Monoterpenoid Indol Alkaloids II

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DRUGS CONTAINING INDOLE ALKALOIDS

APOCYNACEAE

Madagascan Periwinkle Catharanthii herba

***Catharanthus roseus* (*Vinca rosea*)**

Cezayir menekşesi, rozet çiçeği, pervane çiçeği

Catharanthus roseus is probably indigenous to Madagascar, is widespread in all of the tropical regions of the globe. It is cultivated in Turkey and Cyprus as a beautiful park and garden plant.

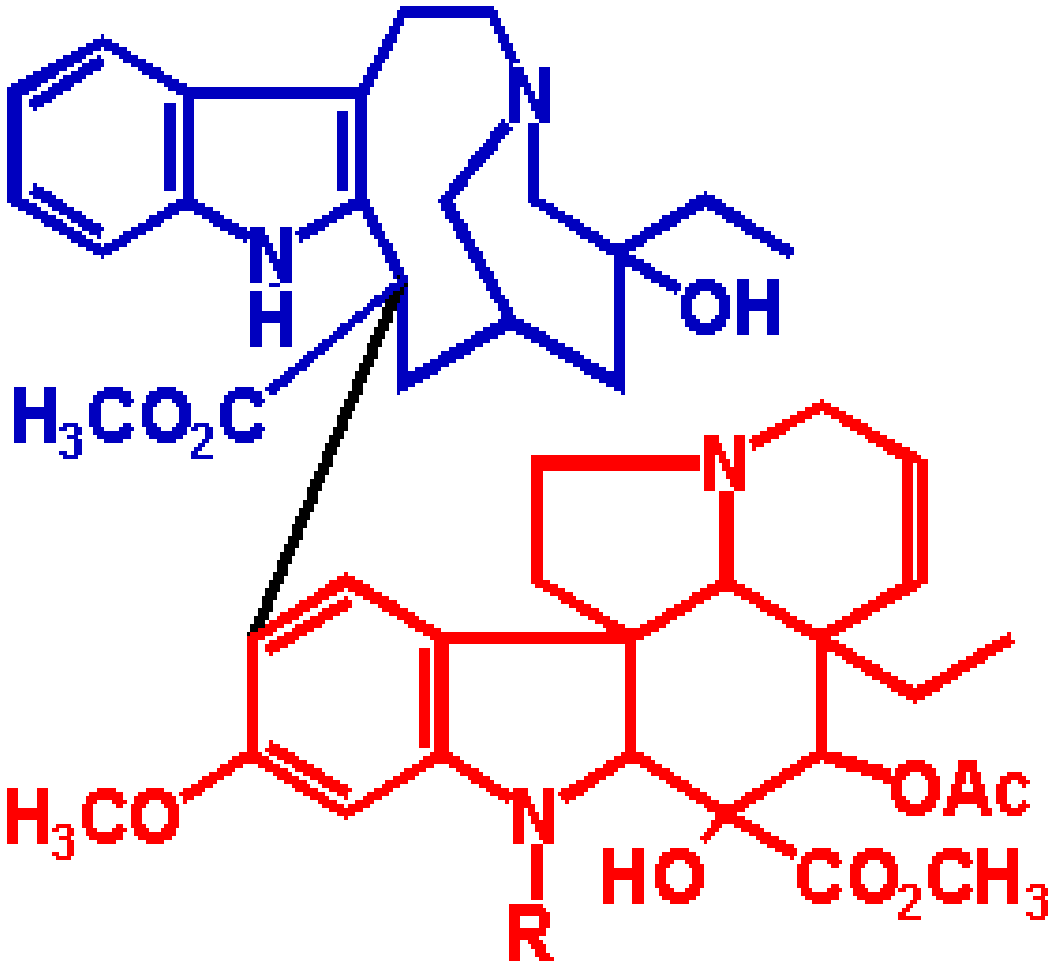
Chemical Composition : The aerial parts contain from 0.2 to 1% alkaloids. These form a very complex mixture in which about 95 constituents have been identified. All of them have an indole or dihydroindole structure (vindoline [the principal constituent], catharanthine, ajmalicine, akuammine, locherine.

The substances of pharmacological interest are the alkaloids formed by the coupling of two “monomeric” alkaloids, an indole and a dihydroindole. This particular structure has led to referring to them as “dimer” alkaloids or else “bisindole” alkaloids. Chemically, they are not dimers, therefore it is better to speak of “binary” alkaloids.

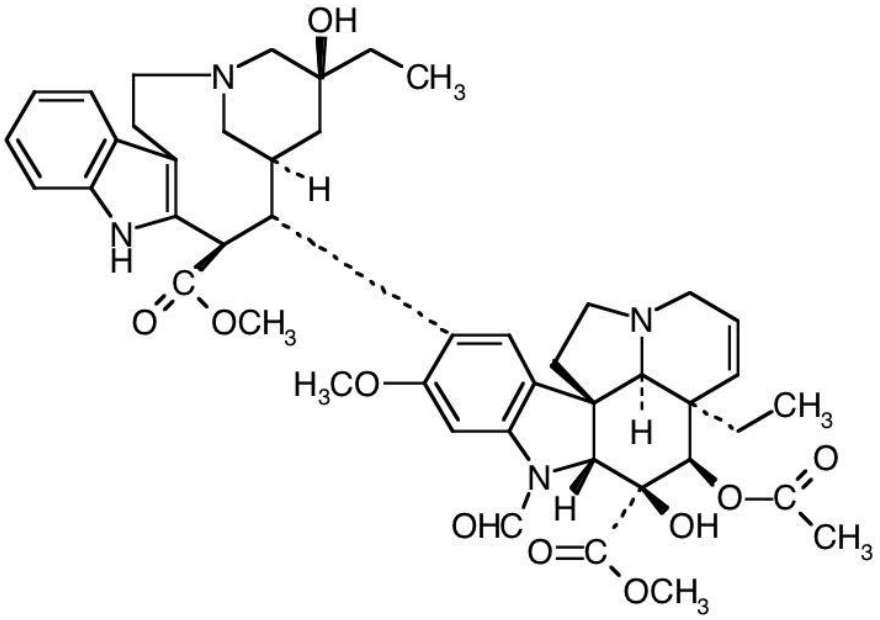
About twenty binary alkaloids heve been isolated from the drug. Several have cytostatic properties especially :

