

## A Natural History of Botanical Therapeutics

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## A natural history of botanical therapeutics

Barbara Schmidt, David M. Ribnicky\*, Alexander Poulev,  
Sithes Logendra, William T. Cefalu, Ilya Raskin

*Biotechnology Center for Agriculture and the Environment, Cook College, Rutgers, The State University of New Jersey,  
New Brunswick, NJ 08901-8520, USA*

*Pennington Biomedical Research Center, Louisiana State University System, Baton Rouge LA 70808, USA*

### Abstract

Plants have been used as a source of medicine throughout history and continue to serve as the basis for many pharmaceuticals used today. Although the modern pharmaceutical industry was born from botanical medicine, synthetic approaches to drug discovery have become standard. However, this modern approach has led to a decline in new drug development in recent years and a growing market for botanical therapeutics that are currently available as dietary supplements, drugs, or botanical drugs. Most botanical therapeutics are derived from medicinal plants that have been cultivated for increased yields of bioactive components. The phytochemical composition of many plants has changed over time, with domestication of agricultural crops resulting in the enhanced content of some bioactive compounds and diminished content of others. Plants continue to serve as a valuable source of therapeutic compounds because of their vast biosynthetic capacity. A primary advantage of botanicals is their complex composition consisting of collections of related compounds having multiple activities that interact for a greater total activity.

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### 1. Natural products and drug discovery

Historically, natural products have provided an endless source of medicine. Plant-derived products have dominated the human pharmacopoeia for thousands of years almost unchallenged [1]. In 1897, Arthur Eichengrün and Felix Hoffmann, working at Friedrich Bayer, created the first synthetic drug, aspirin. Aspirin (acetylsalicylic acid) was synthesized from salicylic acid, an active ingredient of analgesic herbal remedies. This accomplishment ushered in an era dominated by the pharmaceutical industry. In 1928, penicillin was discovered by Alexander Fleming, adding microbes as important sources of novel drugs. The role of plant-derived natural products in drug discovery has recently been diminished by the advent of structure activity-guided organic synthesis, combinatorial chemistry, and computational (in silico) drug design.

Despite drug discovery technology diversification and reduced funding for natural product-based drug discovery, natural products from plants and other biological sources remain an undiminished source of new pharmaceuticals. Industrial funding for natural product-based drug discovery has been declining from 1984 to 2003, yet the percentage of natural product-derived small molecule patents has remained relatively unchanged [2]. A comprehensive review of human drugs introduced since 1981 suggests that, of 847 small molecule-based drugs, 43 were natural products, 232 were derived from natural products (usually semisynthetically), and 572 were synthetic molecules. However, 262 of the 572 synthetic molecules had a natural product-inspired pharmacophore or could be considered natural product analogs [3]. Natural products continue to make the most dramatic impact in the area of cancer. From 155 anticancer drugs developed since the 1940s, only 27% could not be traced to natural products, with 47% being either a natural product or a direct derivation thereof. Only one drug, the anticancer compound sorafenib, could be traced to completely de novo combinatorial chemistry [3]. The above analysis did not include biologics and vaccines, which are derived from nature by definition.

\* Corresponding author. Biotechnology Center for Agriculture and the Environment, Foran Hall, Cook College, Rutgers, The State University of New Jersey, New Brunswick, NJ 08901-8520, USA. Tel.: +1 732 932 8734x227; fax: +1 732 932 6535.

E-mail address: [ribnicky@aesop.rutgers.edu](mailto:ribnicky@aesop.rutgers.edu) (D.M. Ribnicky).

The decline in natural product–based drug discovery is often blamed on the advent of high throughput screening (HTS) [4]. Although well paired with combinatorial chemistry, HTS is not easily adaptable to complex mixtures produced from natural sources. This is mainly due to the high cost per sample, complexity of resupply, difficulty in isolation and characterization of actives, lack of reproducibility, and interference from compounds in complex mixtures [1,2].

