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Lipid-Related Compounds

Alkanes, Alcanols and Esters

WAXES

Waxes commonly occur on the surface of leaves and fruits where they form, with cutin, the very hydrophobic cuticle which limits water losses, controls gaseous exchanges, and participates in the protection against pathogenic agents.

Chemically, waxes are mixtures comprising hydrocarbons, free and hydroxylated aliphatic acids, aliphatic alcohols, aliphatic aldehydes, and aliphatic ketones, β-diketones, and esters. They may also contain terpenoids and flavonoids.

The saturated aliphatic hydrocarbon chains have an odd number of carbon atoms, often between 17 and 37, most often equal to 29 or 31. In some cases the homolog *iso*-C_{27}-C_{33} and *anteiso*-C_{28}-C_{34} series occur. Common esters are derived from 1-alkanols, and may have up to 72 carbon atoms; the most widespread correspond to C_{18}-C_{22} acids and to C_{26}-C_{28} alcohols. Some diesters of diacids are known (e.g., estolides). Terpenoids are frequent and are alcohols, ketones, or acids with a triterpenoid pentacyclic skeleton (oleanane, ursane, lupane, glutinan). Triterpenoid alcohols may be esterified by fatty acids. Waxes are extractible by organic solvents (hexane, chloroform) and amenable to GC analysis.

Except for phytochemical or physiological considerations, waxes and their constituents are of very limited interest.

- **Brazilian Wax Palm = Carnauba Palm,**
  Copernicia prunifera (Miller) H.Moore, Palmae

The wax (Eur. Ph., 3rd Ed.) is obtained from the leaves of this palm tree from the Brazilian northeast (also known as *C. 'cerifera'*). Chemically, it is a mixture of esters of long-chain aliphatic alcohols and aliphatic acids (e.g., C_{30}).

Carnauba wax occurs as a powder, or flakes, or solid lumps. Its identification is accomplished by TLC of the wax dissolved in chloroform (visualized by phosphomolybdic acid). The assay includes a determination of the melting temperature (80-88 °C), acid value, saponification value, and total ashes (<0.25%). The wax is used as a pharmaceutical aid to polish coated tablets and in food techonology (Eur. identification code E903).

- **Jojoba Oil,**
  Simmondsia sinensis (Link.) C. Schneider, Buxaceae

The jojoba is a dioecious bushy shrub widespread in the low-rainfall deserts of the United States Southwest (from Tucson and Phoenix to San Diego) and of the north of Mexico (Baja California, Sonora). It is characterized by blue-green leaves, the color of which is due to the thick cuticle that covers them and drastically limits water losses. It is cultivated in South America, in Israel, and experimentally in some arid regions of the African continent. Typically only female plants are grown since the drug consists of the seeds.

The jojoba seed contains up to 60% of an «oil» that is in fact a mixture of wax esters. Constituents of this «oil» are esters involving eicosenoic (C_{20}) and docosenoic (C_{22}) acids on the one hand, and eicosenol and docosenol on the other hand. In addition to this waxy fraction, these are glycosides with a cyanomethylene-cyclohexyl-substituted aglycone (simmondsin and analogs). A liquid below 10 °C, jojoba oil is barely oxidizable, and its behavior permits its use in place of preparations traditionally obtained from cetaceans (spermaceti). Jojoba production is currently limited in spite of numerous possible applications for the product, and in spite of the potential of this species as a means to enhance the productivity and value of arid regions. In rats fed jojoba oil, changes are observed in the histological and enzymatic activity of the small intestine, which probably preclude any dietary use.

At the present time, cosmetology uses jojoba oil after hydrogenation (it is then a solid up to 65 °C) in the formulation of creams, lotions, soaps, lipsticks, and other preparations designed to be spread onto the skin or the hair; it is a good, non-greasy lubricant.

