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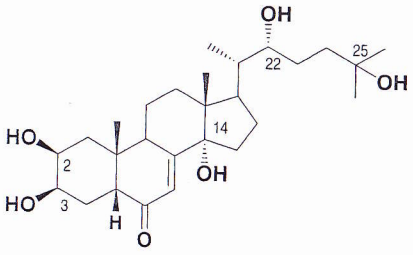
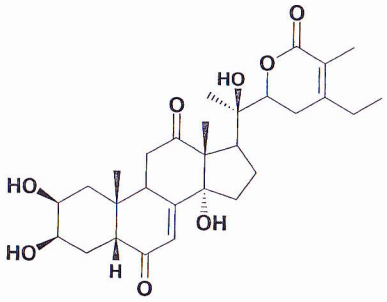
Other Steroids Other Triterpenes

1. INTRODUCTION

Few plant steroids, except for the sapogenins and cardiac glycosides, have established therapeutical applications. From a strictly phytochemical point of view, ecdysteroids deserve to be mentioned here. These compounds, related to ecdysone (= 2β,3β,14α,22*R*,25-pentahydroxy-5β-cholest-7-en-6-one), are characterized by a 7-en-6-one and multiple hydroxyl functions. Nearly one hundred structures have been described in plants, particularly in the Podocarpaceae. In the Arthropods, ecdysone and its metabolites are hormones involved in the regulation of ecdysis and other vital processes (e.g., reproduction, metamorphosis). The occurrence of structural analogs of the ecdysis hormone in plants is a surprise: they may play a defensive role against predators, or a role in the physiology of the plant, or both. Some of these compounds are potential insecticides; various other pharmacological and biological activities are also beginning to be recognized.



Ecdysone



Ajugalactone

Here we shall describe in one group, by arbitrary choice, drugs whose activity is certainly or probably linked to steroids, phytosterols, or related compounds.

2. OTHER STEROIDS

A. Steroid-containing Drugs

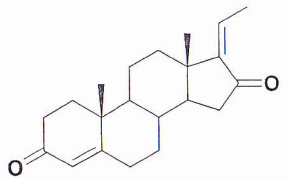
- **MYRRH TREE,**
  Commiphora mukul (Hook. ex Stocks) Engl., Burseraceae

The oleo-gum-resin secreted by this plant from the desert areas of India is a drug used in Ayurvedic medicine to treat, among other ailments, rheumatism, obesity, and miscellaneous disorders of lipid metabolism.

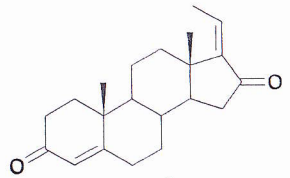
The Plant, the Drug. The myrrh tree is a bushy shrub with thorny branches, with ash-colored bark that peels into thin rolls, 1,3-foliolate leaves, flowers with a fuzzy calyx and a brownish-red corolla, and ovoid drupes that turn red when ripe. The species grows in the arid areas of the northwest of India (Rajasthan, Gujarat) and

as in Pakistan (Baluchistan). The drug is collected at regular intervals for some weeks, following the superficial incision of the bark of the trunk and main branches. Good quality myrrh occurs in vermiculated, translucent, pale yellow or greenish fragments, of aromatic or bitter taste, and of balsamic odor.

Chemical Composition. The constituent polysaccharide of the gummy fraction of myrrh is a highly ramified molecule comprising D-galactose, L-arabinose, and the 4-methyl ether of D-glucuronic acid. The volatile fraction of the oleoresin is chiefly composed of monoterpenes (myrcene). The resinous fraction *per se* contains diarylfuranofuranoid lignans (sesamin and related compounds), macrocyclic diterpenes (cembranes), esters of ferulic acid, and of C_{18}, C_{19}, and C_{20} polyhydroxylated saturated hydrocarbons (the "guggultetrols"), and steroids derived from pregnane and cholestane. The compounds of greatest pharmacological interest are the *E*- and *Z*-guggulsterones, which are geometrical isomers of pregna-4,17(20)-dien-3,16-dione. They occur alongside guggulsterols, which are C_{21} pregnane-type and C_{27} cholestane-type di- or trihydroxylated derivatives.



Z-Guggulsterone



E-Guggulsterone

Pharmacological Properties and Uses. "Guggulipid" (that is, the standardized product of the extraction of the oleo-gum-resin by ethyl acetate) lowers blood cholesterol and lipids in animals. The activity is linked to the guggulsterones and potentiated by the other constituents in the extract. These ketones, like guggulipid and clofibrate, lower blood cholesterol and triglycerides in various animals; they decrease LDL- and VLDL-cholesterol, and increase the HDL-cholesterol/total cholesterol ratio. The guggulsterones are thought to act by stimulation of thyroid function, probably by a direct effect; they are also thought to activate the hepatic membrane receptors that bind LDL, thereby increasing their metabolism. These ketones also induce an increase in the activity of dopamine-β-D-hydroxylase.

