of *Juniperus* (*J. mexicana* Schiede, juniper, *J. virginiana* L., red (pencil) cedar, *J. procera* Hochst. ex Endl., of east Africa).

Regarding the other uses, see the other chapters in this text: *Ginkgo* (flavonoids, p. 329), cypress (proanthocyanidins, p. 399), yews (diterpenes, p. 643). Regarding the applications of the other classes of Gymnosperms, see the uses of *Ephedra* (p. 880) and the toxicity of the Cycadales (cyanogenic glycosides, p. 196). Other anecdotal uses may be mentioned, for example that pine nuts are edible!

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Monoterpenes

Iridoids

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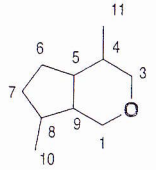
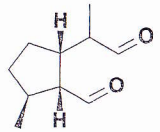
1. GENERALITIES

Iridoids in the strict sense of the term are monoterpenes characterized by a cyclopenta[*c*]pyranoid skeleton, also known as the iridane skeleton (*cis*-2-oxa-bicyclo-[4,3,0]-nonane). In the broad sense, it is acceptable to include in this group the secoiridoids, which arise from the latter by cleavage of the 7,8 bond of the cyclopentane ring. Some authors even limit their definition to the concept of "methylcyclopentane". This group (of about 500 known structures) chiefly

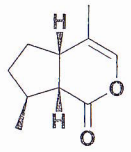
glycosidic compounds (>100). Structurally related alkaloids (e.g., skytanthine) will not be included here: although some are indeed natural products, others are merely extraction artefacts formed by the replacement of the pyran ring oxygen atom by a nitrogen atom; also excluded will be secoiridoid-type sequences combined with an amine derived from tryptophan or phenylalanine (see indole and isoquinoline alkaloids respectively).



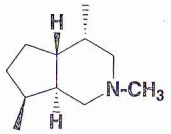
Iridane



Iridodial



Nepetalactone



Skytanthine

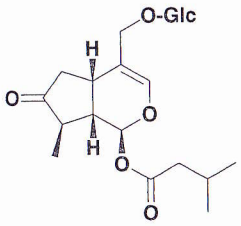
The iridoids were named after ants of the *Iridomirmex* genus, from which were isolated compounds involved in the defense mechanisms of these insects: iridodial, iridomyrmecin, and related compounds. Such simple structures also exist in plants; for example, nepetalactone from *Nepeta cataria* L. (Lamiaceae), or teucriumlactone C from *Teucrium marum* L. have marked properties (the effects of the former on cats earned it some evocative names: catnip, *Katzenmelisse*, *herbe-aux-chats*). In fact, structures that simple are rare: we shall see below that iridoids, which normally contain ten carbon atoms, may also have more, and present multiple structural variations, ranging from simple functionalization to the formation of polycyclic structures.

The group is biosynthetically homogeneous, and is represented, except for the few structures specific to insects, only in the Dicotyledon Angiosperms. They are elaborated preferentially by gamopetalous plants: Dipsacales, Gentianales, Lamiales, Scrophulariales; which makes them interesting chemotaxonomic markers.

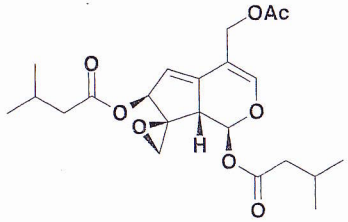
2. STRUCTURE OF IRIDOIDS

The majority of iridoid glycosides in the broad sense of the term are glucosides, with the glycosidic linkage established between the hydroxyl group on the anomeric carbon of D-glucose and the hydroxyl in the 1-position of the aglycone. A small number of structures are now known in which the sugar portion of the molecule is an oligosaccharide (e.g., rehmaniosides). Also known are structures in which the glucose is linked to the 11-hydroxymethyl group (e.g., ebuloside in Caprifoliaceae). Non-glycosidic iridoids may be, among other things, alkaloids (skytanthine), polycyclic compounds (plumericin), polyesters (valepotriates), or intramolecular ethers (rehmaglutin B). Non-glycosidic secoiridoids are exceptional (*Syringa* sp., *Olea* sp. [Oleaceae]).

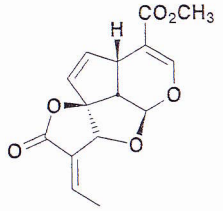
Iridoids generally have ten carbon atoms. When there is a C-11, it is generally part of a carbomethoxyl group (loganin, geniposide) or part of a [illegible]



Ebuloside



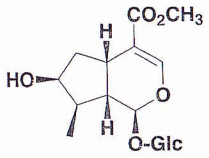
Valtrate



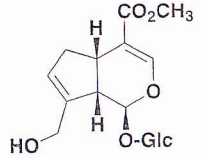
Plumericin

group (monotropein); in rarer cases, this group is replaced by a hydroxymethyl group (Valerianaceae, Caprifoliaceae), or by an aldehyde or methyl group (lamioside). In a certain number of cases, the C-11 is absent (aucubin, catalpol, harpagoside). The pyran ring is only exceptionally open (for example, in the case of the gentiobioside of iridodial and of nepetariaside, the precursor of nepetalactone).

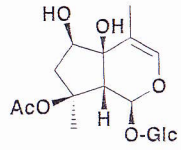
There are multiple structural variations. They have allowed some authors to propose subdivisions within the group. The methyl group which is normally at C-8 can be more or less oxidized: examples include a hydroxymethyl group (aucubin, monotropein) and an epoxide (valtrate); it is rarely absent (deutzioside). There may be an unsaturation at C-7(8) (geniposide, aucubin), which may become a center of oxidation (catalpol) or hydration (lamioside). Note the possible oxidation of C-6 (aucubin, verbenalin, harpagoside) and the potential unsaturation at C-6(7) (monotropein).