Comparative analysis of structural diversity in natural-product mixtures and combinatorial libraries suggests that nature still has an edge over synthetic chemistry, despite the fact that combinatorial libraries use more nitrogen, phosphorus, sulfur, and halogens. Superior elemental diversity does not compensate for the overall molecular complexity, scaffold variety, stereochemical richness, ring system diversity, and carbohydrate constituents of natural product libraries [5-8]. It is generally believed that the complexity of plant-produced secondary metabolites and the vast number of natural products will constitute a resource beyond the capacity of current synthetic chemistry for a long time [9]. Nevertheless, the relative ease and low cost to produce combinatorial libraries, the simplicity and speed of their dereplication (favoring novel bioactive over known compounds) and deconvolution (characterization of unique active molecules), and the compatibility with HTS continue to fuel their widespread use in modern drug discovery.

## 2. Current categories of botanical products in the United States

The use of botanicals for improving human health has evolved independently in different regions of the world. The production, use, attitude, and regulatory aspects of botanicals continue to vary globally. In the United States, botanicals are categorized based on intended use, safety, regulatory status, and degree of characterization. The regulatory aspects of botanical products are an important issue when considering standardization and quality assessment because the regulations dictate some degree of the process. The basic regulatory categories are as follows:

**Dietary Supplements**, also commonly known as *nutraceuticals*, are products consisting of dietary components that are intended to supplement the diet and usually consist of vitamins, minerals, botanicals, and others. Dietary supplements are regulated by the Food and Drug Administration (FDA) under the Dietary Health and Education Act of 1994 (<http://www.cfsan.fda.gov/~dms/lab-qhc.html>), which makes the manufacturer responsible for ensuring the safety of the products but places the burden of proof upon the FDA for enforcement. This creates an unregulated environment where marketing powers retain control. Unless a dietary supplement

contains a new ingredient, there is not even a mandate to register the product.

**Drugs** can be prescription drugs or over-the-counter drugs. These products require the most rigorous testing including 3 distinct phases of clinical testing to ensure safety and efficacy and close scrutiny by the FDA. Although most early pharmaceutical products were botanical preparations and at least 25% of the pharmaceuticals used today are based on plant-derived products [10], only pure compounds isolated from plants and subjected to the same rigors as synthetic pharmaceutical can be conventional drugs. Botanically derived pharmaceuticals that are currently being used today include taxol and morphine [4].

**Botanical Drugs** are complex extracts from a plant to be used for the treatment of disease. The guidelines for this relatively new regulatory category were released in 2004 (<http://www.fda.gov/cder/Guidance/4592fnl.htm>). Botanical drugs are clinically evaluated for safety and efficacy just as conventional drugs, but the process for botanical drugs can be expedited because of the history of safe human use. Botanical drugs are highly but not completely characterized and are produced under the same strictly regulated conditions as conventional pharmaceuticals. Botanical drugs, such as senna and psyllium, can be marketed and sold under the FDA's over-the-counter drug monograph system [11].

## 3. Plant domestication and secondary metabolites

Recent archeological records suggest that modern agriculture started in the Near East 10 000 to 11 000 years ago with the domestication of figs, cereals, and legumes [12,13]. At that time, early Neolithic farmers maintained a subsistence strategy, collecting wild plants for food and medicine while simultaneously domesticating early crops. This point in time marked the beginning of the divergence between medicinal plants and food plants. Centuries of plant domestication improved flavor, color, yield, uniformity, disease and pest resistance, reproductive fitness, and postharvest integrity of crops but has reduced pharmacologically active compounds from major crops to levels where average daily consumption cannot produce a measurable pharmacological effect. The pharmacological side effects of food, frequently residing in poorly palatable compounds, were not likely to be preserved or even considered advantageous by our ancestors. As a result, conventional plant breeding has often reduced the content of bioactive compounds in crops (Table 1).