The purified product seems devoid of acute, subacute, or chronic toxicity (in rats, dogs, and monkeys); it is neither a mutagen nor a teratogen. Several double blind clinical trials using methodology of uneven quality have been conducted in humans and in India: they demonstrate the efficacy, comparable to that of clofibrate, of the prolonged administration of guggulipid in the treatment of certain types of hyperlipidemia (decrease in blood cholesterol and triglycerides). These trials resulted in the marketing of guggulipid in India (500-mg tablets containing 25 mg of guggulsterones). The indications are the treatment of mixed hyperlipidemia, hypertriglyceridemia and hypercholesterolemia. The crude gum may have side

effects (itching, diarrhea); the guggulipid is better tolerated, but it must be used with caution in case of liver disease or intestinal disorders (diarrhea).

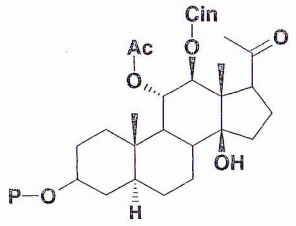
The plant is not listed in the French Pharmacopoeia or the 1998 French Explanatory Note. Further research is needed to demonstrate its true clinical benefits. The myrrh-based preparations that are marketed in France are commonly used in phytotherapy, alone or in combination (with psyllium or field horsetail) to control obesity.

- **CONDURANGO,**
  Marsdenia condurango Rchb. *f.*, Asclepiadaceae

The dried bark of the trunk and branches, still listed in the latest (VII) edition of the Swiss Pharmacopoeia—it must contain not less than 1.8% bitter glycosides—was official in France until 1949; its use is now very limited in Europe. This twining species is originally from the Andes (Ecuador, Peru). Its bark contains phytosterols, triterpenes, phenolic acids, and about 1-3% of a bitter substance, consisting of a mixture of pregnane-type aglycones, polyhydroxylated and partially esterified and glycosylated by a tri-, tetra-, or pentasaccharide comprising 2,6-dideoxyhexoses, namely the condurango glycosides (e.g., A, A0-1, B, C0, D0, E0-3). The structure of the aglycones is fairly close to that of the digitanol glycosides, and their pharmacology has not been studied (all that is known is that the glycosides are toxic to tumor cells *in vitro* [sarcoma 180]). The drug was formerly used as a bitter, appetite-stimulating tonic. In Germany, Commission E authorizes its use for lack of appetite.

- **CHASTE TREE,**
  Vitex agnus-castus L., Verbenaceae

Reputed to be an anaphrodisiac (*agnus-castus*, *chaste tree*, *Keuschbaum*) and traditionally used as an emmenagogue, sedative, and galactagogue, the flowering tops of this Mediterranean shrub contain an essential oil with cineole and sesquiterpenoid hydrocarbons, flavonoids (particularly acylated *C*-glycosides of luteolin and polymethoxylated flavones) and iridoids: aucubin and agnuside, the 4-hydroxy-benzoate (at C-10) of aucubin. The drug extract inhibits the secretion of



Cin = cinnamoyl ; P = pentasaccharide
(D-Glc–D-Glc–[3-OMe-6-deoxy-D-Allose]–D-Ole–D-Cym) :
Condurangoglycoside A1

prolactin *in vitro* (in pituitary cell cultures) and *in vivo* (in rats), probably through a dopaminergic mechanism. Recently, Croatian researchers, postulated that the drug may contain 3-ketosteroids; the presence of these steroids remains to be confirmed, but it would be no surprise, since ecdysones have been shown to occur in other species of the genus *Vitex*. Similar traditional indications (birth control agents) are frequently reported for other species in this genus, in Africa, India, and south-east Asia. In some European countries, particularly Germany, proprietary drugs are sold that contain, among others, an alcoholic extract of the fruit of the chaste tree; they are recommended in the treatment of various premenstrual problems, of symptoms linked to a deficiency of the corpus luteum (e.g., mammary pain, menstrual cycle irregularities *, uterine bleeding), and of acne. Chaste tree flowering tops have recently been approved in France for indications worded as "traditionally used": for menstrual pain; in the symptomatic treatment of neurotonic disorders in the adult and in the child, for example minor sleeplessness (?) [French Expl. Note, 1998].

B. Drugs with Activity Due Entirely or in Part to Phytosterols

Most higher plants elaborate 24α-substituted sterols (24-methyl and 24-ethyl-sterols) **. The β epimers generally occur only in traces, except in the most primitive of tracheophytes, namely mosses and hepaticas ***. Although phyto-sterols play an important role in the physiology of the plant, their potential pharmacological properties have not received much attention.