Loganin

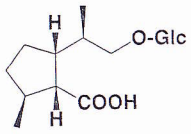


Geniposide

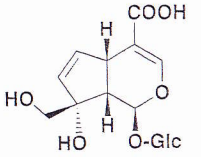


Lamioside

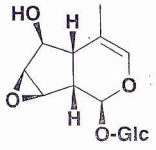
Aucubin



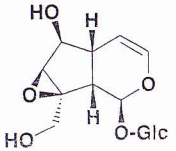
Nepetariaside



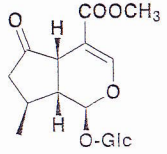
Monotropein



Deutzioside



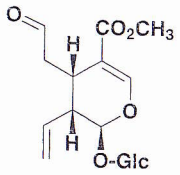
Catalpol



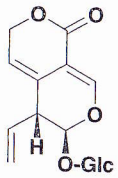
Verbenalin

There are several types of secoiridoid-type aglycones.

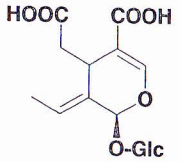
- Those which, like secologanin, have a vinyl group at C-9. Polyfunctionalization of which permits lactonization (gentiopicrin).
- Those which, like oleoside, have an ethylidene or hydroxyethylidene group at C-9. The carboxyl group may be esterified (oleuropein).
- Those which are amidified by an aromatic amine (see alkaloids).



Secologanin



Gentiopicroside



Oleoside

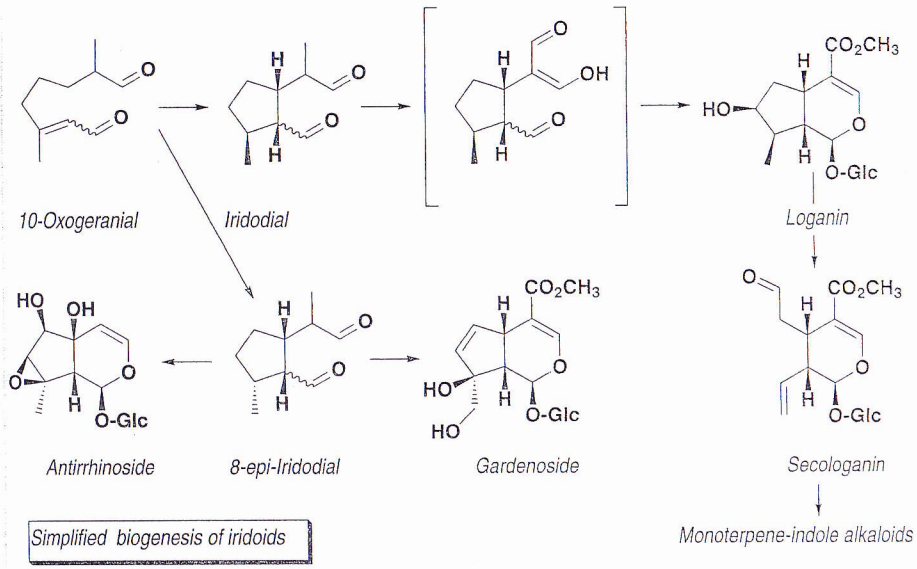
In both groups (iridoids and secoiridoids), dimeric structures are known (e.g., centaurin of *Centaurium erythrea* Rafn.) as well as many structures acylated on the saccharide moiety (Gentianaceae) or on the aglycone (e.g., amarogentin).

3. BIOSYNTHETIC ORIGIN

The study of the biosynthetic origin of iridoids was largely stimulated by the key role played by one compound, secologanin, in the elaboration of indolo-monoterpenoid alkaloids and of certain isoquinoline alkaloids: the condensation of secologanin with tryptamine and with 3,4-dihydroxyphenethylamine leads to strictosidine and desacetylipecoside, respectively, and these are the immediate precursors of the indole alkaloids found in the Apocynaceae, Loganiaceae, and Rubiaceae on the one hand, and of isoquinoline in the ipecacs and in certain other Rubiaceae on the other hand (p. 963).

The incorporation of labeled mevalonic acid, as well as labeled geraniol derivatives, into iridoid-type structures, and into indole alkaloids, demonstrates the terpenoid character of these metabolites. Several mechanisms have been proposed, such as the one—now demonstrated—involving the cyclization of the dialdehyde resulting from the oxidation of 8-hydroxygeraniol to iridodial (or to 8-epi-iridodial). The glucosylation and the oxidation of iridodial leads to loganin, the immediate precursor of most iridoids. The same process applies to 8-epiiridodial to lead, *via* 8-epiloganin, to antirrhinoside, as well as to aucubin and gardenoside.

Loganin is the intermediate that undergoes the ring opening, reaction which leads to the secoiridoids. This step occurs by a mechanism that remains to be elucidated, and affords secologanin, the precursor of all of the secoiridoids, and consequently, of the indole alkaloids that incorporate this pattern.



Simplified biogenesis of iridoids

4. EXTRACTION AND CHARACTERIZATION

Extracting these glycosides is particularly delicate due to their great instability. This instability also explains the darkening that takes place soon after plant collection in many species containing iridoids. In addition, it explains the name of pseudoindican or chromogenic glycoside that used to be applied to some of these compounds.

The extraction is achieved with polar solvents (alcohols of various concentrations), and frequently, an initial separation is obtained by redissolving the extraction residue in water, then re-extracting this with immiscible solvents of increasing polarity. The fractionation *per se* is done by chromatography on alumina, on charcoal (with a risk of irreversible adsorption), on porous polymers (e.g., XAD-2) with polar eluents, and more and more, by reverse phase HPLC. The purification is achieved using classic procedures (TLC, HPLC).

The detection of iridoids in a vegetable drug is most often accomplished by the Trim and Hill color reagent: dilute solution of copper sulfate and hydrochloric acid. To visualize TLCs a non-specific reagent is used: vanillin in the presence of sulfuric acid, or else, more simply, hot HCl.

5. BIOLOGICAL AND PHARMACOLOGICAL PROPERTIES

As one would predict, given the defensive function of this type of compound in ants, numerous iridoids are involved in plant-animal interactions. From the pharmacological standpoint, the applications of this class of compounds are rather

principle. Some iridoids have an anti-inflammatory activity, which is weak by the oral route and stronger by topical application: 1 mg of aucubin, verbenalin, or loganin have an activity almost similar to that of 0.5 mg of indomethacin on the TPA-induced mouse ear edema.

