Animal experiments show that huperzine A has an interesting potential for the treatment of poisoning by soman and other chemical weapons, and that it counteracts the memory loss caused by scopolamine.

According to clinical trials conducted in China, huperzine A is not very toxic and it is thought to have some potential for the treatment of memory loss; it has also been tested in the treatment of myasthenia.

The action of huperzine A is more prolonged than that of physostigmine and it is devoid of the side effects of tacrine (currently used, like donepezil and rivastigmine, to treat Alzheimer's disease). More clinical trials are in the planning stages. Although it has no immediate clinical applications, huperzine is an interesting structural model for the design of molecules with a high affinity for acetylcholinesterase. Synthetic analogs have also been tested and research is in progress in animals, mainly in the context of learning and memorization.

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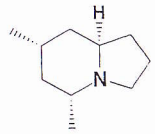
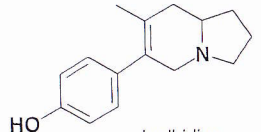
Indolizidine Alkaloids

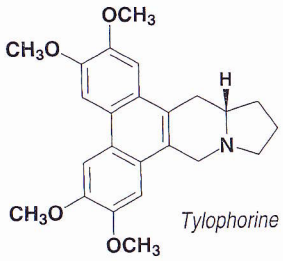
Indolizidine alkaloids are toxic principles occurring in the skin of certain Amphibia (e.g., pumiliotoxins) and are rather rare in plants: alkylindolizidines and bisindolizidines of *Dendrobium* (Orchidaceae), arylindolizidines of certain *Ipomœa* (Convolvulaceae). Although no plant producing alkaloids derived from this bicyclic heterocycle is currently used in therapeutics, compounds such as swainsonine and castanospermine are undoubtedly interesting because of their ability to inhibit glycosidases. We shall not cover here the phenanthroindolizidines of *Tylophora* and of some of the Moraceae (arising from the mixed metabolism of tyrosine and ornithine), the alkaloids of the Elaeocarpaceae, or the alkaloids of *Securinega* (Euphorbiaceae).



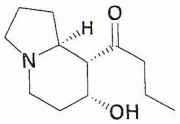
Dendroprimine



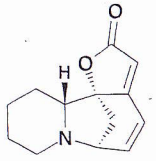
Ipalbidine



Tylophorine

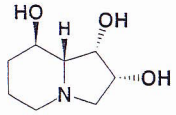


Elaeokanine C

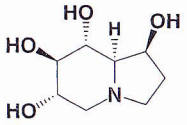


Securinine

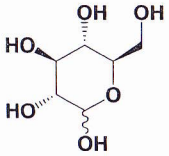
In the past few years, polyhydroxylated indolizidine derivatives have been the focus of attention. Like polyhydroxypiperidines, free necines, or polyhydroxy-*nor*tropanes, most of them were isolated only recently: they are highly water soluble, therefore they are not extracted by the conventional alkaloid isolation procedures; instead, mixtures of alcohols and water must be used. They can be purified by chromatography on ion exchange resins and they are often separated by preparative TLC. They do not react with the classic alkaloid reagents, but under certain conditions, they can be detected after the formation of pyrroles. Methods based on their glycosidase-inhibiting activity can also be used. The best quantitation method is by GC analysis of their trimethylsilyl derivatives. Biochemically, they are derived from L-lysine, *via* pipecolic acid; the other carbon atoms of the pyrrolidine ring are thought to come from a molecule of acetyl-CoA.



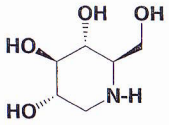
Swainsonine



Castanospermine



Glucose



Deoxynojirimycine

• (–)-SWAINSONINE AND (+)-CASTANOSPERMINE

(–)-Swainsonine has been isolated from several Fabaceae: *Swainsona canescens* (Benth.) A. Lee of Australia, *Astragalus lentiginosus* Dougl. ex G. Don and *Oxytropis sericea* Nutt. of North America; it is also produced by fungi (*Rhizoctonia, Metarhizium*). (+)-Castanospermine is tetrahydroxylated, and has been isolated from the seeds of another Australian Fabaceae introduced in California (*Castanospermum australe* A. Cunn.) and from the leaves and pods of various species of South American *Alexa*.

These two alkaloids are held responsible for the toxic manifestations observed in cattle. In the case of swainsonine, these symptoms (loss of motor coordination, gait abnormalities, and other neurological problems), due to axon alterations in the central nervous system. They are reminiscent of those observed in case of congenital deficiency of lysosomal α-D-mannosidases, whereas the intoxications due to castanospermine are essentially characterized by digestive symptoms. Both alkaloids are potent inhibitors of glycosidases, especially the glycosidases responsible for structural modifications of the oligosaccharide moiety of glycoproteins, with these modifications being required for biological activity: mannosidases (inhibited by swainsonine) and glucosidases (inhibited by castanospermine). Thus, they are valuable tools for the study of the formation and role of glycoproteins in biological systems. The close structural analogy with the

piperidines like deoxynojirimycin *, isolated from *Morus* spp. Biologically, these alkaloids might have an ecological role (plant-insect relationships).

Pharmacologically, compounds like swainsonine have many potential activities: inhibition of tumor proliferation and dissemination (antimetastatic), immuno-regulation, stimulation of interleukin-2 production and T lymphocyte proliferation, and more. Swainsonine has undergone at least one phase I clinical trial.

Castanospermine, a mildly toxic compound (LD50 >0.5 g/kg in mice) displays activity against the human cytomegalovirus and non-negligible activity against retroviruses. Its ability to interfere with the function of the protein envelope of the *human immunodeficiency virus* (= HIV virus) has been demonstrated: it induces substantial perturbations in the synthesis of the glycoproteins of the envelope, which plays a fundamental role in the expression of the cytopathogenicity (CD4+ lymphocytes). *In vitro*, castanospermine and AZT (= *3'-azido-3'-deoxythymidine*) display synergistic inhibition of the HIV virus (types 1 and 2). The low lipo-solubility has led to the synthesis of epimers and structural analogs, particularly derivatives acylated at C-6 such as 6-butanoylcastanospermine: because it enters the cell much better, it is a much more efficacious inhibitor of viral replication. It has been tested in animals as an inhibitor of transplant rejection.

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* A deoxynojirimycin derivative was marketed just recently (October 1998) as an oral antidiabetic drug (prescribed for non-insulin-dependent diabetes that is not fully controlled by diet alone).