ARNICA MONTANA L.

Sesquiterpenoid Lactones

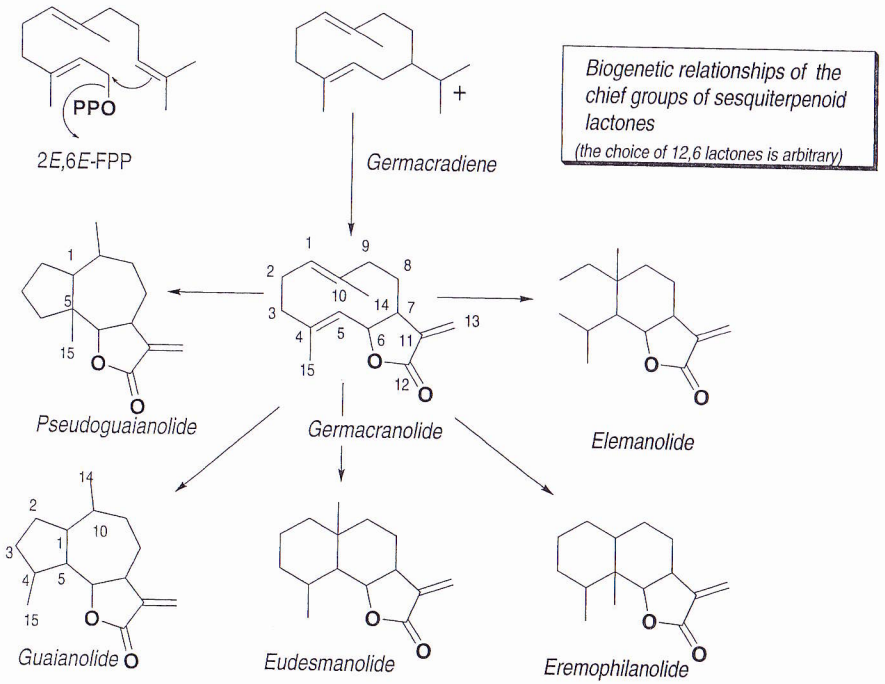
Sesquiterpenoid lactones form a group of substances important by its size — approximately 3,000 known structures—which was described, in the older texts of Materia Medica, under the evocative name "bitter principles *". Sesquiterpenoid lactones have a rather scattered botanical distribution. They occur in the Fungi and Bryophytes, here and there in the Angiosperms (Apiaceae, Lauraceae, Menispermaceae), and chiefly in the Asteraceae. In the latter, the lactones frequently occur in the glandular trichomes located in the leaves, stems, and inflorescence bracts. They are fairly often found in the akenes, but are rare in the subterranean organs (lactucin of chicory roots, helenin of elfdock).

* This obsolete terminology covers a very homogeneous group of compounds: with few exceptions (hops, cinchona), the bitterness of the drugs is due to the presence of terpenoid lactones. These are monoterpenoids in the Gentianaceae (p. 604), sesquiterpenoids in chicory (p. 85) or wormwood (p. 524), diterpenoids such as columbin in *Jateorrhiza palmata* Miers (p. 920), or triterpenoids, such as the limonoids of the Rutaceae and the quassinoids of Simaroubaceae (p. 765). They were formerly used—and, in some cases, continue to be used—

1. STRUCTURE

The skeleta of sesquiterpenoid lactones vary, but they all arise from the cyclodecadiene-type product of the cyclization of 2*E*,6*E*-farnesyl pyrophosphate. Although experimental evidence is rare, it is generally accepted that the chief skeletons arise from the cyclization of the cyclodecadiene-type cation, *via* the germacranolides*.

Quite logically, the structure of the cyclization product depends on the initial conformation adopted by the macrocycle, and on the position of the double bonds which allow various intramolecular electrophilic cyclizations: the enzyme involved in the reaction acts as a matrix for the precursor and determines the stereospecificity of the reaction. Some of the proposed biosynthetic schemes are considered more plausible because they also correspond to *in vitro* syntheses.



There are many secondary structural variations which affect:

- the lactone, which can be *cis*-6,7, *cis*-7,8, *trans*-6,7, or in most cases, *trans*-7,8; it is generally an α-methylene-γ-lactone, and in all cases (except in the Bryophytes), the proton in the 7-position is α;

* Proper nomenclature consists in adding the suffix -olide to the name of the sesquiterpenoid skeleton to indicate the presence of a lactone. In the particular case of germacranolides, the configuration of the double bonds determines four subgroups: germacrolides (*trans, trans*), heliangiolides [1(10)-*trans*,4-*cis*], melampolides [1(10)-*cis*,4-*trans*], and *cis,cis*-germacranolides.

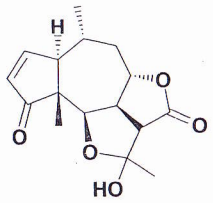
- the methyl groups, which are often functionalized (alcohols, carboxylic acids);
- the unsaturations, which may be reduced or oxidized (epoxides, hydroxyl groups); when hydroxyl groups are present, they are frequently esterified.

