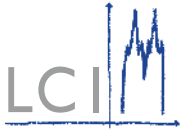


# Tropane Alkaloids and Calystegines

Occurrence, Toxicity, Analytical Methods, Maximum Levels



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## A. What are tropane alkaloids and calystegines?

Tropane alkaloids (TA) are a class of alkaloids and count among the secondary metabolites. They are naturally generated by certain plants. The term "tropane" is derived from atropine (a racemate comprised of (R)- and (S)-hyoscyamine), the active substance of deadly nightshade (*Atropa belladonna*) in whose molecule it is a structural element (see figure 1-2). The class of TA comprises more than 200 compounds which are divisible into various subclasses. They are composed of an azabicyclo[3.2.1] octane ring structure, the tropane skeleton being the most frequently occurring and

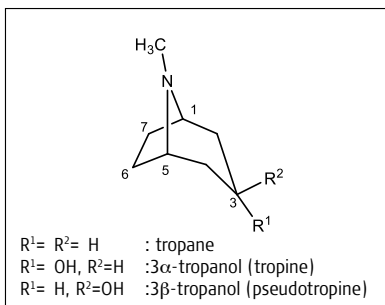


Figure 1 - Structural formulas of tropane and its derivatives

the nitrogen being methylated. A prominent member of the TA family is cocaine, a derivative of ecgonine found in the coca plant (*Erythroxylum coca*).

The calystegines, not discovered till the 1980s, belong to the class of nortropane alkaloids with a low molecular weight and are very polar due to having a minimum number of 3 hydroxyl groups. Around 14 calystegines are currently known (figure 3).

## B. Where do TA and calystegines occur?

TA are formed in plants belonging to the families Brassicaceae, Moraceae, Erythroxylaceae (coca plant), among other groups. They widely occur in the family Solanaceae (e.g. mandrake, black henbane, deadly nightshade, Devil's snare), mostly as esterified tropanol compounds. The

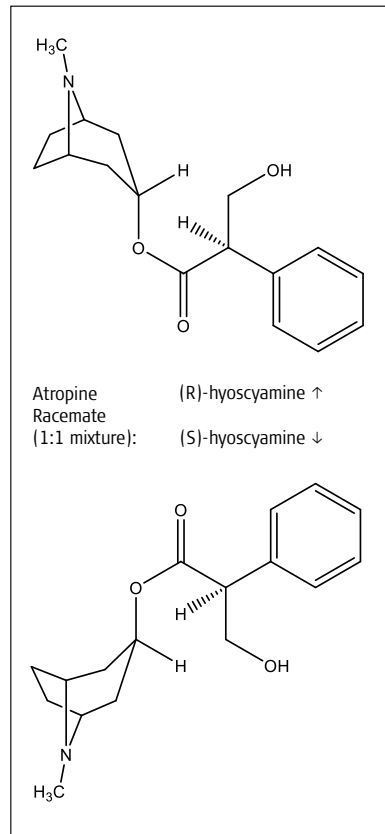


Figure 2 - Structural formulas of atropine

tropane alkaloids are biosynthesised from ornithine and arginine in the plant. The TA are mostly contained in all plant parts in varying concentrations. (-)-Hyoscyamine and (-)-scopolamine (especially in *Brugmansia*, angel's trumpets) are the most frequently occurring and best researched TA compounds.

Calystegines also occur in the Solanaceae family. Particularly in edible plants such as *Solanum tuberosum* (potato), *Capsicum annuum* (peppers, pepper), *Solanum melongenes* (aubergine), and *Convolvulaceae* (incl. sweet potato) they are naturally occurring, where the pattern of occurrence and concentration of calystegines is characteristic of the respective plant part. For example, in potatoes only the calystegines A<sub>3</sub>, B<sub>2</sub>, B<sub>4</sub> are to be found, whereas in aubergines, pepper, and sweet potatoes it is calystegine B<sub>2</sub> that is found.

