresh leaves of *C. cardunculus*, covered with olive oil, are applied topically to relieve infant teething pain.⁴³ The flowers are also processed into a vegetal rennet for cheese making in several regions.⁴ For example *Djben*, a traditional fresh cheese, is made in Algeria with the raw milk of ewe, cow, or goat, coagulated with dried flowers of wild *C. cardunculus* without the use of starter culture.⁴⁴ *Djben* may be made by macerating the flowers of different species (*C. cardunculus*, *C. cardunculus* var. *scolymus*, or *C. humilis*) in different milks, depending on which is available in different regions of the Maghreb countries (Algeria, Libya, Mauritania, Morocco, Tunisia) and Western Sahara, where this cheese is a specialty.⁴⁵

In the early 20th century, the Sicily-born Mafioso Ciro “The Artichoke King” Terranova (1888–1938) ran an artichoke extortion racket in New York City, pocketing an estimated \$1 million annually through the monopoly.⁴⁶ In December 1935, New York City Mayor Fiorello La Guardia (1882–1947) went to the Bronx Terminal Market and, as a tactic to break up the Mafia monopoly, issued an emergency proclamation prohibiting the sale, display, and possession of artichokes in all public places until it was possible to purchase artichokes freely without unlawful restraint, restriction or racketeering, coercion, or duress. Three days after the mayor’s proclamation, the baby artichoke extortion racket was broken up, and the ban was lifted.⁴⁷ In 1948, at the age of 22, Marilyn Monroe (1926–1962) was selected as the inaugural “Artichoke Queen” in Castroville, California, the location of the first artichoke cultivation in the United States and annual Artichoke Festival.⁴⁸

In 1985, a monograph for “Flos Cynarae scolymus” entered volume one of the first edition of *Pharmacopée Africaine*, including tests for identification, composition, purity, and strength, and indicated its use for treating hepatic and renal dysfunctions, as a diuretic, and for arteriosclerosis.⁹ The German Commission E published a positive therapeutic monograph for “Cynarae folium” (*Artischockenblätter*) in 1988 (revised in 1990), in the form of cut, dried leaf, fresh-pressed plant juice, or other galenical preparations, indicated for use as a choleric (promoting bile secretion) drug for dyspeptic problems.⁴⁹

The World Health Organization (WHO) published a “Cynarae folium” monograph in 2009, in volume four of the *WHO Monographs on Selected Medicinal Plants*, listing medical uses supported by clinical data including treatment of digestive complaints (e.g., dyspepsia, feeling of fullness, flatulence, nausea, stomach ache, and vomiting) and adjunct treatment of mild to moderate hyper-

cholesterolemia.⁵⁰ In 2011, and in its 2018 revision, the European Medicines Agency (EMA) published a labeling standards monograph for artichoke that superseded the German Commission E monograph for purposes of product marketing authorization in the European Union (EU).⁵¹ In Canada, a labeling standards monograph for licensed artichoke Natural Health Products (NHPs) was published in 2008 and revised in 2018.⁵² A quality monograph for the dried leaf was first published in the fifth supplement to the fifth edition of the *European Pharmacopoeia* (PhEur 5.5) in 2006.⁵³ A corresponding monograph for the dry extract of artichoke leaf was admitted to PhEur 6.3 in 2009.⁵⁴

In 2010, the European Food Safety Authority (EFSA) issued an opinion that a cause-and-effect relationship had not been established between the consumption of artichoke leaf or extract and a beneficial physiological effect related to an increase in renal water elimination (diuresis).⁵⁵ In the same year, EFSA issued an opinion on proposed antioxidant health claims for dried artichoke leaf that no evidence had been provided to establish that having antioxidant activity/content and/or antioxidant properties is a beneficial physiological effect.⁵⁶ In 2014, the German Federal Office of Consumer Protection and Food Safety (BVL) assessed and classified artichoke leaf as “not novel in food supplements,” but also as a medicinal plant on List B, meaning that restricted use in foods is recommended because pharmacological effects occur at or above the known therapeutic use dosage level.⁵⁷

CURRENT AUTHORIZED USES IN COSMETICS, FOODS, AND MEDICINES

In the United States, artichoke leaf and extracts may be used in dietary supplements, which require Food and Drug Administration (FDA) notification within 30 days of marketing if a structure-function claim is made and product manufacturing that adheres to current Good Manufacturing Practices (cGMPs).⁵⁸ The leaves are also classified as Generally Recognized as Safe (GRAS) by the FDA, but specifically for use as a natural flavoring substance in alcoholic beverages only.⁵⁹

In Canada, the dried leaf is regulated as an active ingredient of licensed NHPs, which require pre-marketing authorization from the Natural and Non-prescription Health Products Directorate (NNHPD). Licensed NHPs prepared from pharmacopoeial quality artichoke leaf may be labeled and marketed for uses including to help relieve digestive upset, such as indigestion, and as a choleric to help increase bile flow, in dosage forms including dried leaf powder and non-standardized extracts (e.g., fluidextract, herbal tea decoction or infusion, tincture, or dry extract).⁵²

In the EU, preparations of artichoke leaf may be used as an active ingredient of registered traditional herbal medicinal products (THMPs) labeled with the therapeutic indication “for the symptomatic relief of digestive disorders such as dyspepsia with a sensation of fullness, bloating and flatulence.” For this use, the artichoke leaf may be prepared in the forms of: (a) cut dried leaves for herbal tea, (b) powdered

dried leaves, (c) aqueous dry extract of dried leaves (drug-to-extract ratio [DER] range 2-7.5:1), (d) aqueous dry extract of fresh leaves (DER 15-35:1), (e) aqueous soft extract of fresh leaves (DER 15-30:1), or (f) ethanol (20% VV) soft extract of dried leaves (DER 2.5-3.5:1).

The dried leaf used for production of registered THMPs must conform to the quality standards monographs of the *European Pharmacopoeia* (*Cynarae folium* PhEur or *Cynarae folii extractum siccum* PhEur).⁸ Furthermore, use of an extract of the leaves in cosmetic products is authorized in the EU specifically for skin-conditioning function.⁶⁰ New potential uses for extracts of the leaves as an “active” component of food packaging to help increase shelf life have been proposed recently.⁴

MODERN RESEARCH

Artichoke leaf preparations have a longstanding use as a traditional medicine for digestive disturbances (e.g., dyspepsia), as a choleric, and for their lipid-lowering, hepatoprotective, antioxidant, diuretic, and anti-atherogenic effects.^{9,49-52,61-63} These health benefits have been reported in multiple studies, including animal models, pre-clinical, phytochemical, laboratory, and human clinical studies.

Artichoke leaf's antioxidant properties and characteristic lipid-lowering and hepatoprotective activities have been attributed to mono- and dicaffeoylquinic acids (cynarin and chlorogenic acid), caffeic acid, sesquiterpene lactones, and flavonoids (including the glycosides luteolin-7-*O*-rutinoside, luteolin-7-*O*-glucoside, and luteolin-4-*O*-glucoside).⁶⁴⁻⁶⁶ Other constituents in the phytochemical profile include phytosterols, tannins, glycolic and glyceric acids, sugars, inulins, and enzymes.⁶⁷ The natural bitter taste of artichoke leaf is attributed to cynaropicrin, a sesquiterpene lactone.^{66,68} This profile is focused on the artichoke leaf (*Cynara folium*), but the high-inulin profile of other *Cynara* plant parts, mostly the inflorescence and external bracts, is also noteworthy. Currently, inulin is researched for its benefits as a prebiotic, which may promote beneficial bacteria found in the gastrointestinal system.^{69,70}

Specifically, recent human clinical trials of artichoke preparations have documented health benefits associated with artichoke's lipid-lowering effects,⁷¹⁻⁷⁴ hepatoprotective effects,⁶⁴ and improvement of gastrointestinal symptoms related to functional dyspepsia^{75,76} and irritable bowel syndrome (IBS).^{77,78} Table 1 summarizes selected clinical studies and the effects of artichoke preparations on these health states.



Artichoke *Cynara cardunculus*
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Table 1. Selected Clinical Trials with Preparations of Artichoke in Chronological Order since 2000

Publication	Study Design	Interventions	Outcome
Englisch et al (2000) ⁷¹	DB-RCT, PC, multi-center, N = 143, 18-70 years of age with hyperlipoproteinemia	Artichoke dry aqueous extract of fresh leaves ^a (each coated tablet contained 450 mg extract; drug-to-extract ratio (DER) range 25-35:1, fresh weight), 1,800 mg per day (2 tablets in the morning and 2 tablets in the evening before meals) for 6 weeks, or placebo	Significant decrease of total cholesterol and LDL-C in the treatment group compared to placebo. Safety review showed 28 adverse events (AEs) with 26 of those mild changes in lab values; authors concluded AEs "unlikely" from the investigational product
Walker et al (2001) ⁷²	R, open-label post-marketing surveillance, N = 279, subgroup reported non-specific gastrointestinal complaints or dyspeptic syndrome (3 out of 5 Rome II criteria met for IBS symptoms)	Artichoke leaf dry aqueous extract ^b (each 400-mg capsule contained 320 mg extract; average native extract DER 4.5:1, dry weight), 2 capsules 3 times a day with meals for 6 weeks	In the treatment group compared to placebo, there was a significant reduction of IBS symptoms reported in individuals with dyspeptic syndrome. Mild AEs reported in the study suggested artichoke leaf extract (ALE) was well tolerated
Holtmann et al (2003) ⁷⁵	DB-RCT, PC, N = 247, 18-75 years of age with diagnosed functional dyspepsia	Artichoke leaf dry aqueous extract ^b (each 400-mg capsule contained 320 mg extract; DER range 3.8-5.5:1, dry weight), 2 capsules 3 times a day for 6 weeks, or placebo	Treatment group showed improved quality of life (QOL) assessed by Nepean Dyspepsia Index (NDI) compared to the placebo group. Authors classified AEs as mild or moderate that resolved by end of the study (45 AEs in 29 patients treated with ALE compared with 25 AEs in 18 placebo patients)
Bundy et al (2004) ⁷⁸	R, open study, N = 208, healthy adults experiencing dyspepsia	Artichoke leaf dry aqueous extract ^c (each 400-mg capsule contained 320 mg extract; DER 5:1, dry weight), 320 mg (1 capsule) or 640 mg (2 capsules) daily for 2 months	After ALE treatment, IBS symptoms incidence significantly decreased by 26.4% ($P < 0.001$) and significant improvement by 20% in the NDI total QOL score
Bundy et al (2008) ⁷²	DB-RCT, PC, N = 131, adults with mild to moderate hypercholesterolemia	Artichoke leaf dry aqueous extract ^c (each 400-mg capsule contained 320 mg extract; DER range 4-6:1, dry weight), 4 capsules/day (1,280 mg/day) for 12 weeks, or placebo	In the treatment group, plasma total cholesterol decreased by an average of 4.2% and increased in control group by an average of 1.9%, no significant differences for LDL-C, HDL-C, or triglyceride levels
Rondanelli et al (2013) ⁷³	DB-RCT, PC, N = 92, adults with primary mild hypercholesterolemia	Artichoke leaf dry extract ^d (each film-coated tablet contained 250 mg extract standardized to > 20% caffeoylquinic acids, > 5% flavonoids, and > 5% cynaropicrin), 2 daily oral doses for 8 weeks (before lunch and dinner), or placebo	In the treatment group, significant increase of HDL-C and decrease in LDL-C and total cholesterol. No AEs reported
Panahi et al (2018) ⁶⁴	Pilot, DB-RCT, PC, parallel-group, N = 100, adults with ultrasound-diagnosed nonalcoholic fatty liver disease (NAFLD)	Artichoke leaf dry extract ^e (each coated tablet contained 200 mg extract standardized to contain minimum of 2 mg cynarin), 600 mg daily in 3 divided doses for 2 months, or placebo	In the treatment group, Doppler sonography showed increased hepatic vein flow ($P < .001$), reduced portal vein diameter ($P < .001$) and liver size reduction ($P < .001$), reduction in serum alanine aminotransferase (ALT) ($P < .001$) and aspartate aminotransferase (AST) ($P < .001$) levels, 90 patients completed study. No AEs reported
Gatmiri et al (2019) ⁷⁴	DB-RCT, PC, N = 38, adults with chronic kidney disease with hypercholesterolemia	Artichoke leaf dry extract ^f (each capsule contained 320 mg extract; composition of extract not disclosed), 2 times daily for 6 weeks, or placebo	Significant decreases in mean total cholesterol and LDL-C, significant difference in appetite, no significant difference in HDL-C and triglycerides. No AEs related to treatment
Rondanelli et al (2020) ⁸⁵	DB-RCT, PC, N = 54, overweight adults, aged 45-55 years of age, with newly diagnosed impaired fasting glucose	Artichoke leaf dry extract ^g (each tablet contained 500 mg extract standardized to $\geq 5\%$ caffeoylquinic acids, $\geq 1.5\%$ flavonoids, and $\geq 1\%$ cynaropicrin), 2 daily oral doses (before lunch and dinner) for 8 weeks, or placebo	ALE treatment group showed improvement on metabolic parameters in impaired fasting glucose individuals. No AEs reported

AE = adverse event; ALE = artichoke leaf extract; DB = double blind; PC = placebo controlled; R = randomized; RCT = randomized controlled trial

^a CY450 extract, tradename: Valverde Artischocke bei Verdauungsbeschwerden, manufactured by aar-Pharma (Remscheid, Germany), marketed by Novartis Consumer Health GmbH (Munich, Germany)

^b Hepar-SL[®] forte (Sertürner Arzneimittel GmbH; Gütersloh/Berlin, Germany)

^c Cynara[™] (Lichtwer Pharma UK Ltd.; Marlow, UK)

^d 250 mg standardized extract in film-coated tablets produced by Indena S.p.A. (Milan, Italy)

^e Cynarol[®] Tablet (Nia Pharmaceutica; Gorgan, Iran)

^f 320 mg undefined extract in capsules

^g 500 mg standardized extract in film-coated tablets produced by Indena S.p.A. (Milan, Italy)

Notes on investigational products of Sertürner and Lichtwer: At the time of these studies, Sertürner was a subsidiary of Lichtwer. In 2004, 3i Group (London, UK) acquired Lichtwer and its subsidiary Sertürner. In 2006, 3i Group sold Lichtwer and Sertürner to MCM Klosterfrau Vertriebsgesellschaft mbH (Cologne, Germany). Klosterfrau Healthcare Group is now the marketer of Hepar-SL[®] forte.

Multiple meta-analyses and systematic reviews have assessed the effects of artichoke preparations on cardiovascular health and related parameters. Sahebkar et al (2018)⁷⁹ performed a meta-analysis and systemic review on the effects of artichoke leaf extract (ALE) on human lipid profiles. From the total of nine trials reviewed and 702 subjects, Sahebkar et al reported significant decreases in total cholesterol and low-density lipoprotein-cholesterol (LDL-C) levels in those taking ALE. No significant effects were reported for triglycerides and high-density lipoprotein-cholesterol (HDL-C) levels. The reviewed studies showed differing dosage levels, durations of treatment, and standardization of the extracts.

A systematic review and dose-response meta-analysis of clinical trials by Hemati et al (2021)⁸⁰ found that artichoke supplementation decreased waist circumference. The data sets, however, did not show significant changes in body weight or body mass index (BMI), with the exception of hypertensive patients in a subgroup analysis that showed significant body weight reduction. Panahi et al (2018)⁶⁴ studied the effects of ALE supplementation on non-alcoholic fatty liver disease and found that both BMI and waist circumference were reduced significantly in the ALE group compared to placebo. Jalili et al (2020)⁸¹ conducted a systematic review and meta-analysis of nine randomized controlled trials (RCTs) and reported that artichoke supplementation correlated with significantly decreased fasting blood sugar.

The results of several studies suggest that artichoke leaf may help decrease gastrointestinal symptoms and improve quality of life in individuals with functional dyspepsia and IBS.^{75,77,78,82,83} Yoon et al (2011)⁸³ and Rahimi et al (2012)⁸² both reviewed the same two studies of ALE for IBS management.

In a 2009 Cochrane systematic review, “Artichoke leaf extract for treating hypercholesterolaemia,” the authors concluded that only mild, transient, and infrequent adverse events (AEs) have been reported for short-term use of ALE.⁸⁴ Authoritative herbal monographs include cautions and contraindications associated with artichoke leaf preparations for individuals with hypersensitivity to the Asteraceae plant family and individuals with hepatobiliary diseases.^{49-52,61-63}

ADULTERATION

According to a 2012 survey of herbalists working in Marrakesh, Morocco, the roots of *Kherchouf* (*C. cardunculus*) are fairly commonly confused in the market with roots of *Tasskra* (*Echinops spinosissimus* subsp. *fontqueri*, Asteraceae).⁸⁶ Artichoke leaf is found as an ingredient of certain types of food supplement products known to be adulteration targets (e.g., weightloss products), and deliberate substitution of other lower-cost ingredients or misidentification of other *Cynara* species is possible. Accordingly, a molecular approach based on real-time polymerase chain reaction (PCR) coupled to high-resolution melting (HRM) analysis was developed for rapid differentiation of *Cynara*

species (*C. cardunculus*, *C. cardunculus* var. *scolymus*, *C. humilis*, and *C. syriaca*) that could be applied to the analysis of commercial products for authentication.⁸⁷

Another study suggested that quantifying the variation in phenolic compounds in artichokes, relative to genetic and environmental factors, could also allow for authentication.⁸⁸ In a study of herbal medicinal products labeled as containing ALE, 7.7% of tested samples (2 of 26) varied significantly from the reference product (i.e., they did not contain the marker chlorogenic acid, and the chromatograms also suggested the presence of synthetic drug substances). The results were inconclusive due to a lack of standards for identifying the synthetic drugs that could be used as adulterants in artichoke extract products.⁸⁹

SUSTAINABILITY AND FUTURE OUTLOOK

The International Union for Conservation of Nature (IUCN) *European Red List of Medicinal Plants* assigns *C. cardunculus* to the conservation category of least concern (LC), meaning that it is not threatened overall in Europe.⁹⁰ However, the species is classified as vulnerable in France.⁹¹ And while this species is not listed in the *Red Book of Italy*,⁹² *C. cardunculus* subsp. *zingaroensis* has been classified as regionally vulnerable in Sicily.⁹³ North Tunisian germplasm of *C. cardunculus* var. *sylvestris* has reportedly been damaged by significant genetic erosion, pollution, urbanization, and poor farming practices.⁵ The main *C. cardunculus* germplasm collections are located in Italy, France, and Spain. However, the expansion of commercial cultivation of single uniform varieties has led to a reduction in diversity. In Italy and France, only a few varieties are cultivated over large areas. And, in Spain, a single ecotype, *Blanca de Tudela*, accounts for 90% of production.¹⁰ Genetic variation analysis of cultivated *Cynara* species and their wild relatives is important for biodiversity conservation, especially with regard to food security,⁹⁴ as the artichoke reportedly ranks as the fourth most important food crop in Europe.¹⁰ *Cynara tournefortii* is classified as a vulnerable species in Portugal,⁹⁵ extremely rare in Morocco,⁹⁶ and critically endangered in Spain.⁹⁷ *Cynara baetica* is extremely rare in Morocco⁹⁶ and vulnerable in Spain, and *C. algarbiensis* is listed as a vulnerable species in Spain.⁹⁷

A 2020 study suggested that *C. cardunculus* could become a model crop for climate change adaptation due to the species' ability to grow in dry and marginal lands.⁹⁸ Seed germination and seedling establishment of *C. cardunculus* typically are not negatively impacted by abiotic stresses (caused in plants by drought, flooding, extreme temperatures) that are further exacerbated by climate change. In a context of uncertainty for farmers due to climate change and environmental pollution, *C. cardunculus* appears to be a crop that can be grown on marginal lands that are predicted to be unsuitable for other crops, thus providing farmers with an economic crop to transition to in the future.⁹⁹ HG

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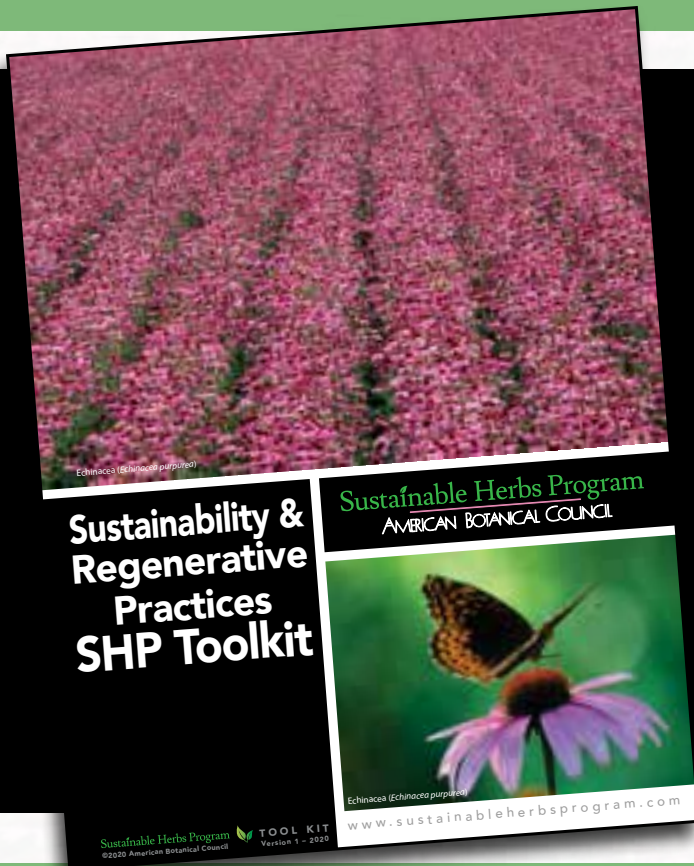
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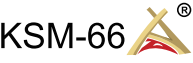
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	Lavender <i>Lavandula angustifolia</i>		Rough Horsetail <i>Equisetum hyemale</i>
	Pomegranate <i>Punica granatum</i>		Saw Palmetto <i>Serenoa repens</i>
	Ashwagandha <i>Withania somnifera</i>		Arnica <i>Arnica montana</i>
	Hibiscus <i>Hibiscus sabdariffa</i>		Coffee Fruit <i>Coffea spp.</i>
	Bacopa <i>Bacopa monnieri</i>		Guayusa <i>Ilex guayusa</i>
	Ginkgo <i>Ginkgo biloba</i>		Hops <i>Humulus lupulus</i>
	Kesum <i>Persicaria minor</i>		Birch <i>Betula spp.</i>
	Tongkat Ali <i>Eurycoma longifolia</i>		Olive <i>Olea europaea</i>
	Acerola <i>Malpighia spp.</i>		Grape <i>Vitis vinifera</i>
	Sceletium <i>Sceletium tortuosum</i>		Devil's Claw <i>Harpagophytum spp.</i>

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ABC Weathers Winter Storm Uri with Damage to Greenhouse and Gardens

By Hannah Bauman

On February 11, 2021, temperatures in Austin, Texas, dipped below freezing. It would remain at or below 32°F for the next 162 hours.¹ Cold weather records in the city were met or broken. Austin-Bergstrom International Airport recorded 6.4 inches of snow, the most in 72 years.² On February 15, the city recorded its first single-digit temperature in 30 years. The culprit of this frigid weather was Winter Storm Uri, which swept across the United States from February 12-16.

At least 111 people in Texas died as a result of the storm, which left 15 million homes without water and almost 4.5 million without power, often for multiple days. The arctic blast caused damages potentially in excess of \$125 billion, according to the *Texas Tribune*, which would make it the costliest disaster in the state's history.^{3,4}

At the American Botanical Council's (ABC's) 2.5-acre Case Mill Homestead, the loss of power and water had dire consequences for some of the infrastructure, and nothing could prepare the gardens for days of freezing weather and snow and ice.

"It made me nauseous," said Toby Bernal, ABC head gardener, upon seeing the gardens (oral communication, March 15, 2021). "It was not pretty. Everything was covered in ice. There was a crust over everything. You couldn't see any damage right off, because it was frozen. When I came back after, you could just tell that some things were automatically damaged."

ABC Education Coordinator Jenny Perez added that "things looked so traumatized" (oral communication, March 15, 2021).