- **Vincristine**, its level dose does not exceed 0.0003% (3 g per t of dried drug)
- **Vinblastine**, which is a little more abundant

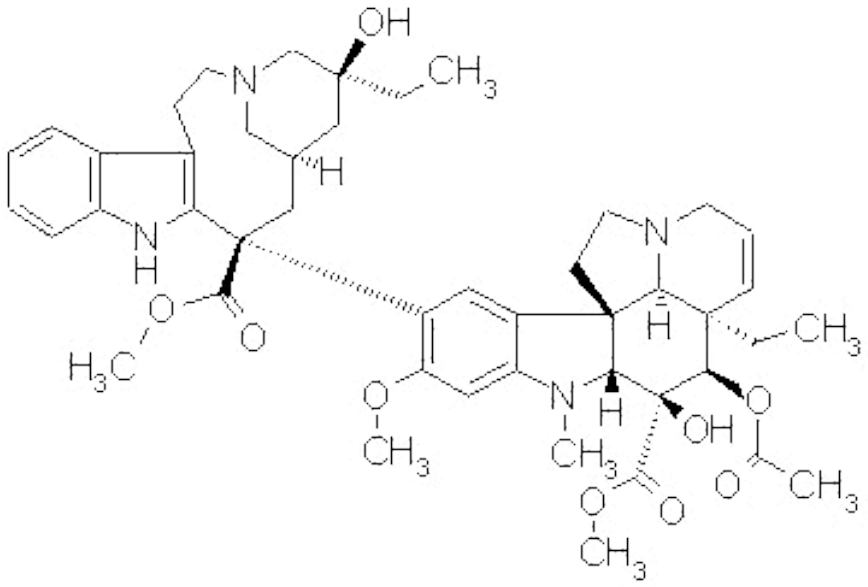
These two alkaloids formally comprise a dihydroindole (vindoline)and an indole (velbanamine) moiety. They differ by the nature of the substituent on the Na of the dihydroindole moiety, which is either a formyl group (**vincristine**) or a methyl group (**vinblastine**).



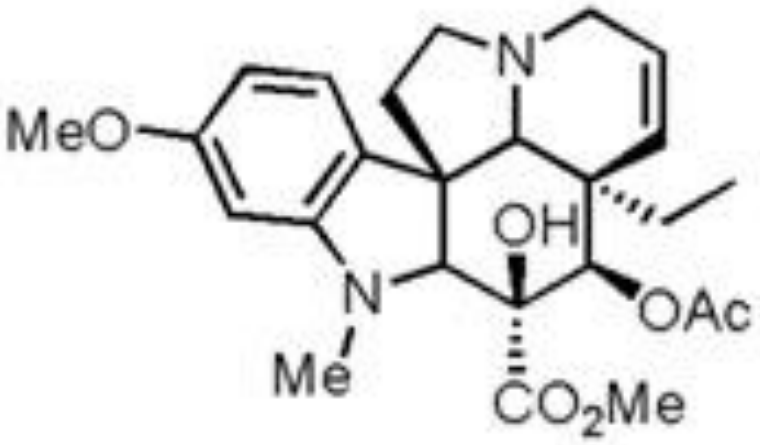
Vinblastine, R = CH_3
Vincristine, R = CHO



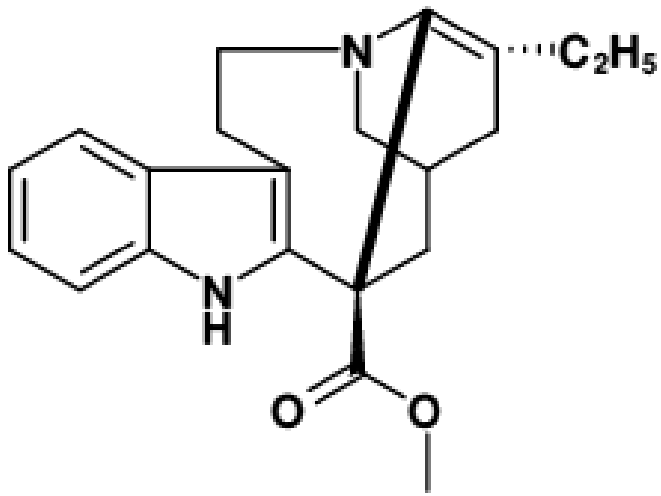
vincristine



vinblastine



Vindoline



Catharanthine

Pharmacological activity :

Vinblastine and vincristine are antimitotics. They bind to tubulin and prevent the formation of the microtubules whose role is well known in the formation of the mitotic spindle. Thus these compounds block mitosis and cause an accumulation of cells in the metaphase. The microtubule assembly also plays a role at other levels, particularly in neurotransmission, hence the neurotoxicity of these alkaloids

Toxicity : Like most compounds with antitumor activity, the binary alkaloids of *Catharanthus* have a high toxicity.

• Vinblastine is highly leucopenic, and this limits the posology. In addition, it induces gastrointestinal distress (nausea, vomiting, constipation). Neurological symptoms can also be observed (headaches, neuritis, loss of the tendon reflexes, depression), as well as respiratory difficulties and alopecia.

• Vincristine mainly has central neurotoxic effects (possible convulsive episodes), peripheral neurotoxic effects (paresthesia, neurolgia, myalgia), and digestive effects (constipation up to paralytic ileus, which is rare). There are multiple side effects: alopecia, (frequent) and less frequently, dyspnea, bronchospasm, headaches, transient blindness, buccal ulcerations, amenorrhea.