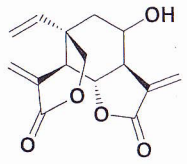
There is no extraction method specific to sesquiterpenoid lactones. They can be extracted with dichloromethane, or with a mixture of diethyl ether, petroleum ether, and methanol, and the extract can be fractionated by the appropriate chromatographic technique. Various reagents are available to visualize the TLC spots, including iodine vapors, a dilute solution of $KMnO_4$, vanillin in the presence of hydrochloric acid, and cobalt chloride in an aqueous sulfuric acid solution.

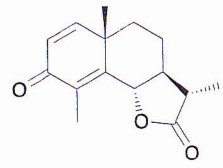
2. APPLICATIONS OF SESQUITERPENOID LACTONES

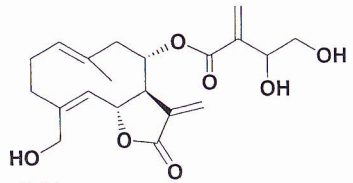
Except in the case of artemisinin derivatives, there are no therapeutic uses for sesquiterpenoid lactones and only a few drugs containing them are used. Although a few drugs with "bitter principles" find some use in folk medicine and in phytotherapy, there is nothing to prove, at least for some of them, that the virtues attributed to them have anything to do with the presence of this type of compound.

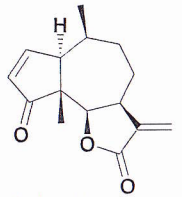
The potential applications of sesquiterpenoid lactones are, however, far from trivial. This is no surprise, considering their high reactivity: the α-methylene-γ-lactone moiety and the epoxides, which are common, are reactive sites for biological nucleophiles, mainly thiol groups and the amines of the active sites of various enzymes (glycogen synthase, DNA polymerase, thymidylate synthase). As a result, these enzymes are irreversibly alkylated, hence sesquiterpenoid lactones have a broad range of biological activities.











Many lactones are antibacterial agents, especially against Gram positive bacteria, for example, the lactones of the elfdock, or cnicin from the blessed thistle, *Cnicus*

to treat wounds and ulcers. Certain compounds in this series are also antifungal agents. Some structures are antiparasitic agents (artemisinin is an anti-malarial of proven efficacy in humans), whereas others are anthelminthics * or toxic to molluscs, for example ambrosin and damsin of *Ambrosia* ** *maritima* L., an herbaceous Asteraceae of the damp coastal areas and river basins of Africa. Some authors have proposed to use this drug to control the molluscs that are vectors of schistosomiasis and distomatosis (*Biomphalaria, Bulinus, Lymnaea*). Its efficacy was confirmed by field tests: 90% of the molluscs disappeared within 3 months from the irrigation canals that were treated.

The alkylating potential of these compounds has led to the study of their cytotoxicity. Although many of them have a strong activity (vernolepin, eupatoriopicrin, tenulin), none has undergone clinical trials, in great part because of their marked toxicity.

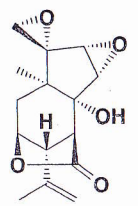
Some of these compounds are interesting tools for biologists: thapsigargin (of *Thapsia garganica* L., Apiaceae) mobilizes intracellular calcium according to a very specific mechanism.

Note that sesquiterpenoid lactone-containing plants represent a serious danger for cattle (*Helenium, Centaurea, Geigeria, Hymenoxys*) but also, on rare occasions, for humans. Examples include polycyclic compounds such as picrotoxinin from a fish

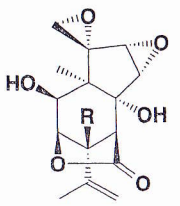
* Santonin belongs to this category: it is the active principle of a drug long used to treat worm infestations, namely wormseed (*Artemisia cina* Berg. Ex Polj., Asteraceae). Its capitulums were used, and contain, in addition to 10-20 mL/kg essential oil with cineole, 2-3% sesquiterpenoid lactones: santonin and other eudesmanolides of closely related structure. Santonin, long prescribed as a nematicide, has been abandoned in human therapy due to its non-trivial toxicity (gastrointestinal distress, visual disturbances, headaches, dizziness).

** While on the topic of *Ambrosia*, and although sesquiterpenoid lactones are not at fault, this is a good place to note that several species in the genus, which are not medicinal, are responsible for allergies to pollen. Examples include *A. trifida* L. and *A. artemisiifolia* L. (common ragweed). The latter is a weed that originally grew on dirt mounds, embankments, and unimproved lands in western Europe, and has been spreading to cultivated land. Worse, the European Union agricultural policy, by requiring that land remain unexploited according to a given schedule, can only promote its dissemination; however, legislation effective on 21 February 1994 requires farmers to maintain the vegetation without allowing it to produce seeds. In France, the spread of common ragweed is particularly rapid along the river Rhône: 6% of the population of the major city of Lyon is believed to be affected by this allergy. Some of the *départements* (counties) in the Lyon *région* have recently launched educational campaigns against this species; since 1995, following the Canadian example, various levels of French local government have passed measures to encourage the eradication of this species. Allergy to *Ambrosia* pollens is a well-known problem in North America where common ragweed and giant ragweed (*A. artemisiifolia* and *A. trifida*, respectively) constitute one of the principal causes of allergy to pollen: in eastern Canada, this plant causes health problems to an estimated 10-12% of the population.

