# Plant Seeds as Sources of Potential Industrial Chemicals, Pharmaceuticals, and Pest Control Agents[⊥]

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Investigations of natural products isolated from seeds have resulted in a remarkable variety of compounds having unusual structures. Seeds of many plant species contain uncommon fatty acids and lipids, some of which have found uses in the cosmetic industry or as renewable (non-petroleum based) industrial raw materials. In addition to proteins and energy storage substances such as carbohydrates and lipids, seeds generally contain, or have the ability to produce, protective compounds that are active as plant growth regulators, fungicides, insecticides, and repellents of herbivores; seeds occasionally contain compounds that are toxic to most other organisms. These compounds may also be present in other plant parts, but often are found at higher concentrations in seeds. Other compounds of interest have been associated with plant−endophyte interactions that are of mutual benefit to both organisms. Tests of seed extracts for cytotoxic and antitumor activity, toxicity to insects, and relationships to several animal disease syndromes have been revealing. Examples of compounds isolated from plant seeds that have served as lead compounds for additional research, or that continue to be of interest to researchers in multiple areas, are reviewed.

## Introduction

Botanists estimate the number of higher plant species to be in the range 300 000−320 000,[1] and only a very small percentage of these have been investigated in some degree for their chemical constituents. Approximately 7000 vegetable crops are utilized by man for food, forage, and fiber throughout the world.[2] A number of other plants are used commercially for various flavor, cosmetic, and construction purposes or as sources of specialty chemicals, medicinal compounds, or pest control agents. However recent emphasis on alternative fuels has attracted considerable attention to plant materials for production of ethanol and to plant seed oils for use as diesel fuel. The use of major food crops such as corn, *Zea mays* L. (Poaceae), and soybean, *Glycine max* (L.) Merr. (Fabaceae), for large-scale production of fuels has marked effects on the price of these commodities and on the price of many common items at the grocery store. Advantages and disadvantages of converting traditional food sources to energy production have been and continue to be the subject of much debate, and such uses are subject to the law of unintended consequences. Alternatively, there could easily be plants yet uninvestigated that would be better choices for alternative fuels and specialty chemicals and which could be managed so that they would produce less negative impact on the food supply and on the environment. Collateral studies of such plants would no doubt reveal other useful and valuable products.

The Northern Regional Research Laboratory (NRRL), now the National Center for Agricultural Utilization Research (NCAUR), a laboratory maintained by the U.S. Department of Agriculture (USDA), Agricultural Research Service (ARS), was established by an Act of Congress in 1938, and the building in Peoria, Illinois, was dedicated in October 1939.[3] Among the objectives of the Laboratory was the development of new products from agricultural commodities such as corn and soybeans, where surpluses were a continuing problem, as well as research on new alternative crops. NRRL was quickly called upon to develop methods for the production of penicillin. Key early contributions included the introduction of submerged culture fermentation, the use of precursors in fermentation, and the discovery of a mold strain that gave higher yields of penicillin. These advances and the use of corn steep liquor[4] in the fermentation process played major roles in the rapid scale-up of penicillin production and in the production of later antibiotics.

The following is a summary highlighting some of the more important and interesting findings in the search for new crops, products, and discoveries concerning little known or under-utilized plants conducted primarily at the NCAUR[5,6] during the last 50 years. Research in several of these areas has expanded and is continuing at the NCAUR and elsewhere.

## New Crops as Sources of Industrial Raw Materials

The search for new crops that would yield products of increased value to farmers and that might be used for industrial purposes rather than food led to a survey of plants growing in the United States and to the establishment of a large collection of germplasm (seeds) at NRRL. During the late 1950s, the program was headed by Dr. Ivan Wolff in what was then known as the Industrial Crops Laboratory. Over a number of years the collection was supplemented by seeds of many unusual and little-known plant species collected by USDA botanists and other botanists primarily from countries that were recipients of aid resulting from Public Law 480 (P.L. 480), also known as the Food for Peace Program. One goal of the program at NRRL was to identify potential new crop species that contained unusual seed oils or lipids as sources of specialty chemicals, value-added materials that would prove more profitable for farmers. It should be possible to manage these renewable resources to reduce the reliance on various specialty materials that are currently imported and to reduce the use of and environmental impact of fossil fuels that are now used to produce some chemicals widely used in industry.

Analyses of seeds in the NRRL collection for oil and protein content began in the 1950s,[7−9] and several dozen previously unknown fatty acids were soon characterized. Included were fatty acids having unusual chain lengths, various positions of double bonds and/or conjugated double bonds, acetylenic fatty acids, and hydroxy or epoxy groups at various positions along the fatty acid chain. Some complex lipids other than the usual triglycerides were also identified. It was soon abundantly clear that seed storage fats were not restricted to the commonly recognized triglycerides consisting primarily of palmitic, stearic, oleic, linoleic, and linolenic acids. A few of the more important and instructive examples resulting from this work are summarized in the following paragraphs.