• Pregnancy and breast feeding are contraindications for both alkaloids. Both are very irritating

Uses :

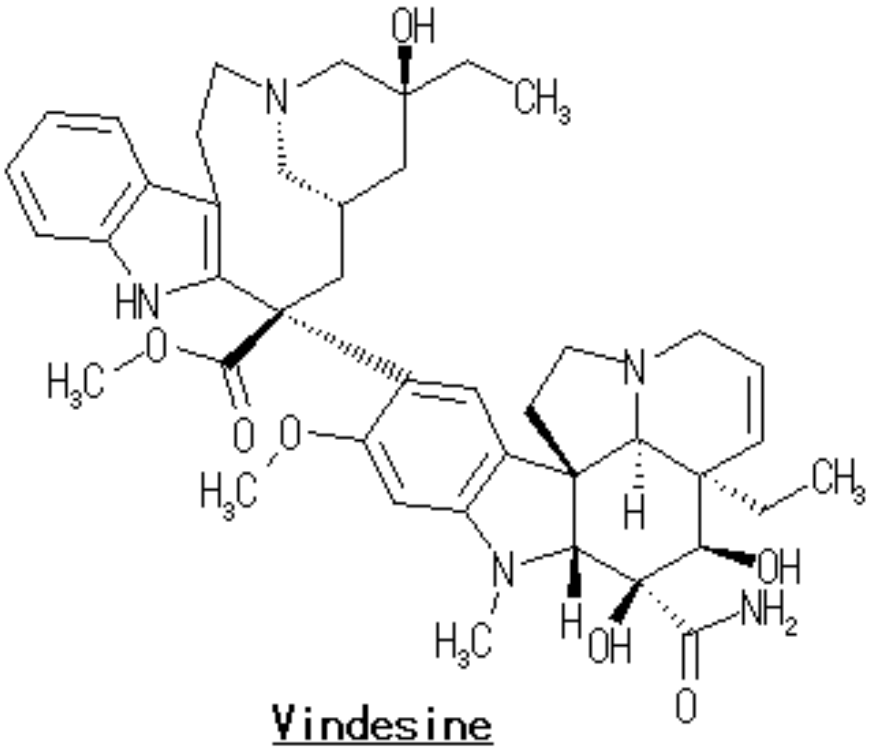
- Vincristine sulfate is indicated in single-drug therapy for acute leukemia. In combination chemotherapy, it is indicated for the treatment of Hodgkin's disease, non-Hodgkin's lymphomes, breast cancer, uterine and cervical cancer, small cell bronchial cancer, rhabdomyosarcoma and various sarcomas.

- Vinblastine sulfate is indicated in the treatment of Hodgkin's disease, of non-Hodgkin's lymphoma, of advanced testicular cancer, of breast and ovary epithelioma, of Kaposy's sarcoma, of choricarcinomas.

Semisynthetic Derivatives of the Binary Alkaloids

Vindesine

This alkaloid can be prepared from vinblastine.

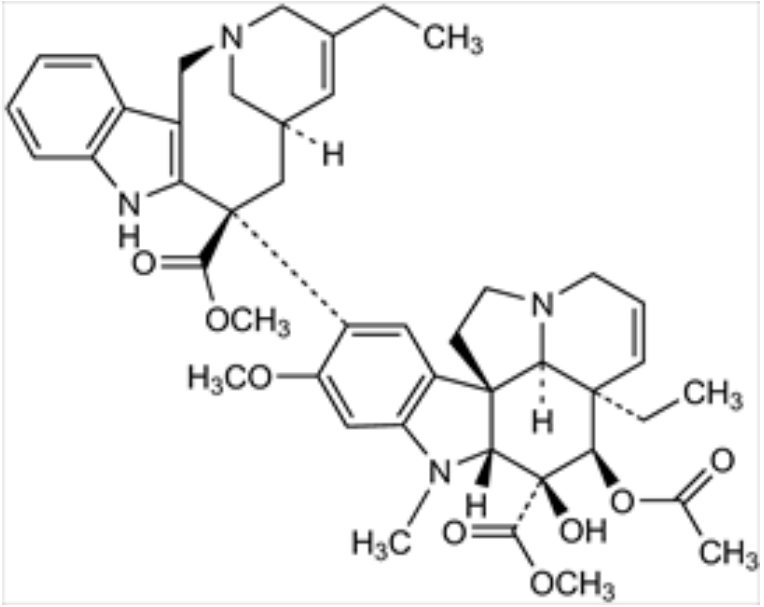


Vindesine

Vindesine is a potent antimitotic. Marketed as a sulfate it is indicated in the treatment of acute lymphoblastic leukemia and refractory lymphomas. Certain solid tumors are also indications : breast, esophagus, upper respiratory and digestive tract, bronchopulmonary cancer.

Like vinblastine and vincristine, this derivative is toxic, and its side-effets include a transient granulopenia, gastrointestinal effects, neurological symptoms less marked than those induced by vincristine, reversible alopecia, weight loss and muscular aches.

Vinorelbine = noranhydrovinblastine



Vinorelbine, marketed as a bitartarate for injecrable solutions acts preferentially on mitotic microtubules and not so much on neuronal microtubules. Its current indications are metastatic breast cancer and bronchial cancer. Although the neurological toxicity is limited, and the severe adverse effects lower than with compound such as vindesine, the hematological toxicity (granulopenia) is substantial and limits the posology. Vinorelbine is more efficacious than vindesine for the treatment of inoperable non small cell lung cancer.