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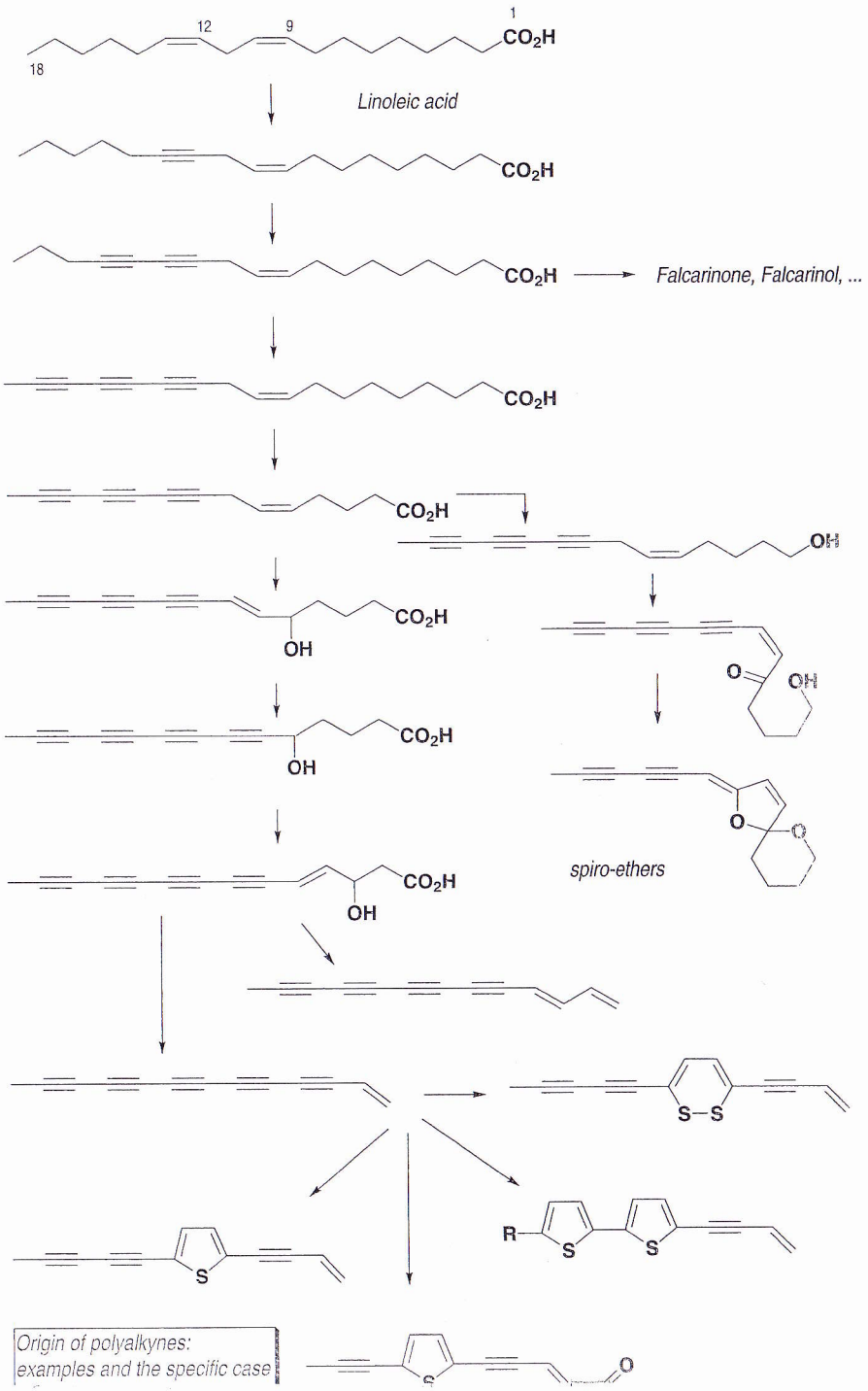
Lipid-Related Compounds