**Medium-Chain Fatty Acids.** Tropically grown coconut and palm kernel, *Elaeis guineensis* Jacq. (Arecaceae), oils are the primary commercial sources of medium-chain fatty acids. Palm oil

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is the second, or possibly now the first, most widely produced edible oil in the world, after soybean oil. The United States imports over one billion pounds of palm oils annually because historically there has been no convenient domestic source for these useful materials. However, seed oils of many species of the genus *Cuphea* contain medium-chain fatty acids.[10–12] For instance, *Cuphea painteri* Rose (Lythraceae) seed oil is rich in octanoic (caprylic) acid (73%), *C. koehneana* Rose (Lythraceae) oil is rich in decanoic (capric) acid (95%), and *C. carthagenensis* (Jacq.) Macbr. (Lythraceae) oil contains dodecanoic (lauric) acid (81%).

*Cuphea* is a genus of low-growing herbaceous or annual plants containing over 45 species. Most species originated in the Americas, especially Mexico, and lack tolerance to frost. Cuphea is only a few years from the wild, and its indeterminate flowering nature, sticky stems, the propensity for seed shattering, and other problems are being addressed. The fatty acids from *Cuphea* species are, however, valuable commodities and could replace imported palm kernel and coconut oil. Lauric acid is used in foods, mostly as vegetable shortenings, as a defoaming agent, and in soaps and detergents. Lauric and myristic acids are used in detergents and in many healthcare and beauty products. Progress in the development of cuphea as a new crop for the Midwest region of the United States is continuing at the NCAUR and elsewhere and is summarized periodically.[13–17]

**Hydroxy Fatty Acids.** Plants of the genus *Lesquerella* are members of the crucifer family (Brassicaceae) and are native to North America. Seed oils of *Lesquerella* species were found to be rich in hydroxy fatty acids.[18–20] The hydroxy fatty acids consist primarily of ricinoleic (12-hydroxy-*cis*-9-octadecenoic), lesquerolic (14-hydroxy-*cis*-11-octadecenoic), densipolic (12-hydroxy-*cis*-9-*cis*-15-eicosadienoic), and auricolic (14-hydroxy-*cis*-11-*cis*-17-eicosadienoic) acids, with only one of these acids predominating in most species.

Castor oil, from *Ricinus communis* L. (Euphorbiaceae), contains approximately 85% ricinoleic acid and is the only commercial source of hydroxy fatty acids. Large quantities of castor oil are imported each year primarily from India, Brazil, and mainland China. *R. communis* could be grown and castor oil produced in the United States; however the seeds also contain the poisonous compound ricin.[21] *Lesquerella* species do not produce ricin and would reduce that problem. Castor oil is generally recognized as safe and effective for over-the-counter use as a laxative, and a derivative (undecylenic acid) is approved for over-the-counter use on skin disorders. Certain lipsticks may contain up to 80% castor oil. Another derivative, Cremophor EL (polyethoxylated castor oil, a nonionic surfactant), is useful as an additive to many modern drugs including the antitumor drug paclitaxel (Taxol).

Castor oil and its derivatives have many applications in transportation and in the cosmetic and manufacturing industries, such as in lubricating greases, machining oils, paints, inks, and waxes and the production of nylon-11. The availability of lesquerella oils should serve as domestic sources of hydroxy acids and provide additional useful products. *Lesquerella fendleri* (Gray) S. Wats. (Brassicaceae), an oil containing in excess of 50% lesquerolic acid, is a developing new crop suitable for temperate growing regions in the United States.[22,23] Some lesquerella and castor oil derivatives, such as estolides and 2-ethylhexyl esters, have recently been evaluated and appear to have potential as additives in biodiesel and ultralow-sulfur diesel fuels.[24]

**Epoxy Fatty Acids.** Gunstone reported vernolic acid (12*S*,13*R*-epoxy-*cis*-9-octadecenoic acid) as a constituent of *Vernonia anthelmintica* (L.) Willd. (Asteraceae) seed oil in 1954.[25] The genus is widespread in India, Pakistan, and certain countries in Africa, but attempts to introduce *V. anthelmintica* into the United States as a new crop have been discouraging. *V. galamensis* (Cass.) Less. (Asteraceae), native to Africa and for which the oil contains 73–80% vernolic acid, may offer better promise as a crop plant.[26] Products that can be made from epoxidized oils include adhesives, varnishes, and paints. A recommended use of vernonia oil as a
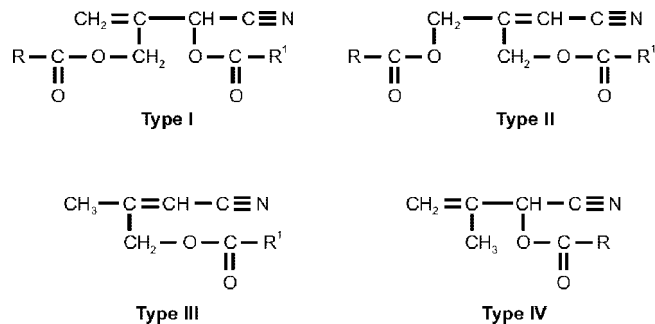


**Figure 1.** Cyanolipid types I–IV. R = alkyl group of a fatty acid.

nonvolatile solvent in oil-based paints offers potential environmental benefits, as it becomes incorporated in the dry paint rather than evaporating into the air.