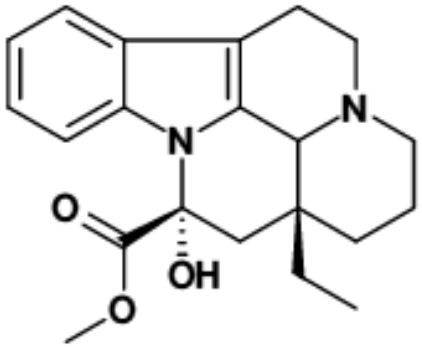
Common periwinkle **rozet** **Vincae herba**

Vinca minor

This herbaceus plant grows in Europe and Turkey. *Vinca major* grows wildly in Cyprus.

Vinca major

Chemical Composition : The drug contains 0.3 to 1% total alkaloids. Vincamine, which represents about 10% of the total alkaloids, occurs alongside approximately thirty other indole alkaloids of the eburnan type (vincine, epivincamine), of the aspidospermane type and related compounds (vincadifformine, vincadine).



Vincamine

Pharmacological Activity : Pharmacology experiments in animals show that vincamine increases cerebral blood flow. Several studies in humans tend to confirm the activity on cerebral blood flow.

Uses : The drug is only used to extract vincamine. The psycological and behavioral problems of cerebral senility (attention deficit, memory loss, dizziness) constitute the chief indication of this compound. Vincamine is contraindicated in the case of cerebral tumor with intracranial hypertension. It must not be taken concomitantly with medicines that might cause wave-brust arrhythmia.

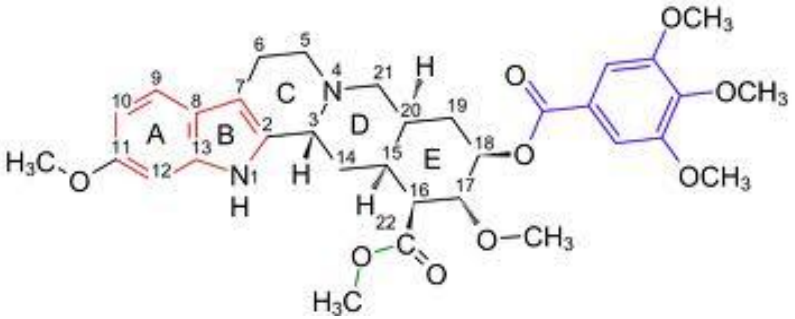
Rauwolfia **Rauwolfiae radix**

Rauwolfia serpentina

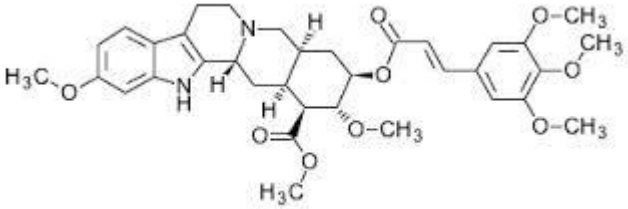
Rauwolfia is an evergreen shrub growing wild in India, Pakistan, Myanmar, Thailand, Malaysia and Indonesia.

Chemical Composition : The total alkaloids (0.5-2.5%) constitute a compolex mixture of nearly thirty different compounds, mostly alkaloids. Of note is the occurence of three main groups of alkaloids.

• Yohimbane-type derivatives : The most interesting ones have six asymmetrical centers (they are substitutied at C-16, C-17, and C-18 : reserpine and rescinnamine occur alongside. Reserpine and rescinnamine are weak beses.



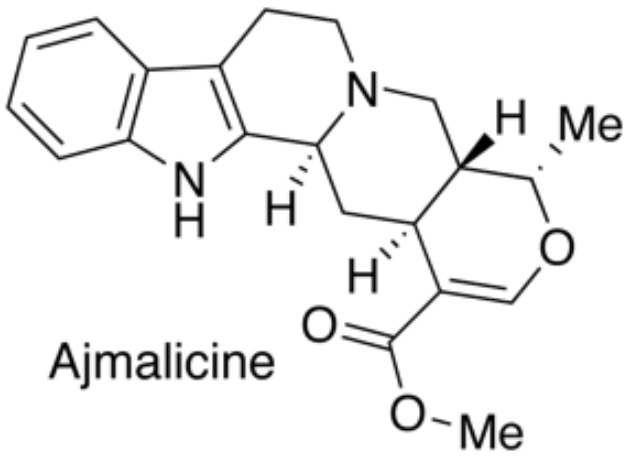
reserpine



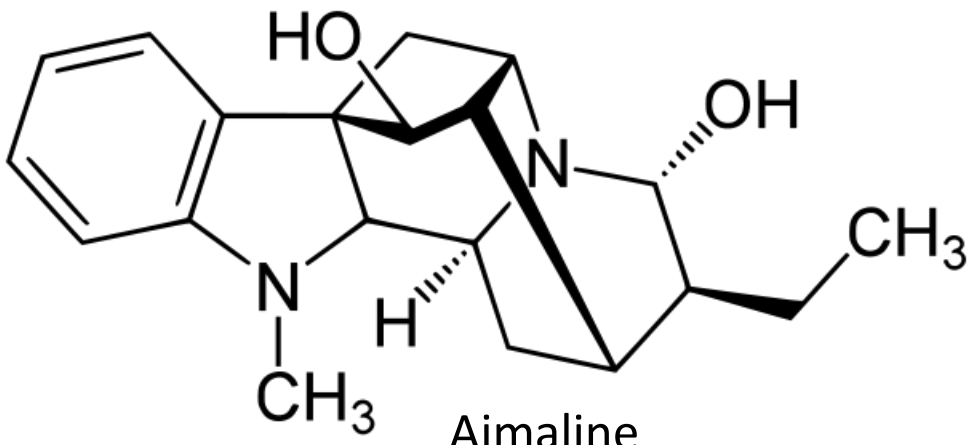
rescinnamine

• Heteroyohimbane Derivatives : These alkaloids, very closed related to the previous ones, have a heterocyclic E ring : Ajmalicine (also known as raubasine) occurs alongside its methoxylated derivatives (reserpiline).