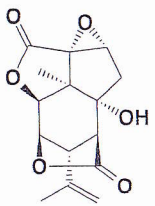
Cf., inter alia, Dechamp, C., Rimet, M.L., Méon, H. and Deviller, P. (1997). Quatorze années de comptes polliniques d'ambroisies (capteur de P. Cour) [illegible]



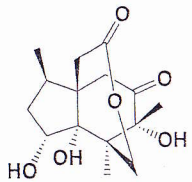
Coriamyrtin



R = H : *Tutin*
R = OH : *Hyenanchin*



Picrotoxinin



Pseudo-anisatine

poison used in India and Indonesia, namely Indian cockles (*Anamirta cocculus* [L.] Wight. & Arn.), tutin and hyenanchin, which sometimes contaminate honeys from New Zealand, and coriamyrtin. The latter is responsible for accidents that are sometimes fatal to children who eat the fruits of myrtle-leaved sumac (*Coriaria myrtifolia* [Bauhin] L., Coriariaceae) in the south of France and in Catalonia. The fruits look somewhat like mulberries and their ingestion induces gastrointestinal, respiratory, and neurological problems, and in some cases, a coma with convulsive episodes. Any serious intoxication requires taking the patient to a hospital emergency room. The structure of these GABA antagonists is related to that of the convulsant sesquiterpenes found in *Illicium* species (anisatin and derivatives, see p. 570).

3. CHIEF DRUGS CONTAINING SESQUITERPENOID LACTONES

Various drugs containing this type of compound are covered in other chapters: artichoke (p. 247), Roman camomile, yarrow (flavonoids, p. 337), matricaria (p. 520), chicory, dandelion (polysaccharides, p. 85), and burdock (p. 173), to name only a few. Here we shall only describe arnica, elfdock, feverfew, and a novel antimalarial, sweet wormwood (*qinghao*).

• Sweet Wormwood (= *Qinghao*), *Artemisia annua* L., Asteraceae

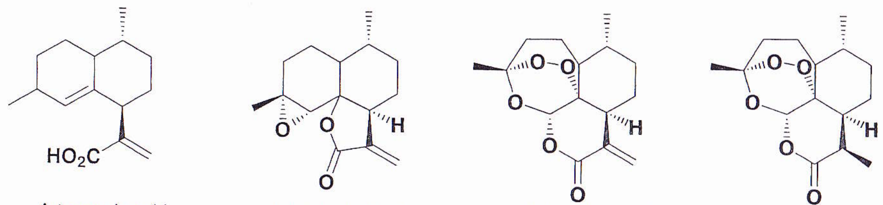
In the early 1970s, the discovery of the antimalarial properties of extracts of this drug led to the isolation of the active principle, artemisinin, as well as to a number of chemical, biological, pharmacological, and clinical studies. The leafy stems are now used to obtain artemisinin, part of which is converted into dihydrogenated ethers and esters.

The Plant, the Drug. In Chinese medicine this drug (= *Qinghao*) is traditionally used to treat fevers and malaria. This wormwood, originally indigenous to Asia, also grows wild in central and southern Europe (for example, in the south of France) and in North America. An annual herbaceous plant with a strong fragrance, it is characterized by large panicles of small globulous capitulums (2-3 mm in diameter), [illegible]

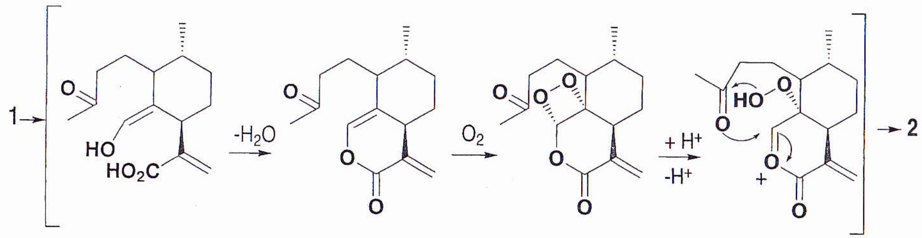
Chemical Composition. The concentration and the composition of the essential oil vary depending on the source of the drug: the Chinese chemotype is very rich in oil (40 mL/kg) and characterized by irregular monoterpenes (artemisia ketone, 64%), whereas the Vietnamese chemotype only contains 14 mL/kg of an essential oil with camphor and germacrene D. Also found are flavonoids, polyalkynes, coumarins, and many sesquiterpenoid lactones with a cadinane skeleton, or a skeleton arising from the rearrangement of a cadinane nucleus: artemisin, artemisic acid (arteannuic acid, up to 2.5%), arteannuin B, and more.