**Acetylenic and Allenic Fatty Acids.** Screening of seed oils for lipid content led to the discovery of crepenynic acid (*cis*-9-octadecen-12-ynoic acid)[27] as the major component (60%) of *Crepis foetida* L. (Compositae) seed oil and to its co-occurrence with 14,15-dehydrocrepenynic acid[28] in *Afzelia cuanzensis* Welw. (Caesalpiniaceae) seed oil. Crepenynic acid has since been reported to be present in a number of legumes and Compositae (Asteraceae) oils.[29] The oil of *Helichrysum bracteatum* (Vent.) Andrews (Compositae) yielded helenynolic acid (9-hydroxy-*trans*-10-octadecen-12-ynoic acid) in addition to crepenynic acid.[30,31]

*Acanthosyris spinescens* (Mart. Et Eich.) Griseb. (Santalaceae) seed oil provided a record number of acetylenic and hydroxyacetylenic fatty acids.[32,33] The most unusual feature was that substantial amounts of odd-carbon (C-17) acids were present rather than the usual fatty acids having even numbers of carbons. The following acetylenic acids were determined to be present in *A. spinescens* triglycerides: 17-octadecen-9-ynoic acid (18%), *trans*-10,16-heptadecadien-8-ynoic acid (10%), *trans*-11,17-octadecadien-9-ynoic acid (4%), 7-hydroxy-*trans*-10,16-heptadecadien-8-ynoic acid (9%), 8-hydroxy-*trans*-11,17-octadecadien-9-ynoic acid (4%), and 7-hydroxy-*trans*-10-heptadecen-8-ynoic acid (6%).

Crepenynic acid, an acetylenic analogue of linoleic acid, was a previously unrecognized biosynthetic intermediate of many polyacetylenic compounds.[34] David Seigler has summarized current understanding of the biosynthesis of polyacetylenes in plants.[35]

*Leonotis nepetaefolia* (L.) R. Br. (Lamiaceae) seed oil was found to contain 16% of a strongly levorotatory allenic fatty acid that was identified as laballenic [(−)-5,6-octadecadienoic] acid,[36] and lamenallenic [(−)-octadeca-5,6-*trans*-16-trienoic] acid was found to co-occur with the former in *Lamium purpureum* L. (Lamiaceae) seed oil.[37] Little is known concerning the biosynthetic pathway to these allenic fatty acids, but they are presumed to be related to the acetylenes.

**Cyanolipids.** Initial screening of the seed oil of *Cordia verbenacea* DC. (Boraginaceae) indicated that it contained ordinary triglycerides and substantial quantities of other lipids. The unusual components of the oil were investigated by David Seigler, then at the NCAUR on a postdoctoral appointment, who first determined that the fatty acids present were esterified to a moiety other than glycerol.[38] Nitrogen was present, as it became apparent that HCN was released upon hydrolysis. Ultimately, it was determined that the cyanolipids consisted of four types (I–IV) (Figure 1).

Cyanolipids are common in oils of the Sapindaceae[39–41] and are based on a five-carbon backbone containing a nitrile moiety together with a methylene group or double bond and one or two OH groups. The OH groups are esterified with long-chain fatty acids, as illustrated in Figure 1. Cyanolipids of types I and IV are cyanohydrins that release HCN on hydrolysis. Type II and III cyanolipids are simply α,β-unsaturated nitriles. Seigler has reviewed the biosynthesis, occurrence, and biological activity of cyanolipids and the more common cyanogenic glycosides.[42]

**Other Seed Lipids.** Several species of the Brassicaceae, such as *Crambe abyssinica*, *Brassica napus*, or *B. campestris* L., are sources of erucic (*cis*-13-docosenoic) acid. Erucic acid converted into erucamide is useful as a slip agent in the manufacture of polyethylene sheets. Cleavage of erucic acid yields brassylic (1,11-undecanedicarboxylic) and pelargonic (nonanoic) acids. Brassylic acid has been used to produce nylon 1313, and both products have commercial uses as plasticizers, lubricants, and surfactants.

The lipid isolated from *Briza spicata*, now *B. humilis* M. Bieb. (Poaceae), seed contains 49% digalactosylglycerides and 29% monogalactosylglycerides,[43] and the predominant fatty acids are palmitic, oleic, and linoleic. The glycolipids appear to be useful as additives to improve breads and various protein-enriched products.[44]

*Trewia nudiflora* L. (Euphorbiaceae) seed oil contains glycerides of α-camlolenic (18-hydroxy-*cis*-9-*trans*-11-*trans*-13-octadecatrienoic) acid that occur primarily as estolides in which the OH group of α-camlolenic acid is esterified to another hydroxy or ordinary fatty acid. Tri-, tetra-, penta-, and hexa-acyl glycerols were isolated.[45] Oils containing conjugated fatty acids are useful in paints and coatings, as they readily oxidize or polymerize on exposure to air.