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* Despite the lack of clinical observations to substantiate the activity of this drug, it is suspected of being at the origin of a syndrome with hyperstimulation of the ovary and multiple follicular development (see Cahill, D.J., Fox, R., Wardle, P.G. and Harlow, C.R. (1994). Multiple Follicular Development associated with Herbal Medicine, *Hum. Reprod.*, **9**, 1469-1470).

** The current international rules of nomenclature recommend referring to the carbon atoms that substitute C-24 as 24^1 and 24^2, instead of C-28 and C-29 as before 1989. This nomenclature has the advantage of being, for the skeleton, parallel to that of triterpenes (the methyl groups at the 4-position are numbered 28 and 29, and the methyl group at the 14-position is numbered 30). These same carbons were formerly numbered 30, 31, and 32, respectively. Furthermore, the *R/S* nomenclature for C-24 is preferred to the α/β nomenclature. The name of the compound is built upon that of a few basic skeletons: cholestane, lanostane, ergostane, or campestane. For example, campesterol is (24*R*)-24-methylcholesta-5,22-dien-3β-ol or, more simply now, campest-5-en-3β-ol.

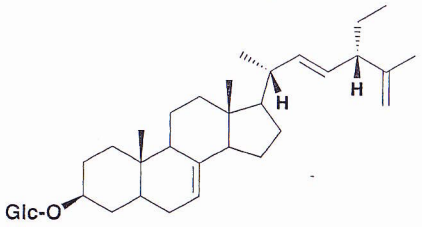
*** At first approximation, the 24β-methyl (or -ethyl) sterols are characteristic of the fungi and of certain algae (particularly the Chlorophyceae). The 25-methylene sterols are found in the brown algae, but also in some families of higher plants (Asteraceae, Cucurbitaceae, and others).

• (Common) Nettle, *Urtica dioica* L., Urticaceae

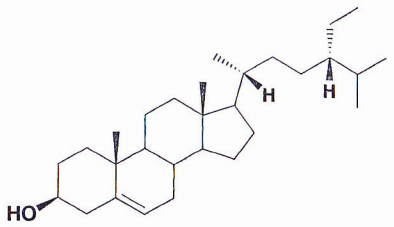
Nettle root is official in Germany (DAB 10). The leafy stem is listed in the BHP (1990).

The Plant. This weed is nitrophilous, therefore it grows wild around rural houses, in piles of rubble, and in ditches. The quadrangular stem bears opposite and dark green leaves with long triangular teeth. The petiole, which is shorter than the blade, the blade, and the stem are covered with fine unicellular, irritating * hairs. The flowers are generally unisexual and are inserted at the base of the leaves as long ramified racemes. The drug consists of the subterranean parts, in other words, the long ramified yellowish rhizomes and roots.

Chemical Composition. The roots of the dioecious nettle contain polysaccharides, (10*E*,12*Z*)-9-hydroxy-10,12-octadecadienoic acid, a low molecular weight lectin, and many phenolics with a C_6-C_3 structure (phenolic acids, scopoletin, phenylpropanoid aldehydes and alcohols), or with a C_6-C_2 structure (free and glucosylated homovanillic alcohol), as well as phenylpropanoid dimers: diarylbutanoid lignans such as secoisolariciresinol and related compounds, or diarylfuranoid lignans such as neo-olivil. Sterols are also found: free and 3-*O*-glycosylated sitosterol, 7α- and 7β-hydroxysitosterols and their glucosides, and the palmitate of sitosterol 3-*O*-glucoside.



Example of Δ^7-sterol glucoside (from Cucurbitaceae)



Sitosterol

Pharmacological Properties. The reputed beneficial effect of the nettle **root** on prostatic adenoma is consistent with the results of animal experiments. The active substances have not been identified rigorously: the polysaccharide fraction is an anti-inflammatory, but what could be the biological activity of the sterols? What about their metabolites?

The possibility of an action *via* aromatase inhibition by the hydroxylated fatty acid has been considered, but deemed unlikely (and no change in prostate volume was observed). Another hypothesis is that the nettle extract would interact with the serum globulin that binds testosterone. This interaction is weak (1-10 mg/mL) and was observed *in vitro*; it is due to the hydrophilic fraction, not to the lectin. The extract does not inhibit 5α-reductase nor the binding of dihydrotestosterone to its receptors in the prostate. Recently, German authors came up with the hypothesis that polysaccharides and the lectin (*Urtica dioica* agglutinin = UDA) are responsible for the activity: the polar fractions are thought to inhibit the growth of prostatic tissue and the lectin is thought to block the binding of the epidermal growth factor secreted by the prostatic tissue onto its receptor. In that case, what is the bioavailability of these polar compounds? The question was not addressed. The results of several clinical trials, published between 1980 and 1990, strongly indicate a rather positive impact of long-term treatment with the alcoholic extract of nettle root on the urinary symptoms associated with prostatic adenoma (improvement of bladder outlet obstruction symptoms and decrease in post-voiding residual urine), but experts find that the methodology used in these trials was not without bias.