Some are ingredients—various forms—of allopathic medications (valerian), others are, typically, phytotherapeutic products (devil's claw, olive tree). Others mostly receive attention for their non-pharmaceutical applications (yellow gentian). Beyond this, it is not known what the role of iridoids may be in folk remedies such as mullein (p. 113), plantains (p. 106), bedstraw and white dead nettle (see below), euphrasia*, veronica **, or the chaste tree (p. 754).

6. CHIEF IRIDOID-CONTAINING DRUGS

• VALERIAN, *Valeriana officinalis* L., Valerianaceae

The drug (Eur. Ph., 3rd Ed.) consists of "the subterranean organs of *Valeriana officinalis* L. *s.l.* including the rhizome, roots, and stolons, carefully dried at a temperature below 40°C. It contains not less than 5 mL/kg of essential oil".

The Plant. *V. officinalis* in the broad sense of the term is a very polymorphic collective species which groups several naturally occurring subspecies that differ from one another by their degree of ploidy. The basic type is diploid, $2n = 14$, (*V. officinalis*), and is a perennial herb with a hollow and grooved stem bearing a rosette of leaves at the base, and opposite pinnatisect leaves on the stem. The leaves comprise 11-19 lanceolate folioles, all of the same width. The flowers are zygomorphous, pentamerous, white or pinkish, and are grouped into terminal cyme-like inflorescences. The gynoecium is three-carpellate and unilocular and leads to an exalbuminous akene. The calyx develops into a feathery tuft (pappus). The species is common in damp woods, ditches, and along the streams of all of Europe, and is cultivated to supply the drug market.

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* EUPHRASIA, *Euphrasia rostkoviana* Hayne = *E. officinalis* L. *nom. ambig.*, Scrophulariaceae. Also known as eyebright, this plant was—and still is on occasion—used in folk medicine, with no pharmacological justification, to treat eye disorders (conjunctivitis, blepharitis, eye strain) and, internally, as an astringent and an anti-inflammatory. The drug is known to contain phenolic acids, a glycosidic phenylpropyl ester (eukovoside), a glucosylated lignan, and many iridoids (aucubin, catalpol, ixoroside, euphroside).

** VERONICA, *Veronica officinalis* L., Scrophulariaceae. In folk medicine, this plant, which grows in open woodlands, is considered an expectorant and a remedy for arthritis and rheumatism. Since none of these activities has been substantiated, the German Commission E cannot approve the therapeutic use of veronica. The drug contains 0.5-1% iridoids (e.g., [illegible] and verproside).

The other valerian subspecies * have very similar characteristics: *V. officinalis* ssp. *collina* (Wallr.) Nyman ($2n = 28$) has leaves with 15-27 folioles, all of the same width, and *V. officinalis* ssp. *sambucifolia* (Mikan *f.*) Celak = *V. excelsa* Poiret, ($2n = 56$) has leaves with 5-9 folioles, with the apical one clearly larger than the others. In contrast to the other subspecies, the rhizome of the latter is clearly stoloniferous (epi- and hypogeous stolons). *V. repens* Host. (= *V. procurrens* Wallr.) could be considered a fourth species, according to the Flora Europaea. Often appended to this species are taxonomic groups of uncertain status and limited distribution (e.g., *V. salina* Pleigel or *V. versifolia* Brügger).

The Drug. Valerian root, whose pungent odor instantly suggests its identity, includes an ovoid to cylindrical rhizome (50 x 30 mm), yellowish-gray, covered by numerous roots of small diameter (1-3 mm), and accompanied by stolons striated between the nodes.

The drug is obtained by cultivating octaploid types. For a few years, optimization attempts have been aimed at increasing the concentration of sesquiterpenoids.

Valepotriate production (see below) remains possible from valerians from various sources that are richer in iridoids:

- Indian valerian—a sedative in Ayurvedic medicine—*V. walichii* DC. (= *V. jatamansi* Jones) is cultivated in several countries, and contains 3-6 (12)% valepotriates, and up to 9% of an essential oil with patchouli alcohol and maaliol;
- the valerians of Central America, such as *V. edulis* Nutt., ssp. *procera* F.G. Meyer, which contain 4-7% valepotriates and whose steam distillate consists almost exclusively of valepotriate decomposition products (isovalerianic acid) and sesquiterpenoid hydrocarbons.

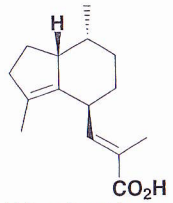
Chemical Composition. The substances (currently known) that may contribute to the valerian root activity are terpenoid in nature: sesquiterpenes and iridoids.

The most important valerian sesquiterpenes are cyclopentanic carboxylic acids. Chemically stable and not volatile, they include valerenic acid, acetoxyvalerenic acid, and in spoiled drugs, hydroxyvalerenic acid. The concentration of valerenic acid and its derivatives (0.2-0.7%) of the best cultivated varieties is maximum in March, when it can reach 0.9%. Other sesquiterpenes are found, that are volatile: valerenal, valerianol, valerenol and its esters (acetate, valerate), valeranone, kessylyl alcohol, eudesmatriene, and other hydrocarbons. These sesquiterpenes constitute a fraction of the essential oil which also contains many monoterpenes (e.g., bornyl acetate, myrtenyl acetate, camphene). The volatile fraction represents 2-20 mL/kg of the dried drug; its composition varies depending on the subspecies, season, cultivation conditions, and most of all, the preparation procedure (dried or fresh drug, steam

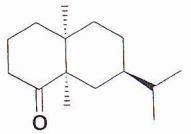
* Here we echo the subdivisions outlined in the Flora Europaea. The "Flore de France" (Guinochet, M. and de Vilmorin, R. (1975), éditions du *Centre National de la Recherche Scientifique* or CNRS, Paris, **2**, p 514 *sq.*) reduces *V. officinalis l.s.* to *V. officinalis* (incl. *V. collina* Wallr.) and to *V. sambucifolia* (incl. *V. procurrens* Wallr.)

distillation or extraction). Valerenic acid and its derivatives are not water soluble and can be extracted with hydroalcoholic solutions containing at least 40% ethanol.