For example, a wild tomato (*Lycopersicon esculentum* var *cerasiforme*) indigenous to Peru produces fruit with very high levels of the bitter glycoalkaloid tomatine (500-5000 mg/kg dry weight) [26]. Tomatine plays a role in pest and disease resistance and also has multiple pharmacological effects in humans including cholesterol-lowering, immunomodulatory,

Table 1  
Bioactive compounds that have been reduced in modern food crops

Crop	Latin name	Chemical class	Examples	Targets	Toxicity	References
Cassava	<i>Manihot esculenta</i>	Cyanogenic glycosides	Linamarin, lotaustralin	Cancer	Block cellular respiration	[14]
Celery	<i>Apium graveolens</i>	Furanocoumarins	Psoralen, xanthotoxin, bergapten	Anticoagulant	Photosensitivity	[15,16]
Broccoli	<i>Brassica napa</i>	Glucosinolates	Sulforaphane	Cancer	Goitrogenic	[17,18]
Potato	<i>Solanum tuberosum</i>	Glycoalkaloids	$\alpha$ -Chaconine, $\alpha$ -solanine	Cancer	Neurotoxin	[19,29]
Tomato	<i>L. esculentum</i>	Glycoalkaloids	Tomatine	Cancer	Neurotoxin	[26–29]
Common bean	<i>P vulgaris</i>	Glycoproteins	Lectins	Cancer, HIV	Agglutination	[30,31]
Soybean	<i>G max</i>	Isoflavones	Genistein, daidzein	Breast cancer	Estrogenic effects	[20,21]
Cotton	<i>Gossypium spp</i>	Phenolic sesquiterpenes	Gossypol	Cancer, male contraceptive	Infertility	[22,23]
Lettuce	<i>Lactuca sativa</i>	Sesquiterpene lactones	Lactucin, deoxylactucin, lactucopicrin	Inflammation, malaria	Allergenic	[24,25]

and cardiotoxic [27,28]. Its ability to inhibit acetylcholinesterase may be responsible for its potentially toxic effects [16]. Not surprisingly, tomatine is considerably lower in sweet fruited tomato cultivars (~30 mg/kg) [26], reducing the bitter flavor but also reducing potential health benefits. Wild potato species also contain considerably higher amounts of glycoalkaloids than modern cultivars [29].

Wild bean species (*Phaseolus vulgaris*) contain many secondary metabolites that are found in lower levels in cultivated species including trypsin inhibitors, tannins, and lectins [30]. These phytochemicals have been called *anti-nutritional* because they may interfere with protein digestion, although they have potential human health benefits as a therapy for cancer, heart disease, and diabetes [31].

Contrary to the trend of reducing bioactives through centuries of plant breeding, some bioactive compounds have been fortuitously enhanced in modern food crops because they impart desirable attributes like color or flavor (Table 2). Examples include pigments such as carotenoids [43,44] and flavonoids [45,46], aromatic constituents of volatile oils like menthol [47,48], and other flavor constituents including gingerols [49] and capsaicin [50,51].

Modern agriculture has also improved various medicinal plants through years of selective breeding for bioactive compounds. For example, foxglove (*Digitalis purpurea*) produces digitoxin and digoxin, cardiac glycosides used to treat congestive heart failure. Modern agriculture has created

uniform cultivars with high digoxin content [52]. Many common cultivated plants are also the source of compounds used as building blocks in the semisynthesis of pharmaceuticals. A number of useful phytochemicals are extracted from soybean (*Glycine max*) including the sterols stigmasterol, sitosterol, and campesterol [53]. Sitosterol and campesterol are esterified into plant stanol and sterol esters, both of which have been shown to lower serum cholesterol [54]. Stigmasterol and sitosterol are used in the semisynthesis of pharmaceutical steroids including progestagens, androgens, and corticosteroids [53,55]. Diosgenin, a structurally related steroid from Mexican yams (*Dioscorea spp*), is also used in the semisynthesis of pharmaceutical steroids [53]. The opium poppy (*Papaver soniferum*) produces morphinan alkaloids including morphine, codeine, thebaine, papaverine, and noscapine [56]. Opioid semisynthetic drugs include dihydrocodeine, fentanyl, and oxycodone [53]. Opioids are widely used as powerful analgesics, cough suppressants, and sedatives.