* The stinging action is due to the liquid contained in the hairs, which is released when their tip is broken off upon contact, so that they essentially act like hypodermic syringes. This liquid contains acetylcholine, histamine, and according to recent work, leucotrienes. On stinging nettle urticaria, see Oliver, F., Amon, E.U., Breathnach, A., Francis, D.M., Sarathchandra, P., Kobza Black, A. et Greaves, M.W. (1991). Contact Urticaria due to Common Stinging Nettle (*Urtica dioica*) – Histological, Ultrastructural and Pharmacological Studies, *Clin. Exp. Dermatol.* **16**, 1-7.

Uses

Nettle Root. In the absence of undebatable clinical trial results, nettle root is traditionally used orally in France [French Expl. Note, 1998] as adjunctive treatment for bladder outlet obstruction symptoms of prostatic origin and to enhance the renal elimination of water. The German Commission E monograph describes that nettle root increases urinary volume and flow rate, and decrease the post-voiding residual urine. Therefore, it is used for the urination difficulties linked to stages I and II benign prostatic hyperplasia. The monograph specifies that since the use of the drug does not decrease the actual hypertrophy, a physician should be consulted on a regular basis. In some medicines marketed in Germany, nettle root extract is combined with the extract of *Prunus africana* (see p. 161).

Nettle Leaf. The nettle ***leaf*** is rich in minerals, proteins, vitamins, and phenolics, and it is said to be edible. It was formerly traditionally used as poultry feed. It is an industrial source of chlorophyll. In some European countries, it is recommended for asthenia and anemia. In France, it is now permitted for phyto-pharmaceuticals based on dioecious nettle *leaf* to claim the following indications for oral and topical administration [French Expl. Note, 1998]: traditionally used for seborrhea, and traditionally used for the symptomatic treatment of minor pain in the joints. The German Commission E monograph describes nettle herb (leafy stem) as used for the adjunctive treatment of rheumatism pain, for the preventive treatment of renal lithiasis, and for irrigation in case of inflammation of the urinary tract. Also in Germany, nettle fruit is used in folk medicine (tonic, "hepatic stimulant").

• β-Sitosterol

Phytomedicines consisting primarily of β-sitosterol have been commercially available in Germany for several years. They are prescribed to improve the symptoms of benign prostate hyperplasia. Faced with the fact that international experts were not taking into account this type ot treatment, the manufacturers of these products began to provide support for clinical trials. The results of randomized double-blind studies indicate that prolonged treatment induces a regression of symptoms that were quantified using a normalized questionnaire (I-PSS), an improvement of the quality of life, and an increase in urinary flow rate. These effects are significantly superior to those of a placebo. No side effects were observed, even at the highest doses (130 mg/day for 6 months).

• Pollen Extracts

In some countries, an extract is marketed that is obtained from the pollen of various plant species from the south of Sweden. Two fractions from this extract are responsible for the biological activity: one is water-soluble, and the other is soluble in acetone and contains sterols. The water-soluble fraction inhibits the growth of prostatic tumor cells and normal cells *in vitro*. Fractionation monitored by checking the biological activity has led to the isolation of a cyclic hydroxamic acid, 2,4-dihydroxy-2*H*-1,4-benzoxazin-3(4*H*)-one, which has the same inhibitory properties. The total extract decreases prostatic hypertrophy in rats. When it is administered to humans, it does not change the blood levels of *luteinizing hormone* (= LH), *follicle stimulating hormone* (= FSH), testosterone, or dihydrotestosterone. In view of the results of trials conducted on patients with prostate adenoma, the total pollen extract is presented as capable of improving nocturia, significantly decreasing the post-voiding residual urine, and in the long run, decreasing the anterio-posterior diameter of the prostate. Its effects on the other common symptoms affecting the prostate are not statistically significant. It does not affect the urinary flow rate.

• Pumpkin, *Cucurbita pepo* L., Cucurbitaceae

Pumpkin seeds were official until the beginning of the twentieth century. They have long been used for their vermifuge properties (a taenicide proprietary product based on pumpkin seeds used to be marketed in France until the early 1980s). For a few years now, some European countries have been marketing the oil of pumpkin seeds as a drug treatment for benign prostate hypertrophy.