Alkyne Derivatives

1. GENERALITIES

Over a thousand substances containing one or several triple bonds are currently known in higher plants, in the Asteraceae, but also in the Apiaceae, Araliaceae, and Campanulaceae. Such compounds have also been described in Basidium fungi and algae. Their limited distribution and structural variety make them good chemotaxonomic markers, especially to distinguish tribes among Asteraceae. In some species they are not normally present, but develop after fungal attack, for



Origin of polyalkynes: examples and the specific case

These alkynes or polyalkynes are often linear, but they can also be partially cyclized. They may contain one or several double bonds and heteroatoms (oxygen, sulfur, chlorine) frequently included in a heterocycle: furan, dihydrofuranone, thiophene, thietanone, or dithiacyclohexadiene. In view of their origin, derivatives such as thiarubrines are also included in this group even though their structure does not possess a triple bond.

Biosynthetically, all of these compounds are related to fatty acids: most arise from linoleic acid through a series of desaturation reactions which lead, *via* crepenynic acid, to a C_{18} triyne acid. The latter leads to compounds of various lengths (see figure on the opposite page). Note especially the enepentyne precursor of the sulfur-containing heterocycles of the Asteraceae.

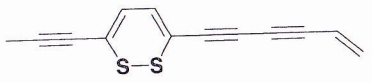
Generally extracted from fresh plants, polyalkynes may be efficiently separated by HPLC and on thin layers of silica containing caffeine, which interacts with the the π electrons of the unsaturated moieties and allows separation of compounds that are structurally very similar (visualization by $KMnO_4$).

2. BIOLOGICAL PROPERTIES

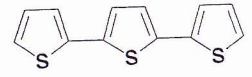
In most cases, polyalkynes and biogenetically related sulfur-containing derivatives are phototoxic. This phototoxic activity is UV A-dependent and particularly pronounced against nematodes, insect larvae, certain fungi (for example *Candida*), some bacteria, and some viruses.

Note the remarkable coincidence between the use, in most traditional medicines, of Asteraceae for the treatment of skin diseases, and the presence in the plants of polyunsaturated or thiophene-type compounds. Thus *Aspilia* of east Africa have an activity due to their thiarubrines *p. 172, which is comparable to that of fungizone on *Candida albicans* or *Aspergillus fumigatus*, and is greater than that of amphotericin.

Another example is *Bidens,* used in China (*B. parviflora* L., *B. tripartita* L.) for the treatment of eczema, wounds and ulcers, and also in South and Central America (*B. pilosa* L.) for candidiasis: in this case the main active ingredient is phenylhepta-triyne. Yet another example is provided by the thiophenes of *Tagetes* (China) or of *Porophylum* (Colombia). In Europe, the reputation of the root of stemless carlina (*Carlina acaulis* L.) for the treatment of skin disorders is to be related to carlina oxide, whose antistaphylococci activity has been demonstrated *in vivo*. A similar

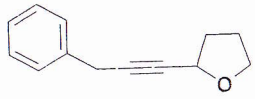


Thiarubrine A



α-Terthienyl

Phenylheptatriyne



Carlina oxide

observation may explain the antifuruncle properties that phytotherapists attribute to burdock.

3. POLYALKYNE-CONTAINING DRUGS

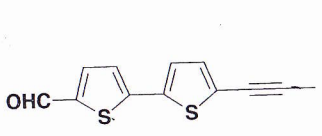
- **BURDOCK,**
  Arctium lappa L. (*Arctium majus* Bernh.), Asteraceae

The dried root of this Asteraceae is the sole part of the plant listed in the 10th edition of the French Pharmacopoeia (although there are still some uses for the leaves).

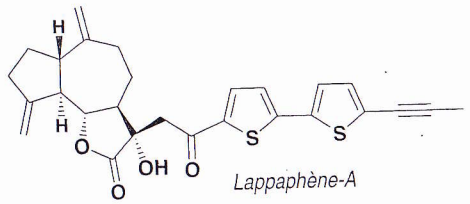
The Plant. This hardy, biennial plant is very common in vacant lots and on trail edges in almost all of Europe. It is easy to identify by its very large cordate leaves (50 x 30 cm) and its capitulums of purple tubular flowers surrounded by green bracts ending in hooks.