• Dihydroindole- Derivatives are chiefly represented by ajmaline, a polycyclic indoline alkaloid.



Ajmalicine



Ajmaline

Pharmacological Activity :

Reserpine : Reserpine was formerly widely used, for its neuroleptic properties and mostly for its antyhypertensive activity. Rescinnamine has the same activities.

Ajmalicine : Ajmalicine is an α-blocking spasmolytic, which at high doses inverts the effects of adrenaline. Ajmalicine (=raubasine) moderates the activity of the vasomotor centers, especially in the brain stem. It causes a transient increase of the blood flow to the brain and is slightly anxiolytic.

Ajmaline : Ajmaline is toxic and no longer used.

Uses :

Reserpine is still marketed in some countries (France) in treatment of arterial hypertension. The presence of reserpine in a medication of this type leads to the following contraindications : depression, combination with MAO inhibitors or levodopa, peptic ulcer, and hypersensitivity to *Rauwolfia* alkaloids.

Ajmalicine is not used by itself. It is currently an ingredient of proprietary products used to treat sequelae of cerebrovascular accidents and proposed to treat the symptoms of senility. It is combined with dihydroergocristine.

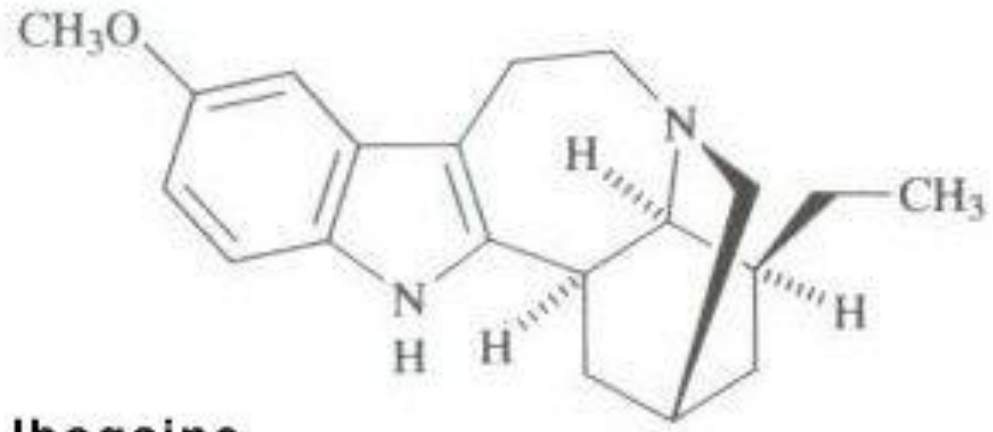
Other *Rauwolfia* Species : The extraction industry mostly uses various species in the genus, particularly *Rauwolfia vomitoria*, an African species with bulky woods and high alkaloid concentration (7-10%), and *Rauwolfia tetraphylla*, a collective species of northern South America.

Iboga

Ibogae radix

Tebernanthe iboga

Iboga is a shrub indigenous to equatorial Africa (Congo, Gabon). It is prized for its big roots whose bark contains 5 to 6% indole alkaloids : ibogaine (principal constituent), tebernanthine and ibogamine. In Gabon the root is used for its antisoporific properties and its ability to increase resistance to fatigue. With a reputation as an aphrodisiac, it has been used during initation ceremonies. Ibogaine is a CNS stimulant. Because of its hallucinogenic activities, ibogaine is prohibited in several countries. High doses in humans can cause paralysis and even respiratory arrest.



Ibogaine

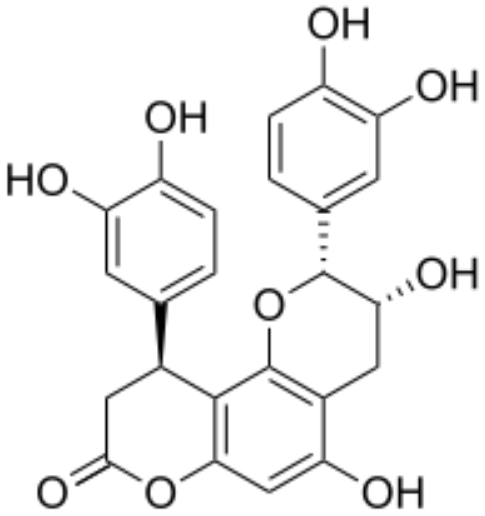
DRUGS CONTAINING QUINOLINE ALKALOIDS

Cinchona Kına kına kabuğu Cinchonae cortex
***Cinchona* ssp. Rubiaceae**

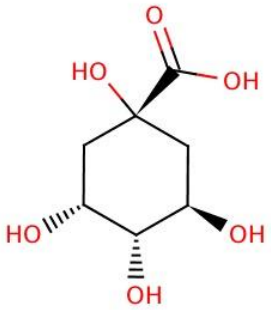
Cinchona consists of the dried bark of *Cinchona pubescens* (= *C. succirubra*). Although only one species is official, others such as *Cinchona ledgeriana*, are used for the extraction of quinine and quinidine. The former is an antimalarial, and remains the treatment of choice for pernicious malaria. For now, the resistance of the parasite to this alkaloid remains very limited. Quinidine is antifibrillant (antiarrhythmic).

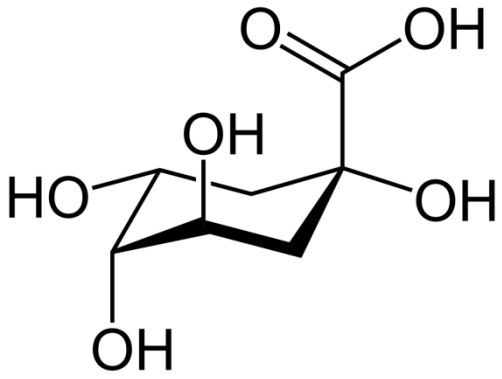
Cinchona pubescens

Chemical Composition : *Cinchona* bark is often rich in phenolics (cinchonaines a-d, quinic acid), it also contains saponins, and essential oil.