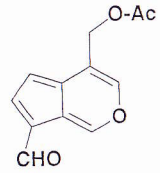
Here, the iridoids are very specific. They are not glycosidic, and are lipophilic esters of triols derived from iridane; they are either 8,10-epoxidized *, or 3(4)-5(6)-dienes (valtrate, isovaltrate, acevaltrate), or 3(4)-monoenes (dihydrovaltrate, isovaleroxyhydroxydihydrovaltrate [IVHD]). Their structures are very close to one another: they differ mainly by the nature of the aliphatic acids (acetic [Ac], isovaleric [isoV]) that esterify the three hydroxyl groups at C-1, C-7, and C-11, and they form a mixture which is difficult to resolve, and in which the valtrate and isovaltrate are largely dominant. The valepotriate level generally ranges from 0.8 to 1.7%. These compounds are particularly unstable: they are hydrolyzed, then they decompose rapidly under the influence of moisture, heat (>40°C), or acidity (pH<3), to yield yellow unsaturated aldehydes (baldrinal, isopropylbaldrinal). A valerian tincture, stored at 20°C for 2 weeks after being prepared, only contains about one-third of the valepotriates initially found. The baldrinals are reactive, which may be why they are no longer detectable under these conditions. It is empirically known that valepotriates, which are not extractible in water, can be extracted from the drug only with hydroalcoholic solutions containing at least 70% ethanol (pure ethanol is the only truly effective extraction solvent).



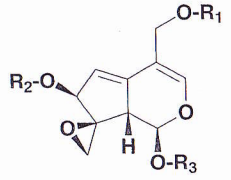
Valerenic acid



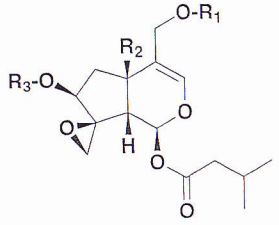
Valeranone



Baldrinal



R_1 = Ac, R_2 = R_3 = isoV: *Valtrate*
R_1 = R_3 = isoV, R_2 = Ac: *Isovaltrate*
R_1 = Ac, R_2 = 3-Ac-isoV, R_3 = isoV: *Acevaltrate*



R_1 = Ac, R_2 = H, R_3 = isoV: *Didrovaltrate*
R_1 = 2-isoV-isoV, R_2 = OH, R_3 = Ac: *IVHD*

In addition, the following compounds have been isolated from the subterranean parts: traces of alkaloids (actinidine, naphthyridyl methylketone), phenolic acids, and γ-aminobutyric acid.

* Valepotriates = valerian epoxide triesters (i.e., triates).

Pharmacological Properties. The literature on the pharmaceutical potential of valerian is plentiful and rich in contradictions. Although the drug is unanimously recognized as a minor tranquilizer, the identity of the substances responsible for this effect remains controversial. The activity was once linked to the esters of borneol, but it was soon reattributed to the valepotriates. Indeed, experimental work conducted with these iridoids on different animal species shows a decrease in locomotor activity (mouse), a spasmolytic effect, a decrease in aggression (cat), but is that really proof of a "tranquilizing" activity? Other authors, who used behavioral tests, found no activity at all. Furthermore, it has long been known that valepotriates are not found in most commercial preparations, including tinctures, and that they are partially degraded and very poorly absorbed in the digestive tract.

Next, the sesquiterpenes were evaluated—valeranone and valerenic acid. Valerenone is a sedative, hypotensive, and anticonvulsant; valerenic acid is a spasmolytic. It was noted that Japanese valerian root, which is used as a sedative, contains practically nothing but sesquiterpenes and that its extracts prolong the duration of barbiturate-induced sleep (kessylic derivatives). The most recent experiments were carried out mostly with total extracts. *In vitro*, the aqueous extract stimulates the release and inhibits the uptake of GABA at nerve endings. Other data show the affinity of aqueous and hydroalcoholic extracts for GABA receptors, and GABA metabolism inhibition by valerenic acid. Tested in mice (IP), the valepotriate-free ethanol extract does not alter motility, nociception, or body temperature, but like valerenic acid (12.5 mg/kg, IP), it counteracts the convulsions induced by picrotoxinin (but not by harman); it prolongs the duration of thiopental-induced sleep. This sleep prolongation may be due to an interaction between constituents of the extract and GABA and benzodiazepine receptors.

The preparation methods of the extracts being tested, their compositions, and the routes of administration were different, which makes it impossible to interpret the divergent data.

Under these conditions, what, if anything, can be said of the clinical data? There are new observations and tests. Unfortunately, these tests are not without bias, and they were often carried out with preparations of poorly defined composition; they attempted to assess the improvement in sleep quality with subjective criteria, or, in some cases, by using electrophysiological recordings. Their results are definitely inconclusive, but they indicate the possibility of a moderate tranquilizing effect and a favorable effect on sleep quality and onset, particularly in subjects who don't sleep much. Among the most recent and most rigorous trials (many of which include only a small number of patients), one trial provides objective proof that slow-wave sleep is increased, and another trial—placebo- and flunitrazepam-controlled—reveals an improvement in the subjective perception of sleep quality, a slight decrease in alertness, and the absence of residual effects upon awakening.

In Germany, where pure valepotriates are used, their psychostimulant, thymoleptic (mood-improving, a property attributed to the diene-esters), and tranquilizing activity (a property attributed to the mono-unsaturated esters) are recognized. These esters are destroyed by gastric acidity, but their degradation products—baldrinal and other derivatives—retain an activity [illegible]

considers them to be the active forms. One thing is certain: valepotriates are inhibitors of nucleic acid synthesis, and they are highly cytotoxic, mutagenic, and teratogenic nucleophiles (hepatoma cells). The baldrinals are also cytotoxic. Until now, these effects have only been observed *in vitro*: the risk to humans, even after prolonged use, is probably negligible. Nevertheless, it should be evaluated.