This large annual plant with procumbent stems is characterized by large leaves covered with stiff hairs, ramified tendrils, large (5-10 cm), pentamerous, unisexual (two pairs of fused stamens + one) three carpels with

flowers, and by a humongous berry containing a large number of seeds within a spongy pulp. The seed is flattened (15-20 x 8-10 x 2-3 mm) and whitish. It is tapered at one end and has a rounded rim.

Pumpkin seeds are rich (30-50%) in unsaturated oil (43-55% linoleic acid). The vermifuge properties of the seed are attributed to a cyclic amino acid: 3-amino-3-carboxypyrrolidine (0.4-0.8%). But it is the sterol composition of the unsaponifiable matter that has retained the attention of chemists. The chief constituents are, as in many other Cucurbitaceae, Δ^7-sterols and their glycosides: spinasterol glucoside, 24β-ethyl-5α-cholesta-7,25(27)-dien-3β-ol 3-*O*-(β-D-glucopyranoside), and the corresponding 7,22*E*,25(27)-trien-3β-ol; they occur alongside Δ^5-sterols (clerosterol, isofucosterol, stigmasterol, campesterol), squalene, and others.

The activity of pumpkin seeds on the symptoms linked to benign prostate hypertrophy is attributed to the Δ^7-sterols, but its mechanism is not known and there are few published clinical studies. The use of pumpkin oil is an ancient and current practice in Germany, and in other countries of central Europe, and Commission E approves the use of the seed, while specifying that is is merely a symptomatic remedy. Pumpkin seed extract is sometimes combined with *Serenoa repens* extract (see p. 162).

3. OTHER TRITERPENES

A. Cucurbitacins

Cucurbitacins are tetracyclic triterpenes arising from a rearrangement of the protostane cation (see p. 665). They are unsaturated and polyfunctionalized—they may include up to nine oxygen atoms—occur most often as glycosides, and are characteristic of several genera in the family Cucurbitaceae. They are particularly toxic substances (LD50 near 1 mg/kg in mice by IP administration), are bitter and cytotoxic, and impart to the drugs that contain them drastic purgative properties: colocynth seeds (*Citrullus colocynthis* [L.] Schrad.), the juice of the fruit of the squirting or wild cucumber (*Ecballium elaterium* [L.] A. Rich.), and the bryony root (*Bryonia cretica* and other species) were formerly used as purgatives. Although these drugs have long been abandoned * by allopathy and phytotherapy, some, like the bryony, are still used in homeopathy.

Cucurbitacins have also been isolated from plants such as the gratiola (*Gratiola officinalis* L., Scrophulariaceae); their presence explains the purgative and emetic action of this old folk remedy which, fortunately, is now obsolete.

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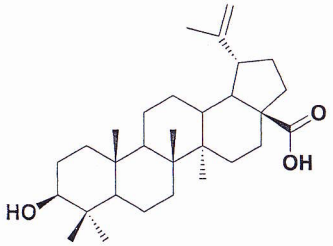
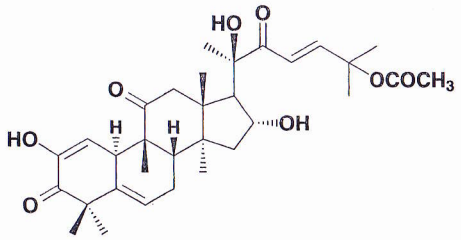
* In some cases, they are still used, either on purpose or by error, and with serious consequences, including death. See: 1° Gálvez Contreras, M. del C., López Gallardo, A., Díez García, F. and Yélamos Rodríguez, F. (1996). Intoxicacíon por coloquíntida, una causa poco frecuente de sindrome diarreico agudo, *Med. Clin.*, (Barcelone), **106**, 599 ; 2° Vlachos, P., Kanitsakis, N.N. and Kokonas, N. (1994). Fatal Cardiac and Renal Failure Due to *Ecballium*

- **Bryony,**
  Bryonia cretica L. subsp. *dioica* (Jacq.) Tutin, Cucurbitaceae

This toxic plant is a perennial dioecious species whose long (5 m) stems bear palmatilobate leaves covered with rough hairs, and tendrils which allow it to climb on nearby supports. The fruit is a berry which is red when ripe and may attract children. The roots, formerly prized for their purgative properties, contain cucurbitacin glycosides, including bryodulcoside, bryoside, bryonoside, cucurbitacin L, bryoamaride, and bryodiosides A-C. All parts of the plant are toxic, however, their composition is not as well known as that of the roots. Upon contact with the skin, the fresh roots cause redness, irritation, and the formation of vesicles. The ingestion of a few fruits (<10 in children) induces vomiting, abdominal pains, diarrhea, and in rare cases, agitation. Bryony appears in the French Pharmacopoeia (10th Ed., IV.7.b), but on *liste B,* which means that it is a species "for which the evaluation of the benefit-to-risk ratio is negative". Currently, the sole use of the drug is in homeopathy. In Armenia, the root of a closely related species, the white bryony, (*Bryonia alba* L.) is considered to be a tonic and an adaptogen.