## Screening of Seed Extracts for Cytotoxic and Antitumor Activity

Research on seed extracts, in cooperation with the National Cancer Institute (NCI) and other agencies, resulted in the discovery of several potentially useful cytotoxic and antineoplastic compounds. Most notable of these were homoharringtonine from *Cephalotaxus harringtonia* (Knight ex J. Forbes) K. Koch (Cephalotaxaceae),[46] cephalomannine from *Taxus wallichiana* Zucc. (Taxaceae),[47] maytansinoids from *Trewia nudiflora* L. (Euphorbiaceae),[48] sesbanimide from *Sesbania drummondii* (Rydb.) Cory (Fabaceae),[49] and acetogenins from the paw paw, *Asimina triloba* (L.) Dunal (Annonaceae).[50] Research on the latter and on other annonaceous species, spearheaded by Jerry L. McLaughlin, has since resulted in identification of over 200 unique annonaceous acetogenins, about half of the acetogenins described to date, and several commercial products as described in detail in his recent review.[51]

***Cephalotaxus* Alkaloids.** *Cephalotaxus harringtonia*, a small tree native to Japan and mainland China, had been introduced as an ornamental but gained little popularity in the United States prior to 1960. This slow-growing tree was low on the priority list as a potential new crop; however, Ivan Wolff and Cecil Smith included an extract of *C. harringtonia* seed as one of the first 200 extracts that were submitted by NRRL around 1960 to the antitumor screen of the National Cancer Institute (NCI). Initial test results were encouraging, as the extract showed significant in vivo activity against L-1210 and P-388 leukemia in mice, and Jonathan Hartwell (NCI) soon placed *Cephalotaxus* on the priority list for identification of the active components. The Paudler group[52] reported cephalotaxine to be the major *Cephalotaxus* alkaloid in 1963; however, cephalotaxine was inactive. By 1970, the cephalotaxine esters homoharringtonine (**1**), harringtonine, and isoharringtonine were identified as the major active principles.[46,53]
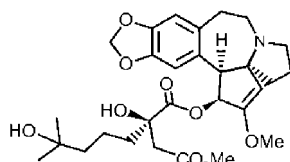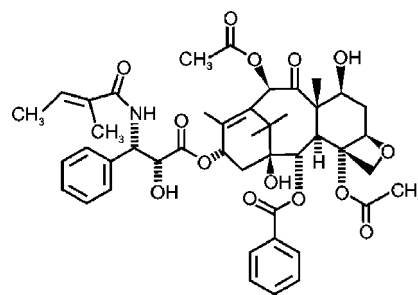
The NCI requested quantities of these alkaloids sufficient for preclinical trials; however, there was no known source of *Cephalotaxus* plants in the United States. Robert Perdue, then of the USDA, Beltsville, MD, in cooperation with NCI, was eventually able to obtain 1000 lbs of *C. harringtonia* var. *harringtonia* cv. *fastigiata*, representing 17 entire trees including roots, from a nursery in Oregon. Extraction of this collection at NCAUR yielded 330 g of mixed alkaloids and, ultimately, 16.6 g of homoharringtonine (**1**), which was selected for preclinical studies.[54] Availability of plant material was less of a problem in mainland China, and George R. Pettit, a member of the National Academy of Sciences Delegation to the People's Republic of China, reported that homoharringtonine was being prepared there for clinical trials in June 1974.[55] The People's Republic of China has continued to be the major supplier of *Cephalotaxus* alkaloids.

Difficulties in obtaining *Cephalotaxus* alkaloids in desired quantities and the novel and relatively complex structures led many to attempt synthetic approaches to cephalotaxine and its esters.[56] Tomas Hudlicky and his group described a stereospecific total synthesis of homoharringtonine in 1983[57] and reviewed synthetic work on these alkaloids in 1987[58] and again in 2007.[59]

Homoharringtonine (HHT) has shown encouraging activity in preclinical and phase I and II trials in patients with hematologic and some solid tumors. Early studies in mainland China reported high response rates in patients with leukemia,[60] and recent studies in the United States and the United Kingdom have shown promising results in patients with chronic myeloid leukemia.[61,62] Itokawa, Wang, and Lee reviewed the chemistry and pharmacology of homoharringtonine and related alkaloids in 2005.[63]

Homoharringtonine has been granted orphan drug status by the FDA, and patents have also been issued for a semisynthetic preparation of HHT and derivatives and for treatments of chronic myelogenous leukemia (CML) that include HHT.[64,65] ChemGenex Pharmaceuticals Ltd., in collaboration with Stratagen Group, is developing omacetaxine mepesuccinate, a semisynthetic formulation of HHT (formerly known as Ceflatonin), as a potential treatment for CML, myelodysplastic syndrome (MDS), and acute myelogenous leukemia (AML). Quintas-Cardama and Cortes have recently published an extensive review of clinical results involving homoharringtonine.[66]

***Taxus wallichiana.*** In attempting to obtain homoharringtonine and related alkaloids in quantities sufficient for clinical trials, various collections of *Cephalotaxus* plant materials were obtained. One of these was collected in the Shillong Forest of India and was identified as *Cephalotaxus mannii*. The extract was quite active in the in vitro and in vivo antitumor screens conducted by NCI; however, no cephalotaxine-type alkaloids were present. The two most active compounds were soon recognized to be paclitaxel (Taxol), previously described in the literature by Wani et al.[67] from a *Taxus* species, and a closely related compound that was given the name cephalomannine (**2**).[68] Taxol had been selected as a high-priority compound for development as an antitumor drug by NCI, and cephalomannine (cytotoxic to KB cells with $ED_{50}$ $3.8 \times 10^{-3}$ µg/mL and in vivo activity against P388 leukemia with T/C 158−180 at 1.0−3.3 mg/kg) possessed similar activity.