Like many cities in Texas, Austin lacks winter infrastructure for snow and extreme temperatures. It has no plows and very little material for treating icy roads. The lack of preparedness and winterization of the state's power grid would make the winter storm even more deadly and destructive.⁵

On Monday, February 15, at 1 am, as electricity use peaked and power plants across the state were going offline because of the weather, the Electric Reliability Council of Texas (ERCOT) made the decision to initiate "rolling outages" to avert what it claimed would be a "catastrophic blackout."⁶ Before these emergency measures, the Texas electric grid was reportedly less than five minutes away from a cascading failure that could have left parts of Texas without power for months.⁷ Trouble compounded as frozen pipes burst, and the lack of power impeded the city's Ullrich Water Treatment Plant's ability to maintain water pressure and supply.

Many members of ABC's Austin-based staff lost water and power. "I live in an older Austin neighborhood just south of the river and early Monday, February 15, I woke up and thought it was colder than it should be in my house," wrote one ABC staff member (email, March 15, 2021). "Our power was out until 3 am Thursday. The temperature in my house during those 73 hours stayed between 34°F and 39°F the entire time." As soon



Damage at the Case Mill Homestead, ABC's headquarters, from the winter storm in February 2021. Photo ©2021 ABC

as the power came back, the city issued a boil-water notice. The staff member noted it was "a miserable experience." Other staff members had to melt snow to have water to flush toilets, including ABC Art Director Matthew Magruder.

"[That was] not how I expected to spend my 43rd birthday," he commented (email, March 17, 2021). "But in the times of COVID-19 and in the wake of 2020, you just never know."

ABC headquarters lost power for at least four days. An external pipe also burst. ABC Customer Service Coordinator Perry Sauls, who lives nearby, walked to the office, as the roads were too icy to drive, to turn off water to the property until the pipe could be fixed almost a week later. However, unlike many in the city who sustained extensive water damage, the main building of the homestead itself, with its recent renovations and well-insulated pipes, escaped unscathed.

Unfortunately, the organization's greenhouse and rainwater collection system sustained severe damage, which is still being assessed. The sub-freezing temperatures burst the system's pipes and damaged its pump system. "I've been in maintenance for over 25 years, and in some pretty hostile environments, like Alaska," said Bernal, "and I've never seen that before, where a solid iron pump broke. Even though we had set up a contingency plan, I don't think we ever [anticipated] losing power for four days."

Pipes also burst in the greenhouse. Bernal described them as "splintered." With no electricity to the computer-based control panel, the natural gas heating system did not turn on. As a result, ABC's collection of tropical plants, many of which were donated from the United States Botanic Garden in Washington, DC, and driven to Austin in the late 1990s, were subject to some decidedly un-temperate temperatures and were not watered during this time.

"We're not willing to say that [any of the plants are gone for good]," said Perez. "Absolutely not." The garden team has started carefully trimming back the plants and giving them seaweed fertilizer and water in small amounts, waiting to see what might show signs of life. The broken pipes have made

this more laborious than normal, as they must manually bring water into the greenhouse. This has not deterred the team, which, along with a few other staff members, continued to work onsite for three days before running water was restored to the house.

The Case Mill Homestead, which dates to an 1853 land grant, has been ABC's home since 1998. ABC has preserved the historic structure while making improvements and cultivating numerous gardens that showcase medicinal plants from around the world. These outdoor classrooms, the heart of the organization's physical headquarters and emblematic of its nonprofit research and education mission, face a long road to recovery. Rarely have this house and the surrounding gardens witnessed winter weather of this severity.

As the snow and ice thawed and power and water returned, the story of the winter storm became that of community interconnectedness. A concerned neighbor initially noted the burst pipe on ABC's property and attempted to help; he contacted ABC Finance Coordinator Cecelia Thompson and, eventually, Sauls was able to turn the water off. One staff member was able to take refuge at a friend's house after enduring no power in his apartment for almost 40 hours.

ABC Development Director Denise Meikel recalled how her neighbors banded together with their limited resources. "My neighbors across the street never lost power, so they took in my mother since my house was really too cold for her," she wrote (email, March 15, 2021). "It got to 39 degrees in my house, probably lower but I stopped checking. Almost everyone in Texas has these stories now, and it proved how much we all need each other. We gave food to people who hadn't stocked up. My friend, with her trusty special tool to turn off water at the water main by the street, helped six of her neighbors get their water turned off quickly once a pipe burst, reducing the amount of damage in their homes. There were tradespeople who live in my neighborhood working for free to help fix water pipes."

ABC Founder and Executive Director Mark Blumenthal said: "All of us here at ABC are grateful that we survived the storm, particularly those who were without power and had to endure near-freezing temperatures in their homes and apartments. Unfortunately, some of our fellow Austinites and other fellow Texans didn't fare so well. At least 111 Texans reportedly died in connection to the winter weather, through exposure, carbon monoxide poisoning, and other causes. We are truly sorry about their passing. With respect to ABC, we are hopeful that many of our plants will regenerate; if needed, we can replace them. But people obviously cannot be replaced."

Now, growth and repair seem more attainable. In the gardens, Perez sees reasons to be optimistic.

"I feel fortunate that we have ... some cuttings of plants that we aren't sure will make it. I feel a lot more hopeful, because I have seen in my own yard that there will be resilience." Though the extended freeze damaged many of the plants above ground, it did not last long enough to freeze the ground itself, and many



The tree on the left is *Tamarindus indica*. The large-leaved plant in the middle is *Anthurium cubense*, which was given to ABC by the United States Botanic Garden. The plant in front of the anthurium is *Murraya paniculata*. Photo ©2021 ABC

root systems are still intact. Plans are being discussed for new equipment and procedures for future freeze events, including the possibility of a back-up generator to help ensure that the greenhouse does not lose heat in the event of a power outage.

"I feel more hopeful than devastated," Perez concluded. "That's just how you have to be."

To donate to help rebuild the gardens, please visit <http://tinyurl.com/wvtaae8t>. All donations are gratefully appreciated. HG

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ABC-AHP-NCNPR Botanical Adulterants Prevention Program Marks 10 Years of Research and Education in the Botanical Ingredients Marketplace

Responsible herb industry members use BAPP publications to set ingredient specifications, authenticate ingredients, and detect and remove adulterated materials from supply chain

By ABC Staff

The ABC-AHP-NCNPR Botanical Adulterants Prevention Program (BAPP) recently announced the completion of its 10th year of research and educational activities in the international herb and medicinal plant communities.

In partnership with consortium members, BAPP was founded by the nonprofit American Botanical Council (ABC) in 2011 as a research and education program to assist members of the US and international botanical industry in authenticating botanical raw materials, extracts, and essential oils, as well as to detect adulteration by some suppliers. The ultimate goal of BAPP is to help ensure the authenticity of botanical ingredients in consumer products.

The BAPP partnership includes the nonprofit American Herbal Pharmacopoeia (AHP), an independent organization that produces high-quality herbal monographs for use by herb industry members, researchers, and regulators; and the National Center for Natural Products Research (NCNPR) at the University of Mississippi, a US Food and Drug Administration (FDA)-funded Center of Excellence for the analysis of botanical dietary ingredients and the development of appropriate laboratory methods for analyzing botanical ingredients and finished products.

As of April 2021, BAPP has published 65 extensively peer-reviewed documents, which are available for free on the BAPP homepage on the ABC website. BAPP documents include Botanical Adulterants Prevention Bulletins (BAPBs), Laboratory Guidance Documents (LGDs), the Botanical Adulterants Monitor e-newsletter, and various articles in ABC's peer-reviewed journal *HerbalGram*. In addition, BAPP representatives have authored or co-authored research papers in other peer-reviewed scientific journals and have participated in many speeches, webinars, and media interviews related to the global challenges associated with economically motivated (i.e., intentional) and accidental adulteration. BAPP publications are reviewed by numerous international experts in academia, industry, and government.

BAPP was founded by ABC Founder and Executive Director Mark Blumenthal, and its first publication was released in *HerbalGram* issue 92 in winter 2011. Writ-



ten by botanist, author, and renowned medicinal plant photographer Steven Foster, the article — “A Brief History of Adulteration of Herbs, Spices, and Botanical Drugs” — provides clear examples of adulteration, counterfeiting, and fraud in the sale of botanical materials since Greco-Roman times. Foster's contributions also include an *HerbalGram* article on the adulteration of skullcap (*Scutellaria lateriflora*, Lamiaceae) with potentially hepatotoxic germander (*Teucrium chamaedrys*, Lamiaceae) and articles on bilberry (*Vaccinium myrtillus*, Ericaceae) and the challenges of ginseng (*Panax* spp., Araliaceae) taxonomy and nomenclature.

In 2013, BAPP expanded by hiring Stefan Gafner, PhD, as ABC's chief science officer and BAPP's technical director. In 2015, BAPP began publishing a series of BAPBs (22 to date) and LGDs (11 to date).

In its 10-year history, BAPP has been supported by more than 200 botanical community and industry entities, including herb companies, trade associations in the United States and internationally, professional research and health practitioner organizations, research centers, and others. A full list is available on the BAPP homepage.

BAPP has been recognized twice by leading industry media organizations. In December 2016, *Nutritional Outlook* magazine presented BAPP with its Best of the Industry 2016 award, and in 2019, BAPP received the Editors Award for Industry Initiative of the Year from NutraIngredients-USA, another leading industry trade publication in the United States. NutraIngredients-USA

recognized BAPP as “an exemplary educational resource about adulteration in the botanical supply chain.”

According to Blumenthal: “Numerous ingredient suppliers and manufacturers in the botanical industry operate ethically and responsibly, producing reliable and authentic botanical and fungal ingredients and various natural consumer products. We are truly grateful for the financial, scientific, and moral support that BAPP receives from these companies and many other parties in the global community who recognize the vitally important research and educational role that BAPP plays in the international medicinal plant industry.”

In an informal survey of 115 BAPP supporters, including 50 members from the dietary supplement industry, nearly half (24) of the industry representatives responded that they had implemented new quality-control measures due to BAPP publications. Fifteen of those 24 revised their ingredient specifications, and 18 changed ingredient suppliers based on BAPP publications. The Botanical Adulterants Monitor was considered the most useful resource by the largest number of these industry members, followed by the more extensive *HerbalGram* articles and BAPBs.

According to Gafner: “For me, this is a moment to look back at what BAPP has achieved over the past 10 years. If, as industry feedback suggests, BAPP has indeed helped bring higher quality supplements and other botanical products to consumers, then I would say it has been successful.”

Ikhlas Khan, PhD, director of NCNPR, stated: “We are very pleased to be part of BAPP, which has been serving the global medicinal plant research and industry communities for a decade, addressing the issue of adulteration and fraud, and providing invaluable and highly reliable educational materials for everyone involved.”

Roy Upton, founder and president of AHP, commented: “AHP has always believed that educating industry about the prevalence of botanical adulteration, and more importantly, providing solutions, is a key to safeguarding public health. After 10 years, I can honestly say that various segments of the industry have made changes needed to minimize the incidence of adulteration. There will always be those who intentionally trade in fraudulent materials for economic gain. For those who want to do it right, BAPP has made

it much easier. For those who don't, the FDA hopefully is watching.”

Industry veteran Loren Israelsen, president of industry trade organization the United Natural Products Alliance, wrote: “Intentional adulteration is the bane of the botanical industry and has been for centuries. ABC recognized this problem as central to their mission and to the reputation of our industry and trust of our consumers. BAPP has now completed its 10th year and has become the essential science-based resource for information and tools to detect and remove adulterants from commerce. This is a major achievement. There is much work to be done. I salute ABC, AHP, and NCNPR for their determination to openly address and commit to resolving this persistent scourge within our industry.”

In addition to providing members of the herb industry and analytical laboratory community with authoritative technical information and guidance on adulteration, BAPP has also created an industry self-regulatory tool to assist botanical industry companies in removing adulterated ingredients (referred to as “irreparably defective articles”) from the global botanical supply chains with the BAPP Best Practices Contract Language and Standard Operating Procedure (SOP) for the Disposal or Destruction of Irreparably Defective Articles. These documents have been submitted for public comment twice and will be published by BAPP in 2021.

Natural product industry regulatory consultant Michael Levin, primary author of the BAPP supply contract language and SOP, stated: “While the dietary supplement industry is required to report serious adverse events to the FDA, there is no similar requirement, or even guidance, for buyers to manage irreparably defective ingredients that are economically adulterated. In 2021, BAPP will empower stakeholders to address this regulatory guidance gap by providing carefully vetted contract and SOP templates that supply chain partners can adapt for use in supply contracts. In so doing, both buyers and sellers of ingredients will have a contractual agreement that mutually assures destruction of defective ingredients that cannot be lawfully remediated, thus preventing their reentry into commerce.” HG

“Intentional adulteration is the bane of the botanical industry and has been for centuries. ABC recognized this problem as central to their mission and to the reputation of our industry and trust of our consumers. BAPP has now completed its 10th year and has become the essential science-based resource for information and tools to detect and remove adulterants from commerce. ... I salute ABC, AHP, and NCNPR for their determination to openly address and commit to resolving this persistent scourge within our industry.”

—Loren Israelsen, president of the United Natural Products Alliance



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Tales from the Elder: Adulteration Issues of Elder Berry

A review of analytical laboratory evidence documenting adulteration and fraud in the international market for elder berry ingredients

By Stefan Gafner, PhD^a; Travis Borchardt^b; Melanie Bush^c; Sidney Sudberg^d; Nicolas G. Feuillère, PhD^e; Mathieu Y.R. Tenon^e; Justine H. Jolibois^e; Pascale J.N. Bellenger^e; Hong You, PhD^f; Rebecca E. Adams^g; Jeremy Stewart, PhD^h; Ido Dagan^h; Timothy Murray, PhD^h; David L. Erickson, PhDⁱ; and Maria J. Monagas, PhD^j

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Botany and Taxonomy

The European elder* (*Sambucus nigra* L., syn. *S. nigra* subsp. *nigra* L., Viburnaceae) is a shallow-rooted tree that can grow up to 10 m (32.8 feet) tall and yields small, round fruit (6-8 mm in diameter) that are dark purple to violet when ripe. The species is distributed throughout most of Europe, from southern Scandinavia to northern Spain, Italy, and Turkey, and east to the Caucasus Mountains.¹ It has been introduced to North and South America and Oceania. The native range of a closely related and morphologically similar species, American elder (*Sambucus canadensis* L., syn. *S. nigra* subsp. *canadensis* (L.) R. Bolli), extends from Nova Scotia and Quebec south through Florida, the West Indies, and Central America, and west from Manitoba to montane Mexico.^{2,3} Other medicinally used elder species include the southern elder (*S. australis* Cham. & Schltdl.), blue elder (*S. cerulea* Raf.), dwarf elder (*S. ebulus* L.), Chinese elder (*S. javanica* subsp. *chinensis* (Lindl.) Fukuoka, syn. *S. chinensis* Lindl.), and Williams elder (*S. williamsii* Hance).⁴

The taxonomy of the main elder species in trade is a matter of debate. The five taxonomic databases⁵⁻⁹ consulted for this article consider *S. cerulea*, *S. nigra*, and *S. canadensis* to be separate species, placing them alternatively into the Viburnaceae^{5,8,9} or Adoxaceae family.^{6,7} (The US National Plant Germplasm System also lists *S.*

* Another common name for *S. nigra* is black elder, or European black elder, to distinguish the species from red elder (*S. racemosa*). Similarly, American black elder is used for *S. canadensis*.

Elder berry *Sambucus nigra*
Photo ©2021 Steven Foster



nigra subsp. *nigra* as a separate species.) This is despite the most recent taxonomic evaluation of the genus by Bolli (1994),¹⁰ who proposed classifying five formerly separate taxa (including *S. canadensis* and *S. cerulea*) as subspecies of *Sambucus nigra*. Bolli also argued for the placement of the genus in a separate family: Sambucaceae. A review of Bolli's work by Applequist¹¹ in 2015 supports the subspecies level of *S. nigra* subsp. *canadensis*, but not that of *S. cerulea*, since the latter is more easily distinguished from *S. nigra* based on its morphological characteristics.

Applequist also argued that the genus *Sambucus* should be placed in the Adoxaceae family.¹¹ However, several publications from 2020 and 2021 place *Sambucus* in the Viburnaceae family,^{5,8,9} while most older publications prior to 2015 place it within the Caprifoliaceae family.^{4,12,13} Weakley (2020) places *Sambucus* in the Viburnaceae or viburnum family (rather than the now obsolete Adoxaceae). It was also formerly placed in the Caprifoliaceae (pink family), or in some treatments in its own separate family, the Sambucaceae.^{3,14}

As if such taxonomic confusion were not enough, sources disagree about the use of the common name "elder" versus "elderberry." The older literature commonly uses the term "elder" for the plant, and specifies the plant parts as "elder berry," "elder leaves," and "elder flowers." More recently, the term "elderberry" has taken hold in the literature for the fruit, while "elderflower" is used for the flower. Some authors even use "elderberry flower" in their publications.^{15,16} The European Medicines Agency takes an interesting approach and uses "elderberry"¹⁷ and "elder flower"¹⁸ in their official texts, while the second edition of the *American Herbal Products Association's Herbs of Commerce*⁴ specifies that the plant name is "European elder" for *S. nigra* and "American elder" for *S. nigra* subsp. *canadensis*.

History of Use

The berries of European elder have been used for various purposes since before recorded history. Archaeological evidence suggests that European elder trees have been cultivated for millennia. For example, elder seeds discovered in what are now Austria, France, Italy, and Switzerland have been dated to the Stone and Bronze Ages (4000–1000 BCE).^{19–22}

Elder berries have longstanding use in herbal medicine. Information on the healing properties of the berry can be found often in writings that date back to antiquity, including in the works of Hippocrates (ca. 460–370 BCE), Pliny the Elder (ca. 23–79 CE), and Dioscorides (ca. 40–90 CE).¹³ All parts of the elder tree were used as medicine in medieval Europe with a wide range of indications. John Parkinson's *Theatrum Botanicum* of 1640²³ includes extensive descriptions of the therapeutic uses of the various parts of the elder tree. Parkinson noted:

[T]he berries also greene or dry, expell the same [choler and tough phlegme†] humors [as the inner bark] and [are] often given with the same successe to helpe the dropsie, by evacuating great plenty of waterish humors. ... [T]he decoction of the roote cured the biting of the viper or adder, and also of a mad dogge, and mollified the hardnesse of the mother, if women sit therein, and openeth the veins, and bringeth downe their courses: the berries boyled in wine performe the same effects; the haire of the head or other parts, washed therewith, is made blacke. ... [T]he juyce of the berries boyled with a little honey, and dropped into the eares, easeth the paines of them; the decoction of the berries in wine, being drunke, provoketh urine.²³

Similarly, several parts of the American elder were used in traditional medicine systems of many indigenous peoples, especially in northern and northeastern North America. The Cherokee and Iroquois nations made preparations of American elder berries to treat fevers, and the Cherokee and Rappahannock for rheumatism.^{12,24} Berries were also used by several tribes (e.g., the Haisla, Hanaksiala, Mi'kmaq, and Paiute) for gastrointestinal problems.²⁴ For example, the Mi'kmaq consumed the berries as a purgative and emetic,¹² and the Paiute ate dried ripe berries to treat diarrhea.²⁴

While many of these uses and indications have disappeared over time, the flowers and fruits of elder trees are still widely used in traditional herbal medicine.²⁵ Elder berries are mostly used in the form of a juice or syrup as a mild laxative, diuretic, and diaphoretic agent for the common cold.^{13,25,26}

Cultivars and Chemistry

Elder trees are grown as ornamental or fruit-producing plants in many areas of Europe, northern Africa, eastern Asia, and North America. Commercial interest in elder berries and flowers has led to the development of many elder cultivars.²⁷ Breeding began in the early 20th century and peaked in the middle of the century and led to the creation of several well-known European elder cultivars (e.g., Haschberg, Korsør, Samdal, Sampo, and Samyl) and American elder cultivars (e.g., Adams, Johns, Nova, Scotia, and York). According to industry sources, several cultivars are currently used for commercial purposes. For European elder, these include Allesoe, Haidegg, Haschberg, Korsør, Rubin, Sambu, Samdal, Sampo, Samyl, and Tattin, with Haschberg being the most widely used (T. Borchardt, email to S. Gafner, January 22, 2021; M. Bush, email to S. Gafner, January 21, 2021). Wyldewood 1 reportedly is the most widely used cultivar of American elder,²⁸ although one industry source suggests that the cultivars Bob Gordon, Pocahontas, and York provide better yields (D. Bennett [INS Farms], oral communication to S. Gafner, February 5, 2021).

† Choler (yellow bile) and phlegm are two of the four medieval humors, or body fluids; blood and black bile are the others. These four humors were believed to have made up the human body's constitution; an imbalance of the humors was believed to be the cause of disease.

Compounds of interest in elder berries include sugars, organic acids, terpenoids, phenolic compounds, and volatile constituents. Several papers have reported the contents of these metabolites, either measured in fresh (fresh weight, FW) or dried (dry weight, DW) fruit. Since elder berries contain between 72% and 78% water,²⁹ a conversion of literature data obtained from fresh fruits to dry fruit can be calculated approximately by multiplying with a factor of four. European elder contains 2.6–10.5 g glucose, 2.6–6.3 g fructose, and 0.05–1 g sucrose per 100 g FW of berries.²⁹ The main organic acids are citric acid (10.4–999 mg/100 g FW) and malic acid (7.4–882 mg/100 g FW), with smaller amounts of tartaric and shikimic acids. Ursolic and oleanolic acids are the most important triterpenoids in the berries.²⁹

With regard to elder berry constituents, the focus has been mostly on the phenolic compounds, which include proanthocyanidins, anthocyanins, flavonol glycosides, and minor amounts of caffeoylquinic acid derivatives (e.g., chlorogenic acid) and simple phenolics. The anthocyanins in European elder are dominated by cyanidin-3-*O*-glucoside and cyanidin-3-*O*-sambubioside, with smaller amounts of cyanidin-3,5-*O*-diglucoside and cyanidin-3-*O*-sambubioside-5-*O*-glucoside. Total anthocyanin contents in European elder berries vary between 149–953 mg/100 g FW,²⁹ or between 250–1,368 mg/100 g FW depending on the authors.^{30–33} Flavonol glycosides include mainly rutin (29–52 mg/100 g FW) and isoquercitrin (6.4–26.5 mg/100 g FW),^{30,33} with small amounts of kaempferol-3-*O*-rutinoside, isorhamnetin-3-*O*-rutinoside, and 3-*O*-glucosides.

American elder berries contain similar amounts of sugars and organic acids. Thomas et al (2015)³⁴ reported glucose and fructose concentrations of 1.4–2.6 g/100 g FW and 1.4–3.1 g/100 g FW, respectively. Citric acid and malic acid contents were 163–501 mg/100 g FW and 194–441 mg/100 g FW, respectively.³⁴ Rutin concentrations reportedly range from 3.5–170 mg/100 g FW.^{34,35} Rutin is the predominant flavonol in American elder berries as well; however, Thomas et al found slightly higher amounts of isorhamnetin-3-*O*-rutinoside (1.4–16.9 mg/100 g FW) in three out of nine cultivars.³⁴ Isoquercitrin concentrations were 0.4–48.5 mg/100 g FW.^{34,35}

Contrary to the European elder, the anthocyanin profile in American elder berries is dominated by cyanidin-3-*O*-[6-*O*-(*E*)-*p*-coumaroyl]sambubioside-5-*O*-glucoside, so the presence of this *p*-coumaroylated compound can be used as a marker to distinguish among the species. Other anthocyanins in

American elder include cyanidin-3-*O*-sambubioside-5-*O*-glucoside, cyanidin-3,5-*O*-diglucoside, cyanidin-3-*O*-glucoside, cyanidin-3-*O*-sambubioside, and cyanidin-3-*O*-[6-*O*-(*Z*)-*p*-coumaroyl]sambubioside-5-*O*-glucoside. Total anthocyanin concentrations in American elder berries range from 208–1,005 mg/100 g FW.³¹ Concentration ranges of individual anthocyanins are provided in Table 1. The anthocyanin profiles of *S. cerulea* and *S. ebulus* appear to be similar to the profile of *S. nigra*. No quantitative data on individual anthocyanins in *S. williamsii* are available, although Feng et al (2016) obtained a total anthocyanin content of 32 mg/100 g FW and included an anthocyanin profile identifying cyanidin-3-*O*-(*E*)-*p*-coumaroylsambubioside-5-*O*-glucoside as the major pigment in this species.³⁶ No other literature references about the anthocyanin profile of *S. williamsii* could be retrieved.

