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*Polyhydroxy*nor*tropanes*

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Pyrrolizidine Alkaloids

1. INTRODUCTION

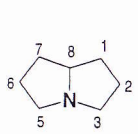
Pyrrolizidine alkaloids have essentially been isolated only from the Asteraceae and Boraginaceae. In both families, they were found in many genera: *Adenostyles, Doronicum, Eupatorium, Farfugium, Petasites, Senecio, Tussilago*, and other Asteraceae, and *Alkanna, Amsickia, Anchusa, Cynoglossum, Echium, Heliotropium, Lithospermum, Myosotis, Symphytum, Trichodesma*, and other Boraginaceae. They have also been characterized, although more sporadically, in about ten other families, including the Apocynaceae, Euphorbiaceae, Fabaceae (*Crotalaria, Cytisus*), Orchidaceae, Poaceae, and Santalaceae.

Therapeutic interest in these alkaloids is almost nil, despite the fact that some are cytostatic *in vitro*. In fact, it is their toxicity which is the focus of attention. Indeed, they are responsible for serious toxic symptoms observed sporadically in humans (careless use of so-called medicinal plants, ingestion of contaminated cereals), and more often in animals. Most of the alkaloids in this group are also mutagens and induce hepatic tumors. Such hepatotoxic and carcinogenic compounds occur in plants that are recommended in traditional medicines, but have no demonstrated therapeutic benefits (coltsfoot, comfrey, borage, crotalaria, heliotropes, hound's tongue, *Senecio*), therefore using these plants seems unwise.

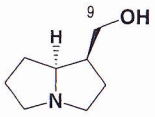
2. GENERAL STRUCTURE OF THE ALKALOIDS

The vast majority of these alkaloids are esters of amino alcohols and of one or two aliphatic carboxylic acids.

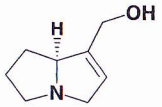
The amino alcohols, also known as necines, are derivatives of pyrrolizidine, in other words azabicyclo[3,3,0]octane. The configuration at C-8 varies, and is most often H-8α. The ring is not always unsaturated at C-1, but it is always substituted by a hydroxymethyl group at this position. Several types of necines can be distinguished as a function of the degree of hydroxylation of the molecule: limited to the primary alcohol of the hydroxymethyl group alone (isoretronecanol, supinidine, laburnine), or with an added secondary alcohol function at C-7 (retronecine, heliotridine, platynecine), and in rare cases, with a third hydroxyl group at C-2 (rosmarinecine) or at C-6 (crotanecine). In some cases, oxidation at C-8 leads to the opening of the bicyclic structure (otonecine).



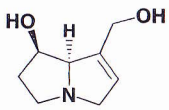
Pyrrolizidine



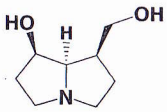
Isoretronecanol



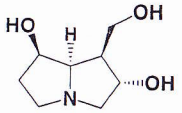
Supinidine



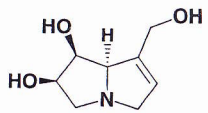
Retronecine



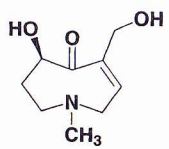
Platynecine



Rosmarinecine

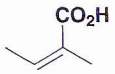


Crotanecine

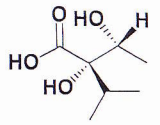


Otonecine

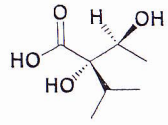
The acids (necic acids in the broad sense of the term) are C_5, C_7, C_8, or C_{10} aliphatic acids. They are sometimes simple (angelic or tiglic acids with five carbons), but they are most often specific to this type of alkaloid, whether they are C_7 hydroxyisopropylbutanoic monocarboxylic acids (lasiocarpic, trachelanthic, viridifloric acids), C8 dicarboxylic acids (monocrotalic acid), or dicarboxylic C10 acids (senecic, jacobinecic, retronecic acids).



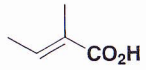
Angelic acid



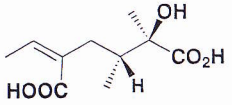
(+)-Trachelanthic acid



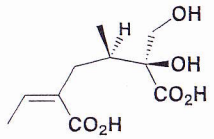
(–)-Viridifloric acid



Tiglic acid



Senecic acid

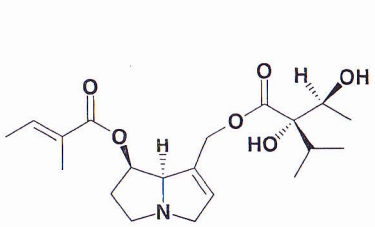


Isatinecic acid

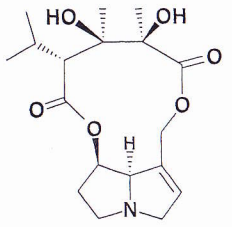
There are many possible combinations of the amino alcohols and necic acids:

- esters of monocarboxylic acids. These compounds are mono- or diesters, and their C-9 hydroxyl group is esterified by a hydroxyisopropylisobutanoic acid (lycopsamine, intermedine). When a second ester function is present, either angelic or tiglic acid esterifies the C-7 hydroxyl group of the amino alcohol (echimidine, symphytine);
- macrocyclic diesters. The pyrrolizidines that are 7,9-diols may be esterified by a dicarboxylic acid, which leads to a macrocycle (senecionine, monocrotaline).