## C. How do TA and calystegines get into foodstuffs?

Tropane alkaloids are undesirable in foodstuffs and feedstuffs and occur as a contaminant of the harvesting process by way of weeds. Conventional processing stages, such as those for cereal grains, are mostly unable to completely remove contamination stemming from the whole plant, parts of the plant, or its seeds. The current contamination of cereal grains in the EU is mostly attributable to *Datura stramonium* (Devil's snare) and *Convolvulus arvensis* (field bindweed). Outside the EU, contamination was observed in peas, soya beans, and French beans via the Solanum species *S. nigrum* (black nightshade), *S. viarum* and *S. torvum* (prickly nightshade). Maize, millet, and wheat can be contaminated by the invasive and widely occurring *Solanum elaeagnifolium*.

The TA get into the foodstuff after the contaminated grain has been processed (e.g. grinding). Since most TA are heat-resilient, the contamination level can still be high even after the product has been heat-treated. Corresponding concentrations detected in foodstuffs range from < 1 to 100  $\mu\text{g}/\text{kg}$ . By contrast, calystegines are only found in plants in which they themselves are also generated. In the edible part of the plant, corresponding concentrations can range from 1 to 100 mg/kg.

## D. Can TA and calystegines pose a health risk?

Research is mostly focused on the toxicological impact of the TA atropine and scopolamine. From the Renaissance period to the present day, extracts of deadly nightshade (belladonna) have been used for pupil dilation. Moreover, since TA are hallucinogenic as of a certain dose/mixture, they are sometimes also used illicitly (i.e. drug abuse).

The tropane alkaloids atropine and scopolamine are antimuscarinic agents, i.e. antagonists to the muscarinic acetylcholine receptor, where only the (-)-hyoscyamine

from the racemate mixture (atropine) has an anticholinergic effect. This means they inhibit the parasympathetic nervous system (vegetative NS) and are active in the central nervous system. The effects most commonly observed include pupil dilation, xerostomia (dry mouth), decreased urine production, cardiac rhythm disturbance, reduced sweat production, and increased body temperature. Greater doses may cause death from cardiac arrest. Due to their sugar-like structure, calystegines are  $\alpha$ -glucosidase inhibitors and act in the intestinal tract, leading to a decreased resorption of carbohydrates.

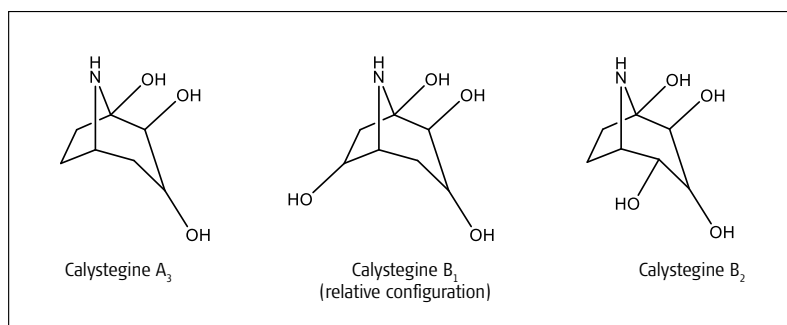


Figure 3 - Structural formulas of calystegines A<sub>3</sub>, B<sub>1</sub>, and B<sub>2</sub>

Correspondingly, the glucose concentration level in the blood (blood sugar) rises less strongly under the influence of  $\alpha$ -glucosidase inhibitors after a meal, opening up the possibility that calystegines might be used to treat diabetes mellitus type II. Intoxications with calystegines have thus far not been observed in humans. The toxicology of other TA is largely unstudied, hence EFSA (European Food Safety Authority) has for the time being classed all TA as being toxicologically relevant.

#### E. How are TA and calystegines analysed?

Two multi-analyte LC-MS/MS methods have been developed for analysing TA. After performing an extraction, 24 TA and 6 calystegines were separately analysed in two different ways. Quantification was performed via external calibration curves using matrix-adjusted standards (MMS).

To balance out the matrix effect, additional isotope-marked (-)-hyoscyamine and (-)-scopolamine are dosed as internal standards.

#### F. Do maximum levels exist for TA and calystegines in foodstuffs?

Under Commission Regulation (EU) 2016/239, a maximum level of 1.0  $\mu\text{g}/\text{kg}$  has been set for the most studied tropane alkaloids (-)-hyoscyamine and (-)-scopolamine in foods. This applies to processed cereal-based foods and baby foods for infants and young children, containing millet, sorghum, buckwheat or their derived products.

No maximum levels are currently set for the TA subclass of calystegines. SW

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