Chemical Composition. The drug may contain over 50% inulin and 2-3% phenolic acids; it is rich in polyunsaturated compounds, polyalkenes, and polyalkynes. The latter are either derivatives of 5'-(1-propynyl)-2,2'-bisthien-5-yl (arctinones, arctinols, arctinal, arctic acid), linear compounds (trideca-1,11-diene-3,5,7,9-tetrayne), or lappaphens, in other words complex molecules that probably result from the addition of arctinal onto an exomethylene-substituted sesquiterpenoid lactone of the guaianolide group. The ash value is high, but not more than 15% in the French official drug. The fruits and seeds are known for their lignan dimers and oligomers, and the bitterness of the leaves is due to arctiopicrin, a sesquiterpenoid lactone of the germacranolide group.

* Note the interesting observations collected—perhaps on the frontier of ethnopharmacognosy? on chimpanzees of Tanzania: these animals consume the leaves of various species of *Aspilia* without chewing them, and this behavior has allowed the authors who observed it to hypothesize that it represents a "medicinal" use of these plants, known for their antibacterial properties. Recent work (1992) failed to confirm the presence in the leaves of thiarubrine A, which had been isolated in 1985 from batches of the same origin. On the other hand, the leaves analyzed contain diterpenoids that stimulate uterine contractions (guinea pig uterus *in vitro*). These authors relate this composition to the fact that female chimpanzees consume *Aspilia* leaves three times as often, and to the fact that in both eastern and western Africa, women use the same *Aspilia* as galactagogue and to stop menstrual cramps. They also reiterate that kaurenol, a diterpenoid of very similar structure, increases progesterone secretion in the rat. In 1993, Rodriguez and Wrangham reviewed the subject and proposed the term «zoopharmacognosy» to describe the process by which wild animals select and use specific plants with medicinal properties for the treatment and prevention of disease. See Rodriguez, E. and Wrangham, R. (1993). Zoopharmacognosy: the Use of Medicinal Plants by Animals, in "Phytochemical Potential of Tropical Plants", Downum, K.R., Romeo, J. and Stafford, H.A., Eds., p.89-106, Plenum Press, New York).



Arctinal



Lappaphène-A

Tests. The French official drug is identified by its morphological characteristics, by the microscopic examination of the powder, by characterizing the polyunsaturated derivatives (which fluoresce after hexane extraction of a aqueous alcoholic extract), and by the characterization of inulin (revealed by resorcinol in the presence of HCl). Since the root has sometimes been confused with that of belladonna, verifying the absence of tropane alkaloids is a requirement (by selective extraction using dilute sulfuric acid solution, reextraction of the bases, and TLC of the residue).

Properties and Uses. The reputation of the drug, traditionally used for the treatment of dermatosis and furunculosis, is in part justified by the presence of polyunsaturated compounds whose antimicrobial and antifungal properties have been demonstrated *in vitro*. Other properties attributed to this drug do not seem to have been confirmed experimentally. The root, rich in fiber, is traditionally consumed in Japan under the name of «*gobo*». Although it is seldom used, in France, burdock root may claim the following indications: for oral or local use, «traditionally used» for seborrheic skin conditions; for oral use, to facilitate renal and digestive elimination functions [French Expl. Note, 1998]. The leaf is approved as a phytomedicine «traditionally used» as an adjunct in the emollient and antipruriginous treatment of skin disorders and as a trophic protective agent for cracks, abrasions, frostbites, chaps, and insect bites. The German Commission E monograph states that the applications that are claimed (gastrointestinal pain, arthritis, rheumatism, skin disorders) have not been substantiated, therefore the therapeutic use of burdock root cannot be approved. Some plant therapists still recommend burdock root& to treat furuncles, whitlows, varicose wounds, pilo-sebaceous infections, and acne.