**1** homoharringtonine

Homoharringtonine was active in the conventional murine leukemia assays, L-1210 lymphoid leukemia (T/C 123−142 at 0.25−1.0 mg/kg) and P-388 lymphocytic leukemia (T/C 244−338 at 0.25−1.0 mg/kg).



**2** cephalomannine

The collection of plant material was then examined by Richard Eyde of the Smithsonian Institute, who determined that it was actually *Taxus wallichiana* Zucc. (Taxaceae) rather than *C. mannii* (Cephalotaxaceae).[47,68] During this time Jerry McLaughlin was at NCAUR on a sabbatical leave from Purdue University, and he further fractionated the extract of *T. wallichiana*. His work resulted in isolation of several taxane diterpenes and additional active compounds including 19-hydroxybaccatin III, 10-deacetylcepha-lomannine, and 10-deacetyltaxol.[69]

David Kingston then requested samples of several of these compounds to be included in the initial structure–activity study of cytotoxicity and microtubule assembly in vitro by Taxol and related taxanes conducted by the Horwitz group.[70] Taxol (paclitaxel) and Taxotere (a semisynthetic analogue) have evolved as antitumor drugs in wide use throughout the world. Kingston recently reviewed the history and status of Taxol and related taxane derivatives,[71] and Hudlicky has reviewed research on the synthesis of these compounds.[72]

***Trewia nudiflora.*** Seed extracts from the collection at the NCAUR continued to be submitted to the NCI antitumor screen during the 1960s and 1970s. One of the most interesting was an extract of *Trewia nudiflora* L. (Euphorbiaceae), a tree that grows in India. James Duke (USDA) arranged for re-collection of the seed (27.2 kg) in 1978, purchased from Pratap Nursery, Dehra Dun, India. The primary active compound isolated from this material proved to be trewiasine (**3**) (800 mg, $3.3 \times 10^{-3}\%$ yield) along with lesser amounts of several closely related compounds.[48,73,74] Trewiasine was cytotoxic to KB cells (ED$_{50}$ $2.0 \times 10^{-4}$ $\mu$g/mL) and active in vivo against PS leukemia (T/C 126–168 at 1.0–31.0 $\mu$g/kg) and B1 melanoma (T/C 165–207 at 4.0–32.0 $\mu$g/kg).
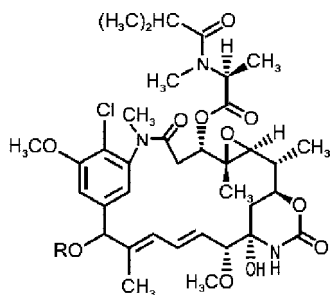


**3**  trewiasine, R = CH$_3$

**4**  colubrinol, R = H

The structure of trewiasine was rather complex, but it soon became evident on consulting the literature. The Kupchan group had isolated maytansine from *Maytenus serrata* (Hochst. Ex A. Rich.) Wilczek (Celastraceae) in 1972[75] and provided details of the structure elucidation of maytansine and related maytansinoids from *M. serrata, M. buchananii* (Loes.) R. Wilczek, and *Putterlickia verrucosa* (E. Mey. ex Sond.) Szyszyl. (Celastraceae) in 1977.[76] Wani, Taylor, and Wall isolated colubrinol (**4**) from *Colubrina texensis* (Torr. & Gray) Gray (Rhamnaceae) in 1973.[77] The NMR and MS data clearly indicated that trewiasine was identical to colubrinol, except that trewiasine possessed an OCH$_3$ at C-15 rather than an OH. The C-15 OCH$_3$ group was present in all of the maytansinoids isolated from *T. nudiflora*.

Maytansine and related maytansinoids appeared promising as antitumor agents, and maytansine was in phase II clinical trials at several cancer centers in the United States by 1978. Maytansine ultimately failed to be useful in cancer treatment due primarily to side effects that were unacceptable to patients. Reports of additional maytansinoids continue to appear in the literature,[78–80] and reviews relating to the maytansinoids also appear periodically.[81–84] It should be noted that maytansinoids are esters of ansamitocin antibiotics that occur in fermentation broths of *Nocardia* species[83] and that

trewiasine has been reported to co-occur with 15-methoxyansami-tosin P-3 in two Japanese moss species.[85]

***Sesbania* Species.** Three *Sesbania* species (Fabaceae) attracted attention, as their seed extracts were cytotoxic to KB cells and were consistently active in the P-388 lymphocytic leukemia in vivo screen.[86] These were *Sesbania vesicaria* (Jacq.) Ell. (= *Glottidium vesicarium* (Jacq.) Harper); *S. punicea* (Cav.) Benth. (= *Daubentonia punicea* (Cav.) DC.); and *S. drummondii* (Rydb.) Cory (= *Daubentonia longifolia* DC.). All three plants occur commonly in disturbed areas along the Southern Atlantic and Gulf Coastal plains in the United States, and the seeds have long been known to be toxic to livestock and birds.[87]