Betulinic acid



Cucurbitacin E

B. Miscellaneous Triterpenes

- **Birch,**
  Betula spp., Betulaceae

The drug (Eur. Ph., 3rd Ed., add. 1998) consists of the dried leaves, entire or fragmented, of *Betula pendula* Roth, or *B. pubescens* Ehrh, or both, or hybrids of the two species. The leaf of *B. pendula* ends in a long acuminate point and is glabrous; that of *B. pubescens* is slightly hairy, and it is neither elongated nor acuminate. The drug contains not less than 1.5% flavonoids, expressed as hyperin (colorimetry after reaction with $AlCl_3$).

Birch leaf contains many flavonoids (2-3%): rutin, quercitrin, hyperin, and other glycosides of quercetin (3-*O*-glucuronyl, 3-*O*-arabinosyl), glycosides of kaempferol and of myricetin, methylated flavones, and more, as well as phenolic acids and triterpenes derived from lupane and dammarane (free or esterified by malonic acid).

In the absence of pharmacological or clinical data, in France the drug is traditionally used orally [French Expl. Note, 1998]: 1. to enhance urinary and digestive elimination functions, and 2. to enhance the renal elimination of water *. The German Commission E attributes a diuretic effect to birch leaf; the monograph specifies that it is used for inflammation and infection of the urinary tract and for urinary lithiasis *. It is also used for the adjunctive treatment of rheumatism pain, although this use is not mentioned on package inserts.

Birch bark contains very large quantities of lupane-type derivatives (lupeol and hydroxylated derivatives, betulinol, betulinic acid) as well as dammaranes, often esterified through the hydroxyl group at C-3 by malonic acid (papyriferic acid). The bark also contains arylbutanoids and glycosidic diarylheptanoids. Like birch leaf, it passes for a diuretic.

Betulinic acid is cytotoxic *in vitro* and *in vivo*: it inhibits the growth of human melanoma in mice selectively, by inducing apoptosis. Certain amides of betulinic acid (amide of 11-amino-undecanoic acid and RPR 103611) are potent and selective inhibitors of HIV-1 replication. Their IC_{50} on some strains is on the order of 10 nM. They are inactive on the viral enzymes (protease, reverse transcriptase), but they prevent the formation of the syncytium and block the entry of the virus into the cells. (Note that the initial experiments that allowed the discovery of these properties were conducted with betulinic acid isolated from plane tree bark, " *Platanus hybrida* Brot. ", Platanaceae).

- **Black Cohosh,**
  Cimicifuga racemosa (L.) Nutt, (= *Actea racemosa* L.), Ranunculaceae

This North American herb, also known as black snakeroot or rattleroot, has a reputation as an anti-inflammatory, diuretic, sedative, and antitussive. The rhizome and roots (BHP 1990) are presented as having an estrogenic activity, and traditionally proposed to relieve various minor gynecological problems. Chemically, the subterranean parts contain formononetin, which may be the basis of the estrogenic activity, since this isoflavone binds competitively to estrogen receptors (ovariectomized female rat uterus). They also contain tetracyclic triterpenes derived from cycloartanol, whose side chain is oxidized and cyclized by ketalization (actein, cimifugoside). In animals, the drug extract is a hypotensive agent, a vasodilator, a spasmolytic, and an anti-inflammatory. In France, the drug is virtually not used any more (except in homeopathy); it is still used in Germany (neurovegetative problems of the menopause, premenstrual syndrome).

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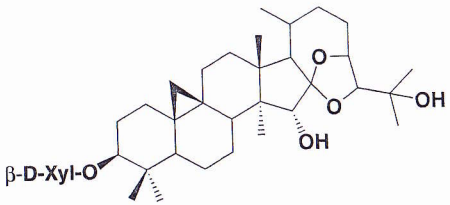
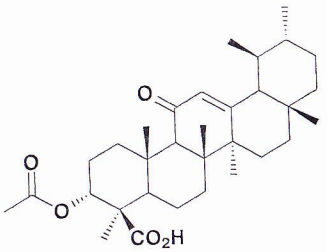
* The same traditional indications may be claimed by cammock root in France and Germany. This European Fabaceae also known as rest-harrow (*Ononis spinosa* L.) contains a triterpene arising from a «double» cyclization of squalene, namely onocerin. There is no proof that onocerin contributes to the activity, which itself remains to be verified. *Ononis* root also contains isoflavonoids (isoflavones, [glycosides of formononetin and of biochanin A], [illegible]) and less than 1 mL/kg of essential oil.

QUASSIA AMARA L.