- ***ECHINACEA*** **or CONEFLOWER,**
  Echinacea spp., Asteraceae

Note: this drug could just as well appear in the chapter on polysaccharides, given the activity attributed to those present by several authors. However, since the lipophilic fractions are also the basis of an activity, *Echinacea* may also be covered here, for its alkenes and alkynes with or without amide functions.

Different species of this genus of North American origin are used in phytotherapy and homeopathy, according to which the subterranean parts possess immuno-stimulatory properties. Three species have undergone chemical and pharmacological studies: *E. angustifolia* DC., *E. purpurea* (L.) Moench (= *Rudbeckia purpurea* L.),

The Plants. *Echinacea* are hardy plants with oval or lanceolate leaves, entire or more or less pinnate (*purpurea*). The large-size capitulums comprise purplish tubular flowers gathered into a sphere and large ligulate dangling, generally pink (or purplish, or very pale) flowers.

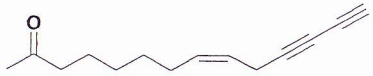
The drug consists of the root, and its microscopic examination is required to identify the species and verify the absence of a common falsification by another Asteraceae: *Parthenium integrifolium* L.*.

Chemical Composition. A substantial number of compounds have been isolated from *Echinacea*, including an essential oil, pyrrolizidine alkaloids, and the compounds in the following list:

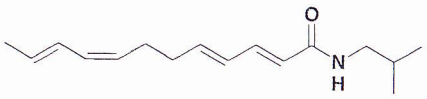
- Phenolic compounds derived from caffeic acid. These include the following:
  - caffeic acid, chlorogenic acid, and dicaffeoylquinic acids (cynarin is specific to *E. angustifolia*);
  - the monocaffeate, dicaffeate, and ferulate of tartaric acid (the dicaffeate [= cichoric acid] is abundant in *E. purpurea* (0.6-2.1%), but practically absent in *E. angustifolia*);
  - sugar esters of caffeic acid (echinacoside: 0.3-1.7% [except in *E. purpurea*]).

- A large number of unsaturated aliphatic compounds. These include aliphatic amides, isobutylamides of polyenyne acids (for example isobutylamide of undeca-(2*E*,4*Z*)-diene-8,10-diynoic acid) and of polyene acids (diene-diynes, for example isobutylamide of dodeca-(2*E*,4*E*,8*Z*,10*E*)-tetraenoic acid). Present in both *E. purpurea* and *E. angustifolia*, their respective structures and levels are slightly different, which is useful for species identification. In *E. pallida*, note especially the

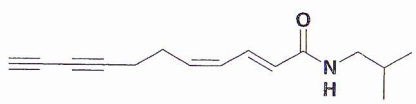
Pentadeca-(8Z,11Z)-dien-2-one



Pentadeca-(8Z)-ene-11,13-diyn-2-one



Isobutylamine dodeca-(2E,4E,8Z,10E)-tetraenoate



Isobutylamine undeca-(2E,4Z)-diene-8,10-diynoate

* In the absence of a monograph, a description of the morphological and microscopic characteristics of the plants and drugs can be found in: Heubl, G.R., Bauer, R. and Wagner, H. (1988). Morphologische und anatomische Studien an *Echinacea purpurea, E. angustifolia, E. pallida* und *Parthenium integrifolium*, *Sci. Pharm.*, **56**, 145-160. HPLC and TLC analysis are also a good means of verifying the identity of the drug: see: Bauer, R. (1997). Standardisierung

presence of ketoalkynes and keto-alkenes. Long-chain fatty acids and alkanes are present in all species in the genus.

- Polysaccharides. Their structure has been studied on cell cultures of *E. purpurea* (fucogalactoxyloglucans, arabinogalactan); the roots of the same species contain a glucuronoarabinoxylan.