Initial attempts to isolate the active components were discouraging, as significant losses in activity occurred at nearly every step in the fractionation process. The active materials were obviously sensitive to mild acid or base and to lengthy standing in certain solvents.[88] After several isolation attempts, the major antitumor active compound in *S. drummondii* was determined to be sesbanimide A (**5**), a glutarimide closely related in structure to the antibiotics cycloheximide (**6**) and streptimidone (**7**).[89] Sesbanimide A was cytotoxic to KB cells (ED$_{50}$ $7.7 \times 10^{-3}$ $\mu$g/mL) and active in vivo against PS leukemia (T/C 140–181 at 8.0–23.0 $\mu$g/kg).
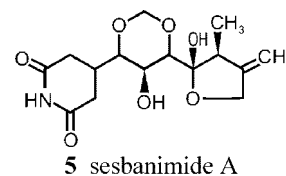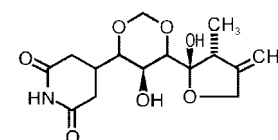


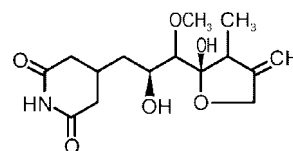**5**  sesbanimide A
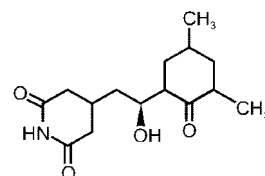


**6**  cycloheximide
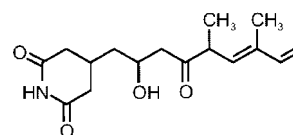


**7**  streptimidone



**8**  sesbanimide B



**9**  sesbanimide C

A re-collection of *S. drummondii* (PR-44884, 454 kg) was obtained by harvesting from the wild in Texas during November 1975, by Robert Perdue, USDA, Beltsville, MD. Extraction and fractionation of this collection was carried out at NCAUR, yielding 250 mg of sesbanimide A (**5**) and two related compounds, sesbanimide B (**8**) (22 mg) and sesbanimide C (**9**) (3.5 mg); yields of $5 \times 10^{-5}\%$, $5 \times 10^{-6}\%$, and $7 \times 10^{-7}\%$, respectively.[49]

An additional collection of seed (560 kg) was arranged for by Matthew Suffness (NCI) and James Duke (USDA) and extracted at Polysciences, Inc. in Warrington, PA, under a NCI contract. The procedure, described in a patent,[90] yielded approximately 1.7 g of **5**, which was used for additional evaluation as an antitumor agent. Ultimately, sesbanimide (**5**) was judged to be unsuitable for use as a cancer chemotherapeutic agent due primarily to excessive general toxicity. At least three groups succeeded in the synthesis of sesbanimide,[91−93] and sesbanimides have since been found to occur in marine *Agrobacterium* strains PH-103 and PH-A034C.[94]

The screening of seed extracts for cytotoxic and antitumor activity in cooperation with the National Cancer Institute attracted widespread interest, and the full impact of these studies remains to be determined.

## Endophyte-Infected Grasses

Tall fescue grass, *Festuca arundinacea* Schreb. (Poaceae), widely grown as forage in the United States, was known to produce a toxic syndrome in cattle in some places during certain times of the year and particularly under stressful environmental conditions. Fescue toxicity often mimics ergotism; however, the ergot fungus, *Claviceps purpurea* (Clavicipitaceae), is usually not present in toxic fescue pastures. Symptoms in cattle during summer months include elevated temperature, poor weight gain, problems with reproduction, and reduced lactation. Loss of weight, rough hair coat, arched back, trembling, and, in severe cases, gangrene of the extremities have been observed during periods of stress due to cold in winter.[95] Economic losses were estimated at $200 million annually in 1984.[96] The problem was traced to an endophyte, *Acremonium coenophialum* (= *Neotyphodium coenophialum*) (Clavicipitaceae), that produced ergot-type alkaloids, and the primary causative agent was identified as ergovaline.[97−99]

The lolines (**10−14**), a group of pyrrolizidine alkaloids, were also present in endophyte-infected tall fescue,[100−102] usually in much higher concentrations. Both alkaloid types were then demonstrated to occur often in other endophyte-infected grasses.[103] The loline alkaloids, though often present in tall fescue at several hundred ppm, appear to have little effect on animals and are mostly excreted in bovine urine relatively unchanged.[104] However, the lolines possess significant insecticidal activity against a variety of insects, and the $LC_{50}$ for *N*-methyl loline, *N*-formyl loline, and *N*-acetyl loline (**11−13**) is essentially equivalent to that of nicotine sulfate for greenbug aphids, *Schizaphis graminum* (Rondani) (Aphididae).[105]
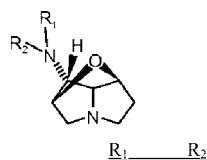
| | | R₁ | R₂ |
|---|---|---|---|
| **10** | loline | CH₃ | H |
| **11** | *N*-methyl loline | CH₃ | CH₃ |
| **12** | *N*-formyl loline | CH₃ | HCO |
| **13** | *N*-acetyl loline | CH₃ | CH₃CO |
| **14** | norloline | H | H |