Cimicifugoside



3-O-Acetyl-11-ketoboswellic acid

• Salai Guggal - Boswellic acids

Boswellic acid (3α-hydroxy-urs-12-en-23-oic acid), 3-*O*-acetyl-11-keto-boswellic acid (= AKBA), and closely related derivatives are the biologically active principles of *salai guggal*, in other words the oleo-gum-resin produced by *Boswellia serrata* Roxb. ex Colebr. (= *B.glabra* Roxb., Burseraceae). A traditional remedy in Ayurvedic medicine, this product is used in India to treat various inflammatory disorders, particularly as an alcoholic extract (Sallaki ®). These boswellic acids are also found in olibanum (frankincense), the oleo-gum-resin secreted by *Boswellia carteri* Birdw. (see p. 580).

The anti-inflammatory activity of the boswellic acids has been studied on different animal models (induced arthritis and edema). It has been established that AKBA, and to a lesser extent, boswellic acid, are specific inhibitors of 5-lipoxygenase *in vitro*, therefore they are inhibitors of leukotriene synthesis.

Preliminary studies in rats indicate that these triterpenic acids have no toxicity, acute or chronic (1 g/kg/day x 6 months). Clinical observations in rheumatoid arthritis patients—but the methodology of these trials was not described—lead some authors to think that these compounds are well tolerated and could be used for adjunctive therapy. It is clear that further trials are necessary to determine if there are real benefits.

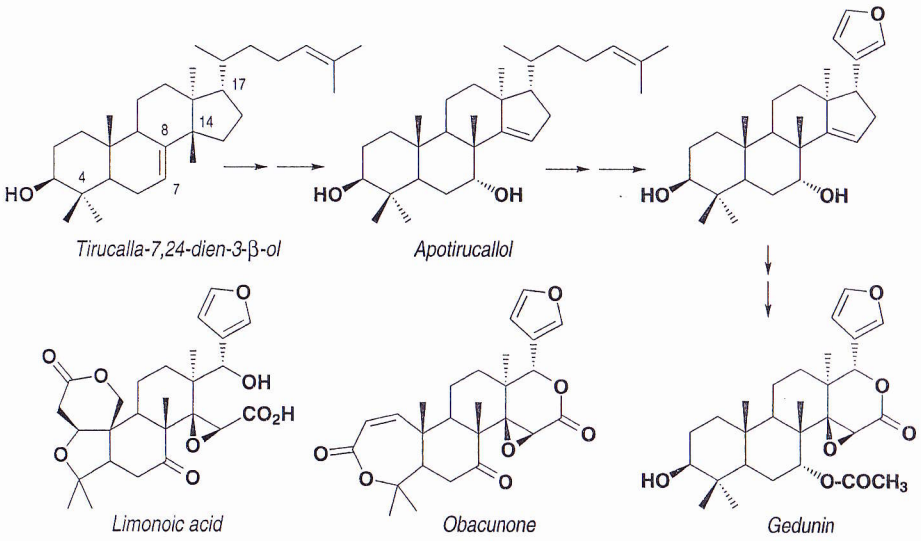
C. Modified Triterpenes

Many genera within families of the order Rutales (Rutaceae, Meliaceae, Simaroubaceae, Cneoraceae) are capable of achieving profound degradations of the triterpenoid skeleton. The chief modifications are a cyclization (limonoids), or an elimination of the C-17 side chain (in most quassinoids), as well as an opening with oxidation of the D ring (quassinoids), or of the A ring (limonoids), or of both (limonoids). In some cases, the modifications are deeper: opening of the B or C ring, sometimes followed by recyclization, and more.

Limonoids

Over 300 limonoids arising from the metabolism of a 4,4,8-trimethyl-17-

(or from Δ^7-euphol): the opening of the 7,8-epoxide allows migration of the methyl group from C-14 to C-8, creates unsaturation at C-14, and always places a hydroxyl group at C-7. The oxidation of the A ring, or of the D ring, or of both, takes place according to a similar mechanism, for example oxidation at the α position relative to the unsaturation and Baeyer-Villiger reaction. Further rearrangements and oxidations are possible (see figure on next page and corresponding references).



Rutaceae. *Citrus* limonoids are of no interest to pharmacy; they are responsible for the bitterness which gradually develops in fruit juices after their preparation. This delayed bitterness is common to all of the *Citrus*, unlike the immediate bitterness which is specific to certain species (grapefruit), and which is due to flavanone glycosides. In the fresh and intact fruit, monocarboxylic limonoic acid occurs as a salt which is not bitter. After the juice is squeezed, acidification leads to its lactonization to limonin, which is bitter. Commercially, this delayed bitterness could cause various problems and justify the biotechnological elimination of the principles responsible for it.