#### 4. The power of biochemical potentiation

A recent review article defined *potentiation* as positive interactions that intensify the potency of a bioactive product [57]. Additive and synergistic effects are subsets of potentiation, where 2 or more compounds in a mixture

Table 2  
Bioactive compounds that have been increased in modern food crops

Plant	Latin name	Chemical	Targets	References
Peppers	<i>Capsicum spp</i>	Capsaicin	Pain	[50,51]
Grapes	<i>Vitis spp</i>	Flavonoids	Cardiovascular disease	[32,45]
Peppermint	<i>Mentha x piperita</i>	Menthol	Decongestant	[47,48]
Tomatoes	<i>L. esculentum</i>	Lycopene	Prostate cancer	[33,34]
Hops	<i>Humulus lupulus</i>	Humulene	Anti-inflammatory	[35,36]
Turmeric	<i>Curcuma domestica</i>	Curcumin	Inflammation, cancer	[37,49]
Ginger	<i>Zingiberis rhizoma</i>	Gingerols	Antiemetic	[38,39]
Saffron	<i>Crocus sativus</i>	Carotenoids	Cancer	[40,41]
Apricots	<i>Prunus armeniaca</i>	Carotenoids	Cancer	[42,43]

Table 3

Bioactive compounds isolated from an extract of *A dracuncululus* L by activity-guided fractionation that inhibit the aldose reductase enzyme, protein tyrosine phosphatase 1B activity and expression, or phosphoenolpyruvate carboxykinase overexpression [59–61]

Isolated compounds	ALR <sub>2</sub>	PTP-1B	PEPCK
4,5-Di- <i>O</i> -caffeoylquinic acid <sup>a,b,c</sup>	Active	–	–
Davidigenin <sup>a,b,d,e</sup>	Active	–	–
6-Demethoxydihydrochalcone <sup>a,b,c</sup>	Active	–	Active
2',4'-Dihydroxy-4-methoxydihydrochalcone <sup>a,b,c,d,e,f</sup>	Active	Active	Active
2',4-Dihydroxy-4'-methoxydihydrochalcone <sup>a,b,c,d,e</sup>	–	Active	–
Sakuranetin <sup>b,c,g</sup>	–	Active	–

ALR<sub>2</sub> indicates aldose reductase; PTP-1B, protein tyrosine phosphatase 1B; PEPCK, phosphoenolpyruvate carboxykinase.

<sup>a</sup> Confirmed with nuclear magnetic resonance.

<sup>b</sup> New compound to *A dracuncululus*.

<sup>c</sup> Activity reported for the first time.

<sup>d</sup> Dihydrochalcone.

<sup>e</sup> New compound to genus *Artemisia*.

<sup>f</sup> First report as a constituent of plants.

<sup>g</sup> Flavonoid.

interact to provide a combined effect that is equal to the sum of the effects of the individual components (additive) or where combinations of bioactive substances exert effects that are greater than the sum of individual components

(synergistic). Potentiation can exist between 2 phytochemicals in a single plant extract, 2 phytochemicals from 2 different plant extracts, or between a phytochemical and synthetic drug. To validate this phenomenon, the bioactive

Table 4

Examples of potentiating interactions between various natural products with other natural products or drugs in the fields of cancer and antibiotic research

