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Alkaloids with Miscellaneous Structures

Derivatives of Spermidine and Spermine

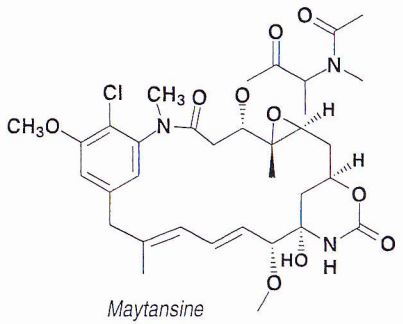
These polyamines formed by the transfer of one (or two) propylamine residue(s) onto putrescine (probably *via* decarboxylated *S*-adenosylmethionine) are widely occuring in plants. They are found in the free state or as amides (e.g., tricoumaroylspermidine of hawthorn flowers). In a smaller number of species, they are the precursors of macrocyclic compounds which react like alkaloids: at least one of the nitrogen atoms reacts with the carboxyl group of an acid, frequently a cinnamic acid (lunarine, pleurostyline, periphylline, homaline). Their pharmacological interest is unclear at the present time.

Macrocyclic Peptides, Peptide Alkaloids

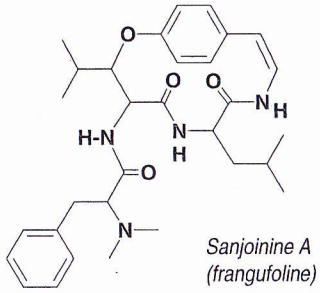
These compounds behave themselves more like peptides than alkaloids, and form a rather limited group of substances isolated from the Celastraceae, Rubiaceae, but most of all, from the Rhamnaceae, including *Ceanothus, Rhamnus*, and *Ziziphus* species. Customarily, the group of "peptide alkaloids" is limited to 10- or 12-membered macrocycles, closed onto the benzene ring in the 1,3-or 1,4-positions.

Thus, we shall exclude the polypeptides responsible for the toxicity of amanitas (*phalloides, verna, virosa*) and found in some lepiotas (*helveola*): amatoxins (octapeptides), phallotoxins (heptapeptides), and virotoxins (nonapeptides). These are not regarded as alkaloids, and moreover, their structure, effects, and mechanism of action exceed the scope of this book.

No compound in this group is currently used, even though some of them do have some activity (e.g., sedative properties of the tripeptides of *sanjoin* and *daechu*, two drugs from the Chinese Pharmacopoeia derived from different *Ziziphus*).

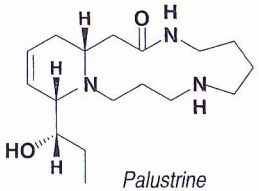


Maytansine



Sanjoinine A
(frangufoline)

7-Hydroxypleurocorine



Palustrine

- **JUJUBE TREE,**
  Ziziphus jujuba Miller (= Z. *vulgaris* Lam.), Rhamnaceae

The jujube tree is small and often thorny. Its fruits are round or ovoid, red when ripe, and edible. Native to China, the jujube tree is acclimatized in southern Europe and in the southern United States. It contains triterpenoid acids and saponins; the seeds contain saponins and flavonoids; the leaves contain saponins and isoquinoline alkaloids. The stem bark and seeds of several species in the genus contain small quantities of peptide alkaloids.

The jujube tree appears on the French Pharmacopoeia liste A of medicinal plants (10th Ed., IV.7.A). The 1998 French Explanatory Note specifies that the part that is used is the fruit without the seed. For the fruit, the following indication may be claimed: traditionally used topically (collutoria, lozenges) as an antalgic for disorders of the mouth, pharynx, or both.

The jujube fruits and the seeds of the thorny varieties (*sanjoin* [Korea], *suanzaoren* [China]) are used in China where, according to tradition, the seeds must be roasted before use as a sedative and for the treatment of insomnia. Interestingly, one of the alkaloids in the drug—sanjoinine A (= frangufoline)—is degraded upon heating to sanjoinine-Ah1, which is much more active, at equivalent doses, than

sanjoinine A. Other authors describe the use of the seeds of thorny varieties for the same indications (*suanzaoren*).

Maytansinoids

Initially referred to—improperly—as ansamacrolides, these substances are closely related to the ansamycines (antibiotics elaborated by micro-organisms).

Isolated from various African Celastraceae in the genera *Maytenus* and *Puterlickia*, these "alkaloids"—contamination by fungal metabolites?—have a complex structure, characterized by a 19-membered macrocycle: a long aliphatic chain comprising an amide bond links two non-adjacent carbon atoms of a chlorinated aromatic ring. These compounds (maytansine, maytanbutine, maytanprine) are of interest because of their antitumor activity: they are active against sarcoma 180, on leukemia L1210 and P388, and on other models, and they interfere with cell growth at concentrations near 1 ng/mL. Their low levels in the plants and their toxicity have inspired many synthetic attempts.

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