The Elder Berry Market

While elder berry has a long history of use in traditional medicine, the appearance of commercial dietary supplements and herbal medicines with the fruit has been a rather recent occurrence in countries with a tradition of Western herbal medicine. The *Galenica Codex* of 1992,³⁸ a book with all medicinally used preparations for pharmacists in Switzerland, does not list any product containing elder berries. One of the first commercial elder syrups, Sambucol® (initially produced by Razei Bar Industries, Ltd.; Jerusalem, Israel; and now owned by PharmaCare; Warriewood, NSW, Australia), was launched in 1992.³⁹

Elder first appeared in the American Botanical Council's annual *HerbalGram* Herb Market Report in 2008, when it ranked as the 16th top-selling dietary supplement ingredient in the mainstream multi-outlet channel, also known as the mass-market channel.⁴⁰ The ranking may be due in part to the popularity of elder flower extracts in many cough lozenges, some of which are also included in the dietary supplement category. A marked increase in popularity was seen from 2017 to 2018 (Figure 1). This may have been caused in part by the severe 2017–2018 influenza season and a 2016 clinical trial showing a reduction in symptoms of the common cold using elder berry.⁴¹ This positive sales trend has continued, and based on available data, 2020 was another record-breaking year for elder product sales, largely due to the COVID-19 pandemic, with an estimated growth of approximately 200% over 2019 sales.⁴²

Table 1. Concentrations of Selected Anthocyanins in Berries from Various Elder Species (in mg/100 g FW)^{30–33,37}

	Cyanidin-3- <i>O</i> -glucoside	Cyanidin-3- <i>O</i> -sambubioside	Cyanidin-3,5- <i>O</i> -diglucoside	Cyanidin-3- <i>O</i> -sambubioside-5- <i>O</i> -glucoside	Cyanidin-3- <i>O</i> -[6- <i>O</i> -(<i>E</i>)- <i>p</i> -coumaroyl]sambubioside-5- <i>O</i> -glucoside
<i>S. canadensis</i>	0.3–62.7	1.7–39.4	6.3–94.6	40.8–195	130.6–594.2
<i>S. cerulea</i>	2.9	63.4	n.d.	n.d.	n.d.
<i>S. ebulus</i>	84.5	244.8	91.6	42.0	n.d.
<i>S. nigra</i>	44.8–739.8	122.2–630.8	5.9–47.1	16.0–82.6	n.d.

n.d. = not determined

Numerous different elder berry preparations are on the market (Figure 2). Many commercial elder berry extracts are standardized to their anthocyanin contents, and extract prices vary based on the concentration of anthocyanins. In 2021, pricing of wholesale bulk elder berry extract containing 7% anthocyanins was between \$160-190/kg, while costs for extracts containing 14% anthocyanins ranged between \$270-300/kg (C. Tower [Artemis International], email to S. Gafner, February 4, 2021). In contrast, “elder berry” extracts that have been found to be adulterated with black rice (*Oryza sativa*, Poaceae) extract are sold for as little as \$14/kg.

Adulteration

As the popularity of elder berry dietary supplements continued to rise during the COVID-19 pandemic due to consumers’ increased interest in herbal ingredients with reported immunomodulatory and antiviral effects, shipments of some elder berry ingredients were delayed due to manufacturing closures in China and India and disruptions of transportation and material processing at customs.^{53,54} In response, some industry members started to raise concerns about demand outpacing supply and that some elder berry bulk extracts and finished dietary supplements offered during the pandemic were of low quality or adulterated.⁵⁵⁻⁵⁸

However, no data explicitly reporting adulteration of elder berries or elder berry extracts could be retrieved in the published scientific literature at the time of this writing (February 2021). On the contrary, some papers suggest that elder berry extracts themselves have been used as adulterants, as undeclared color additives to wine^{59,60} or to adulterate bilberry (*Vaccinium myrtillus*, Ericaceae) extracts.^{61,62} However, the results of the analysis of commercial elder berry products detailed in a 2016 doctoral dissertation by Joseph Galetti, PhD, suggest that, at that time, elder berry product adulteration was common, even if such adulteration appears to have gone unnoticed by the author.⁶³ For his graduate work, Galetti analyzed a total of 33 samples for their content of sugars, anthocyanins, organic acids, vitamin C, and total proanthocyanidins. The samples included 29 commercial elder berry dietary supplements, three samples of bulk fruit, and one sample of bulk powder and were sold in the United States (n = 31), Ireland (n = 1), or Switzerland (n = 1).

The finished dietary supplement samples included 14 syrups, five tinctures, four lozenges, three concentrates, and three capsule products. Eight of these samples (two products each of the syrups, tinctures, capsules, and lozenges) were found to contain peonidin, peonidin-3-*O*-glucoside, or peonidin-3-*O*-galactoside, which are anthocyanins that have not been found in elder berry. Addition-

ally, the elder berry bulk powder contained mainly cyanidin-3-*O*-glucoside and peonidin-3-*O*-glucoside, reminiscent of the main anthocyanins found in black rice extract. In the case of an elder berry capsule supplement, Galetti noted that the product had an anthocyanin composition that was not indicative of elder berry, with 80.5% cyanidin-3-*O*-glucoside, 11.6% cyanidin-3-*O*-galactoside, 3.4% cyanidin-3-*O*-arabinoside, 2.9% cyanidin, and 1.7% peonidin-3-*O*-glucoside (calculated as percent of total anthocyanins).⁶³ The product also had an unusually high level of isocitric acid. Galetti hypothesized that this could be due to the freeze-dried blackberry (*Rubus* spp., Rosaceae) fruit that was also present according to the label. However, peonidin-3-*O*-glucoside is not known to occur in elder berries or blackberries.⁶⁴

Another spurious anthocyanin profile was reported in a 2018 paper on the antioxidant, anti-inflammatory, and cytotoxic effects of an “elder berry” extract.⁶⁵ The extract, described by the authors as a “dietary supplement widely available on the world market, that contains fruit elderberry extract *Sambucus williamsii* Hance” contained 88.2% cyanidin-3-*O*-glucoside and 9.7% peonidin-3-*O*-glucoside, again suggesting adulteration with black rice extract.⁶⁵

Figure 1. US Sales of Elder Dietary Supplements from 2011 to 2019⁴³⁻⁵¹

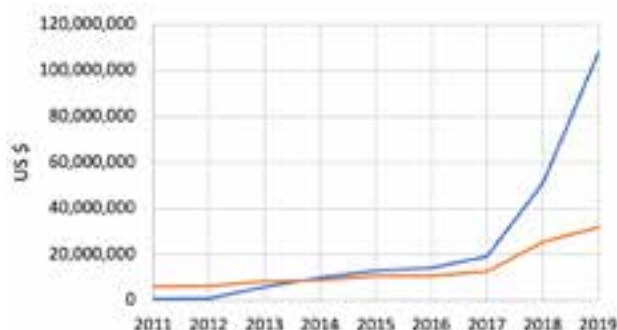
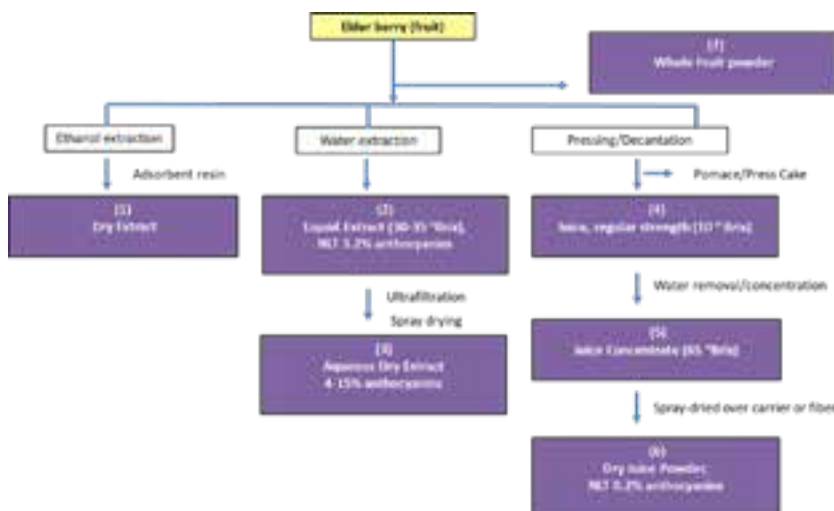


Figure 2. Elder Berry Dietary Supplement Ingredients Available in the United States



The Brix value indicates the number of grams of sucrose present per 100 grams of liquid (e.g., elder berry juice with 10° Brix contains 10 g sucrose in 100 grams of juice). NLT = no less than. This figure has been modified from Monagas (2021).⁵²

Table 2. Results of Elder Berry Product Testing

Company	Method	Adulterated/ Failed Identity Test	Total
Alkemist Labs	HPTLC ^b	32	369
Artemisa*	HPTLC ^b /HPLC ^c	4	11
DNA4 Technologies	WGS ^b	0	2
Eurofins	HPTLC ^b	2	55
Gaia Herbs	UV/Vis ^b	0	6
Nature's Way*	HPTLC ^d /HPLC ^c	16	33
Naturex*	HPLC ^b	4	10
NSF International	HPTLC ^b	0	46
Total		58	532

* These companies included competitors' products in their analyses.

^a Analysis performed by Alkemist Labs (HPTLC) and Complete Phytochemical Solutions (HPLC)

^b Proprietary method

^c United States Pharmacopeia (USP) European Elder berry dry extract monograph⁶⁶

^d Institute for Nutraceutical Advancement method

Current Industry Data Regarding Elder Berry Authenticity

To assess the current market situation with regard to the authenticity of commercial bulk elder berry extracts and finished products, a request for analytical data was sent to manufacturers of elder berry dietary supplements and contract analytical laboratories.

Methods

In total, 14 companies were asked to participate in this initiative, or voluntarily provided analytical data on elder berry quality. This included nine contract analytical laboratories that specialize in identification of botanical ingredients, three manufacturers of elder berry supplements, and two elder berry extract suppliers. These parties were asked to share data on elder berry analysis in unredacted or redacted form, (i.e., without the name of the supplier or manufacturer to respect confidentiality agreements). Eight organizations provided data from elder berry analyses, of which six shared actual reports of the analysis, while the other two shared top-line data on the number of samples that failed identity specifications. The data obtained represent a total of 532 samples, although some of the same samples may have been tested at several laboratories. Test samples included bulk extracts, bulk whole or powdered elder berries, and finished dietary supplement products. Methods of analysis included high-performance thin-layer chromatography (HPTLC, $n = 510$), high-performance liquid chromatography with visible detection (HPLC-Vis, $n = 50$), ultraviolet/visible spectrophotometry (UV/Vis) with chemometric analysis ($n = 6$), and DNA-based identification using whole-genome sequencing (WGS, $n = 2$). Two laboratories used a combination of HPTLC and HPLC-Vis.

Results

A total of 58 (10.9%) of the 532 samples failed the identity test specifications due to differences in the analytical fingerprint when compared to authentic samples. Adulterated materials were more frequently seen when elder berry manufacturers analyzed competitors' products (Table 2).

Identification of Adulterants

Two companies attempted to identify the adulterants. Both companies identified black rice extract as a common adulterant based on comparison of the anthocyanin fingerprint with authentic black rice extract (Figure 3)⁶⁷ or comparison to published data on the anthocyanin composition of black rice

extract. The main anthocyanidin in black rice extract is cyanidin-3-*O*-glucoside. It also contains small amounts of peonidin-3-*O*-glucoside and traces of cyanidin-3,5-*O*-diglucoside and cyanidin-3-*O*-rutinoside, but lacks the characteristic cyanidin-3-*O*-sambubioside present in some authentic commercial elder berry species (Table 1).^{68,69} While other adulterants were detected in some of the bulk extracts, the identities of these ingredients were not determined. Additionally, several commercial elder berry bulk extracts and dietary supplement products were highly diluted or did not contain any detectable anthocyanins at all.

One recent change in the US dietary supplement market is the appearance of extracts labeled to be made from the fruit of Williams elder, which is a red-berried elder species that grows in northeastern China, Japan, and Korea.⁷⁰ Unlike the modern herbal use of European and American elder, where the flowers or the berries are the plant parts of interest, traditional Chinese medicine employs Williams elder twigs. Known as *jie gu mu*, these twigs are used in combination with other herbs to treat bone fractures.⁷¹⁻⁷³ Williams elder stems and branches also are used in Korean traditional medicine to treat broken bones and osteoporosis.⁷⁴ During this initiative, four bulk samples claiming to contain Williams elder berry extract from two different suppliers were analyzed by HPLC-Vis and/or HPTLC (Figure 4). In the case of one supplier, the samples were found to contain either black rice extract or a mixture of black rice and European elder extracts. The samples from the other supplier had exactly the same anthocyanin composition as European elder berry, thus contradicting the findings by Feng et al,³⁶ who reported cyanidin-3-*O*-(*E*)-*p*-coumaroylsambubioside-5-*O*-glucoside as the main anthocyanin of Williams elder (see "Cultivars and Chemistry" section),

with other acylated anthocyanins as minor compounds. As such, it is not clear if the second set of bulk samples were European elder mislabeled as Williams elder or if the research by Feng et al was carried out on the wrong species. To further complicate matters, Williams elder is included in Bolli's very broad circumscription of mostly red-fruited species under *S. racemosa*, along with 34 other synonyms.¹⁰ Clearly, other species or variants could be involved in commercial supply chains or laboratory studies, absent a voucher specimen. Further investigations into the composition of Williams elder berries are needed to provide clear criteria on how to distinguish among Williams elder and other *Sambucus* species.

Stability Considerations

Anthocyanins are known to be prone to oxidation, with light, temperature, water content, and pH affecting their stability,⁷⁵⁻⁷⁸ particularly in liquid formulations.^{63,78} Substantial degradation also has been observed in berries from some suppliers that sterilize fruits, usually by steam, before sending them to manufacturers that then make syrups and extracts. These degraded berries are crispy and have a burnt aroma and flavor (R. Upton [American Herbal Pharmacopoeia], email to S. Gafner, February 8, 2021). Steam sterilization treatments may also noticeably change the anthocyanin profile,⁷⁶ leading to a more brownish colored product due to the loss of anthocyanins and the formation of various types of polymers.^{79,80} As mentioned above, several of the bulk extracts did not exhibit any detectable anthocyanins. It is possible that some of the failing ingredients or products in Table 2 were due to improper manufacturing processes. While not technically adulterated, anthocyanin degradation may compromise the efficacy of the product.

Conclusion

The surge in popularity of elder berry extracts and dietary supplements, combined with supply shortages and increased raw material costs, has created a situation in which some suppliers attempt to gain an unfair market advantage by selling diluted or adulterated elder berry extracts for financial gain. The most common adulterant appears to be black rice extract, but other unidentified materials are used as adulterants as well. While the taxonomic status of American elder and European elder is a matter of scientific debate, the two species can be distinguished based on their anthocyanin profiles. No mislabeling of European elder with American elder, or vice versa, was observed in commercial bulk extracts or finished products. However, one case suggests possible mislabeling of European elder as Williams elder.

Figure 3. HPLC-Vis Chromatogram of Authentic Elder Berry Extract and a Bulk 'Elder Berry' Ingredient Containing Black Rice Extract

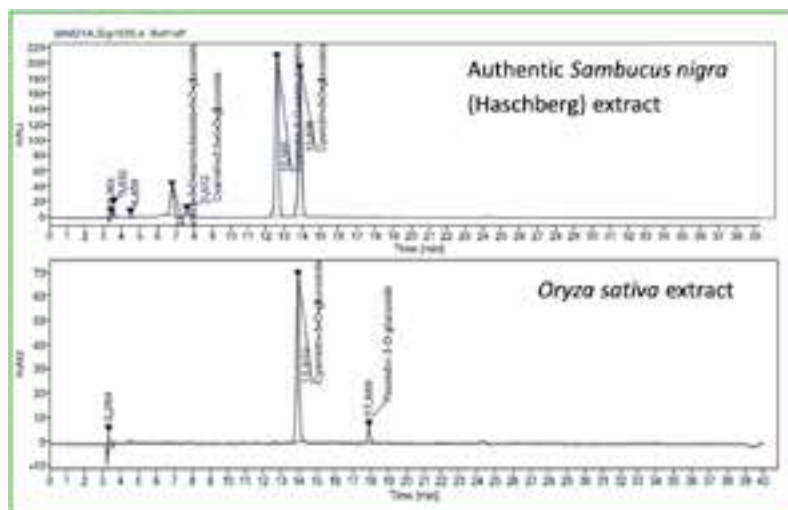
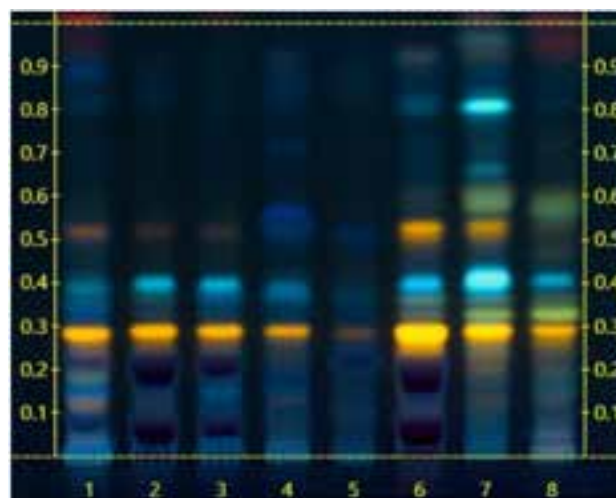


Figure 4. HPTLC Analysis of Commercial Elder Berry Extracts



Lanes 1–2: Authentic European elder berry
Lane 3–6: Commercial elder berry products
Lane 7: Authentic European elder flower
Lane 8: Authentic blue elder berry

The results of this investigation indicate that manufacturers of herbal dietary supplements have to remain vigilant and actively establish quality-control assays that help detect issues with adulteration, such as the undisclosed intentional substitution, dilution, and/or spiking of products, which is particularly relevant during times of extraordinary sales increases and/or sudden supply chain dislocations and shortages. HG

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Elder berry *Sambucus nigra*
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Olivia Newton-John Foundation to Fund Research on Herbal Therapies for Cancer

By Connor Yearsley

In October 2020, Dame Olivia Newton-John and her husband, herbalist John Easterling, launched the Olivia Newton-John Foundation (ONJ Foundation)¹ to fund research on plant-based therapies to treat cancer and improve quality of life in people with cancer.

Newton-John, the British-Australian, Grammy Award-winning singer, songwriter, and actress who co-starred as Sandy in the 1978 film *Grease*, was first diagnosed with breast cancer in 1992 and again in 2013. In 2018, the disease returned for the third time and metastasized to her spine.²

“In the past few years, I have had wonderful success with herbs and cannabis [*Cannabis* spp., Cannabaceae] that my husband grows for me,” Newton-John said (oral communication, December 21, 2020). “I have many friends who are going through cancer, and they ask me about herbs and which ones they can take. A lot of them want the science. We thought it would be wonderful to start a foundation to research plant medicine, so we can show people how this is actually working. It is working for me, and it can work for you. I want to be able to share that knowledge with people.”

Newton-John, who has described herself as a “cancer thriver,” wants to find gentler ways to treat cancer, according to an article published by Good Morning America. “I’ve always thought, ‘Gosh, wouldn’t it be wonderful if we could create kinder therapies that help boost the body’s immune system instead of knocking us down?’” she was quoted as saying.²

The foundation will focus on all types of cancer, not just breast cancer, and Newton-John envisions a world beyond cancer. “That’s everything that drives me forward,” she was quoted as saying.² “To think that we could help people ... live in a world where cancer was just ... something that you could live well with, which I’m doing. And I hope to continue to do that for a long time.”

Because the foundation is so new, it has not yet funded any studies, but Newton-John raised about 1 million Australian dollars (\$764,855) for the foundation by auctioning about 300 items, including artwork and some of her collectible memorabilia. Newton-John and Easterling hope to fund their first study sometime in 2021.

John Easterling and Olivia Newton-John.
Courtesy of John Easterling.



“We would like to find anything that is of interest and value,” Easterling said. “But we want to specifically research some of the things that Olivia has been doing.”

For example, Newton-John and Easterling are interested in funding research on some Amazonian plants. Nicknamed “Amazon John,” Easterling spent many years traveling to and from the Amazon, studying edible and medicinal plants, and previously owned Amazon Herb Company.

Some of the well-known Amazonian plants he uses for Newton-John include *chanca piedra*, or stone-breaker (*Phyllanthus niruri*, Phyllanthaceae); *graviola*, or soursop (*Annona muricata*, Annonaceae); *uña de gato*, or cat’s claw (*Uncaria tomentosa*, Rubiaceae); and *sangre de drago*, or dragon’s blood (*Croton lechleri*, Euphorbiaceae). According to Easterling, preliminary studies

show these plants may have benefits for immune support and may have the ability to compromise cancer cell viability.

Only a small fraction of the many thousands of plant species in the Amazon have been studied for their therapeutic value, Newton-John noted, “so there is a big choice out there, and I’m sure that as we delve into this, we will find other plants that show promise for treating cancer.”

Another of her go-to therapies is cannabis. At their home in California, where cultivation of cannabis for medicinal and recreational use is legal, Easterling breeds different chemovars (chemical varieties) of cannabis with different profiles of cannabinoids and terpenes and formulates them for Newton-John. “We are really confident that she is seeing benefit from the cannabis formula and that other people would also benefit from it,” Easterling said. “We know that there is research to do on some specific cannabis chemovars or combinations of chemovars, and that is one area that we are interested in.”

With cannabis, “the pain relief is something that is obvious really quickly,” he said, but added that the potential benefits are much broader than that. It has anti-inflammatory³ and anti-nausea effects,⁴ and some cannabinoids like

cannabidiol (CBD) have shown the ability to inhibit the migration of cancer cells and induce apoptosis, the natural process of programmed cell death, in cancer cells, as determined in both in vitro and in vivo research.⁵ According to Easterling, other cannabinoids, like cannabichromene (CBC), cannabidivarin (CBDV), cannabigerol (CBG), and tetrahydrocannabivarin (THCV), show potential benefits for cancer as well.

“We started the foundation so we can study these things and show the science, because people like to see the science behind these things,” Newton-John said. “I believe in [cannabis], and I believe it has been working for me really well. And I feel good. [Cannabis] is also good for mood, and mood goes along with pain relief, too.”

Newton-John and Easterling are interested in the possibility of working with the Australian National Institute of Integrative Medicine, which proposed a cannabis study to them. According to Easterling, this study would assess a cannabis product’s effects on circulating tumor cells (CTCs) and quality of life in people with cancer. “It looks very interesting,” Easterling said. “Because [CTCs are] a single marker, it would be more of a simplified study, as far as studies go.”

They are also interested in possibly funding research on fucoidan, a complex polysaccharide that is found in the cell walls of many species of brown seaweed. According to preliminary studies, fucoidan may have benefits for cancer.⁶

Newton-John and Easterling see their new foundation as an extension of the intentions of the Olivia Newton-John Cancer Wellness and Research Centre in Melbourne, Victoria, Australia. Newton-John agreed to lend her name to the center on the condition that it emphasize “wellness” and incorporate other healing methods, including acupuncture, meditation, yoga, art therapy, music therapy, and oncology massage. The wellness center’s philosophy is to treat the mind as much as the body.⁷

According to Easterling, he and Newton-John helped influence the premier of the state of Victoria, Australia, to fund an AU\$1 million study on cannabis and quality of life, which recently started at the Olivia Newton-John Cancer Wellness and Research Centre. This study is separate from the new foundation but may be similar to the type of research that Easterling and Newton-John want to fund through the foundation. “This is a wonderful world emerging here ... as far as people recognizing the benefits of plant therapeutics,” Easterling said. “And we want to take it to a new space of recognition and add to the body of research.”

