Piperidine Alkaloids

Here we shall cover only two drugs of very limited pharmaceutical or historical interest, namely Indian tobacco and pomegranate, respectively.

- **INDIAN TOBACCO,**
  Lobelia inflata L., Lobeliaceae

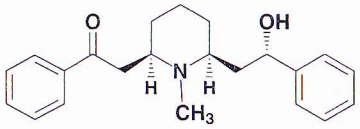
Initially used by Native peoples in North America as a substitute for tobacco, this plant appeared in Europe at the beginning of the nineteenth century, where it was recommended for the treatment of asthma (hence the alternate name asthma weed). The flowering stems were the subject of a monograph in the French Pharmacopoeia until 1972 (9th Ed.).

The Plant. Indian tobacco grows wild in the Appalachian Mountains. It is a small annual herb (20-50 cm) with erect and very ramified stems. The leaves are sessile and the blades have a dentate margin. The flowers are pale blue with foliaceous bracts, and are gathered in terminal racemes; their inflated calyces (hence the name *inflata*) become vesiculose after the floration. The commercial drug comes from North America, where it is cultivated. Generally, it consists of 50-60% stems which are angular, hollow, covered with rough hairs, and mixed with broken leaves.

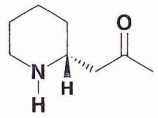
Chemical Composition. The drug contains from 0.2 to 0.5% total alkaloids, including piperidines [(–)-lobeline, *meso*-lobelanine, *meso*-lobelanidine] and piperideines. The chief constituent is (2*R*,6*S*,8*S*)-(–)-lobeline. Biosynthetically, these alkaloids may be formed by a double Mannich reaction between two molecules of phenylalanine (*via* cinnamic acid and benzoylacetate-coenzyme A) and one *N*-pimelidialdehyde cation arising from lysine *via* cadaverine.

Pharmacological Activity. Pharmacologically, lobeline is a respiratory stimulant, which enhances and accelerates the respiratory movements by improving the reactivity of the brain stem centers to carbon dioxide and also acting by a reflex mechanism involving the carotid chemoreceptors. Secondarily, it is a ganglionic stimulant and a β-adrenergic bronchodilator.

Uses. Formerly used (IM or SC) for resuscitation after asphyxia, particularly to treat apnea in newborns, lobeline is no longer used because of its substantial side effects and poor therapeutic index. Lobeline sulfate is still commercialized as an adjuvant in smoking cessation programs (*per os*). Galenicals prepared from Indian tobacco (extract and tincture) are ingredients of a few specialized medications designed for the symptomatic treatment of various bronchopulmonary ailments.



Lobeline



Pelletierine

- **POMEGRANATE,**
  Punica granatum L., Punicaceae

The pomegranate is a shrub widespread in North Africa. Its flowers, which have five to seven bright red petals, and its fruit— a rounded corticous berry with the teeth from the calyx remaining on top—make it easy to identify. The fruit pulp is the starting material for authentic grenadine syrup. The root bark, recommended in 1,550 B.C. in the Ebers Papyrus to treat worm infestations, was used as an anthelminthic, primarily a taenicide, until the first half of the twentieth century. It contains 0.5-0.7% total alkaloids: (–)-pelletierine, isopelletierine, and *N*-methylated analogs. Alongside these piperidines, note the presence of a homotropane, namely pseudopelletierine. The harmful effects due to the fraction absorbed in the intestine have led to the complete abandon (in France) of this drug and its alkaloids.

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Piperidine Amides: Piperaceae

- **BLACK PEPPER,**
  Piper nigrum L.

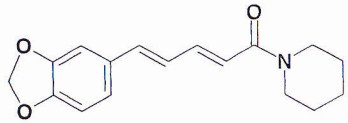
Pepper is one of the most ancient spices. Used since time immemorial in India, it was known in the Greece and Rome of antiquity. It is the fruit of *Piper nigrum*, a perennial plant originally from the south-west of India (Malabar Coast), and now cultivated in India (Kerala), Indonesia, Malaysia (Sarawak), Sri Lanka, and also South America (Brazil). The world production of pepper approaches 230,000 t (1997).

The pepper vines have a ligneous volubile stem affixed to their support by secondary branches. The leaves have an oval acute blade and are alternate. The sessile flowers have no perianth and are grouped by 20 to 30 units into dangling spikes. The fruit is a berry of 4-8 mm in diameter, which turns from green to red as it ripens.