Tests. Valerian is identified by characterizing the valepotriates after extracting them with dichloromethane (blue color in the presence of hydrochloric acid, as a result of the formation, by deacylation and substitution, of dichlorocyclopenta[*c*]pyrilium ions). The assay includes a TLC analysis (to show the presence of valerenic and acetoxyvalerenic acid, and possibly of valtrate and isovaltrate in the dichloromethane extract), an evaluation of the material extractible in dilute ethanol (>15%), sulfuric ashes (<15%), ashes insoluble in hydrochloric acid (<7%), and a quantitation of the essential oil (>0.5%).

Uses. The common usage forms of valerian are simple galenicals, most of which are, as shown by chromatographic techniques, devoid of valepotriates. Only the stabilized drug powder would retain a sufficient level of iridoid-type esters. The nebulisate obtained after hydroalcoholic extraction may also have some activity. Be it as it may, the increasing importance granted to sesquiterpenes (and to potential water-soluble, active substances) displaces the key questions. All of the works and publications reviewed by this author consider the drug nontoxic. Nevertheless, in the current state of knowledge, it is wise to recommend using preparations devoid of valepotriates.

Like the flowers and flowering tops of hawthorn, like the aerial parts of the passion flower, or like many other drugs with which it is frequently associated in herbal teas as well as in simple galenicals, valerian is traditionally used to treat the symptoms of neurotonic disorders in adults and children, especially in cases of minor sleeplessness [French Expl. Note, 1998]. Preparations based on total drug powder and hydroalcoholic extracts of titer >30% must pass basic safety tests and comply with a limit concentration of active substance.

In Germany, package inserts for valerian-based products must list the following indications: nervous tension; difficulties falling asleep; nervous cramp-type pains in the gastric region. The German Commission E monograph lists no contra-indications, side effects, or drug interactions. (But most authors from English-speaking countries discourage the use of valerian in pregnant women.) Medicines with a guaranteed valepotriate titer are used in Germany as tranquilizers, whereas products devoid of valeporiates, which are often combined with other plants, are indicated as sedatives. Pure valepotriates (most often as mixtures) are proposed to treat psychosomatic problems, anxiety, stress, and difficulties concentrating.

Dry extract of valerian. The dry extract of valerian is official in France (Fr. Ph., 10th Ed.). It is prepared by lixiviation with 60c ethanol and dried by an appropriate method (e.g., nebulization) at a temperature lower than 50°C. It must contain 0.25- [illegible]

these acids is done by HPLC of the extract diluted in methanol. In the prescribed experimental conditions, the reaction characteristic of valepotriates is negative (concentration <0.08%).

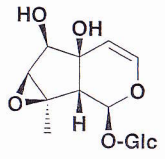
• Devil's Claw, *Harpagophytum procumbens* (Burch.) DC ex Meissn., Pedaliaceae

Introduced in Europe in the late 1960s, the "tuberized secondary root, cut then dried" of this *Harpagophytum*, or devil's claw, is the subject of a monograph in the European Pharmacopoeia (3rd Ed.). In its native area (southern Africa), it is a recognized folk remedy for gastrointestinal problems, fever, and birthing pain.

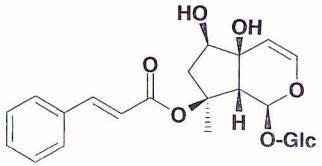
The Plant, the Drug. Devil's claw is a perennial plant with creeping stems which radiate and bear opposite leaves. The large solitary flowers (4-6 cm) have a pale yellow tube which widens into a lobate, deep purplish-red corolla. The fruit is a ligneous capsule armed with spikes ending with a crown of curved and sharp hooks (the name devil's claw reflects the frantic reaction of animals in whose hooves or coat these get caught). This xerophilous species is specific to southern Africa: Namibia, Botswana, and South Africa (Cape Province, Transvaal). They normally grow on the iron oxide-rich soils of the semidesert areas and tend to become ruderal. According to a study published in Nature in 1997, the predictable growth in the current production of the drug (600-800 t/yr) raises questions about the survival of the species, which is only harvested in the wild.

The drug consists of the tuberized secondary roots, sliced to facilitate drying (they contain over 90% water). Macroscopically, they appear as shrunk fragments, shaped like fans or round slices reminiscent of dried mushrooms, light brown, curled on the edges, and marked with radial and concentric lines. Some drug specimens appear coarsely crushed or minced into small slivers (*cossettes* in French). The drug tastes particularly bitter.

Chemical Composition. Rich in sugars (stachyose, raffinose, and simple sugars), devil's claw root also contains free and glycosylated phytosterols, triterpenes (oleanolic acid), flavonoids, phenolic acids, and glycosidic phenylpropanoic esters (verbascoside [= acteoside], isoacteoside). The principles considered responsible for the activity are the iridoids. The chief constituent is harpagoside, the cinnamate of an iridoid hydroxylated at C-8, harpagide. It occurs



Procumbide



Harpagoside

alongside 8-*p*-coumaroyl-harpagide, procumbide, and its 6'-*p*-coumaroyl ester, as well as 3,6-anhydroprocumbide or procumboside. The iridoids represent 0.5-3% of the weight of the dried drug.

Pharmacological Activity. The results of pharmacological research on devil's claw are scarce and appear contradictory, in that the studies were conducted on different animal models (acute or subacute inflammatory processes), and with different extracts administered by different routes. The most recent data show that the aqueous extract is active on the carrageenan-induced edema of the rat paw when administered by the IP route and that the activity is dose-dependent (from 100 to 400 mg/kg). The same extract is inactive by the oral route, apparently because the active principle is destroyed in the stomach. This extract is also inactive by the parenteral route if it is treated with acid before administration. The activity of the extract is intact when administered by the intraduodenal route. Tested under the same conditions, harpagoside is inactive, whereas it participates in the peripheral analgesic activity shown experimentally for the aqueous extract (100 mg/kg, IP). These data led their authors to suggest optimizing and using appropriate galenical forms. The identity of the active principle remains controversial *.