The most challenging part of starting the new foundation has been structuring, Newton-John said. In December 2020, about two months after launching the foundation, Newton-John and Easterling deregistered it in Australia and moved it to the United States, where they live. The COVID-19 pandemic made it difficult “to run the foundation and not be in the same country, and it was much simpler for us to move it [to the United States],” Newton-John said. Tax benefits for US donors was another motivation for the move.⁸

The ONJ Foundation is working with Charities Aid Foundation (CAF) America.⁹ The funding goes through CAF America, which helps find donors and ensures that researchers are qualified to receive funding.

Newton-John and Easterling will consider several criteria when deciding how to allocate funding through the foundation. “It will depend on what kind of research opportunities are presented to us,” Easterling said. “Is it something that rings our bell? Does it have pre-existing science behind it?”

“It is going to be determined by the caliber of researchers behind it, what they have done before, the facility they are working from, and ... the intention [of the research],” Easterling added. “Do the people have plant medicine experience? Another [factor] that is important to us is [plant] extracts as opposed to isolates. I think there is enough science to demonstrate extracts are [often] a better way to go.”

Newton-John said: “We are excited because this is John’s passion for his lifetime, and lucky me gets to marry a man who has such amazing knowledge of plant medicine that I’ve greatly benefitted from. This is a joint venture for us.... I see the improvement in myself, and we see the improvement in our friends when we give them herbs to take. It is very exciting when they call up, and they have used only prescription medicines before and added [herbs] in, and they are seeing improvements. So, we just want to go further with it and contribute to the growing body of plant medicine research for cancer.”

Donations for the ONJ Foundation can be made at www.onjfoundation.org.¹ HG

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Institute for the Preservation of Medical Traditions Seeks New Home for Its Research Collection

By Hannah Bauman

Alain Touwaide, PhD, and his wife Emanuela Appetiti, founders of the nonprofit Institute for the Preservation of Medical Traditions, are seeking a new home for their research collection, *Medicina Antiqua*. This collection is a valuable source of information on the therapeutic uses of plants in the ancient Mediterranean world. The time has come, Touwaide wrote, for the couple to move on after 50 years of acquiring and preserving these materials (email, March 25, 2021). They are now looking for an institution or individual to acquire the collection and give it a permanent home. The couple hopes to keep the entire collection intact, if possible.

“We hope it will continue to grow and, more than anything, to serve the scientific and scholarly community ... and [be] open to all, as we [offered it],” Touwaide wrote.

The cross-disciplinary collection covers aspects of science, medicine, and the humanities and reflects the diverse interests of Touwaide, a classicist, and Appetiti, a cultural anthropologist. The collection contains approximately 30,000 items, including facsimiles of primary sources, catalogs of manuscripts, modern printed versions of ancient texts, and images of early printed herbals. It is currently housed at the Botany Center of the Huntington Library, Art Museum, and Botanical Gardens in San Marino, California.

Touwaide began collecting these works in 1971 as an undergraduate classical studies student at the Catholic University of Louvain in Belgium. Some of the rarer items were acquired through hard work and determination and required Touwaide and Appetiti to seek out small, lesser-known collections and libraries. Their interest lies not only in the knowledge of plants and human health but how this information was transmitted through the centuries and changed as it passed through different hands. Though the acquisition of these works started as a piecemeal effort on a student budget, Touwaide and Appetiti changed their strategy when the value of their collection to the scientific research community became clear, and they moved forward with the goal of creating an open-access academic library.

From 2004 to 2016, *Medicina Antiqua* was available for scholars from around the world through an agreement with the Smithsonian Institution in Washington, DC. In 2007, the Institute for the Preservation of Medical Traditions was formed as an independent research and education center and, in 2016, the collection was moved to its present home in the Huntington. Now, Touwaide and Appetiti hope that their work will remain available for future scholarship.

“We wish to empower the next generation and offer an opportunity to take advantage of our collections, hoping that they will be curated as they deserve and further expanded,” wrote Touwaide (email, March 31, 2021).

Some standouts of the collection include a 1529 edition of the collected works of Italian physician

Niccolò Leonico (1428–1524), who translated into Latin works from the Greek physicians Hippocrates (ca. 460–370 BCE) and Galen (129 CE–ca. 216) and created a cultural shift in the study of pharmacognosy; rare German editions and doctoral theses from the early 19th century; and the 1874 original of *Pharmacographia* by Friedrich A. Flückiger (1828–1894) and Daniel Hanbury (1825–1875). There are also a multitude of floras from regions around the Mediterranean, facsimile replicas of manuscripts in Greek, Latin, and Arabic, early-printed herbals, copies of numerous botanical illustrations, and a special section devoted to Pompeii and the archeological study of its excavation, with all the works of preeminent archeologist and pioneer archaeobotanist Wilhelmina Jashemski (1910–2007).

This collection not only allows scholars to access the information contained within ancient treatises but also to trace these works throughout the centuries, as it contains works relevant to the transmission of ancient texts. These works of textual scholarship (a discipline that covers the description, transcriptions, editing, and annotating of texts and documents) include the inventory and description of the production of Greek, Arabic, and Latin texts with a focus on Renaissance-era scholars, scientists, and printers.

The works Appetiti contributed to the collection cover different sections of the world. Her research interests include Australian Aboriginal populations and related health topics. Non-Mediterranean focuses of the collection also include works on the ethnobotany of Africa, the Caribbean, India, New Zealand, and South America, among others; ethnomedicine of First Nations in Canada, Native Americans in the United States, and traditional practices such as Ayurveda and traditional Chinese medicine; and cultural works of Australian Aboriginal peoples including art, fiction, mythology, and poetry.

These works are a fraction of the 30,000 items in the collection, and only a sample of the topics it spans. More information about the collection is available at <https://medicaltraditions.org/collection>. To contact Touwaide and Appetiti, inquiries can be sent to research@medicaltraditions.org. HG

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The Murder of Guatemalan Maya Spiritual Guide Jesús Choc Yat

By Connor Yearsley

On January 4, 2021, Jesús Choc Yat, a well-known Maya medicine man from Guatemala, was murdered. That is according to a January 7 press release issued by Asociación Maya UK'UX B'E, a Maya advocacy non-governmental organization (NGO). Choc Yat was an *ajq'ij* (spiritual guide) and healer who also used local medicinal plants. He was 57 years old at the time of his death and was from the El Vergel community of La Zona Reina of the municipality of San Miguel Uspantán of the Quiché department of Guatemala.¹

On January 3, Choc Yat reportedly arrived at the community of Lancetillo La Parroquia to celebrate a Maya ceremony where, according to the press release, he was last seen alive. His body was found the next day, allegedly with extensive signs of torture.¹

In the press release, Asociación Maya UK'UX B'E denounced Choc Yat's murder and called on the Guatemalan Public Ministry, which is responsible for the prosecution of criminal cases, to investigate and apprehend those responsible. There were no leads about the murder at the time, but a human rights law office in Nebaj, Guatemala, reportedly was interested in any information on which to investigate. It is unclear if any investigation has been conducted in the meantime. This author made repeated, persistent attempts to obtain more information about and a photograph of Choc Yat from multiple potential sources in Guatemala and elsewhere, but those attempts were unsuccessful. Asociación Maya UK'UX B'E also called for public support to urge the state to stop the persecution of indigenous peoples.¹

Choc Yat's murder is part of a disturbing trend in which indigenous peoples in general and, in some cases, traditional healers specifically are being persecuted and perhaps targeted in Guatemala and elsewhere. In fact, in early June 2020, Domingo Choc Che, 55, a Q'eqchi' Maya spiritual guide and traditional medicine expert, was brutally tortured and murdered after a group of people seized him from his home in Chimay, Guatemala, according to an article in *The Guardian*. Domingo Choc Che's abductors allegedly accused him of witchcraft and performing a ceremony on a grave, beat him for more than 10 hours, and then doused him with gasoline and set him on fire.^{2,3}

An article in *HerbalGram* issue 128 described Domingo Choc Che's murder and included a Q&A with two of his colleagues, who provided insights about what should be learned from his murder and what can be done to prevent similar crimes from happening in the future. Some or many of those insights may also be relevant and applicable to the murder of Choc Yat. At the time of the *HerbalGram* article (November 2020), three people were awaiting trial for Domingo Choc Che's murder,³ but the status of the trial is still unknown despite follow-up inquiries by this author.

In a tribute article published in April 2021, Cultural Survival (an NGO that advocates for indigenous peoples' rights and supports indigenous communities' self-determination, cultures, and political resilience) states that it documented 56 murders, 11 disappearances, and 23 violent attacks against indigenous human rights and environmental defenders in Latin America in 2020. Some of those, includ-

ing Domingo Choc Che, are described in the tribute.⁴ While Domingo Choc Che's role as a religious leader and spiritual guide apparently played a part in his murder, the circumstances and motivations behind Choc Yat's murder, on the other hand, are not clear.¹⁻⁴

The murders of Choc Yat, Domingo Choc Che, and others, are a harsh reminder of Guatemala's 36-year genocidal civil war, which lasted from 1960 to 1996. During that time, more than 200,000 people were killed and an additional 45,000 disappeared, according to *The Guardian*. Eighty percent of victims during the war reportedly were indigenous. The 1996 Guatemalan peace accords recognized the rights of indigenous peoples to their traditions, but prejudices and persecution continue.² And, in some or many cases, like Choc Yat's, information and justice are apparently scarce and elusive.¹ His death has attracted far less international attention than Domingo Choc Che's, maybe because he did not have the national and international links that Domingo Choc Che had, according to a peer reviewer of this article who knew Domingo Choc Che.

"Indigenous peoples of tropical America are suffering from two plagues: political killings and COVID-19," wrote Mark Plotkin, PhD, an ethnobotanist and president of the Amazon Conservation Team (email, April 23, 2021). "The rate of infections in Amazonia is about twice that of urban centers. And the spate of killings of political leaders and environmentalists, both indigenous and not indigenous, is further compounding the negative effects of the current day and age." HG

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The Autumn Crocus and Its Constituent Colchicine: The Story of a Late Bloomer

Recent studies show potential benefits for patients with COVID-19

By Stefan Gafner, PhD

In January 2021, several media reports put a spotlight on colchicine, an alkaloid from the autumn crocus (*Colchicum autumnale*, Colchicaceae), after a randomized, double-blind clinical study with 4,488 patients with COVID-19¹ showed a reduction in hospitalization and death rates in the colchicine group, according to the preprint conclusion.^{2,3} While the authors of the study reported this as a major breakthrough, many scientists pointed to the lack of statistical significance between the colchicine and placebo groups in the primary endpoints of the study and emphasized the need for more data.⁴⁻⁶ Nevertheless, the results seem promising and reinforce that plant constituents can be important sources of medications.

Historical Uses

The autumn crocus has been known for centuries, but many older medical texts mainly mention its toxicity. In his *De Materia Medica*, Greek physician, pharmacologist, and botanist Pedanius Dioscorides (ca. 40–90) describes a plant named *ephemerum*, also referred to as *colchicon*, which flowers in fall and has flowers like a crocus (*Crocus* spp., Iridaceae). He wrote, “when eaten, it has a fatal effect by choking, as is with mushrooms.” Ingestion of small amounts (less than five grams) of autumn crocus, all parts of which contain colchicine,⁷ can cause gastrointestinal symptoms with diarrhea and loss of fluids, followed by life-threatening complications (e.g., heart failure, arrhythmias, renal failure, hepatic injury, respiratory distress, impaired blood clotting) and possibly death.⁸

However, the Greek physician Alexander of Tralles (ca. 525–605) also noted the benefits of a plant known to him as *hermodactyl* for the treatment of gout, an inflammatory condition caused by the crystallization of monosodium urate in and around joints. Since he did not provide any botanical descriptions, the identity of *hermodactyl* is debatable, but many scholars believe that it was a *Colchicum* species.^{9,10} This is supported by the writings of Arab physicians such as Serapion the Younger (ca. 12th century) and Ibn al-Baitar (1197–1248), who treated the name *hermodactyl* as a synonym for the Arab name *surugen*, which al-Baitar described as “similar to the saffron, has leaves like the onion, a stem one span long, and a white root with a red cover, the root being soft, sweet, and toxic as mushrooms.”⁹

The plant was almost absent in early European medical writings until Anton Freiherr von Störck (1731–1803), a physician in Vienna, Austria, wrote a book about the usefulness of autumn crocus for the treatment of edema. But it was not until 1780, when Nicolas Husson, an officer in the French army, introduced a medicinal water that contained an infusion of *C. autumnale* as the main ingredient and successfully used it to treat patients with gout, that the potential medicinal virtues of the plant started to spark the interest of the European medical community.⁹

The main active alkaloid in autumn crocus was isolated in 1820 by French pharmacists Pierre-Joseph Pelletier

(1788–1842) and Joseph-Bienaimé Caventou (1795–1877).^{11,12} They gave it the name veratrine due to its similarity with a constituent from the roots of white hellebore (*Veratrum album*, Melanthiaceae) and sabbadilla (*Schoenocaulon officinale*, syn. *V. sabbadilla*, Melanthiaceae). After further inspection, German pharmacist and chemist Philipp Lorenz Geiger (1785–1836) noticed that veratrine was different from the constituents obtained from white hellebore and named it “colchicine.”^{9,12} However, the structure of colchicine was not fully confirmed until 1952.¹³

Colchicine and Inflammatory Conditions

Prescription drugs containing colchicine started to be used in the 1950s for the treatment of gout, but use declined due to the narrow therapeutic index (the difference between effective and toxic doses). In 2010, the US Food and Drug Administration (FDA) banned the manufacture, distribution, and marketing of unapproved oral colchicine (i.e., medications that had been grandfathered due to longstanding use without going through the FDA drug approval process). One company, URL Pharma (Philadelphia, PA), successfully took colchicine through the FDA approval process, and even-



Autumn Crocus: A 'Late Bloomer'

The 2006 Swiss movie *Late Bloomers* (originally titled *die Herbstzeitlosen*, the German name of the autumn crocus) tells the story of 80-year-old Martha, who, after her longtime husband dies, starts a business making underwear. Before her marriage, Martha had been a seamstress for a lingerie company, and for many years had been dreaming of returning to her craft. However, the new boutique with risqué apparel made by the octogenarian does not please everyone in the small rural village where Martha lives, especially not her son, the village priest, and the president of the local conservative political party, who consider such a store morally objectionable and an eyesore for the quaint little village.

Like the movie's heroine, the autumn crocus is also a late bloomer. It produces flowers in late fall in fertile meadows and pastures in Europe, from southeastern Ireland to central Bulgaria, and from northern Greece to central Germany. Naturalized populations have been found as far north as southern Scandinavia.⁷

Autumn crocus *Colchicum autumnale*
Photo ©2021 Steven Foster



tually received three years of market exclusivity for Colcrys® for the treatment of gout, as well as a seven-year exclusivity period for its use to treat familial Mediterranean fever (FMF), an autoinflammatory disorder that causes recurrent fevers and painful inflammation of the abdomen, lungs, and joints.¹⁴

While generally known as an agent that inhibits cell division, colchicine's anti-inflammatory properties have been the subject of much interest in recent years as a first line treatment for gout. Colchicine is able to prevent the formation of pro-inflammatory signal molecules and restricts the movement of cells of the innate immune system that can exacerbate inflammatory processes.^{15,16} This has led to a number of new uses, such as the treatment of FMF, pericarditis (inflammation of the pericardium fibrous membrane surrounding the heart), and Behçet's disease, a rare disorder that causes blood vessel inflammation.¹⁷ In addition, a 2020 study of 5,522 patients with coronary heart disease found a significant reduction in the risk of death in patients taking 0.5 mg oral colchicine per day compared to placebo.¹⁸

Colchicine and COVID-19

Based on the promising results of clinical studies in these inflammatory conditions, researchers started to investigate if colchicine could help prevent or limit complications resulting from the inflammatory effects known as cytokine storm in patients with COVID-19.¹⁹ In July 2020, Schlesinger et al¹⁶ listed 10 registered clinical studies that were investigating the usefulness of colchicine for patients with COVID-19, including two large clinical trials with a targeted enrollment of 2,500 (COLCOVID trial) and 6,000 (COLCORONA trial) patients. By November 2020, the total number of trials had grown to 22.¹⁷ The initial results of two studies suggest that patients treated with 0.5–1 mg oral colchicine per day had a longer survival time²⁰ and a lower risk of death.²¹

The COLCORONA trial

A preprint of the results of the COLCORONA clinical study was published in January 2021.¹ This randomized, double-blind, placebo-controlled trial compared 0.5 mg oral colchicine (twice daily for the first three days and then once daily for 27 days thereafter) to placebo in 4,488 patients who had been diagnosed with COVID-19, either by polymerase chain reaction (PCR) testing or using clinical criteria. While the study initially planned to enroll 6,000 patients, the investigators terminated the study once 75% of the planned patients were recruited due to logistical issues and the need to provide results in a timely fashion given the urgent need for therapeutic options for patients with COVID-19. The study assessed hospitalization and death rates as the primary endpoints and the need for mechanical ventilation as the secondary endpoint.

Of the 2,235 patients in the colchicine group, 101 patients were hospitalized and five patients ultimately died, compared to 128 hospitalizations and nine deaths in the placebo group (n = 2,253). Mechanical ventilation was necessary for 11 patients in the colchicine group and 21 in

the placebo group. Among the 4,159 patients with PCR-confirmed COVID-19, death or hospitalization occurred in 4.6% and 6.0% of patients in the colchicine and placebo groups, respectively (odds ratio, 0.75; 95% CI, 0.57-0.99; $P = 0.04$).¹

Serious adverse events were reported in 4.9% of the colchicine group and 6.3% in the placebo group ($P = 0.05$). Pneumonia occurred in 2.9% and 4.1% of patients, respectively ($P = 0.02$). Diarrhea was reported in 13.7% and 7.3% of patients, respectively ($P < 0.0001$). Among patients with diabetes, hospitalization or death occurred in 6.1% of those in the colchicine group and 9.6% in the placebo group (odds ratio, 0.61; 95% CI, 0.37-1.01), possibly because the primary endpoints are more likely to occur in high-risk patients.

The initial results of the COLCORONA trial suggest that colchicine may be able to reduce hospitalization and death rates.¹ As the paper has not yet been peer reviewed, the results should be interpreted with caution. Additional findings from other studies of colchicine in patients with COVID-19 are expected to be published later this year.

Conclusion

The medicinal value of the autumn crocus and colchicine is closely linked to their toxicity. Ingestion of any parts of this plant can be fatal. Due to the small difference between the effective and toxic dosages, the medicinal use of colchicine has been limited to patients with gout and pericarditis. However, new clinical research on colchicine's anti-inflammatory effects using lower doses has brought a renewed interest in the drug. Its potential benefits for life-threatening diseases such as COVID-19 may lead to wider professional use of this fascinating plant constituent. More research to confirm colchicine's benefits to treat symptoms of inflammation in patients with COVID-19 is needed to establish its suitability as a valuable therapeutic agent. HG

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Systematic Review Shows Oral Intake of Ginger May Improve Postpartum Nausea and Vomiting, Digestion, Inflammation, and Colorectal Cancer Risk Markers

Reviewed: Anh NH, Kim SJ, Long NP, et al. Ginger on human health: A comprehensive systematic review of 109 randomized controlled trials. *Nutrients*. January 2020;12(1). doi: 10.3390/nu12010157.

By Samaara Robbins

Ginger (*Zingiber officinale*, Zingiberaceae) root traditionally has been used to relieve common gastrointestinal (GI) issues, including abdominal pain, nausea, and vomiting. Some studies have shown that the anti-emetic properties of ginger may be an effective treatment for motion sickness, post-operative nausea, and chemotherapy-induced nausea and vomiting (CINV). This systematic review aimed to summarize the effects of oral ginger consumption on any clinically studied aspect of human health, provide direction for future clinical research, and discuss the shortcomings of the available randomized controlled trials (RCTs).

Four English and two Korean databases were searched through July 2019: PubMed, EMBASE, Cochrane Central Register of Controlled Trials, Clinical Trials, Korean Studies Information Service System (KISS), and National Digital Science Library (NDSL) of Korea. RCTs investigating the efficacy of ginger on human health and disease were included. After excluding ineligible articles (e.g., duplicates, case reports, commentaries, reviews, etc.), a total of 109 articles were included in this systematic review and organized into six subsections: anti-emetic ($n = 47$), GI ($n = 12$), analgesic ($n = 16$), anti-inflammatory ($n = 8$), metabolic improvement ($n = 16$), and others ($n = 10$).

Most of the included RCTs had a sample size of less than 60 participants. The effects of ginger were assessed using various controls, including placebo ($n = 73$), medications or other functional materials ($n = 14$), both placebo and medication or other functional materials ($n = 16$), or no treatment ($n = 6$). Ginger was administered in daily doses that typically ranged from 500 mg to 1,500 mg. More than half of the studies were conducted in Iran or the United States.

Anti-emetic Effects

Of the 47 RCTs that evaluated the anti-emetic effects of ginger, 16 studies investigated CINV. Eight demonstrated a positive effect of ginger on the prevention or alleviation of CINV as well as reduction of acute and delayed CINV in both children and adults.

Hyperemesis, or nausea and vomiting of pregnancy (NVP), was evaluated in 14 RCTs. Eight studies compared ginger to a placebo, demonstrating significant effects in the ginger group (P value not given). In general, ginger

Study Details: At a Glance	
Study Design	Systematic review
Included Studies	109 studies
Interventions	Various ginger products
Controls	Various
Disclosures	The authors declared no conflicts of interest.

showed similar effects when compared to other medications including dimenhydrinate and metoclopramide.

Post-operative nausea and vomiting (PONV) was evaluated in 11 RCTs. Five showed no significant benefits using ginger to treat PONV. One study demonstrated ginger's effectiveness in treating nausea and vomiting induced by antiretroviral therapy ($P = 0.001$).

GI Effects

Ginger also was assessed for its protective effects on the GI system. Seven RCTs studied gastric function, mainly gastric emptying and gastric dysrhythmia (abnormal frequency of gastric contractions). Ginger was reported to enhance gastric emptying. Ginger proved beneficial in the prevention of slow-wave gastric dysrhythmias induced by acute hyperglycemic events ($P < 0.05$).

Four RCTs evaluated the risk of colorectal cancer, and there were mixed results with the ginger treatments. Ginger was shown to have a beneficial effect on colorectal cancer by reducing tumorigenic risk factors; however, there was no difference in these risk factors between the ginger and placebo groups for those with average risk of colorectal cancer.

One study determined no difference between the ginger and placebo groups in reducing the symptoms of irritable bowel syndrome.

Analgesic Effects

Seven RCTs examined the analgesic effects of ginger on primary dysmenorrhea. Four compared ginger to other medications (e.g., mefenamic acid and ibuprofen) and found similar efficacy between the two groups. Three trials compared ginger to a placebo and measured the decrease in pain using a visual analog scale. These studies reported contradictory results, with two studies in favor of ginger and the other reporting no difference between the groups.

Four RCTs evaluated muscular pain. Two of these studies indicated a lack of evidence supporting ginger's effect on muscular pain, and two reported that ginger partially relieved muscular pain when compared to placebo.

Migraines and headaches were studied in three RCTs that reported significant differences in symptom attenuation ($P < 0.05$ for all). Two studies demonstrated that ginger may be beneficial for reducing low back and chest pain associated with transluminal coronary angioplasty (a procedure used to open blocked coronary arteries).

Anti-inflammatory Effects

Eight RCTs evaluated the anti-inflammatory effects of ginger in arthritis-related diseases, particularly osteoarthritis (OA). Six studies reported that ginger consumption improved symptoms of OA when compared to placebo. Additional studies demonstrated potential pain reduction with ginger supplementation in patients diagnosed with OA and rheumatoid arthritis.

Metabolic Effects

Ginger was assessed in patients with type 2 diabetes mellitus (T2DM) and obesity. Five studies evaluated the effects of ginger on diabetes-related indices including glycemic markers, lipid levels, and blood pressure. Ginger supplementation did not have a significant effect on blood pressure in T2DM, and only minimally reduced weight in obese women.

Four studies examined conditions related to obesity including cardiovascular disease, serum adipocytokines, and breast cancer. Among these studies, three demonstrated that ginger had a positive effect on fasting blood sugar, hemoglobin A1c (HbA1c), insulin sensitivity, and insulin resistance.

In terms of obesity and cardiovascular health, ginger was beneficial in lowering risk factors including body fat mass, body fat percentage, total cholesterol, waist circumference, waist-to-hip ratio, and insulin resistance. Ginger may have antioxidant and anti-dysmetabolic effects in obese women diagnosed with breast cancer. Additional studies showed that ginger may reduce risk factors of metabolic syndrome.