Meliaceae. The chief economical interest of this family is that it produces the finest of woods: African mahoganies (*Khaya grandifolia* DC., *K. ivorensis* A. Chev., *K. anthotheca* (Welw.) DC, and more), Honduran mahogany (*Swietenia macrophylla* King), a west African timber of mahogany type (*Entandophragma utile* [Dawe & Sprague] Sprague) and various species of *Turraeanthus, Guarea*, and *Cedrelus*.

The handling of these woods often causes allergic reactions: contact dermatitis or respiratory symptoms. In most cases, these effects are attributed to modified triterpenes (e.g., anthothecol).

• NEEM, *Azadirachta indica* A. Juss., Meliaceae

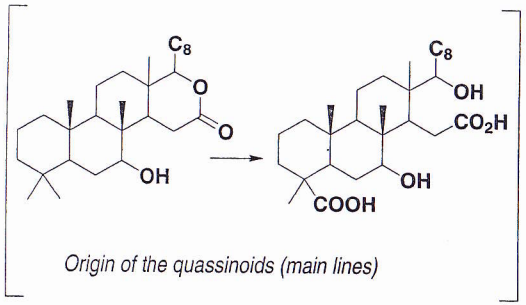
A. indica is a tree common in India and acclimatized in tropical Africa. The bark, the leaves, and the oil from the seeds are widely used in folk medicine: the bark has a reputation for being a tonic, the leaves and the oil from the seeds are recommended as anthelmintics, antiseptics, and antiparasitic agents. Many terpenoid constituents have been isolated from the different drugs: diterpenes (abietane derivatives), and, most of all, more than fifty highly oxidized tetranortriterpenoids, including azadirachtin, nimbolide, nimbidinic acid, azadirone, and nimbin. Some of the activities attributed to this drug have been investigated (antimalarial, anti-inflammatory, CNS activity), but it is mostly the activity of azadirachtin that has been the focus of attention. This compound acts on insects as an antifeedant. In addition, at low doses, azadirachtin, by a complex mechanism of action on the insect's neuro-hormonal regulation, interferes substantially with larval growth and insect development; it delays growth, inhibits ecdysis, and induces malformations, all of which make it an insecticide that is all the more interesting because its environmental impact is much smaller than that of synthetic pesticides. Several products are now commercially available in the United States (e.g., Margosan-O, Azatin); they contain azadirachtin, and some contain *Azadirachta* seed oil, which is thought to potentiate the activity.

Quassinoids (see formulas p. 766)

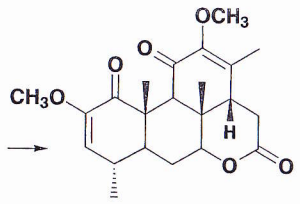
Most of these bitter principles from the Simaroubaceae have a C_{20} (or a C_{19}) skeleton; some of them retain part of the side chain from the common precursor, and therefore, have a C25 skeleton. All of the compounds in this group are highly oxidized and include lactones as part of their structure.

Various quassinoid-containing drugs were formerly used for their tonic or insecticidal properties, for example the quassias. Surinam quassia (*Quassia amara* L.) and Jamaican quassia, two tall Caribbean trees, were formerly used for their wood, rich in quassin, itself considered bitter and aperitive*. The potential applications of the Simaroubaceae are linked to the marked biological activities of a certain number of quassinoids. An example is that of the C_{20} quassinoids isolated from *Brucea, Ailanthus, Simarouba, Castela*, and *Simaba*, which have cytotoxic properties. This activity is due to compounds that are bridged (8,11 or 8,13), esterified (at C-15 or C-6), and have an unsaturated A ring and hydroxyl groups at C-11 and C-12, for example bruceantin. Several quassinoids, mostly with 20 carbon atoms and a bridge, are antimalarials *in vitro* and at very low doses (IC_{50}<0.02 μg/mL). Some are also amebicides.

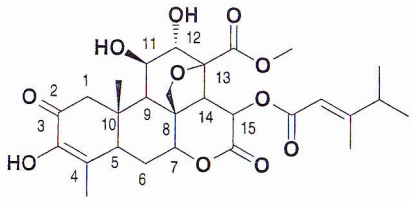
* One of the rare proprietary drugs containing quassia wood (but also yellow gentian root, cinnamon, bitter orange peel, cinchona bark, kola nuts, *nux vomica* extract, and calcium glycerophosphate) has been on the French market since 1910! Its brand name is Quintonine®.



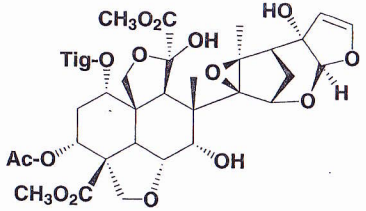
Origin of the quassinoids (main lines)



Quassin



Bruceantin



Azadirachtin

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