For some authors, studies in humans tend to indicate that long-term use of devil's claw preparations (e.g., nebulisate titrated for harpagoside) is capable of markedly improving arthrosis. However, an indomethacin-controlled trial showed no benefit in arthritic patients. More recently, a double-blind trial in patients with back pain gave inconclusive results; yet it gave some indication of an activity for the aqueous extract (6 g/day x 4 weeks), to be confirmed or not by further trials. In any event, the origin of the activity has yet to be explained: all that is known is that the prolonged administration of powder to healthy humans (2 g/day, *per os* x 21 days) does not alter the metabolism of arachidonic acid. The drug is apparently devoid of acute short-term toxicity (rodents, dog), and the observations recorded in humans have revealed no side effects of note. The long-term toxicity has not been studied.

Tests. Devil's claw is identified by microscopic examination of the powder (fragments of cortical parenchyma with large cells, some of which contain reddish-brown granular inclusions and yellow droplets, ducts with thickened areas and

* It was recently established that the aqueous extract of *Scrophularia frutescens* is an anti-inflammatory (rat, carrageenan-induced edema, *per os*), unlike the harpagoside that it contains [Garciá, D., Fernández, A., Sáenz, T. and Ahumada, C. (1996). Antiinflammatory Effects of Different Extracts and Harpagoside Isolated from *Scrophularia frutescens* L., *Il Farmaco*, **51**, 443-446]. Several species in the genus *Scrophularia* are reputed to be anti-inflammatory. One example is the wood figwort (*S. nodosa* L.), which may claim, in France, indications identical to those of devil's claw; it is also traditionally used topically against sunburns, superficial and limited burns, and diaper rashes [French Expl. Note, 1998]. Its chemical composition is close to that of devil's claw and includes phenolic acids, flavonoids, harpagoside, harpagide, aucubin, and catalpol. The pharmacology and toxicity of wood figwort are not known.

tracheids) and by TLC analysis of a methanolic extract (visualization with phloroglucinol and hydrochloric acid). The assay includes a search for starch and a quantitation of harpagoside by HPLC after extraction with methanol; the drug contains not less than 1.2%.

A study published in 1997 showed that some commercial extracts are probably prepared from a mixture of *H. procumbens* and a close species, *H. zeiheri* Decne. The latter contains less harpagoside (0.7-1.4%), but it contains 0.9-1.8% 8-(4-coumaroyl)-harpagide. Experiments in rodents have shown that the analgesic and anti-inflammatory activities of the *H. zeiheri* root extract are not significantly different from those of the official drug extract (*H. procumbens*).

Uses. Despite the reservations expressed by some, and although conclusive clinical data are lacking, contemporary phytotherapy makes extensive use of the nebulisate, the dried extract, the powder, or the infusions and decoctions of the drug for benign rheumatic disorders. In France, phytopharmaceuticals based on devil's claw are traditionally used [French Expl. Note, 1998], orally and topically, for the symptomatic treatment of minor painful joint disorders. No safety/toxicological tests are required for any form (aqueous or hydroalcoholic extract, drug powder). In any event, it seems reasonable to not use the drug alone, but to complement the customary therapy. Physicians can also prescribe it in cases that do not immediately require anti-inflammatory agents, which are not without side effecs. It can induce diarrhea in some patients.

The German Commission E attributes to devil's claw the following properties: choleretic, appetite-stimulating, anti-inflammatory and weakly analgesic. This is why the Commission E monograph specifies, under uses: lack of appetite, gastrointestinal pains, treatment of the degenerative disorders of the locomotor system. A gastroduodenal ulcer is a contraindication (this information is also in the *British Herbal Compendium*). Some authors recommend against using this drug in pregnant women.

• Olive Tree, *Olea europæa* L., Oleaceae

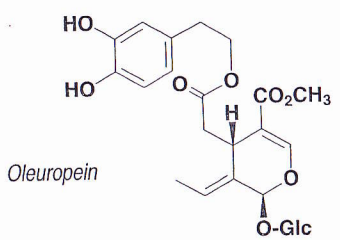
Cultivated as an oil crop (see p. 143), this Mediterranean tree is official for its dried leaves (Fr. Ph., 10th Ed.), to which phytotherapists attribute hypotensive properties.

The Plant, the Drug. This species is characterized by a gnarly trunk with a cracked bark, indeciduous leaves, and small white tetramerous flowers grouped in racemes. Its fruit is notorious: the olive, an ellipsoid drupe with a hard pit and a mesocarp rich in oil (see p. 143). The leaves are opposite, subsessile, entire, and coriaceous, have a grayish-green upper side and a whitish underside with a sheen to it, a result of the presence of a fine down which can easily be scraped off. The drug tastes bitter. It can be identified by its microscopic [illegible]

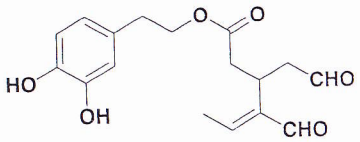
presence of many shield-shaped covering trichomes and of sclerites clearly visible in the powder; these are long, have thick walls, are bent here and there, are highly refringent, and end as if they were truncated.

These characteristics allow verification of the identity of the drug, which in addition, is characterized by the presence of triterpenes (by the red color developed by an ether extract in the presence of acetic anhydride and sulfuric acid). The assay includes TLC (to show the presence of oleuropein).

Chemical Composition The olive tree leaf is characterized by the presence of several secoiridoids: oleuropein (the main constituent, 60-90 mg/g), 11-demethyl-oleuropein, the 7,11-dimethyl ester of oleoside, ligustroside, oleuroside, and unconjugated secoiridoid-type aldehydes (oleacein). Triterpenes and flavonoids, namely rutin and the glycosides of apigenin and luteolin, are also found.



Oleuropein



Oleacin

Pharmacological Activity. Although tradition attributes to the olive tree leaf numerous properties (febrifuge, hypoglycemic, hypotensive, diuretic, and more), few of them have been studied experimentally. The infusion and the decoction of olive tree leaf are hypotensive in the dog: the same activity is observed with oleuropein in the hypertensive dog (IV) and also in the normal cat (IV). Both the infusion and oleuropein are coronary vasodilators and antiarrhythmics, but the iridoid is probably not the sole active constituent of the drug. The methanolic extract inhibits the potassium-induced contractions of the isolated rabbit aorta; fractionation experiments show that the activity is mainly due to 3,4-dihydroxyphenylethanol. Tested on the isolated guinea pig auricle, oleuropein decreases the amplitude of the contractions and slightly decreases the heart rate (the negative inotropic, chronotropic, and dromotropic activities had been observed previously on the isolated heart of several animal species). The effects do not seem to result from an action on calcium channels. It is also known that, *in vitro*, the aqueous extract inhibits angiotensin converting enzyme and that this property is due to oleacein; the products of enzymatic hydrolysis of the secoiridoids also have this activity.