The different kinds of pepper are well recognized.

- Green pepper consists of whole fresh berries. Generally conserved in acidic aqueous solution (or frozen, or pasteurized), it is highly aromatic.
- White pepper consists of the fruits collected at full maturity. After being soaked in water for several days, the fruit pericarp and the external layers of mesocarp are removed, and the fruits are dried.
- Black pepper is prepared from the spikes collected immediately after the first berries turn red. After drying, the fruits are separated from the stalks. The dried fruits are spherical (3-6 mm) and particularly hard. Their surface is brownish black and extremely wrinkled.

The peppery odor is due to 1 to 3.5% of an essential oil rich in terpenoid hydrocarbons, and the pungent taste to amides (5-10%). The chief constituent is piperine, an amide of piperidine and of piperic acid. The other amides are piperidines (piperanine, piperettine), pyrrolidines (piperyline), or isobutylamines; the acid which is part of their structure has a side chain of variable length (5 to 10 carbon atoms).



Piperine

Peppers (*P. longum, P. nigrum*) are frequently used in Ayurvedic medicine; in several cases, it appears that they increase the bioavailability of active ingredients with which they are mixed, perhaps by increasing intestinal absorption, or by exerting an antioxidant effect during the first pass through the liver.

Piperine is a CNS depressant and an anticonvulsant in rats. Some of its synthetic derivatives have been used in China as anti-epileptics.

Other *Piper* spp.

***Piper* spp. for Dietary Uses.** A certain number of species in this genus are used as black pepper substitutes: with few exceptions, they are consumed where they are produced and are not exported. Examples are (Indian) long pepper, *P. longum* L., *P. officinarum* C. DC., but also *P. retrofractum* Vahl., *P. saigonense* DC. or, in Africa, Ashanti pepper, *Piper guineense** Schum and Thonn., and in South America, *P. aduncum* L.

***Piper* spp. for Other Uses.** Note: 1. betel pepper or betelvine, *Piper betle* L., of India and southeast Asia, whose leaves are masticated (see areca nut, p. 871); 2. kava-kava, the dried root of *Piper methysticum* Forst., used in the islands of the Pacific Ocean to prepare an inebriating beverage (see styrylpyrones, p. 304); 3. tailed pepper or cubebs, *Piper cubeba* L. *f.* of Indonesia, with a reputation as an antiseptic, used as such in aromatherapy (do not confuse with the African cubeb, *P. clusii* C. DC.); and 4. matico pepper, *P. angustifolium* Lam., a spice and medicinal plant in South America.

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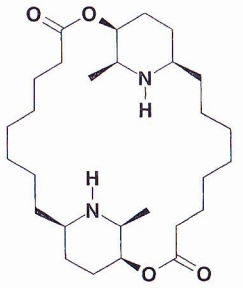
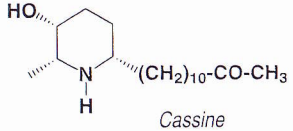
* Not to be confused with malaguetta pepper which is not a *Piper* but an Annonaceae: *Xylopia æthiopica* A. Rich. This species is not the only one to usurp the name pepper: Cayenne pepper (*Capsicum*, Solanaceae), Jamaica pepper [*Pimenta*, Myrtaceae (but true pimentos are *Capsicum*!)], knotweed (*Persicaria* [*Polygonum*] *hydropiper* [L.] Opiz), prickly ash (*Zanthoxylum* spp.), pepper tree (Schinus molle L.), and others, without forgetting, for the sake of anecdote, black cumin, the seed of *Nigella* sp. (Ranunculaceae).

Piperidine Alkaloids
not from the Metabolism of Lysine

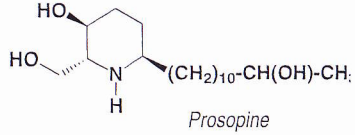
This is a limited group comprising piperidines substituted by a short aliphatic side chain (coniine, pinidine) or a long one (carpaine, cassine, prosopine). These alkaloids are elaborated from a polyacetate unit which incorporates a nitrogen atom; in the case of coniceine, there is a transamination between alanine and 5-keto-octanal formed from capric acid. This biosynthetic route also exists in other series (e.g., alkaloids of the Himantandraceae) as well as in some insects (ants, ladybugs). There is no therapeutic interest in these alkaloids, even though some of them are not devoid of activity (amebicidal and bradycardic activity of carpaine from the leaves of *Carica papaya* L.). Some are toxic, for example coniine and coniceine from poison hemlock.