Other Effects

The authors also reviewed RCTs that evaluated the use of ginger for thermoregulatory, thrombotic, and respiratory functions. Ginger demonstrated mixed results for thermoregulatory function (maintaining normal body temperature). However, ginger may reduce the use of mechanical ventilation and length of stay in intensive care in patients diagnosed with acute respiratory distress syndrome (ARDS) and asthma.

Two studies reported little to no effect of ginger on thrombotic reaction (blood clot formation). However, one study using a single dose of 10 g powdered ginger showed a significant reduction in adenosine diphosphate-induced and epinephrine-induced platelet aggregation in patients recovering from myocardial infarction (P value not given).

Ginger was shown to significantly reduce menstrual bleeding in teenagers aged 15 to 18 years ($P < 0.001$). Another study showed that ginger significantly increased milk volume on the third day postpartum compared to placebo ($P < 0.01$).

Adverse Events and Study Quality

Only 17 studies reported adverse events. Heartburn was reported in 16 studies in which participants received a daily dose between 500 mg and 2,000 mg of ginger. The remain-



Ginger *Zingiber officinale*
Photo ©2021 Matthew Magruder

ing side effects were not conclusively assigned to ginger due to small sample size. GI-related side effects included heartburn, nausea, abdominal pain, bloating, gas, and epigastric distress. Diarrhea was reported in two studies that evaluated heavy menstrual bleeding after elective cesarean section. Patients that underwent laparoscopic surgery reported cardiovascular and respiratory symptoms with ginger treatment.

The majority of the studies did not describe the blinding of assessors or methods for random sequence generation and allocation concealment, and fewer than half of the studies were classified as having a low risk for selection and detection biases. Most of the studies were classified as having a low risk of performance, attrition, and reporting biases, with 101 and 103 studies assigned to low risk of attrition and reporting bias, respectively. Using the Cochrane Collaboration's quality assessment tool, only eight studies were assessed as having a low risk for every type of bias.

The majority of RCTs evaluating the efficacy of ginger on human health focused on nausea and vomiting, GI function, pain, inflammation, metabolic syndrome, and other symptoms. Most of the studies showed that ginger had a positive outcome on the selected measure, especially those studies that evaluated NVP, digestive function, markers for colorectal cancer risk, and anti-inflammatory functions. Limitations include relatively small sample sizes, inconsistent evaluation systems or parameters, and general quality of the trials. The authors recommend that future research include detailed descriptions of the methodology and a sufficient pool of participants to address the functional characteristics of ginger. HG

Dark Chocolate Improves Verbal Episodic Memory Compared to White Chocolate in Healthy Young Adults

Reviewed: Lamport DJ, Christodoulou E, Achilleos C. Beneficial effects of dark chocolate for episodic memory in healthy young adults: A parallel-groups acute intervention with a white chocolate control. *Nutrients*. February 14, 2020;12(2):483. doi: 10.3390/nu12020483.

By Shari Henson

Flavonoids and flavonoid-rich foods are associated with various health benefits. In particular, the consumption of cocoa (*Theobroma cacao*, Malvaceae) flavonoids is reported to benefit cardiovascular health and cognitive function. These authors conducted a parallel-group, acute intervention trial to compare the effects of dark chocolate (DC) and white chocolate (WC) on episodic verbal memory and mood in healthy young adults.

The study was conducted at the University of Reading School of Psychology and Clinical Language Sciences in Reading, United Kingdom, and included 57 females and 41 males recruited from the university student population through posters and online notices. Forty-nine participants were assigned “according to a predetermined alternating order” to one of two groups to consume either DC or WC bars (Green and Black’s; London, UK) that were matched for calories (203 kcal) and weight (35 g). The DC contained 70% cocoa; its specific flavonoid content was not assessed. Based on analyses of DC from other peer-reviewed studies, the authors estimated that the DC bar used in their study contained 83 mg flavonoids (assuming 100 mg of DC contains 237 mg total flavonoids). WC does not contain flavonoids.

Outcome measures were assessed at baseline before the participants ate the chocolate and two hours afterward. The Rey Auditory Verbal Learning Test (RAVLT) tool was used to measure episodic memory. For the RAVLT, subjects listened to a list of 15 nouns and, immediately after, were asked to recall as many words as possible; this process was repeated four additional times using the same words. Next, the subjects listened to an “interference” list of 15 different nouns and, immediately after, were asked to recall as many of the new words as possible. After a 20-minute delay, subjects were then asked to recall words from the first list. RAVLT scores included immediate word span,

Study Details: At a Glance	
Study Design	Parallel-group, acute intervention trial
Participants	98 healthy university students
Test Material	35 g bar of organic dark chocolate (Green and Black’s; London, UK)
Control	35 g bar of organic white chocolate (Green and Black’s)
Disclosures	The authors declared no conflicts of interest.

words learned, final acquisition, total acquisition, proactive interference, retroactive interference, delayed recall, and total recall. The authors noted the fact that all subjects were enrolled in a university degree program “enabled control over educational attainment, which is a predictor of episodic memory performance.”

Subjective mood was assessed using two self-report measures: the Positive and Negative Affect Schedule (with higher scores representing higher levels of affect) and the Bond-Lader scale, which assesses alertness, contentment, and anxiety (with higher scores indicating higher levels of each variable).

Upon arriving at the test site, during session one, participants were measured for height and weight, completed the outcome assessments, and then ate their assigned chocolate. They returned to the laboratory two hours later after fasting and completed the outcome assessments for a second time. Laboratory conditions remained consistent during the trial.

Two hours after consumption of the chocolate, greater improvements in RAVLT scores were observed in the DC group compared to the WC group for immediate word span, words learned, final acquisition, total acquisition, delayed recall, and total recall (Table 1). These results indicate an increased ability to learn words initially and throughout the task. A lack of any effect on interference in the DC group suggests that the DC did not reduce the process of forgetting caused by learning new words or reduce the effect of old learning on new learning.

No significant effects were observed for the subjective mood outcomes. Positive affect (the extent to which one experiences positive emotions and interactions) and anxiety increased and negative affect decreased in both groups from baseline to two hours after chocolate consumption. The authors note that the reported anxiety may be related

Table 1. Mean Number of Words Recalled Two Hours Post-Consumption

	Dark Chocolate	White Chocolate	Interaction P-value
Immediate Word Span	6.53	4.94	$P = 0.00005$
Words Learned	5.59	4.14	$P = 0.0004$
Final Acquisition	12.1	9.1	$P < 0.00001$
Total Acquisition	50.3	38.7	$P < 0.00001$
Delayed Recall	10.6	7.41	$P < 0.00001$
Total Recall	67.4	51.1	$P < 0.00001$

to anxious feelings associated with anticipating performing the RAVLT.

The authors suggested that an increase in cerebral blood flow following the consumption of flavonoid-rich cocoa, which has been observed in other studies, may be a possible mechanism of action for the episodic memory improvements seen after two hours in the DC group.

A limitation of this study is that sensory properties, such as taste and pleasure, may have affected the cognitive effects; however, the authors state this is somewhat countered by the lack of differences in positive and negative affect between the two groups. Another limitation is

the lack of assessment of lifestyle factors (e.g., sleep quality, diet, and physical activity) and hormonal variations, which could have contributed to differences in cognitive function. The study is further limited by the fact that the flavonoid content of the DC was not measured.

The authors conclude that “70% cocoa dark chocolate consumption appears to benefit verbal episodic memory two hours post consumption in healthy young adults relative to a white chocolate control. These findings support the notion that everyday available portions (35 g) of dark chocolate might confer benefits to the brain in healthy consumers.” HG



Cacao *Theobroma cacao*
Photo ©2021 Steven Foster

Systematic Review of Human Trials Regarding Dosage, Efficacy, and Safety of CBD in Adults

Reviewed: Larsen C, Shahinas J. Dosage, efficacy, and safety of cannabidiol administration in adults: A systematic review of human trials. *J Clin Med Res.* March 2020;12(3):129-141. doi: 10.14740/jocmr4090.

By Mariann Garner-Wizard

Cannabidiol (CBD), a psychoactive but non-intoxicating cannabinoid in cannabis (*Cannabis sativa*, Cannabaceae), has promise in somatic and psychiatric disorders. Cannabis research and clinical use have been limited by concerns about its effects on the central nervous system (CNS), abuse potential, and legal status. CBD is well tolerated, has low abuse potential, and is being studied actively. In vitro and in vivo studies suggest that it has analgesic, anti-epileptic, anti-inflammatory, anti-psychotic, and immunomodulatory effects.

Despite regulatory issues, CBD is sold in many products that are used for various indications. It is unclear what formulations and doses should be used in trials. However, dosages in many over-the-counter (OTC) products (typically 20-25 mg) are far less than dosages used in clinical trials. This systematic review summarizes evidence on CBD administration, dosage, efficacy, and safety in humans.

A search of electronic databases revealed, after removal of duplicates, 362 studies in English published from 2000 to November 5, 2019. Included studies had at least 10 partici-

Study Details: At a Glance	
Study Design	Systematic review
Included Studies	25 studies (N = 927), including 22 controlled clinical trials and three observational studies
Interventions	Various CBD formulations
Controls	Placebo or active control (amisulpride in one study)
Disclosures	The authors declared no conflicts of interest.

pants each and evaluated CBD alone. Pediatric trials were excluded, which eliminated many studies on epilepsy.

Of the studies retrieved, 25 were included in the review. Of these, 22 were controlled clinical trials and three were observational studies. Of the controlled trials, 20 were randomized (RCTs) and two were not. Of RCTs, 14 were individually randomized parallel trials, five were individually randomized crossover trials, and one was a cluster randomized crossover trial. Studies were conducted in five

Cannabis Cannabis sativa
Photo ©2021 Brian Shamblen



nations, mostly the United Kingdom. The risk of bias in RCTs was assessed via the Cochrane tool. Heterogeneity, assessed by grouping studies by indication, outcomes, and mode of administration, was too great for data to be pooled. Grading of Recommendations Assessment, Development, and Evaluation (GRADE) criteria were used to rate quality of evidence for given outcomes.

Most studies used pure CBD, one used cannabis seed CBD oil, and one used a CBD-rich botanical extract. Most used oral capsules. Vaporization and sublingual oil also were used. Placebo was the most-used comparator, and only one study had an active control. Among the RCTs, three had low risk of bias, eight had high risk, and nine had uncertain risk. Major potential sources of bias were in randomization and selection of reported results. Some studies did not report outcomes specified in their methods or changed the main outcome after registering the trial.

Anxiety, assessed in 11 studies (358 participants), was the main outcome in eight studies. Two studies were limited to patients with anxiety disorders, and one was limited to those with non-clinical paranoia. Four individually randomized parallel controlled trials studied CBD's effects on subjective anxiety. In two of those trials, people with social anxiety disorder (SAD) taking 600 mg and healthy individuals taking 300 mg reported reduced anxiety as assessed by a visual analog scale (VAS) vs. placebo. In a third trial, 150, 600, and 900 mg doses failed to affect anxiety as assessed physiologically. The fourth trial found that 600 mg CBD reduced anxiety according to the Beck Anxiety Inventory compared to placebo. Two crossover RCTs using 400 and 600 mg CBD reported reduced anxiety and increased mental sedation. Two non-RCTs gave 600 mg to healthy individuals. One study found no difference in anxiety and the other found less anxiety compared to placebo. In two studies, 16 or 32 mg CBD, administered in one study via inhalation, enhanced fear extinction (a reduction of previ-

ously acquired conditioned fear responses). The evidence supporting the anxiolytic effect of acute CBD intake is of low quality according to GRADE criteria.

Four parallel-group RCTs (196 participants) assessed the effects of CBD on cognitive impairment and psychotic symptoms in people diagnosed with schizophrenia. CBD at 600-1,000 mg per day for up to six weeks was compared to placebo and active controls. One RCT found no differences between CBD and placebo at six weeks. One found that CBD was as effective as amisulpride at four weeks in improving symptoms, with "marked tolerability and safety." One RCT found 1,000 mg per day CBD an effective adjunct to antipsychotic drugs, significantly improving symptoms and clinical impressions. In a study of single doses (300 or 600 mg), no improvement was seen in selective attention on the Stroop Color and Word Test. Evidence of benefits for this indication is of moderate quality by GRADE criteria.

Three studies assessed the use of CBD in substance use disorders. Single oral doses (200, 400, and 800 mg) of CBD did not reduce reinforcing effects of cannabis smoking. Both inhalation of CBD for one week and single oral doses (800 mg) had possible benefits in reducing tobacco (*Nicotiana tabacum*, Solanaceae) use. In single RCTs of type 2 diabetes, Crohn's disease, and ulcerative colitis, no benefits were seen. Single arm trials assessed oral CBD as an adjunct to anti-epileptic treatment and reported fewer seizures ($P = 0.01$); a topical cream for serious skin inflammation, with good results; and sublingual oil drops as an adjunct treatment for adverse effects (AEs) of human papilloma virus vaccine, again with positive results.

CBD AEs, reported in 10 studies, were generally mild and brief. Higher-quality and consistently reported RCTs, as well as more research on single cannabinoids vs. whole-plant extracts and different modes of administration, are needed. HG

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China aster (*Callistephus chinensis*) engraving from Redouté's *Choix* (1827-1833). Courtesy of Taschen, Cologne.

Radiant Redouté

Botanical Artwork of ‘the Raphael of Flowers’

By Connor Yearsley

All botanical engravings courtesy of Taschen, Cologne.

Nicknamed “the Raphael of Flowers,” Pierre-Joseph Redouté (1759–1840) is widely considered one of the greatest botanical artists ever. During his long life, he produced more than 2,000 botanical paintings of more than 1,800 plant species. Some of these had not been depicted for publication before, and many were published in volumes as copper stipple engravings. Redouté was one of few botanical artists to work independently of botanists, yet his work is highly faithful to nature.^{1,2}

Unlike some of his colleagues, who at least sometimes worked from dried, pressed herbarium specimens, Redouté depicted mainly live plants from gardens around Paris, which allowed him to achieve a remarkable level of refinement. Also, unlike many of his contemporaries who often worked on an individual commission basis, Redouté had a studio with employees and numerous pupils, both young men and women, some from upper-class Parisian society.¹

Partly due to his pleasing personality, Redouté had rich and influential patrons from both the *ancien* and *nouveau régimes* who were willing to pay high prices for his artwork. These included Queen Marie Antoinette (1755–1793), wife of King Louis XVI (1754–1793); Empress Joséphine Bonaparte (1763–1814), first wife of Napoleon I (1769–1821); Empress Marie Louise (1791–1847), second wife of Napoleon I; and Queen Maria Amalia (1782–1866), wife of Louis Philippe (1773–1850), the last king

of France.^{1,2} Redouté was highly influenced by the Dutch painters Jan van Huysum (1682–1749) and Rachel Ruysch (1664–1750).³

In 2019, Taschen, an art book publisher based in Cologne, Germany, published *Pierre-Joseph Redouté: The Book of Flowers*. This beautiful, 608-page catalog includes a selection of some of the finest engravings from Redouté’s *Les Liliacées* (*The Lilies*),⁴ all 169 engravings from his *Les Roses* (*The Roses*), and all 144 engravings from his *Choix des plus belles fleurs et des plus beaux fruits* (*Selection of the Most Beautiful Flowers and the Most Beautiful Fruits*),⁵ or “*Choix*” for short. Published in Redouté’s later years, between 1827 and 1833, *Choix* mainly contains works that were selected to appeal to viewers and often printed from reworked plates from his earlier publications.¹



Cover of *Pierre-Joseph Redouté: The Book of Flowers*. Courtesy of Taschen, Cologne.

Oil painting of Pierre-Joseph Redouté (1759–1840) by Baron François Gérard (1770–1837), a French Neoclassical painter and portraitist who was born in Rome and also painted portraits of Napoleon and Joséphine Bonaparte, among other prominent figures. Kodak Ektachrome photographic reproduction provided by the Royal Museums of Fine Arts of Belgium.



Map showing some of the locations referenced in the article.



Taschen's book provides a glimpse into the gardens and greenhouses of a bygone Paris. The text (in English, French, and German) includes biographical information about Redouté and was written by H. Walter Lack, DPhil, a professor at the Free University of Berlin and former director at the Botanical Garden and Botanical Museum in Berlin.¹ Some of the depicted plants in the book have ethnobotanical (including medicinal) uses, and 11 of these prints are featured here. *HerbalGram* is grateful to Taschen for generously providing these beautiful, historical engravings.

Redouté was born on July 10, 1759, at Saint-Hubert, a village in the Ardennes (then part of the Austrian Netherlands but now in the province of Luxembourg, Belgium, which borders the present-day country of Luxembourg). His father was a painter, and eventually so were his two brothers. He spoke Walloon, a Romance language spoken in the Wallonia region of Belgium, and he had little formal education. At age 13, he left home with his paintbox to explore Flanders and other parts of the Low Countries (including present-day Belgium and the Netherlands). For the next decade, he was a wayfaring artist, gained some training in Liège (in present-day Belgium) and discovered the work of van Huysum in Amsterdam.^{1,2,6}

In 1782, he joined his older brother, Antoine-Ferdinand, in Paris, designing scenery for theaters. He began painting flowers at the *Jardin du Roi*, which was created by King Louis XIII (1601–1643) in 1626 as a royal garden of medicinal plants and is now called the *Jardin des Plantes* (part of the French National Museum of Natural History).⁷ Redouté's

artwork apparently caught the attention of Charles Louis L'Héritier de Brutelle (1746–1800), a wealthy official and botanist who took Redouté under his wing, taught him about botany and botanical illustration, gave him access to his large botanical library, and commissioned some of Redouté's works. Redouté also met and befriended Dutch painter Gerard van Spaendonck (1746–1822), professor of flower painting at the *Jardin du Roi*, who had a large influence on Redouté and taught him about watercolor technique.^{1,2,6}

In 1787, Redouté went to London, where he depicted plants at the Royal Botanic Gardens, Kew, and learned about intaglio printing and how to create stipple engravings based on his paintings.^{1,2,6} With intaglio printing, the image is incised into the plate, and these incisions hold the ink (the opposite of relief printing, in which the raised areas of the plate are inked and printed). Stipple engraving uses dots instead of lines and allows for subtle nuances and elegant shading. This involves a roulette, a tool with a revolving textured wheel on a shaft with a handle. By carefully rolling the roulette over the copper plate in different directions, many dot-like depressions are created. The density of the dots determines the relative lightness or darkness of specific areas of the print.^{1,2,8}

For printing, the various colors of ink are applied by hand into the recessions of the plate, and the excess ink is wiped, often with tarlatan fabric, so ink is left only in the recessions. The plate is then put on the printing press with a sheet of dampened paper over it, and the immense pressure from the rollers presses the paper into the recessions, pull-

ing the ink into the paper. The paper is then carefully and evenly peeled off to reveal the print. Each plate is printed (or “pulled” in printmaking terms) just once before it needs to be cleaned and re-inked for the next pull.^{1,8} Redouté mainly used this method for publishing his work. The process is time-consuming and therefore costly, so patrons had to be wealthy, and publication was by subscription.¹ According to Lack, the copper plates, as a rule, were melted down after use.

In the late 1780s, probably at L’Héritier’s suggestion, Redouté was named draftsman to the cabinet of Marie Antoinette.^{2,6} He was then asked to assist van Spaendonck in contributing paintings to the *Collection des Vélins* (“the Parchment Collection”), which included depictions of plants from the Jardin du Roi and animals from the *Ménagerie du Roi*, the royal zoo in Versailles. After the French Revolution, commissions remained high, as members of the nouveau régime took over the gardens of the ancien régime and wanted their plants captured for posterity. Around that time, Redouté collaborated on *Plantarum historia succulentarum*, a work on succulent plants, with text by Swiss botanist Augustin Pyramus de Candolle (1778–1841). This included more than 170 copper engravings of Redouté’s work and was published in installments between 1799 and 1837.^{1,2}

Between 1802 and 1815, *Les Liliacées*, with 486 engravings of Redouté’s work, was published in many installments. Despite the title, it contains, in addition to lilies (Liliaceae), other plants found around Paris at the time, including irises (Iridaceae) and exotics like bromeliads (Bromeliaceae) and orchids (Orchidaceae). The texts were provided by de Candolle, Swiss botanist François Delaroché (1781–1813), and French botanist Alire Raffeneau Delile (1778–1850). Eighteen engravers contributed. Showing the significance of the work, Napoleon reportedly ordered two of his ministers to each subscribe to 80 copies of *Les Liliacées* and give them as diplomatic gifts of state.^{1,2,9}

In 1799, Joséphine purchased Château de Malmaison, an estate near the left bank of the Seine in Rueil near Paris. For her lavish gardens and greenhouses at Malmaison, Joséphine spent huge sums on the procurement and cultivation of rare, novel, and exotic plants from around the world and hired Redouté to depict them in watercolors. This resulted in *Jardin de la Malmaison*, which was published in installments between 1803 and 1805. It contains 120 engravings of Redouté’s work and text by French botanist Étienne Pierre Ventenat (1757–1808). Like *Les Liliacées*, this work was used as official diplomatic gifts. Joséphine paid Redouté a lavish salary of 18,000 francs per year, which allowed him to buy a small estate at Fleury in 1804.^{1,2}

Recording of plants at Malmaison continued with *Description des plantes rares cultivées à Malmaison et à Navarre* (*Description of Rare Plants Cultivated in Malmaison and Navarre*), for which Redouté painted 55 watercolors. French botanist Aimé Bonpland (1773–1858), who had traveled with Alexander von Humboldt (1769–1859) through South America, provided the text. After Joséphine’s death in 1814, Redouté would never have another patron who paid so well.^{1,2}

Between 1817 and 1824, Redouté’s most famous work, *Les Roses*, was published in installments. It includes 169 stipple engravings of roses (*Rosa* spp., Rosaceae) from Malmaison and other gardens around Paris. Claude Antoine Thory

(1759–1827), a wealthy botanist and Redouté’s friend, provided the text. Some of the depicted rose cultivars reportedly no longer exist. The popularity of *Les Roses* may partly be explained by its pleasing style, which largely avoided overly detailed botanical representation. The work became a symbol of the *Restauration*, the peaceful period after the French Revolution, Reign of Terror, and Napoleonic Wars.^{1,2,9}

In 1825, Charles X (1757–1836), king of France, made Redouté a member of the *Légion d’honneur*, France’s highest order of merit. Later, Leopold I (1790–1865), the king of the Belgians, made him a knight of the Order of Leopold. Despite his notoriety, however, Redouté spent his later life in debt and thus worked right until his death. In June 1840, at age 80, he died from a stroke at his Paris studio. In 1985, almost 150 years later, 468 of his watercolors sold at auction for \$5 million, demonstrating the longevity of his work. As no buyer would acquire the entire collection, it was scattered.^{1,2,9} Now, Taschen’s book makes available a large sample of Redouté’s work, so what originally only the wealthy could enjoy can now be enjoyed by many.