Pharmacological Activity. Known to Native American Indians, echinaceas were used externally as wound-healing agents, as well as internally for headaches, stomach aches, or as antitussives. Pharmacology has not confirmed these indications, but it presents echinacea-based preparations as immunostimulatory, based on various experiments: carbon clearance test in the mouse (detects an increased phagocytosis), phagocytosis test for granulocytes and macrophages, induction challenge for mediators (interferon, interleukins). What are the substances responsible for the responses observed (inconsistently) during these tests? The polysaccharides are active, but, in many tests, the lipophilic fraction is also active, and sometimes more so. In 1994, a critical analysis of clinical data obtained in humans showed that these data were not sufficient to make therapeutic recommendations on what type of preparation to use or what doses to use for specific indications: the products tested were different, they were often part of combinations, and in general the quality of the methodology left much to be desired.

Uses. Echinacea is not official in France, nor is it listed in the Annex to the French Explanatory Note published in 1998. The German Commission E monograph (1992) states that *E. pallida* root is used as a supportive treatment for flu-type infections and must not be used in case of tuberculosis, multiple sclerosis, AIDS, and other conditions. According to Commission E, the properties that are claimed for *E. angustifolia* (plant and root) and *E. pallida* (plant) have not been demonstrated, therefore the Commission does not recommend therapeutic use. In addition, it specifies that parenteral use is proscribed given the risks (chills, short-lived fever, nausea, vomiting, immediate allergic reaction in rare cases). Package labels must include the wording «to enhance resistance to upper respiratory tract infections (e.g., colds)»; labels must state that the use of these products by medical prescription «does not exclude the use of antibiotics or other anti-infectious agents.»

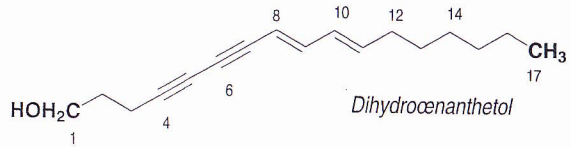
Many German practitioners, on the basis of possible immunostimulating effects of *Echinacea*, recommend its use as a tincture, mother tincture, or extract, alone or in combination (e.g., *Baptisia*, *Thuja*) to stimulate defense mechanisms: for the prevention and treatment of colds, of the flu, and of various respiratory disorders, as adjunctive therapy to chemotherapy for common ailments, or as a prophylactic treatment against opportunistic infections in high-risk patients. The drug and its preparations seem devoid of toxicity.

4. TOXIC OR ALLERGENIC POLYALKYNE-CONTAINING PLANTS

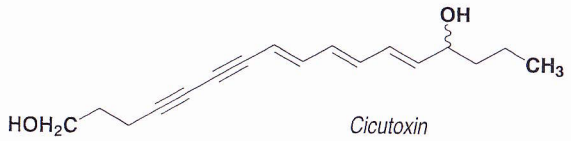
• European Water Hemlock, *Cicuta virosa* L., Apiaceae

A plant of swamps and of muddy ditches, the European water hemlock is a large size (1 m and more) herbaceous species with a cylindrical and hollow stem, reddish at the base and at the knots, with tri- and bitripinnatisect leaves. The compound umbels are without involucre and with involucels with 3-5 acuminate bracts. The voluminous root is hollow and septate. Chemically, the root is rich in acetylenic compounds. The major one is (–)-cicutoxin or heptadeca-(8*E*, 10*E*, 12*E*)-trien-4,6-diyn-1,14-diol; it occurs alongside cicutol, cicudiol, their isomers, falcarindiol, and other C17 isomeric polyalkynes. The effect of (–)-cicutoxin is reversible potassium channel blockade.