Uses. Although the potential toxicity of the drug is not well known, and although observations in humans are rare, old, of weak methodology, and sometimes unconvincing, phytotherapists gladly resort to the olive tree leaf to help maintain a reasonable blood pressure range. Iridoids are not very stable, therefore stabilized [illegible] indications

for the drug by the oral route: 1. traditionally used to enhance the urinary and digestive elimination functions, and 2. traditionally used to enhance the renal excretion of water.

• YELLOW GENTIAN, *Gentiana lutea* L., Gentianaceae

According to the European Pharmacopoeia (3rd Ed.), the drug consists of the dried fragments of the subterranean parts.

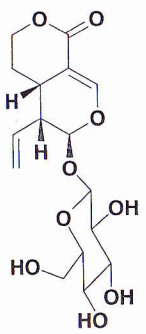
The Plant. A tall and hardy herb (1-1.5 m), the yellow gentian possesses leaves with parallel venation, opposite and decussate, sheathing at the top of the stem, and yellow flowers pseudowhorled at the base of the leaves. This species grows wild in the mountain areas of Europe, most often at elevations between 1,000 and 2,500 m (about 3000-8000 ft). The major part of the French consumption (1,000 to 1,500 metric tons) is supplied by collecting wild plants, mostly in the Auvergne region. There is some cultivation, although the plants can only be harvested after 7 to 10 years.

The Drug. The drug consists of wrinkled, hard, and hardy roots (10-40 mm in diameter), which are brittle and break with a short, more or less reddish-yellow (not brown) fracture. The official drug must not contain other gentians (TLC analysis of a methanolic extract); its bitterness value must be not less than 10,000 (relative to that of quinine). It must contain not less than 33% material extractible in water.

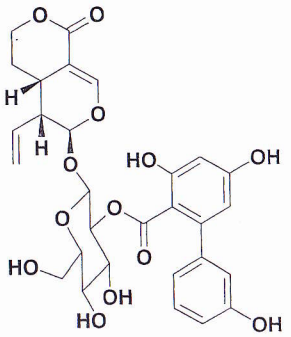
Chemical Composition. The bitter taste of the drug is due to 2-3% secoiridoids: gentiopicroside (the chief constituent), amarogentin, and other esters of sweroside and swertiamarin. The yellow color is linked to the presence of xanthones (gentisin, isogentisin, gentiin). Note also the presence of phytosterols, of phenolic acids, of oligosaccharides, and of pectin; the drug contains no starch.

Uses. Traditionally used orally to stimulate the appetite [French Expl. Note, 1998], the yellow gentian is chiefly used in the liquor industry. Other species in the genus find similar applications (*G. pannonica* Scop., *G. punctata* L., *G. purpurea* L.). The German Commission E monograph specifies that the bitter substances in the drug stimulate salivary and gastric secretions—*via* a reflex activity—and that this tonic is used for gastrointestinal pain and lack of appetite. Package inserts must mention the possible side effects (occasional headaches in sensitive persons) and the contraindications (gastroduodenal ulcers).

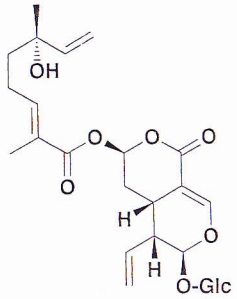
* Annex II of this French government text does not include indications using the terms «hypotensive» or «antihypertensive». This is probably a consequence of item 3 of paragraph 2.2 of chapter 1: «Certain uses have been purposely excluded because they correspond to pathologies for which it would be dangerous to not apply the therapies whose efficacy has been established in accordance with current standards.»



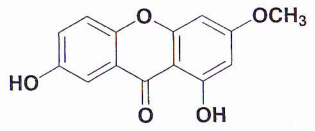
Sweroside



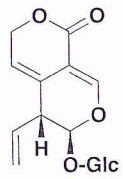
Amarogentin



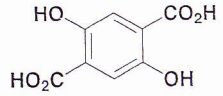
Menthifolin



Gentisin



Gentiopicrin



2,5-Dihydroxy-terephthalic acid

• EUROPEAN CENTAURY, *Centaurium erythræa* Rafn., Gentianaceae

The Plant, the Drug. It is the flowering tops of *C. erythræa* (= *Erythræa centaurium* [L.] Persoon) that are listed in the French Pharmacopoeia (10th Ed.) for medicinal use. This small herb is annual or biennial, and grows wild in the meadows and forest clearings of Europe and of North America. It is characterized by an erect stem with opposite decussate leaves, which ends with a corymbiform cyme of pink tubular flowers. The drug is identified, among other criteria, by its macro- and microscopic characteristics, and is evaluated by TLC: presence of swertiamarin in the 6% ethanol used for maceration.

Chemical Composition and Pharmacological Activity. The drug is rich in phenolic acids (terephthalic acids and acids with a C_6-C_1 or a C_6-C_3 unit). It also contains flavonoids, and like many Gentianaceae, it contains polysubstituted xanthones (methylbellidifolin, eustomin). The presence of several secoiridoids explains the bitter taste of the drug: swertiamarin, sweroside, gentiopicrin, centaurin, centapicrin, and desacetylcentapicrin. The literature on the pharmacology of the European centaury is slim. Very recently, it was shown that the aqueous extract of the drug possesses, in animal models, anti-inflammatory and antipyretic properties. Swertiamarin and gentiopicrin are antibacterials; it is also known that swertiamarin is metabolized in the intestine to gentianine, which is a CNS sedative.

Uses. Phytopharmaceuticals based on the European centaury, like those based on the yellow gentian, are traditionally used orally to stimulate the appetite and facilitate weight gain [French Expl. Note, 1998]. In Germany, its uses are also identical to those of gentian.