Keith Clay, of Indiana University, had observed that *Balansia obtecta* Diehl (Clavicipitaceae), an endophyte of *Cenchrus echinatus* L. (Poaceae), one of the world's most persistent and troublesome weeds, known as "sandbur", "burgrass", or "sandspur", produced alkaloids that had not been identified. The predominant alkaloids were determined to be ergobalansine (**15**) and its C-8 epimer ergobalansinine,[106] lysergic acid peptide alkaloids that differed from the usual ergot alkaloids in that alanine was present as the starter unit for the peptide moiety rather than proline. Ergobalansine and its isomer are also produced by *B. cyperi* Edgerton (Clavicipitaceae), an endophyte of *Cyperus virens* Michx. (Cyperaceae), and ergobal-
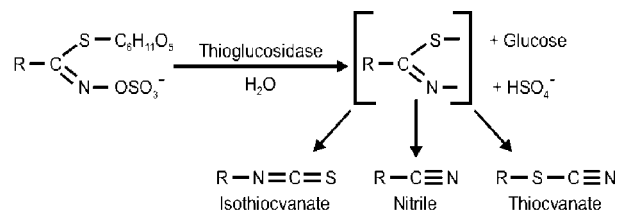


**Figure 2.** Major product classes from enzymatic hydrolysis of glucosinolates.

ansinine was later reported to occur in seeds of *Ipomoea piurensis* (Convolvulaceae) (reidentified as *Ipomoea asarifolia*).[107,108]
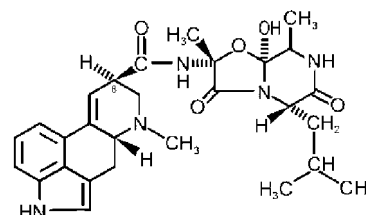


**15** ergobalansine

Sleepygrass, *Stipa robusta* (Vasey) Scribn. (Poaceae), from the Sacramento and Sierra Blanca Mountains of New Mexico, was known to produce a profoundly somnolent or stuporous condition in horses lasting up to several days.[109,110] When fully recovered, no serious aftereffects were observed; however, once poisoned horses tended to avoid eating the plant again. The primary active constituent in sleepygrass (or sleepy grass) was demonstrated to be lysergic acid amide.[111,112] Sleepygrass now is known as *Achnatherum robustum* (Vasey) Barkworth, and the toxic alkaloids are found in plants infected with a *Neotyphodium* endophyte. The focal point for high toxicity levels is near Cloudcroft, New Mexico.[113]

## Compounds and Plants of Interest for Pest Control or Other Purposes

**Glucosinolates and Isothiocyanates.** Glucosinolates occur in at least 11 plant families and in virtually all members of the mustard family (Brassicaceae or Cruciferae). Although leaves usually contain approximately 0.1% glucosinolates, their concentration in seeds of some species may range as high as 10% dry weight.[114] A study of glucosinolates from seeds of 297 species of wild plants illustrates the wide occurrence of glucosinolates and the variety of their hydrolysis products[115] (see Figure 2). The chemical diversity and distribution of glucosinolates and isothiocyanates among plants has been reviewed by Fahey et al.[116]

Glucosinolates are water-soluble polar compounds that occur in plants as salts. The plants contain a number of enzymes, or thioglucosidases, that are activated on disruption of plant tissues and release isothiocyanates, thiocyanates, nitriles, and various other compounds. Many common garden vegetables are members of the Brassicaceae family, and their characteristic odors and flavors are due primarily to glucosinolate hydrolysis products. These include edible and nutritious vegetables such as mustard greens (*Brassica juncea* (L.) Czern.); broccoli, brussel sprouts, cabbage, cauliflower, kale, kohlrabi, collards (all *Brassica oleracea* L.); horseradish (*Armoracea rusticana* P.G. Gaertn.); radish (*Raphanus sativa* L.); rutabaga (*Brassica napobrassica* Mill.); and turnip (*Brassica rapa* L.). Glucosinolates are also present in oilseed crops such as crambe (*Crambe abyssinica* L.), canola (*Brassica napus* L), and various *Lesquerella* species.

Glucosinolates and their hydrolysis products have long been known for their fungicidal, bacteriocidal, nematocidal, and allelopathic properties and have recently attracted attention due to their potential cancer chemoprevention attributes.[117] Benzyl isothiocy-

anate strongly inhibited germination of seeds of velvet leaf, *Abutilon theophrasti* Medik. (Malvaceae), at $4 \times 10^{-4}$ M.[114] Vaughn et al. demonstrated that the major phytotoxins of pennycress, *Thlaspi arvense* L. (Brassicaceae), 2-propen-1-yl (allyl) isothiocynate and allyl thiocyanate, completely inhibit seed germination of several other plant species at concentrations of 5 ppm or less.[118] It was suggested that pennycress seed meal may have potential as an environmentally friendly biofumigant for high-value horticultural crops. Seigler has provided an excellent summary of the occurrence, chemistry, and range of biological effects of glucosinolates and their hydrolysis products.[114]