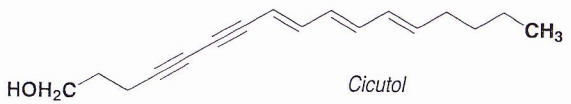
All parts of the plant are toxic, especially when fresh. Intoxication occurs following the ingestion of the subterranean parts mistaken for edible roots, and although it is rare, it is often fatal (respiratory arrest, ventricular fibrillation). Intoxication initially manifests itself by profuse salivation and abdominal pains,



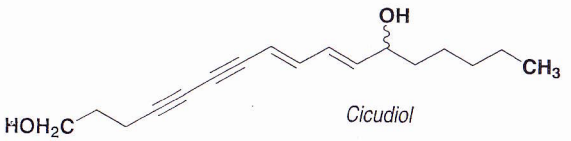
Dihydrocœnanthetol



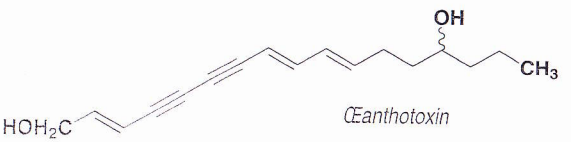
Cicutoxin



Cicutol



Cicudiol



Œanthotoxin

followed by prolonged vomiting and violent convulsions at regular intervals. The essential part of the treatment—when it is not too late—consists of stomach pumping with activated charcoal and prevention of the convulsions (thiobarbiturate, flunitrazepam), and if necessary, assisted ventilation and fluid administration. The species common to North America (*C. douglasii* [DC.] Coulter J. & Rose, *C. occidentalis* Dougl. ex Heynh.) have an identical composition and toxicity.

• Hemlock Water Dropwort, *Œnanthus crocata* L., Apiaceae

This common plant of the European southwest is abundant in the meadows and damp ditches of western France. The leaves are bipinnatisect (radical leaves) or bitripinnatisect (cauline leaves), with oval corner segments. The root consists of clumps of tubers (hence the name dead men's fingers), exudes an orangy-yellow juice, and the whole plant smells somewhat like celery. The substance responsible for the toxicity is a polyenyne that is unstable when exposed to air: (+)-œnanthotoxin. Concentrated in the roots, its level is maximal in the winter and at the beginning of the spring. In the 1990s, rare intoxications were observed among «natural» food advocates (due to confusion with the wild carrot, or attraction to the smell). The symptoms observed in case of intoxication are identical to those due to the European water hemlock; the treatment is similar. Like European water hemlock, hemlock water dropwort sometimes causes the loss of cattle.

• Ivy, *Hedera helix* L., Araliaceae

Repeated contact with the leaves of this common species (see p. 701) may cause erythematous or vesiculous reactions of the face, hands, and arms, sometimes 48 hours after contact. It appears that no experimentation has been conducted to identify the substance(s) responsible for these dermatitic effects. Note, however, that in the case of other Araliaceae of the genus *Scheflera* [*Brassaia*], the agent responsible for the dermatitis has clearly been shown to be falcarinol, a polyalkyne whose presence in ivy leaves has been established.

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Toxic polyalkyne-containing plants

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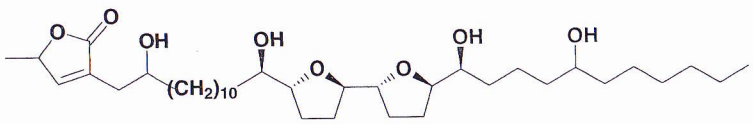
Lipid-Related Compounds

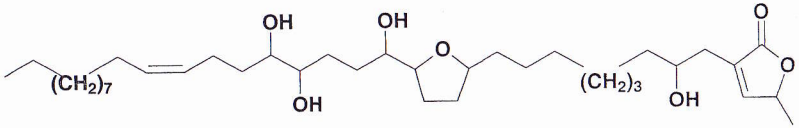
Acetogenins

This name designates long-chain aliphatic compounds with 35 or 37 carbon atoms, ending with a γ-lactone most often unsaturated and cyclized into one (type A) or two tetrahydrofuran rings that may (type B) or may not (type C) be adjacent. The carbon chain generally has several oxygen-containing substituents and the γ–lactone is sometimes hydroxylated. Biosynthetically, the tetrahydrofuran rings probably arise from the enlargement of the two or three epoxide rings of an intermediate arising from the oxidation of 1,5-dienes and 1,5,9-trienes. The terminal lactone may result from an aldol condensation between a C_3 unit and a long-chain fatty acid.