• BUCKBEAN, *Menyanthes trifoliata* L., Menyanthaceae

Several authors place this genus in a small family (five genera) separate from the Gentianaceae and that Cronquist classifies within Solanales: the Menyanthaceae; in contrast to the Gentianaceae, their leaves are alternate.

The leaf of this perennial species with white flowers and purplish-red anthers is official (Fr. Ph., 10th Ed.). A plant from very damp areas, buckbean is a very common herb in Europe, except in the Mediterranean area. The leaf is trifoliolate, and its petiole widens into a sheath at the base. The drug contains many phenolics (phenolic acids, scopoletin, flavonoids), as well as iridoids, responsible for its bitterness: loganin, menthiafolin, and dihydromenthiafolin. The drug is recommended in Swedish folk medicine to treat glomerulonephritis. Experiments on the rat kidney, rendered ischemic then perfused, show a beneficial effect of the rhizome decoction, which could act by inhibition of biosynthesis of prostaglandins, of LTB4, and of the PAF.

In France [French Expl. Note, 1998], buckbean leaf, like European centaury flowering tops, is traditionally used orally to stimulate the appetite and facilitate weight gain. It is also for lack of appetite that it is used in Germany, and the Commission E monograph specifies that it stimulates salivary and gastric secretions. In the United Kingdom, the leaf (BHP 1990) also is used in the composition of antirheumatic medicines; they are contraindicated in case of diarrhea.

• EUROPEAN VERVAIN, *Verbena officinalis* L., Verbenaceae

In contrast to the lemon verbena (*Aloysia triphylla* [L'Hérit.] Britt.) with which it should not be confused, this common perennial herb is not listed in the latest edition of the French Pharmacopoeia.

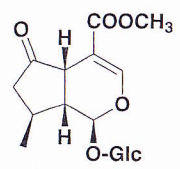
The drug consists of the aerial parts. It is known to contain 0.2-0.5% iridoids, including verbenalin and hastatoside, and phenylpropanoid glycosides (verbascoside [= acteoside], eukovoside). In France, the aerial parts are traditionally used orally to enhance the renal excretion of water, and it is used locally for the adjunctive emollient and itch-relieving treatment of skin disorders, as a trophic protective agent for cracks, bruises, frostbite, and insect bites, and for sunburns, superficial and limited burns, and diaper rash [French Expl. Note, 1998]. The German Commission E recognizes that the drug is secretolytic and lists numerous uses in the monograph, but the Commission finds it impossible to recommend its therapeutic use, since none of the indications

have been justified. Nothing is known about the side effects and potential toxicity of this species. It seems wise to discourage its use by pregnant women.

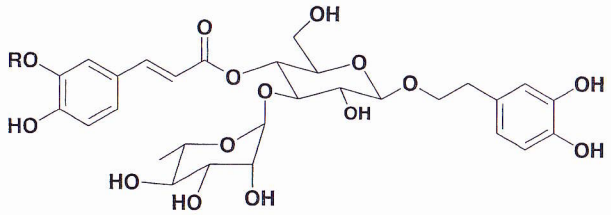
• White Dead Nettle, *Lamium album* L., Lamiaceae

The white dead nettle was official during the nineteenth century for its flowers. In 1989, the dried and peeled corolla was listed in the French Pharmacopoeia (10th Ed.). A common plant on the edges of country roads and in hedges, the white dead nettle is a perennial herb whose leaves, which are acuminate-dentate but not stinging, are reminiscent of those of nettles.

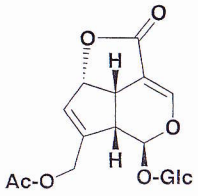
The only constituents whose occurrence and structure are well established are chlorogenic acid, flavonoids (rutin, tiliroside), phenylpropanoid glycosides (acteoside, galactosylacteoside [= lamalboside]), and iridoids (lamalbide, 6-desoxylamalbide, albosides A and B, and caryoptin). In the absence of reliable pharmacology studies, the drug is traditionally used orally to enhance urinary and digestive elimination functions, and to enhance the renal excretion of water [French Expl. Note, 1998]. Locally, it can be used to relieve scalp itching and peeling with dandruff. In folk medicine, the drug has long been used in vaginal injections to treat leucorrhoea. In Germany, this use is mentioned in the Commission E monograph, which lists internal use for catarrh of the upper respiratory tract and topical use for mild inflammation of the throat, mouth, and skin. The plant is also used in cosmetic formulations (shampoos, lotions).



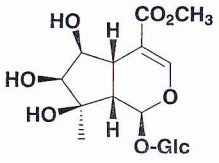
Verbenalin



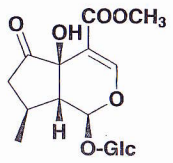
R = H : *Verbascoside (= acteoside)*
R = CH_3 : *Eukovoside*



Asperuloside



Lamalbide



Hastatoside

• Bedstraw, *Galium* spp., Rubiaceae

The 1998 French Explanatory Note specifies that bedstraw may be employed in the composition of phytomedicines traditionally used in the symptomatic treatment of neurotonic disorders in the adult and in the child, for example in case of minor sleeplessness. Which bedstraw is this all about? It is a pity that the text is not more specific because common usage and botany manuals refer to several species of *Galium* as bedstraw: *G. mollugo* L. (white bedstraw), *G. verum* L. (lady's bedstraw, yellow galium), *Cruciata laevipes* Opiz (= *G. cruciata* [L.] Scop.) (crosswort), *G. aparine* L. (catchweed bedstraw), *G. palustre* L. (marsh bedstraw), *G. uliginosum* L. (swamp bedstraw), and more. The first four species are on the revised French government list of January 1, 1993. In any event, there is no pharmacological or clinical justification for their use. In the United Kingdom, *G. aparine* L. is on the list of plants that may claim to be herbal medicines (General Sale List, 1-R1a); it is the subject of a BHP monograph (1990) in which the microscopic characteristics are described.

Although these species have not undergone many chemical investigations, they are all known to contain phenolic acids, flavonoids, and iridoids, particularly asperuloside. In the United Kingdom, *G. aparine* passes for a mild diuretic (with no justification) and it is used to treat various skin disorders.

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