Cinchonain 1b



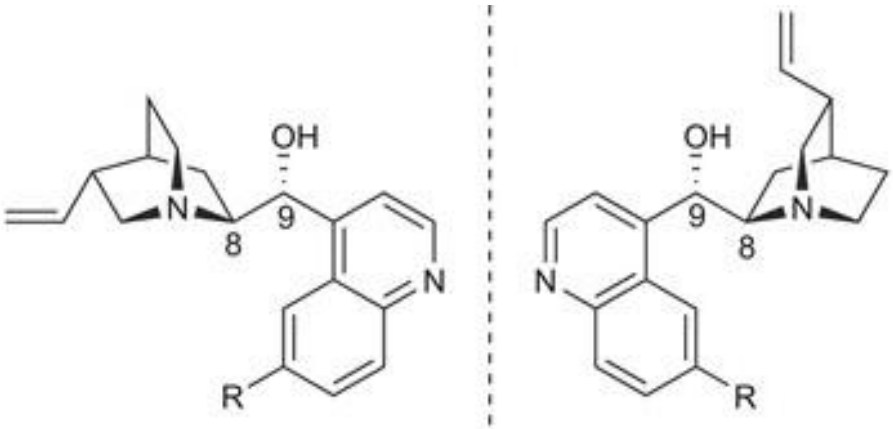


Quinic acid

The concentration of total alkaloids and quinine varies depending on the species

Species	Total alkaloids (%)	Quinine (%)
C. calisaya	3-7	0-4
C. pubescens	4.5-8.5	1-3
C. officinalis	5-8	2-7.5
C. ledgeriana	5-14	3-13

The principal alkaloids of the bark have a quinoline structure, they are stereo-isomers quinine, and quinidine and their 6'-demethoxylated homologs cinchonine, and cinchonidine



1a, R = OMe, (−)-Quinine (*QN*)
1b, R = H, (−)-Cinchonidine (*CD*)

2a, R = OMe, (+)-Quinidine (*QD*)
2b, R = H, (+)-Cinchonine (*CN*)

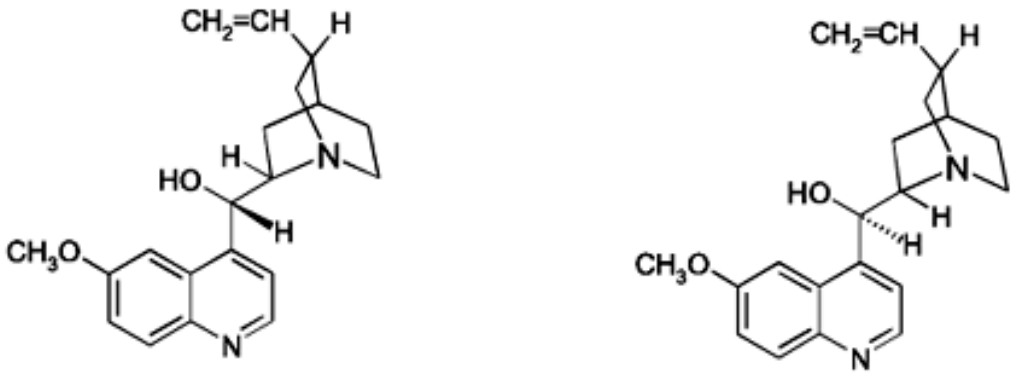


Fig. 1 - Quinine (a) and quinidine (b).

Physico-chemical Properties of the Alkaloids :

Quinine gives two series of salts, the “basic” and the “neutral” salts. “Neutral” salts are far more soluble in water than “basic” salts. This difference in solubility between the two series of salts can be the basis for the extraction and purification of quinine.

Color reactions have long been known and are still useful. Quinine and quinidine in solution in dilute sulfuric acid can be treated by bromine until the fluorescence disappears. The addition of aqueous ammonia causes the development of an emerald green color, which can be extracted with chloroform (thalleiquin test); the addition of potassium ferrocyanide in alkaline medium leads to a purplish-red color that can also be extracted with chloroform.

Pharmacological Activity :

Quinine : This alkaloid is most of all an antimalarial. It is active on the erythrolytic forms, up to the young trophozoite stage. It is active on *Plasmodium vivax, P. falciparum,* and *P. malariae.* The action of quinine on the myocardium, as well as of quinidine, but to a lesser extent, is a decrease in excitability, conductibility, and contractility. Quinine is only modestly antipyretic and analgesic; it has a weak curare-type activity on the motor end-plate.

Quinidine : This compound, essentially produced by semisynthesis from quinine, is an antiarrhythmic. By interfering directly with the electro-physiological properties of the cardiac cells, it inhibits the rapid sodium influx, decreases the rate of depolarization, and increases the refractory periods, it decreases cardiac automacity, contractility, and decreases the atrial and intraventricular conduction velocity.

Uses: *Cinchona* galenicals are only used sporadically and their use in homeopathy only accounts for a small amount of the bark, quinine and quinidine constitute the major part of the cinchona products currently used in pharmacy.

Quinine : The current indications of quinine include the following

a- The treatment of malaria attacs. The normal dose for a curative treatment in adults is per os 25 mg/kg. Quinine is contra indicated in case of A-V conduction abnormalities, and can cause at high doses, nervous and sensory side effects (partial loss of hearing, ringing in the ears and gastrointestinal distress

b- The symptomatic treatment of the fevers and aches as well as flu-like states

c- Other pharmacological uses include older medications with miscellaneous indications: cardiac rhythm abnormalitis, palpitations, precordial pain; quinine is generally combined with papaverine, phenobarbital, or hawthorn (*Crataegus*) extract.