Known since the mid-1980s—over 200 have been described—acetogenins are characteristic of the Annonaceae *, where they are mostly concentrated in the seeds



Rioclarin (threo/trans/threo/trans/erythro)



Glaucaflorin

* Annonaceae are mostly known for their edible fruits, including *Annona cherimolia* Miller (cherimoya), *A. muricata* L. (soursop, guanabana), *A. squamosa* (sugar apple, sweetsop, custard apple), *A. reticulata* L., *Asimina triloba* (L.) Dunal (pawpaw), *Rollinia mucosa* (Jacq.) Baillon (biribá). They are sometimes used for their essential oils. For example, the fresh flowers of *Cananga odorata* (Lam.) Hook. & Thomson produce the essential oil of ylang-ylang.

(*Annona, Asimina, Goniothalamus, Rollinia, Uvaria*). The potential applications of these molecules are linked to their marked properties: cytotoxic and antitumor (gigantecin, bullatacine, rolliniastatin), antiparasitic (annonacin, cherimolin), and insecticidal (asimicin, annonin). Biochemically, acetogenins block mitochondrial respiration by inhibiting NADH-cytochrome C oxidoreductase; this would explain their insecticidal activity, among others.

"Gluco-resins" of Convolvulaceae

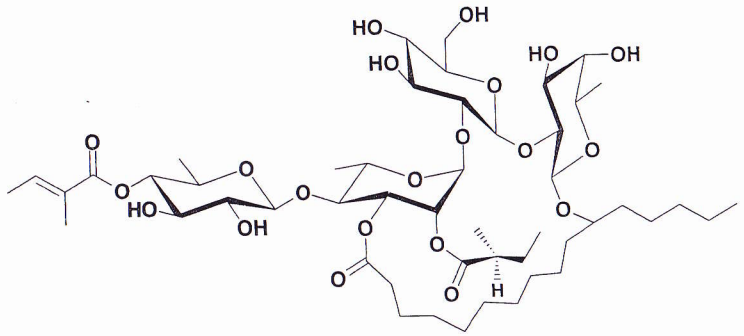
Convolvulaceae containing cathartic gluco-resins have been known since ancient times and have long been prized for their cathartic properties. They include the following:

- Ipomœa (Orizaba Jalap, Mexican Scammony Root), *Ipomœa orizabensis* (J. Pellet.) Steudel;
- Jalap, *I. purga* (Wender.) Hayne;
- Scammony glorybind, *Convolvulus scammonia* L.;
- «*turbith*», *Operculina turpethum* (L.) Silva Manso.

All of these species, mostly native to the intertropical regions, are voluble herbs characterized by flowers with a gamopetalous funnel-shaped or tubular, abruptly flared corolla, and by leaves most often cordate at the base. The drug consists of the subterranean parts rich (10-18%) in gluco-resin. The structure of these active ingredients has long remained poorly-known, until the use of the appropriate techniques showed that the diethyl-oxyde-soluble fraction of these resins consists of complex glycosides characterized by the presence of an oligosaccharide chiefly composed of 6-deoxy-hexoses (rhamnose, fucose, and more). This oligosaccharide constitutes the sugar moiety of a glycoside whose aglycone is a hydroxylated fatty acid (e.g., 11*S*-hydroxy-decanoic acid or «jalapinolic acid»). This acid, through its carboxyl group, forms an intramolecular ester with a hydroxyl group on the oligosaccharide, and this ester turns out to be a macrocycle. Other hydroxyl groups on the oligosaccharide are esterified by fatty acids (*n*-decanoic, *n*-dodecanoic) or by lower molecular-weight acids (including tiglic, isobutyric, and 2-methylbutyric acid).

Gluco-resins are contact cathartics which cause an increase in water elimination and in peristalsis. Their use [illegible]

convolvulus of western Europe, especially bear's-bind, *Calystegia sepium* (L.) R.Br., have an activity of the same type, although weaker, and their use must also be proscribed.



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