The active principle is artemisinin or *qinghaosu* (*qinghao* extract). Its concentration in the dried aerial parts varies, in the Chinese drug, from 0.01 to 0.08% as a function of the source, edaphic and climatic conditions, and vegetation period. It has been shown in plants cultivated in Vietnam, that the highest yield in artemisinin and in leaves is obtained at an early vegetative stage (five-months-old, yield = 0.86% of the dry weight, i.e., 4.6 g of artemisin per square meter cultivated), and decreases afterwards. According to other authors, the concentration could exceed 12% in some Chinese clones.

Biogenesis. Artemisinin is an endoperoxide, probably formed from artemisinic acid (= arteannuic acid) *via* arteannuin B: the opening of the epoxide is thought to yield a dihydroxycadinanolide, which in turn would fragment o give a seco-4,5-cadinane, whose enol form has been isolated from the plant. The latter lactonizes readily and would then get oxidized and converted, *via* artemisitene, to artemisinine.



Arteannuic acid (= artemisinic acid) — *Arteannuin B* : 1 — *Artemisitene* : 2 — *Artemisinin (qinghaosu)*



Proposed mechanism to explain the conversion of arteannuin B into artemisitene

Pharmacological Properties. Artemisinin is an antimalarial agent. It is selectively toxic to various species of *Plasmodium* (*falciparum, vivax, ovale*) *in vitro* and *in vivo*, including at nanomolar concentrations against chloro[illegible]

strains. Artemisinin is effective against blood-stage parasites; the activity is maximum on the ring-stage parasite and the trophozoites during the growth stage. Toxic to the first stages of the gametocyte, artemisinin is inactive against the merozoites, the pre-erythrocytic forms, and the mosquito-stage sporozoites. Artemisinin and its derivatives prevent cell adhesion to the vascular endothelium, and if administered early, they prevent rosetting. The activity against the parasite manifests itself rapidly, and the elimination of the parasite and improvement of the symptoms occur sooner than with chloroquine. The mechanism of action remains to be demonstrated and may be linked to the peroxide structure: formation of radicals and reactive decomposition products, activated by iron (mechanism analogous to that of the Fenton reaction for hydrogen peroxide decomposition); the products are thought to damage the parasite by rapidly alkylating its proteins and altering its membranes. In parallel, artemisinin forms adducts with hemin (ferriprotoporphyrin IX) and its ferrous form (ferroprotoporphyrin IX), which result from the digestion of hemoglobin by the parasite: it is possible that artemisinin inhibits the polymerization of hemin to hemozoin, in other words its detoxification by formation of "malarial pigment".

Synthetic efforts aimed at improving bioavailability and efficacy have yielded active derivatives, including α- and β-artemethers (methyl ethers, epimers of dihydroartemisinin), arteether, and sodium artesunate (i.e., the hemisuccinate of dihydroartemisinin), and sodium artesunate. In the body, all of these derivatives release dihydroartemisin, which is thought to be the active form.

In the mid-1990s, over 1.5 million persons had been treated with artemisinin, essentially in east and southeast Asia, but also in Gambia and Kenya. The health benefits of this compound and of its derivatives can be evaluated better now. They act very rapidly, particularly on resistant strains of *falciparum* and on pernicious malaria: in the latter case, clinical trials show that the artemether is as efficacious as or more efficacious than quinine administered parenterally. However, artemisinin does not appear to reduce the high mortality significantly.

Artemisinin and its derivatives have not yet induced resistance. Their drawback is a high recrudescence rate, which can be decreased by use in combination with mefloquine. The peroxides appear to be devoid of toxicity in animals and no major side effects have been noted in humans. Neurological lesions observed in dogs (10 mg/kg) and rats undergoing long-term treatment with the ethers are a good reason to exercise extreme caution* and to develop toxicological studies (especially because the signs of encephalopathy due to the parasite may mask the potential neurotoxicity of the compounds of interest).

Tests. Sweet wormwood sesquiterpenes can be extracted with petroleum ether and analyzed by TLC (visualization by vanillin or anisaldehyde in the presence of sulfuric acid, or by iodine vapors). There are several methods of quantitation by

* In fact, artesunate was recently incriminated: Miller, L.G. and Panosian, C.B. (1997). Ataxia and Slurred Speech after Artesunate Treatment for *falciparum* Malaria. *New Engl. J. Med.*, 336, 1328.

HPLC with UV detection at 220 nm, with or without conversion to derivatives which absorb in the UV, by opening the oxygen-containing heterocycles in alkaline medium, then forming lactols in acidic medium. An alternative approach to HPLC detection is with a method sensitive to the peroxide moiety of artemisin (electrochemical detection). GC-MS analysis is efficient despite the thermal instability of artemisinin (detection of degradation products). LC-MS and immunochemical analysis are also useful to detect the minute quantities of lactones and their metabolites.