Quinidine : The different quinidine salts are prescribed to treat cardiac arrhythmias, to maintain the sinus rhythm after normalization of atrial filtration, or tachicardia; they are also indicated in the case of atrial and ventricular extrasystoles. The physician must take into account the contraindications (wave burst arrhythmia, A-V blocks, cardiac insufficiency, hypersensitivity to quinidine) and the drug interactions which constitute further contraindications (ritonavir, antiarrhythmic or other drug interactions which cause wave burst arrhythmia, bepridil, sotalol, vincamine, sultopride) or which are subject to

precautions (urinary alkalinizing agents, digoxin, β-blockers. The principal side effects are minor gastrointestinal symptoms. Massive overdose is marked by dizziness, sensory problems (photophobia), respiratory difficulties (apnea).

Camptothecae cortex, radix, fructus

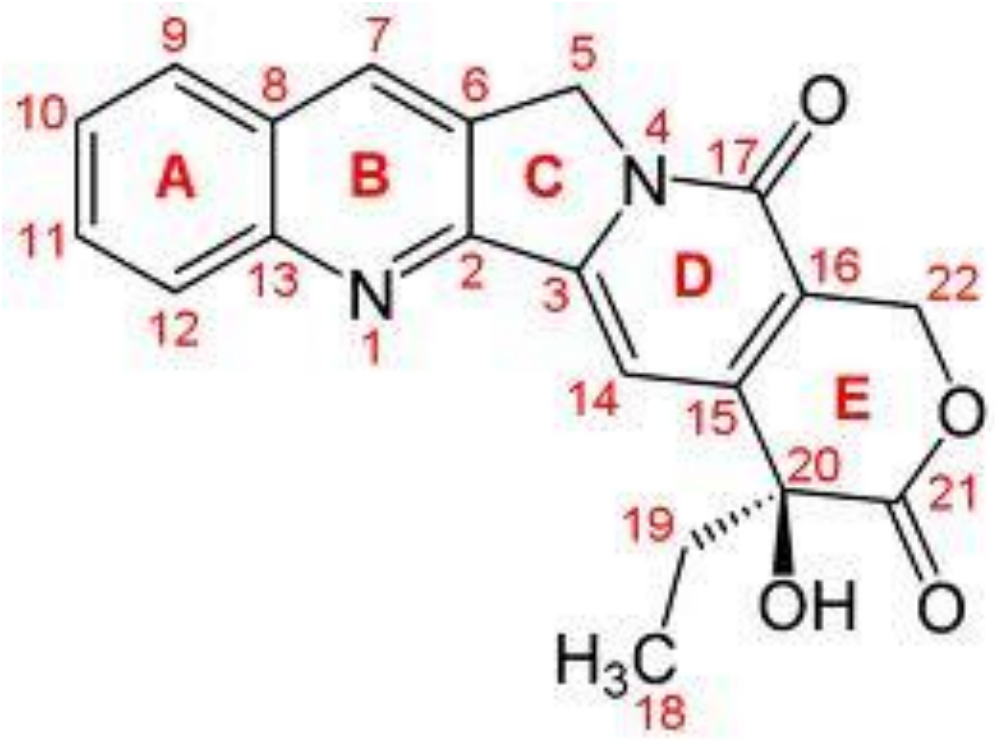
Camptotheca acuminata Nyssaceae

The trunk bark, root bark and the fruits of *Camptotheca acuminata* contain 0.001, 0.02 and 0.03% camptothecine respectively; this is a compound that has been found in some Icacinaceae roots and a Rubiaceae.

- ***Mappia foetida*** (Icacinaceae), 0.1% camptothecine

- *Merrilliodendron megacarpum* (Icacinaceae)
- *Pyrenacantha klaineana* (Icacinaceae)
- *Opiorrhiza mungos* (Rubiaceae)

Mappia foetida = Nothapodytes foetida



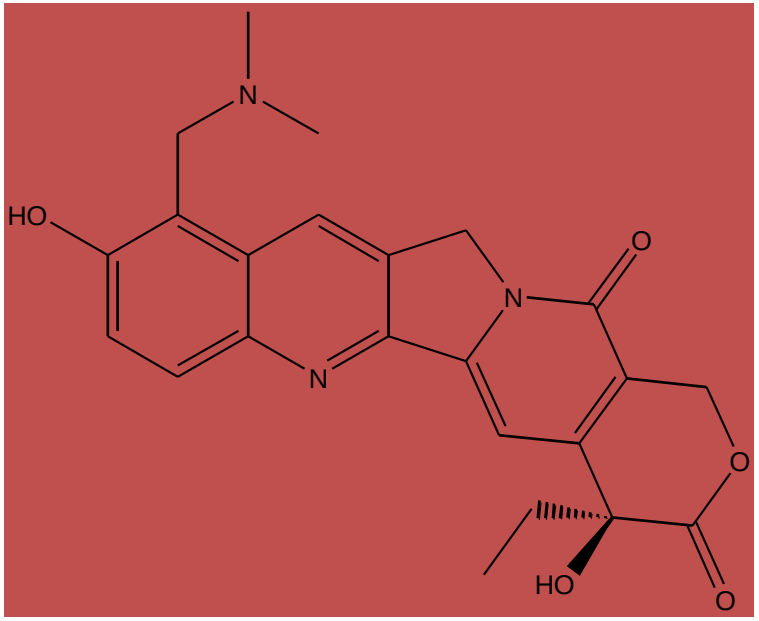
camptothecine = camptothecin = (20S)-camptothecine

Camptothecine, the neutral lactam (it does not react with the general reagents for alkaloids and does not form stable salts) is particularly insoluble in conventional solvents. It is related to the indol group.