Maritime Squill/Sea Onion

Drimia maritima, Asparagaceae

from *Les Liliacées*

“Squill” may derive from the Greek *skilla*, possibly related to Scylla, a sea monster in Greek mythology that terrorized the strait through which Odysseus traveled. In spring, maritime squill’s large bulb bears a rosette of broad, thick, leathery, dark green leaves. In early autumn, after the leaves have died down, a tall raceme (flower cluster) emerges with small, whitish flowers. These racemes are notable on dry, barren hillsides of coastal areas of the Mediterranean, where the species is native. A variety with red-tinged flowers is called red squill.¹⁰ The Ebers Papyrus, a 16th-century BCE Egyptian medical papyrus, reportedly mentions this species as a treatment for dropsy (edema, which is sometimes caused by heart failure).^{11,12} Greek physician Hippocrates (ca. 460–370 BCE) prescribed it for asthma, convulsions, and jaundice. It also has been used as a diuretic, expectorant, and purgative.¹⁰ Use of this species, however, declined in the 19th century after digitalis, derived from purple foxglove (*Digitalis purpurea*, Plantaginaceae), was deemed preferable for treating heart failure.¹¹ All parts of maritime squill contain cardiac glycosides, which are toxic to humans, rodents, and many other animals. Its bitterness prevents most animals from eating the plant, or it induces vomiting, but rats seem undeterred. In fact, Greek botanist Theophrastus (ca. 371–287 BCE) recommended the plant as a rat poison, and it is one of the oldest known rodenticides. Its major toxicant is the cardiac glycoside scilliroside. Interest in maritime squill was renewed in the United States in the 1980s, as rats had developed resistance to anticoagulant poisons.^{10–12} This species also has shown insecticidal activity.¹³



Salvia Montana

Salvia Maritima

Autumn Crocus/Meadow Saffron

Colchicum autumnale, Colchicaceae

from *Les Liliacées*

Although toxic, autumn crocus/meadow saffron has long been used for gout (a form of inflammatory arthritis)

and other conditions. All plant parts contain the alkaloid colchicine.^{14,15} It is native to Europe and, like saffron (*Crocus sativus*, Iridaceae), flowers in autumn. Despite its name, it is not closely related to saffron or true crocuses, which belong to the Iridaceae family. The plant's star-shaped pink flowers emerge without foliage, hence its other name "naked ladies."¹⁶ The genus name *Colchicum*

derives from "Colchis," the Black Sea region of Georgia, possibly by association with mythological poisoner Medea of Colchis, as the plant is poisonous.^{14,16} First-century Greek physician Dioscorides reportedly noted the plant's toxicity. In the sixth century, Greek physician Alexander of Tralles recommended a plant, possibly a *Colchicum* species, to treat gout. In the 18th century, Nicolas Husson, a French Army officer, made a medicinal water that reportedly contained an autumn crocus infusion and used it to treat gout. Colchicine's use eventually declined due to the narrow therapeutic window between its effective and toxic dose.¹⁴ Now, however, it is used to treat other inflammatory conditions, like Behçet's disease (causes blood vessel inflammation), familial Mediterranean fever (causes recurring fevers and abdominal pain), and pericarditis (inflammation of the thin, sac-like membrane surrounding the heart).^{15,17} According to the preprint conclusion of a 2021 randomized trial on people with COVID-19, hospitalization and death rates were reduced in those who received a low dose of colchicine compared to those given a placebo,¹⁸ but more research is needed (see pages 40–43 in this issue for more details about colchicine and COVID-19).





Courtesy of Taschen, Cologne.

Wild Pineapple/Pinguin Bromelia/Piñuela

Bromelia pinguin, Bromeliaceae
from *Les Liliacées*

Native to the Caribbean, Central and South America, and Mexico, this bromeliad is a long-lived tropical perennial shrub that grows to two meters (6.6 feet) tall and three meters (9.8 feet) in diameter and often forms dense colonies. Its spiny leaves form a rosette that exceeds the inflorescence, its central leaves are bright scarlet during blooming, its flower petals are white with a pinkish blotch, and it has globose yellow berries. It is cultivated for ornament and was introduced to other Caribbean islands, Florida, Hawaii, India, and Sri Lanka. In some places, it

is invasive; it displaces native plants and shelters invasive animals. It also hosts a virus that causes mealybug wilt of pineapple (MWP), a disease that can cause pineapple crop losses of up to 40%. This species often is used as a living fence on pasture and agricultural lands due to its dense leaves and rapid spread by stolons (runners), so the risk of MWP spread is greater if these hedgerows are near pineapple orchards. Leaves of *B. pinguin* are used for textiles. Its edible, acidic fruits reportedly taste like pineapple and usually are roasted or boiled to avoid mouth irritation.^{19,20} They contain vitamin C, ash, crude fiber, calcium, magnesium, manganese, and zinc²¹ and have been used to treat arthritis, intestinal parasites (possibly due to the presence of the proteolytic enzyme pinguinain²²), and ulcers, and to make a diuretic “wine.”¹⁹ Fruit pulp preparations also have shown activity against several human-pathogenic bacteria.²¹

Banana

Musa × paradisiaca, Musaceae

from *Les Liliacées*

Banana (*Musa*) species likely were domesticated millennia ago at the Kuk Early Agricultural Site, a UNESCO World Heritage Site, in New Guinea.²³ *Musa × paradisiaca* is a hybrid of *M. acuminata* and *M. balbisiana*, the parents of most edible bananas. Its fruits are berries and usually sterile and seedless.²⁴⁻²⁶ The sheaths of its huge leaves overlap to help form a false stem, or pseudostem, which dies after flowering and fruiting. However, the roots send out suckers (offshoots) that form new pseudostems.²⁶ Use of “elite” banana clones creates concerns, because a lack of genetic diversity may increase vulnerability to diseases like *Fusarium* wilt, a fungal disease.²⁷ *Musa × paradisiaca* fruits are often

plantains, or cooking bananas, which are high in tannins and, because of astringency, usually are cooked before eating, which turns their starch into sugar. Bananas are used in various dishes and to make alcohol, snacks, and flours. They provide potassium (which can reduce risk of heart disease and lower blood pressure), vitamins B₆ and C, and more. The pulp of unripe bananas is high in cellulose (which aids digestion), hemicellulose, lignin, and starch.^{24,25} The leaf and stem of *M. × paradisiaca* have been used to treat diarrhea, the stem for asthenia (weakness) and wounds, and the leaf for inflammation, headache, and rheumatism. Parts of *M. × paradisiaca* may have analgesic, antibacterial, antidiabetic, and anti-ulcer effects,²³ but more human studies may be needed. Research also has explored uses for banana waste. Banana peel powder, for example, can reduce silver ions to form silver nanoparticles, which show antibacterial and antifungal effects.²⁵



Courtesy of Taschen, Cologne.

Pineapple/Ananas

Ananas comosus,
Bromeliaceae

from *Les Liliacées*

Europeans first cataloged pineapple on the Guadeloupe archipelago in the Caribbean during Columbus' second voyage in 1493. Columbus named the fruit *piña de Indes* because it resembles a pinecone (from pine [*Pinus* spp., Pinaceae] trees). This explains the name "pineapple," although in many languages it is called *ananas*, which derives from the Tupí term for the fruit.²⁸ Like a pinecone, pineapple fruit exemplifies the Fibonacci sequence, a well-known mathematical sequence in which each number is the sum of the previous two (0, 1, 1, 2, 3, 5, 8, 13, 21, 34, etc.). Pineapple's rind has three spirals of "hexagonal" scales, with eight parallel rows spiraling gradually, 13 spiraling moderately, and 21 spiraling steeply. These are Fibonacci numbers.²⁹ Pineapple originates from the Paraná-Paraguay river basin of Brazil and Paraguay. The Tupí-Guaraní peoples were possibly the first to domesticate pineapple, which was widespread in tropical America before Columbus arrived. Cultivation spread across the tropical world before the end of the 16th century, and pineapple came to symbolize wealth.^{28,30} In the 18th century, the Dutch and English discovered how to grow pineapple in temperate climates using hothouses called "pineries,"³¹ and pineapple was introduced to Hawaii. It is high in potassium and vitamins A and C. Native Americans have used it as food, to make alcoholic beverages, expel parasites, treat stomach complaints, and stimulate menstrual flow. The fruit and stem contain bromelain, a group of enzymes that breaks down protein. Bromelain may inhibit clotting and growth of malignant cells, reduce inflammation, and help treat wounds, and has been used to tenderize meat.²⁸



Bromelia Ananas
Michx. & Peck.

Ananas cultivi
P. B. G. & Peck.

Courtesy of Taschen, Cologne.

Grape

Vitis vinifera, Vitaceae

from *Choix*

Vitis vinifera, the common grape, is a woody vine native to southwestern Asia. Its tendrils (coiling thread-like appendages) allow the species to climb to treetops or grow horizontally across low-growing plants. Its small, greenish flowers give way to big, sweet, brightly colored fruits (berries) that attract animals, which disperse the seeds.³² Today, about 10,000 varieties of this species are cultivated.³³ Its fruits are used mostly for making wine but also eaten fresh or dried (as currants, raisins, or sultanas).³² Grape was among the first domesticated fruits. Dated to about 8000 BCE, pottery shards of vats that once held wine were found in present-day Georgia in

Transcaucasia.³⁴ Impressions of grape leaves on the bases of ceramic pots (often created when prehistoric Greek potters stood the pots on mats of leaves to dry before firing) indicate grape's use in places like southern Crete in the Early Bronze Age (ca. 3000 BCE to 2400 BCE).³⁵ Wine plays a part in the *Epic of Gilgamesh* (ca. 2100 BCE), an ancient Mesopotamian poem that is among the earliest known literary works.³⁶ *Vitis vinifera* also has been used medicinally for millennia. Ancient Greeks reportedly made use of wine's antiseptic properties. Dioscorides noted medicinal uses for grape flowers, leaves, stalks, and tendrils.³⁷ Much later, 18th-century Swedish botanist Carl Linnaeus noted the leaves as a treatment for stranguria (slow, painful urination) and tussis (cough). Both the fruit and seed contain polyphenolic compounds with beneficial antioxidant activities, and grape seed extracts may have cardiovascular benefits.³³





Fig

Ficus carica,
Moraceae

from *Choix*

With about 750 species, the *Ficus* genus is one of the largest genera of flowering plants. Of these species, *F. carica* is among the most significant. Native to parts of Asia, it is a fast-growing shrub or small tree known for its foliage and fruit. The fruit is a syconium (a fleshy receptacle with many tiny flowers) and is pollinated only by the female fig wasp *Blastophaga psenes*, which enters the fruit to lay eggs. This fig-wasp relationship has existed for more than 80 million years.⁴⁵ Early evidence of human fig consumption comes from Pre-Pottery Neolithic A (ca. 10000-8800 BCE) archaeological sites in the Jordan Valley, north to the Upper Euphrates region of Turkey.⁴⁶ In the biblical book of Genesis, Adam and Eve cover themselves with fig leaves after realizing their nakedness, though the biblical fig may be *F. sycomorus*.⁴⁵ Excavations of the Uluburun shipwreck, thought to be from the 14th century BCE and discovered in 1982 off the Mediterranean coast of Turkey, yielded fig remains among the cargo.³⁵ Carbonized fig remains were found at Pompeii, which was destroyed/preserved after Mount Vesuvius' eruption in 79 CE.⁴⁷ Now, human clinical trials show that fig may effectively treat atopic dermatitis, constipa-



Courtesy of Taschen, Cologne.

tion, and warts. Fig is dense in nutrients and a good source of vitamins, minerals, carbohydrates, other sugars, organic acids, fiber, polyphenols, and the phytochemical abscisic acid (ABA).⁴⁸ ABA may stimulate cellular uptake of blood sugar, which may be why a sweet fruit like fig seems to have better glycemic responses than refined sugars.⁴⁹



Courtesy of Taschen, Cologne.

Stemless/Trumpet Gentian

Gentiana acaulis, Gentianaceae

from *Choix*

The roots of gentian (species in the genus *Gentiana*) contain some of the most bitter known natural compounds. The genus is named for King Gentius of Illyria on the Balkan Peninsula, who ruled circa 180–168 BCE and reportedly discovered the medicinal value of yellow gentian (*G. lutea*) root. Like yellow gentian, stemless or trumpet gentian has been used in bitter tonics (to stimulate appetite, aid digestion, and treat digestive ailments) and anti-smoking formulas. It also has been used to treat arthritis, jaundice, sore throat, and wounds. This perennial is found in rocky meadows, on screes (slopes covered

with small loose stones), and in alpine/subalpine coniferous forests up to about 3,000 meters (9,843 feet) in European mountain ranges (the Alps, Apennines, Cantabrians, Carpathians, Cévennes, Pyrenees, and Sistema Ibérico). It typically grows to only four inches and is noted for its striking, upward-facing, trumpet-shaped, deep blue flowers with green spots in the throat. Due to the plant's short stem, the flowers appear to sit directly on the glossy, evergreen basal leaves, which grow in a rosette that forms a tufted "carpet" or "mat." The species name *acaulis*, meaning "stemless," is also a group name that refers to multiple short-stemmed gentian species, but stemless gentian differs from these other species in the shape of the leaves and flowers and markings inside the flowers. Stemless gentian is cultivated for ornament and depicted on the back of the Austrian one-euro cent coin.^{50,51}



Courtesy of Taschen, Cologne.

Pomegranate

Punica granatum, Lythraceae
from *Choix*

Possibly native to Persia, this small tree can be 20 feet tall and is grown for ornament and its edible fruits.⁵² Pomegranate pieces from the Early Bronze Age were found at Jericho and Arad, both in present-day Israel. Excavations of the Uluburun shipwreck yielded pomegranate remains. To the ancient Egyptians, pomegranate apparently symbolized the promise of an afterlife, and a pomegranate-shaped silver vase was entombed with King Tutankhamun (died ca. 1325 BCE). Pomegranate remains from Motya, a Phoenician site in western Sicily, indicate its cultivation there in the eighth century BCE.⁵³ When Persian King Xerxes invaded Greece in 480 BCE, pomegranates, symbolizing strength, reportedly adorned his soldiers' spears. The

Romans called pomegranate *malum punicum*, meaning "apple of Carthage,"^{52,54} and it is depicted in Roman iconography, including at the Villa of Livia and the Temple of Venus Genetrix, both in Rome.⁵⁵ In ancient Greece and Rome, pomegranate symbolized fertility, perhaps due to its many seeds ("pomegranate" derives from Latin for "seeded apple"). In Greek mythology, Persephone was forced to spend part of each year in the Underworld after eating pomegranate seeds.^{54,56} Pomegranate is also significant in many religions. Some scholars suggest that a pomegranate, not an apple (*Malus* sp., Rosaceae), tempted Eve in the biblical book of Genesis.^{53,54} The biblical book of 1 Kings states that pomegranates decorated the capitals of the pillars of King Solomon's temple. Pomegranate has been used to treat digestive and skin disorders, intestinal parasites, and more. It is rich in antioxidant polyphenols like ellagic acid and punicalagins and may help prevent cancer, cardiovascular disease, and diabetes.^{56,57}

Opium Poppy

Papaver somniferum,
Papaveraceae

from *Choix*

The opium poppy is among the oldest sources of medicinal and recreational drugs. Opium (the dried, milky latex from the unripe seed capsules) has analgesic, anti-diarrhea, hypotensive, and sedating effects. It contains the anodyne alkaloids morphine, codeine, thebaine, and more. Theophrastus, Greek physician Galen (129–ca. 216), and Persian polymath Avicenna (980–1037) all wrote about opium. Swiss physician Paracelsus (1493–1541) reintroduced opium to Western medicine. In the 1600s, English physician Thomas Sydenham introduced laudanum, an alcoholic tincture of opium, to treat pain, insomnia, and diarrhea.⁵⁸ Around 1804, German pharmacist Friedrich Sertürner isolated morphine from opium and named it after Morpheus, the Greek god of sleep and dreams. Morphine likely was the first alkaloid isolated from a plant,^{59–61} and its isolation helped launch the modern pharmaceutical industry, wherein the first “modern” drugs were based on plant-derived isolates. Chinese immigrants brought opium smoking to the United States when they came to work on railroads and goldfields during the 1849 California Gold Rush.⁶¹ During the US Civil War (1861–1865), morphine and the hypodermic syringe, recently introduced by Scottish physician Alexander Wood, aided many life-saving amputations but also caused a wave of “morphinism” (addiction).⁵⁸ In 1874, English chemist C.R. Alder Wright refined heroin



Courtesy of Taschen, Cologne.

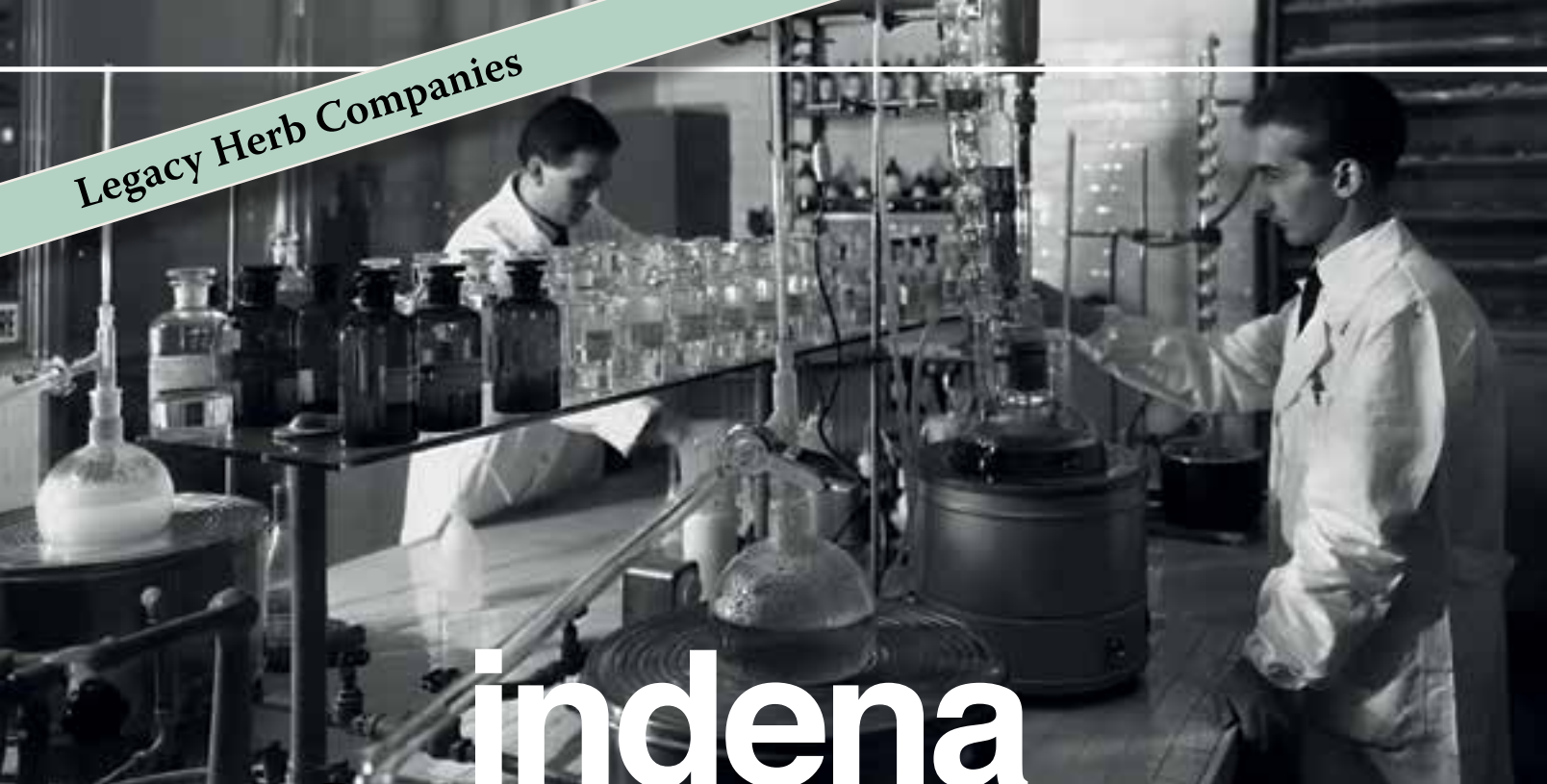
from morphine. In the early 1900s, heroin was touted as a nonaddictive morphine substitute and was marketed as a cough medicine for children before its addiction potential was realized.^{58,60,61} British chemist Sir Robert Robinson determined morphine's chemical structure, which partly earned him the Nobel Prize in Chemistry in 1947.⁵⁹ Today, morphine, codeine, and Paregoric (an elixir containing camphorated tincture of opium) are still used in conventional medicine.⁵⁸ HG

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Common primrose (*Primula vulgaris*) engraving from Redouté's *Choix* (1827–1833). Courtesy of Taschen, Cologne.



indena

CENTENNIAL

Finding Quality in Nature and Science

By Karen Raterman

In a world in which nations and companies compete for and capitalize on natural resources, sustainability may not always be a top consideration. This makes the qualities of a company like Indena SpA even more prescient. It touts a decades-long commitment to sustainable sourcing and views the connection between science and the natural world as a means to nurture invaluable resources that are of utmost importance for human health.

The Milan, Italy-based pioneer in identification, development, and production of botanical active ingredients celebrates its centennial anniversary in 2021. That is a rare industry landmark. The company was founded in 1921 as Inverni Della Beffa at the dawn of an era of burgeoning modernity and optimism. Since then, it has weathered a century of wars, economic crises, scientific discoveries, and astonishing technological advancements. Today, Indena still stands as a company that is thriving and relevant.

“Today, we manage, from our headquarters in Milan, four production sites around the world and five international subsidiaries, employing a total of more than 900 people (most of them in the strategic fields of Innovation and Quality),” wrote Indena CEO Daniele Giavini (email, April 28, 2021). “We also have about 100 patent families and more than 1,000 scientific studies published with qualified research groups.”

Despite its deep Italian DNA, Indena has always valued international expansion, and today international markets, including collaborations with several partners in

innovative fields, account for about 90% of its business, Giavini added.

From the beginning, the founding fathers of the company, Carlo Boccaccio Inverni and Biagio Alberto Della Beffa, brought a new, modern approach to the business of medicinal plants. Their initial aim was to provide not only high-quality medicinal plants but also standardized plant extracts, which helped pave the way for enhanced chemical characterization and more accurate dosing.¹

Since its early days, the company has had many firsts. Inverni Della Beffa was a pioneer in standardized extracts, and Indena became the first company to introduce the concept to the US market.¹ During the 1960s, the growing insights of its scientific team led to the publication of the renowned reference book *Medicinal Plants: Their Chemistry, Pharmacology and Therapy* (Messaggerie Italiane, 1962).² In the 1970s, Inverni Della Beffa was the first company

in the herbal industry to use mass spectrometry (MS) and nuclear magnetic resonance (NMR) machines in its quality-control laboratories, which helped scientists better analyze



the structures of complex plant extracts and overcome the skepticism of those in the conventional pharmacology field.²

The importance of such developments is far reaching. “Standardization means that you can trust your botanical ingredient in terms of safety and effectiveness,” wrote Antonella Riva, Indena’s product research manager (email, March 3, 2021). “A standardized extract is a complex matrix well characterized for its phytochemical profile. This profile [is] the identity card of the Indena extract and will be the same, batch after batch, allowing customers and consumers the same quantity of active principles,” she explained.

Other important firsts over the decades include Indena’s biomedical documentation, such as research studies that support the use of the company’s ingredients for various health conditions. Indena also paved the way for increased bioavailability of botanical ingredients with the develop-

Left photo: Indena’s chemical laboratory on Via Ripamonti in the 1960s.

Right photo: Biagio Alberto Della Beffa and Carlo Boccaccio Inverni, co-founders of Indena.

Bottom photo: Settala pharmaceutical pilot plant in Milan, Italy. Photos ©2021 Indena





Indena's Settala production plant.
Photo ©2021 Indena

ment of a proprietary, scientifically proven food-grade delivery system, Phytosome, which optimizes bioavailability and efficacy and has allowed for the translational success of natural products like curcumin and quercetin, Riva added.

Today, the company continues to make significant advancements. Most recently, it announced it has become the first Italian company authorized by the Italian Ministry of Health to manufacture cannabinoid-based cannabis (*Cannabis sativa*, Cannabaceae) extracts. Indena received additional permission from the Italian Medicines Agency (AIFA) to manufacture these extracts, making it one of only a few companies in the world to produce cannabidiol (CBD) for the pharmaceutical market.³

In 1977, Inverni Della Beffa became Indena (INdustria DERivati NATurali) and invested in technological innovation for development of botanical derivatives like extracts, while the production of finished plant-based, mainly prescription medicines, was maintained under the brand name of Inverni Della Beffa.¹

Indena's success is deeply rooted in its foundational pillars, which include quality, research, technological innovation, and solutions designed to make safe and more effective products available for peoples' wellbeing, noted Fran-

cesca de Rensis, Indena's marketing director (email, March 3, 2021).

"Attention to quality and the quest for excellence have been company hallmarks since the beginning, as well as the innovative approach to business, which has characterized the company throughout its history," de Rensis wrote. Today, she added, Indena "continues to draw inspiration from the spirit of its founders a century on. Their vision, forward thinking, scientific rigor, and stability remain the ingredients of quality for a major player in a global market."

By the 1980s, Indena was experiencing growth and an expanding global footprint.