Natural products	Drug/natural product	Target	Summary	Reference
<i>Cancer</i>				
Apple extracts <sup>a</sup>	Vitamin C	Liver cancer	Apple extracts, containing vitamin C, had greater antioxidant activity and reduced in vitro tumor proliferation greater than vitamin C alone.	[65]
Soy extract, genistein	Tamoxifen	Breast cancer	Combination of tamoxifen with genistein or soy extract had synergistic effects on delaying the growth of MCF-7 tumors in mice.	[66]
Tomato powder <sup>b</sup>	Lycopene	Prostate cancer	Tomato powder inhibited prostate cancer more than pure lycopene in NMU rats, suggesting that tomato powder contains compounds in addition to lycopene that modify prostate carcinogenesis.	[67]
Tomato powder, broccoli powder, combination of tomato and broccoli powders	Lycopene, finasteride	Prostate cancer	Tomato powder, broccoli powder, and combination treatments all significantly reduced Dunning rat prostate tumor size more than finasteride or lycopene. The tomato/broccoli combination treatment had the greatest antitumor effect.	[33]
<i>Antibacterial</i>				
<i>Acorus calamus</i> , <i>Hemidesmus indicus</i> , <i>Holarrhena antidysenterica</i> , <i>Plumbago zeylanica</i> extracts and fractions	Ceftazidime, cefuroxime, chloramphenicol, ciprofloxacin, tetracycline	MRSA <sup>c</sup>	Extracts and fractions from 4 plants demonstrated synergistic antibiotic activity against various strains of MRSA when used in combination with each other and in combination with synthetic antibiotics.	[68]
	Tetracycline, ciprofloxacin	ESβL-producing <i>E coli</i>	Extracts and fractions from 4 plants demonstrated synergistic antibiotic activity against ESβL-producing <i>E coli</i> when combined with tetracycline or ciprofloxacin.	[70]
Bidwillon B	Mupirocin	MRSA	When bidwillon B and mupirocin were combined, synergistic effects were observed for 11 strains of MRSA.	[72]
<i>Camellia sinensis</i> , <i>Lawsonia inermis</i> , <i>Punica granatum</i> , <i>Terminalia belerica</i> , <i>Terminalia chebula</i> extracts	Tetracycline, ampicillin	MRSA	The <i>C sinensis</i> extract showed synergism with ampicillin; <i>L inermis</i> , <i>P granatum</i> , <i>T belerica</i> , and <i>T chebula</i> extracts showed synergism with tetracycline.	[69]

MRSA indicates methicillin-resistant *S aureus*; ESβL, extended spectrum beta-lactomases; NMU, *N*-methyl-*N*-nitrosourea.

<sup>a</sup> Apple extracts contain naturally occurring vitamin C.

<sup>b</sup> Tomato powder contains naturally occurring lycopene.

phytochemical(s) in a mixture must first be identified and isolated. Afterward, plant extracts or mixtures of phytochemicals must be tested side by side with the single bioactive compounds to see which one has greater bioactivity. Only then can clear conclusions be made whether or not a mixture of compounds actually intensifies the potency of a single bioactive product. A good example of the multicomponent nature of botanicals is illustrated with an extract from *Artemisia dracuncululus* L that is being researched as a botanical therapeutic for diabetes and metabolic syndrome. The extract decreases blood glucose in hyperglycemic animal models of diabetes and seems to enhance insulin sensitivity as a mode of action [58]. Based on 3 of the diabetes-related activities identified for the extract, together with activity-guided fractionation, 6 active compounds were isolated and identified (Table 3). Therefore, the activity of the total extract is the combined result of at least 6 different compounds and at least 3 different activities. The precise nature of their interaction has not yet been defined.

In the field of cancer research, phytochemicals have been shown to affect various parts of signal transduction pathways including gene expression, cell cycle progression, proliferation, cell mortality, metabolism, and apoptosis [62]. Combination chemotherapy has been the mainstay of cancer treatment for 40 years [63]. It is therefore reasonable to assume that a mixture of compounds (phytochemical or synthetic) would have greater bioactivity than a single compound because a mixture of bioactive compounds has the ability to affect multiple targets [62,64]. Studies have documented synergistic anticancer effects of phytochemicals including quercetin, catechins, resveratrol, and curcumin with various cancer drugs and/or other phytochemicals [62]. A few other examples of synergistic anticancer activity are shown in Table 4. In addition, natural products have been shown to overcome multiple drug resistance in tumors when used in combination with other natural products or drugs [62]. Similar observations have been made in the field of antibiotic research (Table 4). A number of plant extracts and natural products have been shown to work synergistically with existing antibiotics, restoring antibiotic activity against resistant strains of *Staphylococcus aureus* (methicillin resistant), *Escherichia coli*, and *Shigella* [70–72].

## 5. Conclusions

Plants must maintain and protect themselves through diverse arrays of complex natural products that they make from the inorganic components of air, soil, and water because they lack the flight response. Remarkably, the oldest known living eukaryotic organism, turning 4772 years old in 2007, is a specimen of a bristlecone pine, *Pinus longaeva*, growing in the White Mountains of Inyo County, California [73]. Many other plants can live hundreds of years without succumbing to diseases or predation. It should come to no

surprise that some of the compounds that have enabled plants to survive may also be used to maintain the health and well-being of humans.

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