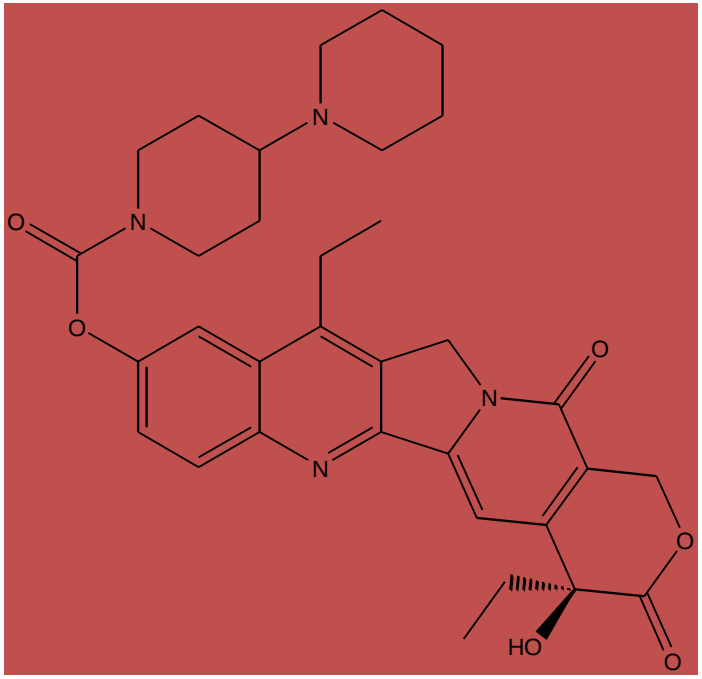
Pharmacological Activity : The recognized cytostatic and antitumor activity of camptothecine led, in the 1970's to preliminary clinical trials which were abruptly interrupted because of the substantial toxicity was observed, and in view of this, research resumed, especially to obtain synthetic analogs with reduced toxicity.

Several products are now on the focus of attention and have in fact undergone preclinical or clinical investigations :

- 9-amino-20S-camptothecine
- 9-dimethylaminomethyl-10-hydroxy-20S-camptothecine (**topotecan**)
- 7-ethyl-10-[4-(1-piperidino)-1-piperidino] carbonyloxy-camptothecine (**irinotecan**)
- 9-nitro-20S-camptothecine



topotecan



irinotecan

Uses : Irinotecan was marketed with the following indication : second-line treatment of metastatic colorectal cancer after failure of a previous valid treatment including 5-fluorouracil. Irinotecan is particularly toxic : neutropenia and in over 80% of the patients, acute cholinergic syndrome, nausea, vomiting, and delayed diarrhea

Topotecan is indicated for metastatic ovarian cancer after failure of one or more lines of chemotherapy. Because of its toxicity (severe neutropenia and thrombopenia), it is necessary to monitor hematological parameters regularly. It is also indicated for small cell bronchial cancer.

Uncariae folium

Cat's claw

Una de gato

Uncaria tomentosa (Rubiaceae)

The plant, a vine shrub, grows in Sauth America (Peru and Amazon forests.

The drug is used traditionally for 2000 years against cancer, asthma and gastric ulcer.

Uncariae folium

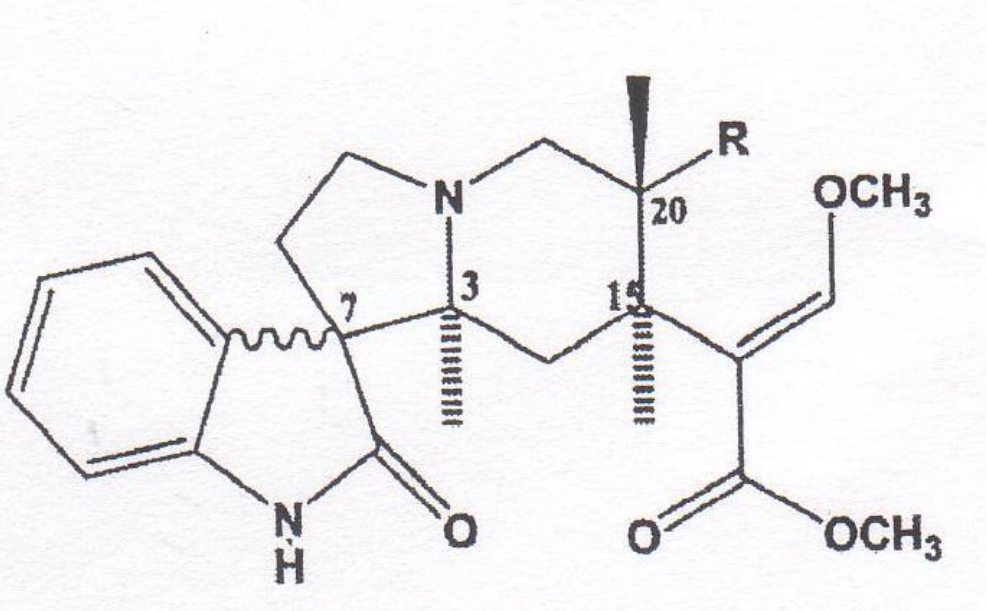
Cat’s claw

The plant contains in the leaves, and also in barks and roots indole alkaloids.

Major alkaloids : Rhynchophilline and isorhynchophylline

Uncariae folium

Cat's claw



Rhynchophylline

Isorhynchophylline

7	3S, 7R, 15S, 20R	R= ethyl
8	3S, 7S, 15S, 20R	R= ethyl
9	3S, 7R, 15S, 20R	R= vinyl
10	3S, 7S, 15S, 20R	R= vinyl

The drug is used in the therapy today especially for its antiinflammatory, immunostimulant and also antitumoral activities

Although the drug has no serious side effects and toxicity, it is not recommended in pregnant women and infants under age 3.

Cat's claw can be used in forms of herbal teas, tinctura and capsula.

Reference Books :

Main Book

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