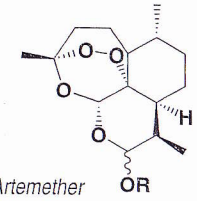
Uses. Sparingly soluble in water and in lipidic phases, artemisinin may be administered in aqueous or oily suspension (IM), or in tablets or suppositories. Since 1993, the WHO has recommended against the use of artemisinin and its derivatives for prophylaxis, and to reserve its use for the geographical areas with multiresistant *falciparum*, by prescription. The following compounds can be used:

1. artemisinin, initially prescribed at 50 mg/kg for a 3-(5-) day treatment (orally). It is also used by the IM route or as suppositories (2.8 g/3 days, convenient in a rural environment);

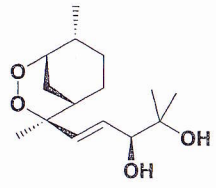
2. since 1994, the β-artemether has been marketed in part of Africa (Paluther ®). The product—an 8% injectable solution in peanut oil—is packaged in ampules containing 80 mg. It is used by IM injection: 160 mg on the first day and 80 mg on each of the next four days (this is for adults; for children the total curative dose is 9.6 mg/kg). If necessary, the total curative dose (480 mg) can be administered within 3 days. The therapeutic indications are the treatment of severe malaria due to *Plasmodium falciparum*, or when resistance to other antimalarials is suspected.

3. artesunate. Prepared extemporaneously by reacting sodium bicarbonate with artesunic acid, then administered by the IV or IM route (severe malaria: 2.4 mg/kg at 12 and 24 hours, then 1.2 mg/kg/day). It is also available in 50-mg tablets (Arsumax ®): 2 x 100 mg on day 1, then 2 x 50 mg (day 2 to 5). Artesunate is sometimes used in combination with mefloquine to decrease relapses.

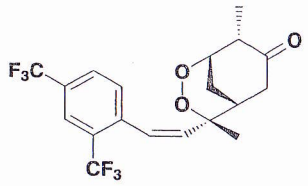
Artemisinin has generated much attention and much chemical research: total synthesis from (*R*)-pulegone or (–)-β-pinene (not cost effective), semisynthesis from artemisinic acid (a 40% yield can be achieved), synthesis of derivatives and studies of structure-activity relationships. There is also ongoing research on various promising trioxanes and tetraoxanes, and on analogs of natural peroxides (e.g., arteflene [=Ro 42-1611], an analog of yingzhaosu A, isolated from the root of an Annonaceae, *Artabotrys uncinatus* [L.] Merr.). So far, attempts to produce artemisinin by tissue or cell culture have been disappointing.



R = CH_3 : *Artemether*
R = C_2H_5 : *Arteether*
R = $COCH_2CH_2CO_2Na$: *Artesunate (Na)*



Yingzhaosu



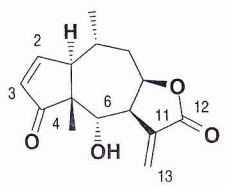
Arteflene (Ro 42-1611)

• ARNICA, *Arnica montana* L., Asteraceae

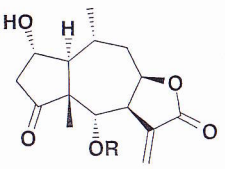
The drug (Fr. Ph., 10th Ed.) consists of the dried capitulums. It is used externally for its "vulnerary" properties (*vulnus, eris*, wound—> *vulnerarius*: wound healing). This plant is rare and protected, and in several European countries, a closely related species is used as a substitute: *A. chamissonis* Less. ssp. *foliosa* (Nutt.) Maguire (DAB 10).

The Plant, the Drug. Arnica is a species indigenous to mountain areas, easy to identify by its large (60-80 mm) orangy-yellow capitulums, on a 2-3-cm peduncle, surrounded by an involucre of 18-24 acute bracts covered with yellow hairs. The flowers are ligulate (20-30-mm long) with 7-10 veins and 3 teeth. In the tubular flowers (15-mm long) as well as the ligulate flowers, the ovary has a pappus of whitish bristles that are not feathery.

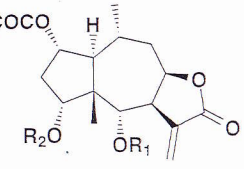
Chemical Composition. The color of arnica drug is due to carotenoids. Its odor is due to 5 mL/kg essential oil of pasty consistency because of a high concentration of fatty acids; it contains, among others, terpenoid hydrocarbons and thymol derivatives. The bitterness is due to sesquiterpenoid lactones (0.2-0.5% helenalin, dihydrohelenalin, and their esters: acetates, isobutyrates, tiglates, isovalerates, and more): their proportions vary depending on the geographic origin (central Europe and Spain). Note also the presence of triterpenoids, phytosterols, fatty acids, polysaccharides, phenolic acids, coumarins, polyalkynes, and of 0.2-0.3% flavonoids (glycosides of hispidulin, patuletin, betuletol, spinacetin, quercetagetin). *A. chamissonis* can contain more lactones (up to 1.5%) and in addition to the above compounds, it can contain their 2,3-dihydro-2α-hydroxylated homologs (arnifolins) and their 2,3-dihydro-2α,4α-dihydroxylated homologs (chamissonolides). Again, the proportions of the different compounds vary widely, with some batches closely resembling *A. montana*. The two species also differ by their flavonoid composition: *A. chamissonis* is characterized by glycosides of flavonoids acylated by acetic acid or 2-methylbutyric acid.