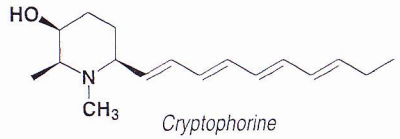
Carpaine



Cassine



Prosopine



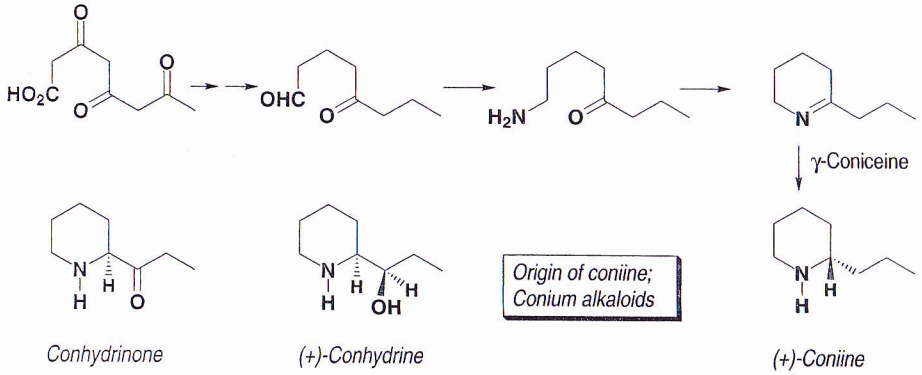
Cryptophorine

• POISON HEMLOCK, *Conium maculatum* L., Apiaceae

Famous for having caused the death of Socrates, the fruit of hemlock was used for two millennia for its antineuralgic properties and was official in France until 1949. Although the use of the plant has now been abandoned, it ought to be known because of its toxicity.

The Plant and its Composition. A tall biennial herb (1-2 m), hemlock has a hollow, grooved stem, marked at the base with purplish-red spots; the sheathing leaves have a tripinnatisect blade with acute lobes. The umbel has an involucre and involucels consisting of two to six short curved bracts. When crushed, the whole plant releases an unpleasant "mouse" odor . The species is not rare: it is found in piles of rubble and along country roads in all of Europe.

The chief alkaloids found in the plant are coniine (a volatile alkaloid that can be steam distilled), γ-coniceine, conhydrine, *N*-methylconiine, *N*-methylconhydrine, pseudoconhydrine, and conhydrinone. The ripe fruit can contain more than 1.5% alkaloids located in the epicarp and endocarp, and mostly represented by coniine (but the concentration varies greatly as a function of the time of collection). In the vegetative parts, γ-coniceine is the chief constituent, especially at the beginning of the growth phase (furthermore, it is six to eight times more toxic).



Toxicity. Coniine blocks neurotransmission in ganglions and neuromuscular junctions. The classical example of its toxicity is the death of Socrates: "But he walked about, until he said that his legs were getting heavy; then he lay down upon his back, as he had been directed, and the man at intervals examined him, feeling of his feet and legs. Then, pressing hard against his foot, he asked him if he felt it. Socrates said, 'No'; and after that he did it to his shins, and moving upwards, showed us that he was growing cold and stiff, and, touching Socrates, he said that when it reached the heart, he would be gone. [...] but in a little while there was a convulsive movement, after which the man uncovered him. His eyes were fixed." (Plato, Phaedo, LXVI, translated into English by Lane Cooper (1941), p. 192, Cornell University Press, Ithaca, New York).

The description provided by Plato is a good illustration of the decrease in mobility and sensitivity, the progressive paralysis of the muscles, and the progressive cooling of the extremities. On the other hand, the dizziness, mydriasis, tonic and clonic convulsions that are also symptoms of the intoxication are not mentioned; moreover, Socrates does not lose speech (an instant before his death, he expresses concern for

his debts to Asclepios); if we believe some authors, the deadly beverage brought "all crushed in a cup" by Crito's slave must have contained some opium.

Human intoxications by poison hemlock, which is sometimes confused with chervil, require rushing the victims to a hospital emergency room. The case reports of poisoning published most recently describe lethargy as the main symptom (the patient falls asleep or loses sensitivity).

All animals can be intoxicated by the plant, but their susceptibility varies with the species. Poison hemlock can induce congenital malformations in pregnant females.

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