The company was at the forefront of product research and development and produced complex extracts such as multicomponent ingredients used in food (dietary) supplements. In 1989, the company opened Indena USA led by Greg Ris, vice president of sales, to introduce the concept of standardized herbal extracts in the US market.

Preserving success also means addressing many challenges. For example, it is difficult to maintain continuity in personnel and vision. For Indena, this came from the Della Beffa family: the company's origin and inspiration, the engine of its development, and a crucial source of internal cohesion, Giavini explained. The company has always been aware that establishing structured corporate governance would provide the opportunity to innovate the typical relationship between family and business that is common in Italy, he added. "The Della Beffa family has always had a long-term vision for the company's growth," Giavini added. "For this purpose, top management figures were entrusted with leading the organization and [were] stably kept in place. This is a key factor that allowed Indena to grow and succeed."

This consistency in management and philosophy helped Indena nurture strong relationships around the world and a reputation for integrity and leadership. "A longtime member of [the Council for Responsible Nutrition (CRN)], Indena is one of the highest quality herbal ingredient firms in the industry and widely respected as a leader in quality and innovation for both nutraceuticals and pharmaceuticals," noted Steve Mister, president and CEO of CRN, a leading industry trade organization in the United States (email, April 20, 2021). "As Indena is based in Italy, CRN has had the privilege of working with Greg Ris, the company's lead US contact, as well as other Europe-based staff. We congratulate Indena on its centennial anniversary and look forward to continued collaboration in the future."

Loren Israelsen, executive director of the United Natural Products Alliance, an industry trade group, also praised Indena's engagement with the US market and its experienced staff's deep understanding of the United States' regulatory and compliance requirements. "This is quite unusual for a non-US-based company to have that level of domestic engagement and competence," he wrote (email, March 15, 2021).

Indena: By the Numbers¹

- Business sectors in 2020: 60% pharmaceutical, 40% health food
- Cultivation, production, and sale in more than 80 countries around the world
- International markets (outside Italy) account for 90% of company business
- Production sites: 4
- Produces about 20,000 tons of raw material annually
- International branches across Europe, Asia, North America, and South America: 5
- Ca. 900 employees
- 100+ primary patents and 1,000+ published scientific studies
- 120 plant species grown in 60 countries around the world

Israelsen called quality the company's chief legacy. "Indena has a golden reputation for quality that is so trusted that many companies use Indena extracts as the benchmark against which other ingredients are judged," he wrote. "Indena's [research and development] has led to breakthroughs in botanical extract efficacy. They relentlessly pursue innovation and technological improvements, which is one of the reasons they remain such a vital company."

The Meaning of a Century

Perhaps the underlying secret to Indena's success goes back to its vision about nature and science. "Since the beginning of our company's life, Indena's approach to phytotherapy added something fundamentally new to the medical knowledge of the time. Phytopreparations were being scientifically screened in the laboratory and would become companions to modern medicine," wrote Stefano Togni, Indena business development and licensing director (email, March 3, 2021). "In other words, individual active ingredients and their specific pharmacological profile were being identified, as were the multicomponent extracts with a much greater degree of complexity. This valuable information, supported as it was by scientific criteria, was made available to the public and professionals alike."

In the case of a company, one could suggest many different attributes as important to stay relevant for 100 years. "Few companies survive to be 100, and far fewer natural product companies have been able to adapt and evolve to be world leaders in the way that Indena has," Israelsen noted. "There are a few other examples. Schwabe, of Germany, is 150+ years old, and Indiana Botanic Gardens is 110+ years old, but this is such a rare achievement. It certainly deserves to be celebrated."

Gabriele Fontana, Indena – business and innovation intelligence, said that the company's history has shown Indena to be a reliable, financially solid, and flexible company, ready to adapt to environmental changes. "Being a company with a century of experience means being a solid company that has gone through a hundred years of social, economic, financial, and legislative changes," he wrote (email, March 3, 2021).

"The solidity [derives] from ... being a family company since its foundation and is proof of its healthy way of doing business. The flexibility derives from its proprietary technical know-how accumulated in 100 years of activity. The course of the last century has seen the tightening and sharpening of regulatory and quality requirements by authorities, and Indena has always been able to invest in its technology and meet the demand. There is no company that can survive for such a long period of time and miss just one of those attributes." Fontana added.

Presentation at the Via Ripamonti facility in Milan, Italy, in the 1960s.
Photo ©2021 Indena

When asked what sets Indena apart, Ris suggested that it comes down to the company's pharmaceutical roots. "We have higher standards and quality systems we adhere to. I highly doubt if other botanical companies are screening for 450 pesticides," he wrote (email, February 25, 2021). Secondly, he added, Indena is a privately owned business, and "the Della Beffa family from the beginning insisted that the company do it better than anyone else. Second best was never an option."

Indena: A History through Plants

Indena has experienced many key advances in its history, and its journey is perhaps best memorialized by its enduring bond with the plant world and the important botanical derivatives it has developed for the pharmaceutical and nutraceutical industries.

The company founders brought intuition and vision to the business, and their revolutionary approach to the medicinal plants sector brought immediate and ongoing significance to the market.³ This helped create a new scientific and industrial model that would lead to the standardized production of active principles from plants. One of the first was the horse chestnut (*Aesculus hippocastanum*, Sapindaceae), often called the "green umbrella of boulevards," lining the streets of many European cities.² Among the company's first products in the 1920s was an extract known as escin derived from the bark of horse chestnut branches. The vasoactive substance was used to produce preparations for edema and capillary fragility.⁴ The development of this raw material illustrates the importance of the scientific and quality strides from the early days of Inverni Della Beffa.

The company was also consistently ready with the right botanical ingredient at the right moment. Such was the case in the 1940s, as war descended on Europe. To ensure the safety of its production and employees, Inverni Della Beffa left its Milan facility for a temporary location in the hillside town of Alzano, in the province of Bergamo.² These years of hardship and disruption prompted demand for valerian



(*Valeriana officinalis*, Caprifoliaceae), a medicinal plant long known for its calming properties.⁵ Even through this difficult time, Inverni Della Beffa met this demand and provided a gentle remedy to help ease the tension of both military and civilian populations at the time.

Scientists at Inverni Della Beffa had also discovered that valerian's qualities were not caused by a single active ingredient but rather the synergism of several compounds.⁵ This discovery compelled the company to begin producing standardized fluid extracts in addition to isolated active ingredients. This also led to production of purified natural derivatives reduced to a single molecule that formed the basis of conventional pharmaceutical medications with well-characterized applications.

With the war over, the 1950s marked a period of expansion, change, and opportunity for Inverni Della Beffa. During these years, the company expanded internationally and continued to add to its body of research.²

One of the actives that became important at the time was from *Gloriosa superba* (Colchicaceae), a climbing plant sometimes referred to as flame lily, with a long stem and large orange-red flowers. This plant contains the alkaloid colchicine, which initially was derived from the autumn crocus (*Colchicum autumnale*, Colchicaceae) and, despite its toxicity, has well-documented anti-inflammatory properties that are useful for the treatment of gout.⁶ It eventually was discovered that flame lily provides other health benefits including muscle-relaxant properties. However, because thiocolchicoside (a derivative of colchicine) was available only in the seeds, much of the unused portions of the plant were wasted. This prompted Inverni Della Beffa scientists to develop a new fermentation process to transform colchicine present in the plant into thiocolchicoside, thus creating the active compound for muscle relaxation more efficiently. This effort was the foundation for the company's mission to source ingredients sustainably and ethically.

The expansion and development of opportunities continued for Inverni Della Beffa in the booming 1960s, as Luigi Della Beffa took the company's helm. In addition to producing active ingredients, Inverni Della Beffa began producing finished herbal medicines. A flagship product at the time was the antiarrhythmic agent (used to treat heart rhythm disorders) derived from the roots of *Rauwolfia serpentina* (Apocynaceae), an evergreen shrub sometimes called Indian snake root that is native to India and sub-Himalayan regions.² The finished herbal extract contains alkaloids like ajmaline, which can address tachycardia (rapid heart rate), premature heartbeat, and fibrillation (quivering or irregular heartbeat).⁷

The 1970s was a decade of technological progress across the world and at Inverni Della Beffa. The company began using MS and NMR machines to analyze the structure of complex extracts like silymarin from milk thistle (*Silybum marianum*, Asteraceae) fruits more accurately. Silymarin has antioxidant actions and is well known for its support and regeneration of the liver.² This allowed the company to demonstrate a plant's healing properties in an analytical way. It was to become a hallmark of Indena.

The blossoming 1980s health aesthetic based on natural principles for fitness and diet left Indena poised for further success. There was now demand for complex, effective, well-tolerated plant extracts that could complement synthetic drugs and/or mitigate their effects.² Indena's long history of research and laboratory work allowed it to meet this need and demonstrate efficacy of multicomponent derivatives — an important prerequisite for safe and reliable products in the emerging nutraceuticals market.

A plant that exemplified this concept was bilberry (*Vaccinium myrtillus*, Ericaceae), a shrub-like plant native to northern areas of Europe, Asia, and North America that has been used for medicinal purposes since the Middle Ages.⁸ Rich in antioxidants such as flavonoids and anthocya-



Pacific yew *Taxus brevifolia*
Photo ©2021 Steven Foster

nins, it is thought to have benefits for the digestive system, oral health, and vision. In the 1980s, Indena developed a new method to map and characterize the anthocyanins in bilberry, and that method remains an industry standard today.

In the 1990s, Indena continued to invest in botanical research and innovation. The yew tree (*Taxus* spp., Taxaceae) is another example.² This long-lived conifer, common in Italy and throughout Europe and North America, is also known to be highly poisonous. However, it contains important chemicals known as taxanes that have promising anti-cancer properties.⁹

The problem was that taxanes are in the tree's bark and extracting them meant destroying the entire tree. The need to find a sustainable manufacturing process became urgent at the beginning of the 1990s when the US company Bristol Myers Squibb (BMS) obtained the registration of Taxol®, the anti-cancer agent paclitaxel for ovarian and then breast and lung cancer. Indena was the first company to offer BMS a sustainable plan for manufacturing paclitaxel. First, the Della Beffa family invested in five-year cycle term plantations of yew tree for the extraction of paclitaxel from the bark. Then, Indena researchers were the first to industrialize the extraction of 10-deacetylbaccatin III (10-DAB III, a precursor of clinically used paclitaxel analogs) from the leaves of *T. baccata*, the European yew tree. That was one of the greatest achievements in the field of industrial natural products manufacturing at that time. The leaves are a renewable source and do not require the sacrifice of the tree. Furthermore, the large-scale availability of 10-DAB III paved the way for the industrialization of the semi-synthesis of the taxane family of drugs.⁹

According to Giavini, “the cooperation with Bristol Myers Squibb for the industrial manufacturing of paclitaxel was a key turning point for Indena, as it introduced in the company the concept of high-containment facilities [an ensemble of buildings, equipment, devices, and operating procedures in place for handling harmful substances in conditions that are safe for workers and the environment] for highly potent API [active pharmaceutical ingredient] handling. And, beyond that, Indena started a unique experience in dealing with the US regulatory framework for natural-derived pharmaceutical substances.”

Ris also thinks this development was important. “Indena was able to demonstrate to Bristol Myers Squibb ... that there was a more environmentally friendly way to collect the active — from needles and twigs,” he wrote. “You create the precursors from this sustainable source and then add the side chain. We became their principal supplier. This also led to a new taxane discovery for Indena and second- and third-generation products.”

Indena Today

These stories illustrate Indena's century-long commitment to preserving the balance of nature and its ongoing awareness of the connection between the health of people and the planet. The company has also made a commitment to country, people, and corporate responsibility that goes above



and beyond business norms. In its literature, the company describes being proud of its past and responsible for its future.

This notion views the nature of business and success as circular, according to Laura Bo, Indena – communications and sustainability (email, March 3, 2021). “Indena has always been conscious of how important it is to preserve the natural balance of nature and how the health of people and planet are strictly interconnected,” Bo wrote. “For a century, the company has been learning from plants, producing precious extracts and derivatives for human health, ... guaranteeing the safety of employees and people engaged in the supply chains, [and] safeguarding biodiversity and environment.”

“Of course, procedures, certifications, and a dedicated management [team] are essential to reach the goal to contribute to sustainable development,” Bo continued. “This is ... why Indena [has] a committee [that oversees] environmental, health, and safety issues with the focus to reduce CO₂ emissions and build a circular economy.”

Today, Bo added, Indena considers circularity an innovative and wealthy paradigm that brings together and reconciles nature, technology, and people in a “precious circle and evolutionary journey.” Indena has started a new Corporate Social Responsibility program, which aims to widen this circle and help the company meet its responsibilities to the environment, society, and its stakeholders.

From Ideas to Reality

Indena moves from ideas to practice with the help of bright minds. The company describes its research and development department as “an internal think tank that is dedicated to phytochemical engineering as a means to explore how humankind in the next few decades might take care of its health by reconnecting with the natural world.”¹⁰

With a shared belief that nature provides inspiration for brilliant ideas and that there is no limit to what can be achieved, Indena scientists combine intuition and know-how to solve human health issues.¹⁰ This involves studying both biological activities and underlying molecular mechanisms to identify new principles.

A big challenge, de Rensis noted, is attracting and retaining skilled workers and understanding that skillsets and thinking styles are essential. “We have a team of key people with soft and hard skills who are committed to a common purpose, performance goals, and approach, for which they hold themselves mutually accountable.”

From there, the company develops new ideas to advance both efficacy and safety of medicinal plant derivatives. For example, Indena’s proprietary Phytosome system for the formulation of extracts uses 100% natural food-grade ingredients to help enhance the bioavailability and pharmacokinetic profile of active compounds.¹ This is important, explained Riva, because if a botanical active ingredient is poorly soluble in water, it cannot cross the intestinal barrier and is not able to express its biological activities. “Thanks to our food-grade delivery system called Phytosome, insoluble botanical [active compounds] have the chance to reach the gut in the lecithin matrix with a major possibility to cross gastrointestinal epithelium.”

Bioabsorption is only the first step, she added, because the active ingredient then needs to reach the tissue where biological activity occurs. Phytosome technology allows this to happen.

Quality Control and Supply Chain Management

According to de Rensis, quality is a constant and unavoidable requirement for products, processes, technologies, services, and solutions at Indena. “We always strive to dissect, analyze, and constantly evolve our quality system, ensuring even more fairness in the system itself. As for botanical extracts, quality means the quality and control of the entire production chain, from the procurement of vegetal raw materials to checks on the finished product,” de Rensis wrote. Indena has always managed all stages of the manufacturing process in strict accordance with the most accredited protocols, she added.

Quality is particularly important now, as the industry emerges from the COVID-19 pandemic and a year of record growth, Ris noted. “The fact that new consumers are purchasing supplements, taking more responsibility for their own health during and post lockdown, is encouraging. ‘Underlying conditions’ became a classification consumers want to avoid.” Unfortunately, he added, the industry “is still plagued by products that are either adulterated or don’t meet label claims.... This has been a longstanding problem that is exacerbated when there are raw material shortages.”

Along with quality, Indena has long sought to manage its supply chain in ways that align with its circular business model. This involves full traceability, supplier qualification, and good agricultural and collection practices (GACPs).

It starts with a solid chain of custody. “One critical issue for the botanical products industry is to guarantee continuity and integrity in the supply chain together with high standard levels in terms of quality, safety, and sustainability,” Fontana wrote.

Regarding the procurement of ingredients, he added, despite the challenging times, the company’s reliable and robust partners, which have been in place for decades, have added value for Indena. Furthermore, due to its longtime experience with herbal materials, Indena is well acquainted with sourcing activities and how to maintain enough stock, which help prevent or limit shortages.

“Indena knows that paying attention at every step of the way positively impacts the quality and effectiveness we can offer,” Fontana added. “That is why we have established more than 30 quality checks, spanning the entire process, from seed to finished product, allowing us to have full traceability and complete control for a strong chain of custody.”

Environmental and Social Responsibility

The company also cares about where plants are grown, how they are handled, and the people along the supply chain, which adds another level of complexity. In fact, Bo explained, “many criteria have to be considered in a risk assessment of social and environmental impact in the supply chain.” In 2013, she said, Indena launched the Sustainable Sourcing Program to ensure the safety and wellbeing of the communities involved in its supply chain and to conserve biodiversity.

Indena also created a multidisciplinary team composed of a botanist, quality system manager, regulatory experts, a sociologist, and communications experts. This team analyzes the supply chains and their possible risk factors and then develops complex projects involving local communities, suppliers, institutions, and nongovernmental organizations (NGOs), generating positive social and environmental impacts.

Indena also has developed many programs throughout the world. Among them is the *Centella asiatica* Project in Madagascar.¹⁰ Established in 2015, in the Alaotra-Mangoro region of Madagascar, where most of the gotu kola (*C. asiatica*, Apiaceae) processed by the company is harvested, the program’s goal is to improve living conditions and decrease poverty in these local communities by promoting higher quality education and attendance rates among children, Bo explained.

Indena partnered with the Italian NGO Volontari nel Mondo RTM to help provide school kits and teaching materials to almost 3,000 children and 84 teachers in 10 elementary schools every year, organize didactic and linguistic training for teachers, build toilets and water wells or pipelines to provide clean water, and renovate and maintain school buildings.^{10,11}

The results have been encouraging, Bo noted, improving attendance rates in participating schools to 90%, as

Looking forward, the Indena team still sees many challenges and opportunities. Addressing authenticity of plant materials continues to be a focus ... as the company plans to develop and apply various techniques, including botanical, chemometric, and genetic analyses, to ensure authenticity and quality of plant materials and their derivative products.

compared to 80% in other parts of the country, increasing student enrollment by more than 10% compared to the previous year, boosting school literacy rates and exam results, and supporting teacher motivation. The project won the Convention of Pharmaceutical Ingredients (CPhI) Award for Excellence in Pharma: Corporate Social Responsibility in 2016.

The Path Ahead

Looking forward, the Indena team still sees many challenges and opportunities. Addressing authenticity of plant materials continues to be a focus, Riva wrote, as the company plans to develop and apply various techniques, including botanical, chemometric, and genetic analyses, to ensure authenticity and quality of plant materials and their derivative products.

Single- and multiple-locus DNA barcode markers, for example, are used to distinguish authentic products from counterfeits, combining standard and innovative technologies such as bCUBE® from the biotechnology company Hyris Ltd. (London, UK). Moreover, Riva noted, Indena has developed and tested an innovative DNA-based method that can strongly correlate the final product (dry extract) to the plant material used to produce it.

The need for personalized integrated solutions represents another opportunity, noted Togni. “Moving away from the ‘one-size-fits-all’ traditional concept implies having a diagnostic and tracking system and powerful algorithm to process individual data collected to elaborate personalized solutions. These [solutions] have to rely not only on drugs and supplementation, but also on dietary interventions and lifestyle changes for optimal health.”

Accordingly, the company has entered a development program with health intelligence company Onegevity (New York, NY) to further expand its commitment to innovative approaches for preventive health. “We are proud to cooperate with Onegevity,” wrote Giavini. “Our project with Onegevity is perfectly in line with Indena’s approach and with our continuous focus on research and development of highly effective solutions that are synergistic to the Onegevity wellness plan. The collaboration is allowing us to process certain botanical ingredients [in] Indena’s portfolio through the Onegevity AI platform, with the aim of discovering novel potential indications and beneficial effects for new or known botanical ingredients, as applicable to the pharmaceutical or nutraceutical market. This project fits very well with our credo ‘Science is our Nature.’”

Another increasingly important area of research is healthy aging. “Prevention and supplementation play a pivotal role in this,” Giavini added.

Whatever the future holds, Indena has never considered botanicals to be a trend and will keep looking ahead, Togni noted. “Indena’s expertise has always been creating phytochemical solutions that are versatile and timeless, evolving with people’s changing needs, with high quality, reliability, traceability, and integrity.

“The plant kingdom is still largely unexplored,” Togni added. “It expresses very high chemical diversity and complexity, developed over millions of years of evolution interacting with a surrounding challenging environment. They are very difficult to replicate synthetically. Furthermore, we see a paradigm shift in health care, moving from treatment of disease to prevention, maintenance of wellbeing, and increase of resilience.” HG

Disclosure

Indena is a long-time Sponsor Member of the American Botanical Council (ABC) and supporter of several key ABC programs. This article has been formally reviewed for accuracy by Indena staff.

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Cannabis Healing: A Guide to the Therapeutic Use of CBD, THC & Other Cannabinoids by Franjo Grotenhermen. Rochester, VT: Park Street Press; 2020. Softcover; 231 pages. ISBN: 978-1-62055-831-7. \$19.99.

By Nishi Whiteley

Franjo Grotenhermen, MD, has been a leading medical cannabis (*Cannabis sativa*, Cannabaceae) researcher for two decades. He has authored more than 50 peer-reviewed journal articles, has written or edited 11 cannabis science books, and serves on various scientific review committees. He is the founder and executive director of the highly regarded, clinically focused International Association for Cannabinoid Medicines and is the president of the German Association for Medical Cannabis. His leadership in the space has garnered him high regard among his peers as a leading authority on cannabinoid pharmacology. A practicing family physician in Germany, Grotenhermen has observed how cannabis has impacted his patients. As a result, he is an advocate for safe, legal access to cannabis for anyone who may find therapeutic benefit from its use. This book was originally published in German in 2015 and expanded and revised in French in 2017. This 2020 edition was translated into English by Jack Cain from the expanded French edition.

Cannabis Healing is well organized. It starts with the historical global uses of cannabis, followed by a basic review of plant chemistry with short explanations of how the different chemical components of cannabis interact with the human body, how different ailments may benefit from cannabis use, dosing, intake methods, and precautions. It ends with nutritional information about hemp seed and oil. The appendix offers tips on growing cannabis.

The book covers the effects of cannabis on the different physiological systems of the body and tackles the controversial issues of cannabis addiction (which is uncommon), risk of use during pregnancy, how cannabis use affects fertility, cannabis and children, and the risks of early pre-teen and teen use on brain development (an area of increasing, recent concern). While the overarching theme of the book is about the therapeutic benefits of cannabis, Grotenhermen does not shy away from sharing anecdotal and clinical data about potential risks and side effects of cannabis use, which, in this

reviewer's opinion, gives the reader a balanced viewpoint from which to make an informed assessment about whether cannabis may be beneficial for them or their patient(s).

Throughout the book, Grotenhermen shares real experiences from his patients. He weaves these anonymous patient stories with clinical and observational research study outcomes, making it easy for readers to quickly understand how cannabis may affect someone with a particular condition or symptom. Clear guidance is given for dosing, intake methods, contraindications, and how to mitigate potential risks and/or adverse side effects. Additionally, the book is well referenced with peer-reviewed journal articles for those who wish to dig deeper. For these reasons, this book achieves its purpose of being a therapeutic guide to cannabis.

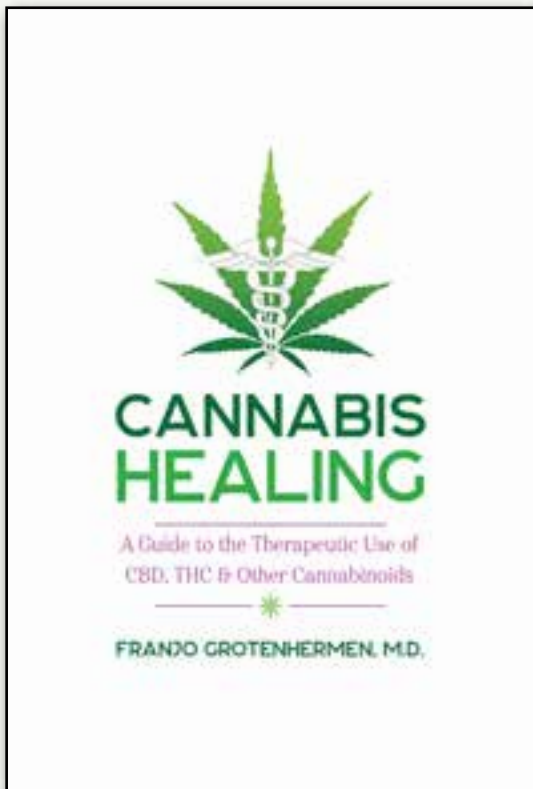
The cannabinoid tetrahydrocannabinol (THC), the primary psychoactive and intoxicating component of the cannabis plant and the most-studied cannabinoid, is the primary focus of the book, although there is some coverage throughout about cannabidiol (CBD) research and use cases.