Helenalin



Arnifolins



Chamissonolides

Pharmacological Properties - Toxicity. Anti-inflammatory, analgesic, and anti-ecchymotic properties are traditionally attributed to arnica. We cannot exclude that the sesquiterpenoid lactones are in part responsible for this activity: they are known to inhibit the migration of polymorphonuclear leukocytes and the rupture of lysosomal membranes. An inhibitory activity on platelet aggregation has also been reported. Experiments have shown that arnica preparations and constituents are antimicrobial, antifungal, anti-inflammatory, and cytotoxic for various cell lines. All of the galenical forms of arnica cause allergic reactions, and in sensitive subjects, cross-reactions with Asteraceae and other lactone-containing species are frequently observed.

The systemic toxicity of the lactones is also known: in his review of the literature, Hausen [1992] lists case reports of vomiting, respiratory and cardiac difficulties, bloody sputum, cerebral problems, and even deaths following the administration of arnica preparations for the purpose of abortion.

Tests. Arnica is identified by its microscopic characteristics, particularly by paired covering trichomes with a punctate common wall. The drug is official only if it contains <2% akenes (total foreign matter <4%). Although the French Pharmacopoeial monograph only requires one TLC analysis of phenolics and the verification of the absence of marigold (absence of rutin), it is perfectly feasible, by TLC as well as by HPLC, to distinguish *A. montana, A. chamissonis*, and other species (e.g., *Heterotheca inuloides* Cass., but also marigold), based on their flavonoid and/or sesquiterpenoid lactone content.

Uses. Arnica and its preparations are reserved for external use, because when they are taken orally they can cause headaches, abdominal pains, as well as vasomotor problems (palpitations) and breathing difficulties. A common form of utilization is the tincture, diluted with water or a dilute alcohol, and applied in a compress onto bruises, ecchymoses, petechiae, sprains, and strains; this is acknowledged by the 1998 French Explanatory Note, which authorizes "traditional use for the symptomatic treatment of ecchymoses". Arnica and its preparations are also traditionally used for sunburns, superficial and limited burns, and diaper rashes. Arnica preparations should not be applied on open wounds or near the eyes or mouth.

The German Commission E monograph on arnica specifies that application to damaged skin can induce edematous dermatitis, that prolonged use can induce eczema, and that the most concentrated forms can cause the formation of vesicles and even necrosis. In Germany, the common indications are the same as in France. Package inserts must list contraindications (hypersensitivity to Asteraceae), side effects (allergy), and the need to use the product only for external application.

In homeopathy, arnica passes as an agent that promotes the resorption of extravasated blood and prevents hemorrhages. A 1993 Canadian clinical trial showed the lack of statistically significant effect of arnica 5 CH on bleeding time and other blood clotting parameters [Baillargeon *et al.*, 1993].

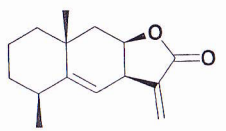
• ELFDOCK, *Inula helenium* L., Asteraceae

The dried root and rhizome of this perennial plant with large (6-8 cm) yellow capitulums are said to be diuretics, bechics, and anthelminthics (Fr. Ph., 10th Ed.).

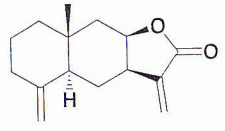
The drug contains eudesmanolides (alantolactone, isoalantolactone, and their more or less hydrogenated derivatives), a germacranolide, triterpenes, sterols, and depending on the season, 20-45% inulin. Steam distillation of the subterranean parts yields 1-3% of an odoriferous fraction which partially solidifies at ambient temperature.

The elfdock rhizome and root consist of irregular fragments with a balsamic odor, and an aromatic and bitter taste. They are frequently excoriated, and this reveals a grayish cortical parenchyma. Under the microscope, the cut and the powder show inulin grains and resin-containing cells. Three TLC analyses allow:

1. the verification of the absence of alkaloids (contamination by belladonna roots);
2. the visualization of the sulfuric acid hydrolysis products of inulin;
3. the study of the sesquiterpenoid lactones after steam distillation, including the characterization of alantolactone.



Alantolactone



Isoalantolactone

Alantolactone and isoalantolactone are cytotoxic and display antibacterial and antifungal properties *in vitro*: at concentrations of 10 µg/mL they inhibit the growth of *Microsporum cookei, Trichophyton mentagrophytes, Trichothecium roseum*, and other Fungi which are pathogenic for humans (*Trichophyton, Epidermophyton*). These lactones are also reputed to be anthelminthic and hypotensive: their anthelminthic properties are weak and vary widely, maybe because of a rapid absorption in the digestive tract.