Consumption of cruciferous vegetables has been linked to a decreased incidence of colorectal tumors in humans; however, excessive amounts of glucosinolates may have detrimental effects. Sulforaphane (**16**), or (−)-1-isothiocyanato-(4R)-(methylsulfinyl)butane, present in broccoli, has been identified as a compound that induces enzymes protective against cancer,[119] induces cell-cycle arrest and apoptosis in human lung adenocarcinoma LTEP-A2 cells, and retards growth of LTEP-A xenografts in mice.[120] Iberin, containing one less methylene group than sulforaphane and isolated from *Lesquerella fendleri* seeds, inhibits growth and induces apoptosis in human glioblastoma cells.[121]
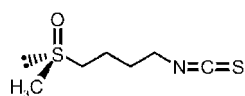


**16** sulforaphane

**Seed Components Effective against Insects.** Seed extracts of selected species were prepared for observation of their effects on a variety of insects. Seeds of the Mexican oleander, *Thevetia thevetioides* Adans. (Apocynaceae), yielded the cardiotonic glycosides neriifolin and 2′-acetylneriifolin, which were insecticidal, LD$_{50}$ of 30 and 192 ppm, respectively, when incorporated into the diet of the European corn borer (*Ostrinia nubilalis*).[122] McLaughlin and Mikolajczak investigated different parts of the paw paw plant (*Asimina triloba*) and collaborated to report the extremely cytotoxic and insecticidal properties of asimicin, the first annonaceous acetogenin.[50,123] Trewiasine (**3**) and related maytansinoids acted as antifeedants, disrupted the life cycle, or were toxic to insects including the codling moth (*Laspeyresia pomonella*), spotted cucumber beetle (*Diabrotica undecimpunctata*), European corn borer (*Ostrinia nubilalis*), redbanded leaf roller (*Argyrotaenia velutinana*), plum curculio (*Conotrachelus nenuphar*), and chicken body louse (*Menacanthus stramineus*).[124] Significant levels of several phytoecdysteroids, which act as insect molting hormones in many insects and crustaceans, were isolated from *Diploclisia glaucescens* (Bl.) Diels (= *Cocculus macrocarpus* W. & A. (Menispermaceae)) seed.[125] Dithyreanitrile (**17**), an indole alkaloid containing a nitrile and two S-methyl groups, was isolated from *Dithyrea wislizenii* Engelm. (Cruciferae) that inhibited feeding of fall armyworm and European corn borer larvae.[126] Synthesis of dithyreanitrile was then reported by Mantus and Clardy.[127]
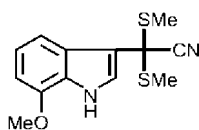


**17** dithyreanitrile

**Other Compounds of Interest.** Of particular importance to plant science was the isolation and structure determination of brassinolide (**18**) by Grove et al.[128,129] Brassinolide, from *Brassica napus* (Cruciferae), or rape, pollen, was the first plant growth regulating substance shown to have a steroidal structure and the first naturally occurring steroid that had a seven-membered lactone ring as part of the fused ring system.
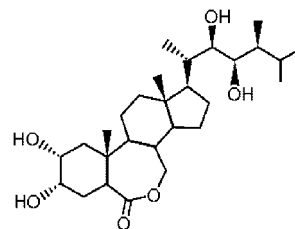


**18** brassinolide

Extracts of *B. napus* pollen had been reported to produce a novel growth-promoting effect when applied to young pinto bean plants. However, isolation of brassinolide from the extract was complicated by the presence of chromatographically similar glucose esters of long-chain fatty acids,[130] and the initial yield from 230 kg of pollen was only 10 mg. Since the discovery of brassinolide, over 70 brassinosteroids have been isolated from plants.[131] The brassinosteroids have been shown to be involved in plant processes such as cell expansion and elongation and pollen tube formation and to provide some protection to plants during chilling and drought stress.[132]

Drummondol (**19**), a compound encountered during the isolation of sesbanimide (**5**) from *Sesbania drummondii* seeds, was obviously related to phaseic acid (**20**) in a manner similar to the relationship of vomifoliol (**21**) to the plant growth regulator abscisic acid (**22**). Two compounds isomeric with **19**, drummondones A (**23**) and B (**24**),[133] were also isolated. Drummondone A and drummondone B had unusually high melting points (170−172 and 185−187 °C, respectively) for molecules of such low molecular weight (C$_{13}$H$_{20}$O$_4$, MW 240), and this was attributed to the rigid bicyclo[2.2.2]octane ring system. The drummondones may be catabolites or artifacts of isolation, but drummondol (**19**) has since been isolated from
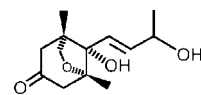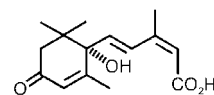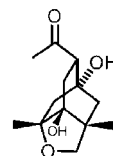


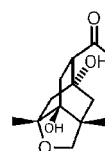**19** drummondol
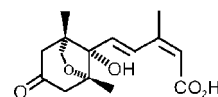


**20** phaseic acid
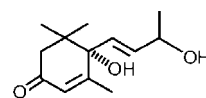


**21** vomifoliol



**22** abscisic acid



**23** drummondone A



**24** drummondone B

*Capsicum annuum* L. (Solanaceae),[134] and from fruits of *Capparis spinosa* Linnaeus (Capparaceae) as the glucoside.[135]

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