Covering all the potential therapeutic uses of cannabis in one book is an impossible task. This book, however, does a good job of providing a basic overview of how patients with some of the most common chronic illnesses might benefit from cannabis in general. I appreciate that the author consistently communicates that the use of cannabis and cannabis products is not a one-size-fits-all approach, but that through thoughtful and measured experimentation patients are empowered to safely find the best dose for them. To that end, the guidance in the book gives readers

sufficient information to make judgements about where to start and how to escalate the dosage in increments to ultimately help them get the relief they seek.

This practical book covers a tremendous amount of information in a concise, easy-to-follow format. It can be used as a desk reference or read from beginning to end. Either way, the cannabis-naïve and the most experienced cannabis educators, researchers, and health care providers will find this book useful. HG

Nishi Whiteley is a cannabis science writer, author, and educator based in Austin, Texas. She is also the COO of CReDO Science, a cannabis-based formulation consulting and biopharma IP development company. She recently co-authored a review article on CBD, which was published in HerbalGram issue 127.



Natural Woman: Herbal Remedies for Radiant Health at Every Age and Stage of Life by Leslie Korn. Boulder, CO: Shambhala Publications, Inc.; 2020. Softcover, 320 pages. ISBN: 9781611806717. \$24.95.

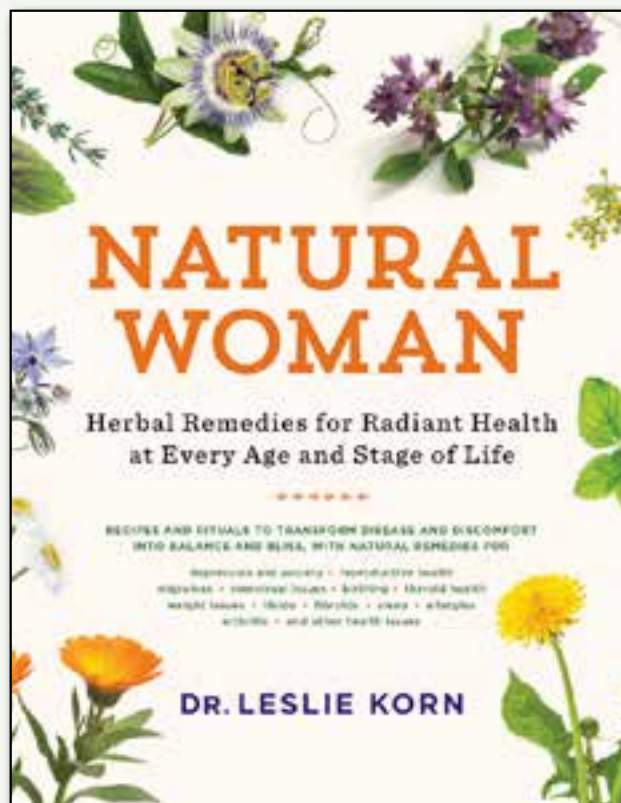
By James Lake, MD

Author Leslie Korn, PhD, MPH, is both an expert healer with deep sensibilities and a scholar of the first order with impressive academic credentials. Her career has been devoted in equal measure to treating patients and educating herbalists and physicians on safe, evidence-based uses of herbs, other natural products, and a wide range of other complementary and alternative medicine (CAM) options. In her new book *Natural Woman*, Korn offers a range of herbal remedies for maintaining well-being and treating maladies of the body, mind, and spirit. Korn's book is more than yet another compendium of reviews of herbs. In addition to featuring concise sections on the science supporting different herbal remedies, the book is filled with a wealth of practical advice on how to select safe and effective herbal products (e.g., powders, tinctures, teas, and salves).

Chapter 1, "How Herbs Heal," is a concise overview of the historical evolution of herbal medicine. Korn frames the wisdom of traditional herbal healing practices in the context of the benefits and limitations of modern science. The chapter also provides important caveats against combining certain herbs and medications, which may result in adverse effects, and a glossary of common herbal actions (e.g., adaptogen, bitter, galactagogue, nervine, etc.).

Chapter 2, "Preparing Your Herbal Medicines: Tools and Methods," introduces readers to practical methods of growing, harvesting, and preparing herbs and describes the steps involved in creating herbal medicines for improving health and vitality. In simple language, Korn describes what goes into preparing a simple herbal bath soak from rose (*Rosa* spp., Rosaceae) attar, cordials for relaxing the mind and enhancing the digestive process, slippery elm (*Ulmus rubra*, Ulmaceae) lozenges for soothing a sore throat, a topical garlic (*Allium sativum*, Amaryllidaceae) ointment for treating fungal infections, and more. Chapter 2 also introduces readers to plasters, poultices, rubs, salves, suppositories, syrups, teas, tinctures, and vaginal douches. My favorite part of this chapter was a section on the medicinal uses of honey, which has established antibacterial and antiviral properties and has been used since ancient times to treat skin infections and various ailments.

Chapter 3, "Herbs for Day-to-Day Healing and Seasonal Rhythms," describes the uses of herbs and essential oils for treatment of common physical maladies such as asthma attacks, headaches, colds, burns, and insect bites. Korn outlines the essential components of an herbal medicine first aid kit including tools and supplies for making and storing tinctures, teas, and salves. She describes the goals of seasonal cleanses for achieving optimal health and vigor at different times of the year. The steps involved in making various herbal preparations are presented in simple language. Korn's description of a "spring cleanse" for nourishing and cleans-



ing the organs following a prolonged period of inactivity is especially enjoyable and relevant.

Chapter 4, "Herbal Medicines for Everyday Use and Special Purposes," is the heart of Korn's new book. The chapter contains extensive discussions about various herbs and herbal formulas for treating everyday maladies and restoring optimal health. Korn describes a tea made with alfalfa (*Medicago sativa*, Fabaceae), nettle leaf (*Urtica dioica*, Urticaceae), and red clover (*Trifolium pratense*, Fabaceae) flowers for menopausal symptoms, artichokes (*Cynara scolymus*, Asteraceae) combined with garlic and ghee for strengthening the heart, and how to make an herbal soup for immune support and a "happy liver" smoothie to boost liver function.

Chapter 5, "Spice Medicine," describes uses of common spices such as marjoram (*Origanum majorana*, Lamiaceae), oregano (*O. vulgare*), paprika (*Capsicum annuum*, Solanaceae), rosemary (*Salvia rosmarinus*, Lamiaceae), cilantro (*Coriandrum sativum*, Apiaceae), and savory (*Satureja* spp., Lamiaceae), and some spices that are less well-known in the United States, such as tamarind (*Tamarindus indica*, Fabaceae), star anise (*Illicium verum*, Schisandraceae), and epazote (*Dysphania ambrosioides*, Amaranthaceae). Korn then provides recipes for juices, soups, teas, and smoothies that are both tasty and have health benefits. As a grilled cheese sandwich fanatic, I was intrigued by the recipe for grilled cheese and epazote and am looking for a local source of this widely used herb native to Mexico.

Chapter 6, "Spirit Plants: Finding the Goddess Within," discusses ritual uses of psychoactive plants, some of which have been used to expand consciousness in different healing traditions. The chapter begins with comments on the

appropriate, safe uses of psychoactive plants and encourages readers to work with a qualified guide if/when using any spirit plant. Korn then describes the potential physical and psychological benefits of ayahuasca (*Banisteriopsis caapi*, Malpighiaceae), cannabis (*Cannabis* spp., Cannabaceae), kava (*Piper methysticum*, Piperaceae), kratom (*Mitragyna speciosa*, Rubiaceae), peyote (*Lophophora williamsii*, Cactaceae), salvia (*Salvia divinorum*, Lamiaceae), and other spirit plants.

Chapter 7, “Herbal Medicines for Life’s Cycles, Health, and Dis-ease,” reviews herbs as aids for digestion, management of hypoglycemia and non-insulin-dependent diabetes, as tonics for stress, depression, and insomnia, for enhancing immune function, treating autoimmune conditions (e.g., lupus and some thyroid disorders), and managing pain and headaches. Other sections address bone health, postpartum depression, and female reproductive health issues, including premenstrual syndrome, irregular or heavy menstrual periods, endometriosis, polycystic ovarian syndrome, and fibroids. The chapter also includes reviews of remedies for enhancing heart health and reducing high blood pressure using recipes that are simple to prepare and contain herbs with established anti-inflammatory and/or anti-hypertensive effects. Korn also covers herbal remedies with known neuroprotective and anti-inflammatory benefits that can potentially enhance cognitive performance in some elderly individuals.

As a physician, I found the section in Chapter 7 on herbal remedies for childhood health problems especially informative. After remarking on “Clark’s rule” for adjusting herbal medicine doses in children to ensure safety, Korn introduces practical tips for managing common childhood ailments using low doses of widely available herbal remedies to minimize risk of side effects. Examples include an asthma mocha smoothie to calm inflammation in the lungs; the “bellyache rock” in which chamomile (*Matricaria recutita*, Asteraceae) oil is applied to the child’s belly followed by light pressure with a damp towel; a lavender (*Lavandula angustifolia*, Lamiaceae) diffuser for night terrors; a Chinese medicinal herb for bedwetting; and slippery elm bark pudding for colic in infants. The final section of Chapter 7 introduces readers to herbal remedies for enhancing comfort, reducing distress and anxiety, and alleviating physical pain that many individuals experience toward the end of life.

Chapter 8, “Herbal Rituals,” introduces readers to rituals in which herbal medicines are used to promote healing, celebrate important life transitions, and achieve heightened awareness. Korn distills practical suggestions on ritual uses of cedar (*Cedrus* spp., Pinaceae), copal (*Bursera* spp., Burseraceae), sandalwood (*Santalum* spp., Santalaceae), and sweetgrass (*Hierochloa odorata*, Poaceae) from her in-depth knowledge of Native American indigenous cultures, and describes how to use herbs ritually to mark different life stages including birth, coming of age, menarche and menstruation, wedding ceremonies, welcoming an animal companion, and the loss of an animal or human. Rituals are described in simple steps and are accessible to readers who have no prior knowledge of such practices.

Although *Natural Woman* is about herbal remedies for women, the book is much more than a repository of information on herbs alone. Korn weaves an integrative tapestry that encompasses a range of healing approaches informed by her expertise as a master herbalist, nutritionist, spiritual healer, massage therapist, and yoga practitioner.

The publication of *Natural Woman* is an important milestone in women’s health care. I bow to Leslie Korn for her tireless work bringing practical knowledge of healing herbs to the public, and, with this book, to women everywhere. HG

James Lake, MD, is the founder and former chair of the American Psychiatric Association Caucus on Integrative Psychiatry and author of a series of 10 short self-help books on alternative approaches in mental health care and five textbooks on integrative mental health care. His most recent book is *An Integrative Paradigm for Mental Health Care: Ideas and Methods Shaping the Future* (Springer, 2009).

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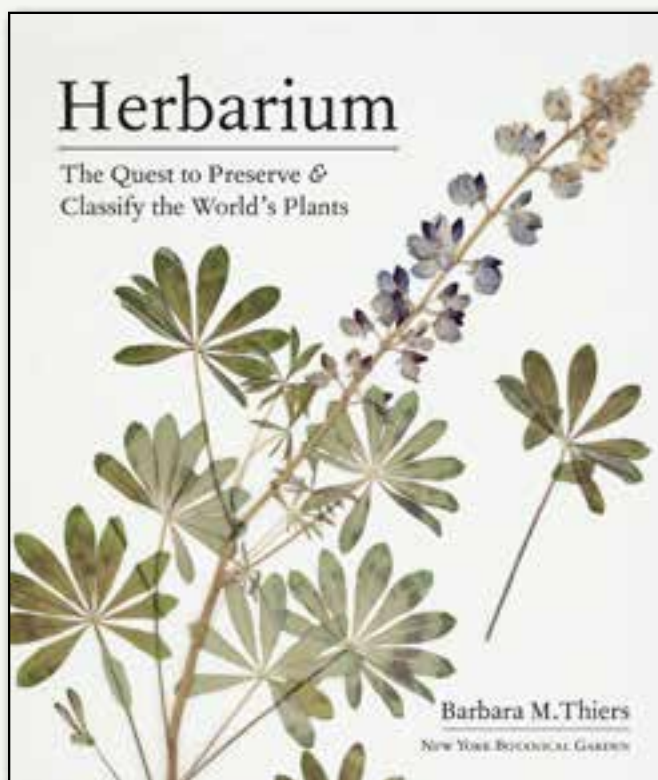
Herbarium: The Quest to Preserve and Classify the World's Plants by Barbara M. Thiers. Portland, OR: Timber Press; 2020. ISBN: 978-1-60469-930-2. Hardcover, 304 pages. \$40.00.

By Michael J. Balick, PhD

This elegantly written and lavishly illustrated book takes readers through time and place in an exploration of how herbaria (collections of preserved plant specimens used for scientific study) were first created as simple teaching tools, to their evolution as essential scientific resources that document the world's plant and fungal biodiversity and help shape our response to global change. Luca Ghini (1490–1556), an Italian physician who received his medical degree from the University of Bologna in 1527, is recognized as the first to use dried, pressed plants in his university teaching. At that time, medicine depended heavily on plants, and physicians who used these modalities were also trained in botany. After all, the misidentification of a plant that a physician prescribed for a common condition could, in the worst case, lead to the patient's death. Ghini was the first person who is documented to have taught a medicinal plant course in a European medical school. He realized that he could not always depend on book illustrations to identify medicinal plants, so he began to use living plants in his classes, giving medical students the opportunity to touch, smell, and taste the therapies that they would be prescribing.

But in winter, many living plants were unavailable, so his bold step was to create an herbarium of dried, pressed, preserved plants, first known as a *Hortus Hiemalis* (winter garden) or *Hortus Siccus* (dry garden). His technique was to take fresh plants and arrange them on paper to simulate, to the extent possible, the way they looked in nature. Then he dried the plants by applying pressure on the specimens to release the moisture these materials contained, resulting in flattened dried plants, many of which retained an element of their original colors. When properly dried and preserved, the specimens were glued onto the pages of a blank book, in which Ghini could write notes about the plants to further inform his students. Plants prepared this way and properly curated (e.g., kept from moisture, high temperatures, and insects) will last almost indefinitely. These newly created resources were far more valuable to medical professionals than the simple illustrations in medical books of the day. Ghini then went on to teach at the University of Pisa, where he created the first known botanical garden for the purpose of training physicians. Known as the *Orto Botanico di Pisa* today, this historically significant garden is open to the public, free of charge. From their initial use in teaching medical students, preserved plant collections now known as herbaria can be found around the world, furthering our understanding of botanical diversity.

Readers may remember a childhood school assignment to collect colorful leaves in the fall and press them between paper, so they could be observed with delight and studied.



With this assignment, students made an herbarium specimen, although not always with the scientific rigor necessary for proper use of the material.

This book is an extraordinary and most engaging tour of the history of botany and the establishment of herbaria. It covers botanical exploration and the remarkable and sometimes unexpected personalities who expanded our understanding of the diversity, beauty, uses, and distribution of plants and fungi. The next sections of the book discuss the development of herbaria in the United States and around the world. The final section is devoted to the future of herbaria and the relevance of these natural history collections that now hold and carefully curate an astonishing total of about 390 million individual specimens. With new technology, scientists are putting these collections to use in ways unimagined by Ghini, using data to understand global change, classifying plants by analyzing their DNA, detecting and remediating pollution, documenting and predicting threats from invasive species, and understanding atmospheric conditions of the past, all through use of these specimens. Those in the herb and supplement industries, or people who simply admire and use plants in their daily lives, will find this an important resource. This book gives life to botanical collections and is a brilliant work that can be read, understood, and enjoyed by everyone. HG

Michael J. Balick, PhD, is an ethnobotanist at the New York Botanical Garden, specializing in diversity, distribution, and traditional uses of plants.

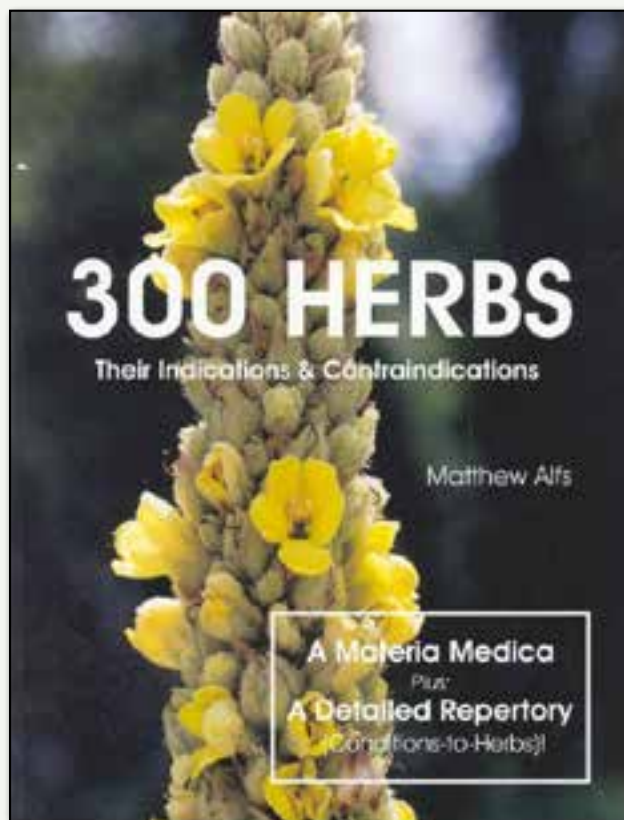
300 Herbs: Their Indications & Contraindications, 2nd ed., by Matthew Alfs. New Brighton, MN: Old Theology Book House; 2020. ISBN: 978-0-9612964-8-3. Softcover, 216 pages. \$25.00.

By David Winston, RH (AHG)

The number of books on the medicinal use of plants seemingly grows exponentially every year. Unfortunately, many offer little in the way of new, unique, or clinically useful information. In fact, most of the new books rehash the same basic information, the same “herban” myths, and generalized, often clinically irrelevant data. When Matthew Alfs first published his book *300 Herbs* in 2003, it was obvious that this was not a run-of-the-mill herb book. It is a work of serious scholarship that is also highly useful for clinical herbalists, NDs, and other medical professionals who want to deeply understand the complexities and unique qualities of the plant medicines they use.

The second edition of this book has been modestly expanded and revised to make it more relevant to today’s world of herbs. At-risk species or herbs no longer in commerce have been deleted, while increasingly popular herbs from Ayurvedic and traditional Chinese medicine (TCM) systems have been added, making it even more useful than the original work.

The book first provides an overview of differential diagnosis/assessment and energetic concepts of Greek medicine, Unani-Tibb, TCM, Ayurveda, and Eclectic medicine. This is followed by an extensive *materia medica* of 300 herbs and a repertory section that arranges herbs



by indications and health conditions. A *materia medica* (the materials of medicine) is a detailed exploration of the medicinal substances used in clinical practice. Unlike many current *materia medica*, Alfs’ book gives clear and

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precise information on each herb's energetic qualities, indications for use according to various traditional medical systems, specific indications for each organ system, and a clear description of each herb's actions.

For example, the entry for nutgrass (*Cyperus rotundus*, Cyperaceae) lists its indications for edema, premenstrual hyperhydration, and genitourinary conditions such as amenorrhea (absence of menstruation), dysmenorrhea (painful menstruation), and irregular menses caused by blood stasis. These entries also include information on typical dose and dose form. Finding this information in one concise book is rare, and it makes this an essential text for serious clinicians. Most of the rest of the book is a repertory.

The repertory not only lists herbs that affect various aspects of the musculoskeletal system, for example, but also differentiates those that are useful for different types of musculoskeletal pain. For example, black cohosh (*Actaea racemosa*, Ranunculaceae) is indicated for heavy, tensive, aching muscles, while boneset (*Eupatorium perfoliatum*, Asteraceae) is for deep and aching pain, and wild yam (*Dioscorea villosa*, Dioscoreaceae) or nutgrass is used for smooth muscle pain. The clear differentiation according to symptom picture, energetics, or location enhances practitioners' ability to make accurate and patient-specific choices in recommending the most appropriate herbs.

Repertories are common in homeopathic literature, but in the herbal literature they are few and far between. I can think of only a few examples: the rather difficult-to-use *Prescriber and Clinical Repertory of Medicinal Herbs* by F. Harper-Shove (Health Science Press, 1938), the late Michael Moore's wonderful but slim booklet *Herbal Repertory in Clinical Practice* (Southwest School of Botanical Medicine, 1990), Matthew Wood's excellent

book *The Earthwise Herbal Repertory* (North Atlantic Books, 2016), and, of course, Matthew Alfs' *300 Herbs*. These last three titles by Moore, Wood, and Alfs form a cornerstone of Western herbal knowledge to help practitioners understand the unique qualities of each herb and their specific applications for truly effective treatment. This allows clinicians to think beyond "this herb is good for pain" and start to see how one herb may be a much better choice for the exact type of pain a patient is experiencing.

The only criticism I have for the second edition of this book is that according to the bibliography, only one new reference has been added since the original edition. This is appropriate for long-gone medical traditions such as the Eclectics or Physiomedicalists where no new material has been published in the past 100 years. However, it neglects more recent texts covering TCM, Ayurvedic, African, and European *materia medica* that have been published in the 17 years since the first edition. Many of these recent texts are more authoritative than those listed in the current bibliography. HG

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Classifieds

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Perilla *Perilla frutescens*
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FOOD AS MEDICINE

PERILLA

Perilla (*Perilla frutescens* var. *crispa*, Lamiaceae) leaf has a long history of use in traditional Chinese medicine and cuisine but is relatively unknown in the West. However, the perilla plant is of interest to researchers, who see in its phytochemical profile possible treatments for food poisoning, allergic reactions, and cognitive decline. This colorful, spicy herb has flavorful, vitamin-packed leaves and oil-rich seeds that contain more omega-3 fatty acids per serving than flax (*Linum usitatissimum*, Linaceae).

Fast Facts

- In Japan, Korea, and much of southern Asia, perilla is an important, widely consumed, and easily cultivated food plant, whose leaves and seeds have a long history of use as a warming, pungent food and medicine.
- The flavor of red perilla is described as anise (*Pimpinella anisum*, Apiaceae)-like with hints of cinnamon (*Cinnamomum* spp., Lauraceae) and mint (*Mentha* spp., Lamiaceae), whereas green leaves have a stronger cinnamon spice flavor.
- Perilla appears to have therapeutic potential for treating food poisoning, influenza and respiratory viruses, asthma, diabetes, and heart disease.
- Perilla seed oil is commercially available as a dietary supplement, offering a plant-based source of omega-3 fatty acids.

Nutrition Profile

Per 100 grams of perilla leaves

Excellent source of

Vitamin K	690 mcg	575% DV
Manganese	2.01 mg	87.4% DV
Chromium	17.6 mcg	50.3% DV
Vitamin C	42.8 mg	47.6% DV
Folate	110 mcg	27.5% DV
Vitamin A	236 mcg	26.2% DV
Riboflavin	0.34 mg	26.2% DV
Vitamin E	3.9 mg	26.0% DV
Copper	0.20 mg	22.2% DV

Very good source of

Iron	2.69 mg	14.9% DV
Zinc	1.30 g	11.8% DV
Thiamin	0.13 mg	10.8% DV
Potassium	500 mg	10.6% DV

Phytochemical Focus

- Perilla seed oil contains more alpha-linolenic acid (ALA, an omega-3 fatty acid) than any other known plant source, including flax seed oil, the most widely used source of ALA in dietary supplements.
- Perilla leaf contains more beta-carotene per serving than carrots (*Daucus carota*, Apiaceae) and more lutein per serving than spinach (*Spinacia oleracea*, Amaranthaceae) or broccoli (*Brassica oleracea*, Brassicaceae).

About ABC's Food as Medicine Series

Every other month, the American Botanical Council's monthly e-newsletter HerbalEGram highlights a conventional food and explores its history, traditional uses, nutritional profile, and modern medicinal research. The articles, written by ABC Education Coordinator Jenny Perez, also feature a nutritious recipe to encourage readers to experience the extensive benefits of these whole foods.

The full "Food as Medicine: Perilla" article with references is available on ABC's website in the HerbalEGram section (March 2021 issue).

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