In the absence of truly demonstrated properties, the rhizome and roots of the elfdock, as well as their preparations, may be "traditionally" used in France (French Expl. Note, 1998) by the oral route: 1. to enhance urinary and digestive elimination functions, and 2. to treat the symptoms of cough (forms based on total drug powder must pass basic safety tests). The German Commission E monograph lists uses for respiratory, gastrointestinal, renal, and urinary disorders, and states that none of these indications has been completely validated. After a reminder that lactones can cause allergic reactions and that high doses of elfdock can induce vomiting, diarrhea, and other problems, Commission E concludes that the therapeutic use of elfdock cannot be justified. In the United Kingdom, where the drug is used (BHP 1990) for bronchitis and cough, pregnancy and breast-feeding constitute contraindications. Several authors also discourage abusive or prolonged use.

INULA HELENIUM L.

Alantolactone and isoalantolactone are responsible for the allergic dermatitis observed with this Asteraceae.

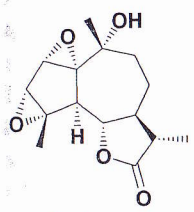
• FEVERFEW, *Tanacetum parthenium* (L.) Schultz-Bip., Asteraceae

The drug (Fr. Ph., 10th Ed.) consists of the dried aerial parts, whole or in fragments. In France, this drug was introduced in phytotherapy relatively recently.

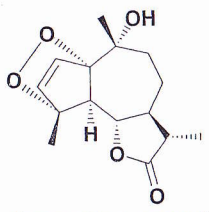
The Plant, the Drug. Feverfew is a tall (70-80 cm) perennial herb, originally indigenous to Asia Minor, and fairly common in the neglected fields of Europe. The stems, almost quadrangular and more or less ramified, bear polymorphic leaves, which are pinnatisect or bipinnatisect, and divided into 5-9 segments with a crenate margin. The capitulums of yellow tubular flowers and white ligulate flowers are grouped in corymbs of 5-30 capitulums on long pedicels, with a diameter ranging from 12 to 22 mm. The fruit is a brown akene with 5-10 white ribs, surmounted by a membranous crenate crown.

Under the microscope, the pulverized drug is characterized by numerous covering trichomes, 5-7-cellular, uniseriate, with a trapezoidal basal cell, ending with an element often bent at a right angle, very long, flat, tapered, and with a thin wall.

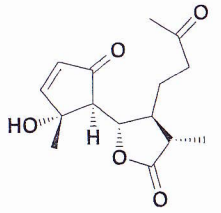
Chemical Composition. The strong odor of feverfew is due to an essential oil (3-8 mL/kg in the leaves) containing camphor and chrysanthemyl acetate as major constituents (the latter can be found partially hydrolyzed to chrysanthemol in the dried drug). Flavonoids, water soluble flavone glucuronates, and lipophilic di-3,7- and tri-3,7,3'-methylated flavonols are also found. A sesquiterpenoid lactone, parthenolide, is thought to be the active principle. This is a germacranolide that has been isolated from European and North American batches, but has not been found in



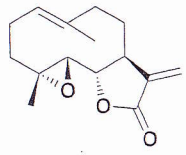
Canin



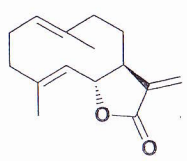
Tanaparthin α-peroxyde



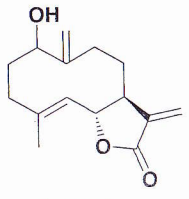
Seco-tanapartholide A



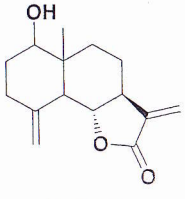
Parthenolide



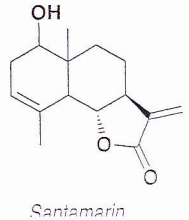
Costunolide



Artemorin



Reynosin



Santamarin

Mexican samples in which a eudesmanolide occurs, namely santamarin (santamarin is also found alongside parthenolide in North American plants). In practically all of the batches analyzed, other germacranolides are also found (costunolide and derivatives, artemorin), as well as eudesmanolides (reynosin), and guaianolides (canin, artecanin, anaparthin, a derivative of cumambrin B). Some varieties are particularly rich in parthenolide (f. *floculosum*) and the concentration of this lactone varies as a function of the vegetative cycle (maximal at the time of blooming) and also as a function of the organ: it is concentrated in the flowering tops (1.38%) and leaves (0.95%), but not in the stems (0.08%), and it is virtually absent from the roots (0.01%; values determined on a batch of plants from the United Kingdom). It has been shown empirically that the parthenolide concentration drops by nearly 50% in 9 months in the crushed drug stored with no particular precaution.

Pharmacological Properties. Feverfew extracts inhibit platelet aggregation and the ADP- or adrenalin-induced release of serotonin (=5-HT), which would explain the activity against migraines traditionally attribued to the drug. It has been shown that parthenolide has a—weak—affinity for 5H2A receptors. There is also inhibition of the degranulation of polymorphonuclear leukocytes, of the release of enzymes involved in the inflammatory process, of phospholipase A2 and of prostaglandin synthesis, as well as a protective effect on vascular endothelial cells. The observed activity seems to result from the Michael-type addition of the methylene lactone onto the enzyme thiols groups (cysteine inactivates parthenolide and cancels its effects). A very recent study of the effect of the extracts on smooth vascular muscle has shown that although the chloroform extract of the fresh plant does inhibit contractions induced by various agonists in a non selective and irreversible fashion, extracts prepared from the dried drug do not, in fact their action is opposite—but their analysis shows that they contain no parthenolide. This reversible stimulation of smooth vascular muscle fiber contraction appears to be linked to a potassium channel blockade induced by a unidentified substance. Is this vasoconstriction involved in the antimigraine effect, as it is in the case of ergot alkaloids or sumatriptan? This is one hypothesis. It is worth noting that the properties of parthenolide have been studied *in vitro,* but that the bioavailability of this very reactive compound remains to be determined. We cannot exclude that other constituents contribute to the activity, for example the flavonoids (?) or chrysanthemyl acetate, which is known to inhibit prostaglandin synthetase.

The initial clinical trials tended to show that feverfew leaf powder had an interesting potential to prevent the onset of acute attacks of migraine headache, but these trials were criticized for their patient selection methods. A more recent double blind trial on about 40 patients treated with ethanolic extract capsules titrated to contain 0.5 mg of parthenolide led to the conclusion that the capsules had no beneficial effect in preventing the attacks. Therefore, further research is needed. The only study conducted to evaluate the effect of feverfew on rheumatoid arthritis showed that it had none.

Tests. Feverfew is identified by macro- and microscopic examination, and by characterizing parthenolide by TLC analysis of a methanol extract with visualization by spraying with vanillin in the presence of sulfuric acid. The assay *per se* includes foreign matter (<12%; stems of diameter >5 mm: <10%), total ashes (<12%), and parthenolide quantitation (HPLC, methanolic extract, not less than 0.2% of the drug weight).

Uses. In France [French Expl. Note, 1998], the flowering tops of feverfew are used orally for the following indications: traditionally used 1. to prevent headaches *; 2. to relieve menstrual pain. Medicines based on total drug powder and hydroalcoholic extracts of alcoholic titer >30% must pass basic safety tests. In Canada, the marketing of a non-prescription (over-the-counter = OTC) product claiming efficacy in the prophylaxis of migraine headaches has been authorized.

Feverfew causes no serious side effects in regular users (ulcerations of the mouth, abdominal pain). Experts from English-speaking countries agree that pregnancy is a contraindication and in Canada, the recommendation is to not prolong treatment beyond 4 months without medical advice. It is rare for this Asteraceae to cause allergic dermatitis. Yet the risk exists, especially for all persons who are hypersensitive to sesquiterpenoid lactones (cross reactions).

Comment. A systematic analysis of commercially available leaves, powders, capsules, tinctures, and other forms showed that their quality varied widely (in 1991): parthenolide could not be detected in about one-third of the preparations for the oral route; its concentration ranged from 0.01 to 1% in the other two-thirds. Several types of adulteration were documented (*Matricaria maritima* L., *M. recutita* [L.] Rausch., *Tanacetum vulgare* L.). The standards that are now in place (France, Canada) should help improve the quality of commercial products.

4. SESQUITERPENOID LACTONES AND ALLERGY

Asteraceae containing sesquiterpenoid lactones are frequently responsible for dermatitis of allergic origin. These compounds act as haptens and bind to proteins to form allergens, which in turn induce the sensitization of lymphocytes. Of course, this is due to the reactivity of the α-methylene-γ-lactone. Produce species (e.g., artichoke, cardoon [cynaropicrin], endive [lactucopicrin]), ornamental species (e.g., mums [arteglasin], daisies, asters, cosmos, gaillardia, rudbeckia), sunflowers [niveusin], and certain medicinal species (e.g., Roman camomile [p. 335], matricaria [p. 520], yarrow [p. 337], feverfew, arnica, or inula [see above]) have caused various cases of occupational papulous dermatitis and conjunctivitis in farmers, horticulturists, and florists.

* Until February 1998, the wording of the French regulation was "to prevent acute attacks of migraine headaches".

Asteraceae are not the only species that contain allergenic lactones. Dermatitis can also be observed after contact with laurel (costunolide and other lactones) or hepaticas of the genus *Frullania* (*F. dilatata* [L.] Dum., *F. tamarisci* [L.] Dum., and others [frullanolide and other lactones, eudesmanolides, eremophilanolides]).

Also responsible for allergic dermatitis are perfumery products based on Asteraceae (e.g., arnica, camomiles).

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