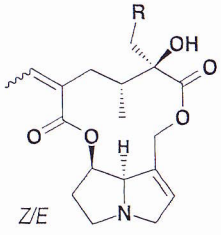
The mono- and diesters of monocarboxylic acids are characteristic of the Boraginaceae, and the macrocyclic diesters are, for the most part, constituents of the



Symphytine

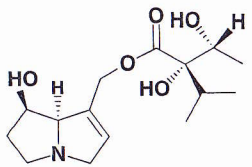


Trichodesmine

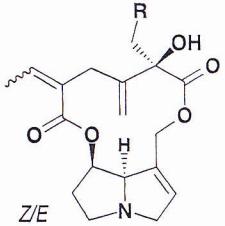


Z/E

Z
R = H : *Senecionine*
R = OH : *Retrorsine*

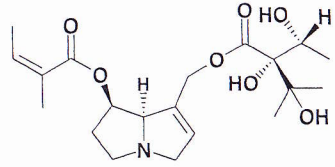


Intermedine



Z/E

Z
R = H : *Seneciphylline*
R = OH : *Ridelliine*



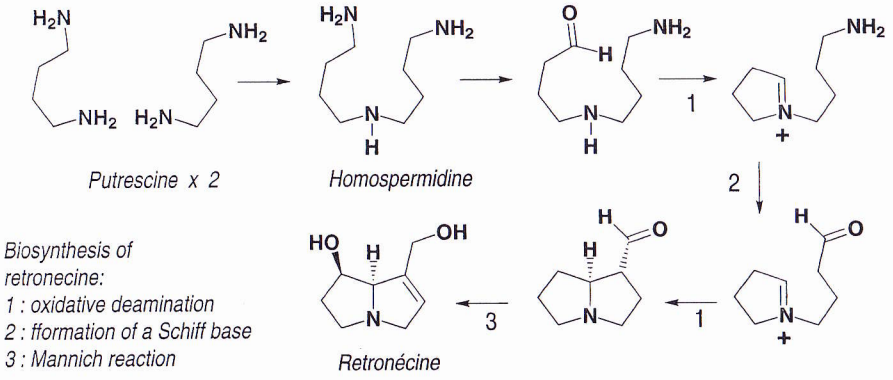
Echimidine

Asteraceae. In exceptional cases, the amino alcohols can be esterified by aromatic or arylalkyl acids (Orchidaceae).

From an analytical standpoint, it is possible to characterize these compounds by oxidizing them (chloranil, hydrogen peroxide), then by reacting the resulting pyrrole with *p*-dimethylaminobenzaldehyde (condensation in the α position relative to the nitrogen atom). Since alkaloids often occur as *N*-oxides, their transformation into pyrroles requires using a ferrous complex in the presence of ascorbic acid. Alkaloid quantitation is done by HPLC or GC.

3. BIOSYNTHESIS

A detailed study of the biosynthesis of necines has shown that the formation of these compounds does not go through the (theoretical) condensation of one molecule of putrescine with its deamination product. In fact, the NAD^+-dependent condensation of two molecules of putrescine (or of one molecule of putrescine and one molecule of spermidine) yields a symmetrical intermediate, namely homospermidine (= *N*-[4-aminobutyl]-1,4-diaminobutane). The latter is subsequently cyclized according to a classic sequence: oxidative deamination, formation of a Schiff base, another oxidative deamination, and intramolecular Mannich reaction.



4. TOXICITY

A. For Animals

Although the Boraginaceae and Asteraceae species containing pyrrolizidine alkaloids are not normally grazed by animals, the absence of other food, and especially contamination of fodder and silage can lead to accidental consumption, and therefore to chronic or acute intoxications, for which no truly efficacious treatment is possible. The toxicity is chiefly hepatic: swelling of the hepatocytes,

centrolobular necrosis, caryomegaly, thrombosis of the hepatic vein, increase in bilirubinemia (with jaundice as a result), and liver failure. The symptoms of intoxication can vary as a function of the structure of the alkaloids at fault, the subacute or chronic character of the intoxication, and the animal species. For example, horses display mainly a neurological syndrome: the animal presses its head against obstacles and makes random movements. This syndrome is linked to an increase in ammoniemia subsequent to the alteration in hepatic function.

Many plant species can cause these intoxications, including *Senecio jacobaea* L. (Europe, North America, New Zealand) and other species in the genus (e.g., *alpinus* Scop., *douglasii* DC., *lautus* Sol.); various *Crotalaria* (North America, South Africa) which cause poisonings marked by hepatic *and* pulmonary toxicity; *Heliotropium europaeum* L., which is a real danger to swine and poultry in Australia because it contaminates grain; and *Echium* sp. (Australia). Fodder contamination has decreased, at least in western Europe, with the use of weed-killers selective for the Dicotyledons.

B. For Humans

The various plants in this group have apparently never caused any acute intoxication in humans. They are, however, responsible for chronic intoxications marked by loss of appetite, abdominal pains and swelling, ascites, and hepatomegaly. Biochemically, there is a substantial increase in transaminases, alkaline phosphatase, and γ-glutamyltransferase. A biopsy reveals a veno-occlusive syndrome: the centrolobular veins are obliterated by reticulated fibrosis.

Such chronic intoxications due to pyrrolizidine-containing plants have been reported in areas of the world where these plants are traditionally used as remedies. For example, in Guadeloupe, the flowers of what the French call "*thé à sonnettes*" (= literally tea with small bells), *Crotalaria retusa* L., are traditionally used for the flu or pulmonary ailments. In the United States and Europe, comfrey preparations (*Symphytum officinale* L.) are traditionally used for therapeutic effects that have yet to be substantiated. The veno-occlusive syndrome can also be the consequence of drinking infusions of misidentified plants (e.g., not *Gnaphalium* but *Senecio*, not *Tussilago* but *Adenostyles*) or adulterated plants (*Petasites*). In 1988, the *World Health Organization* (= WHO) documented 280 species in 40 different genera containing pyrrolizidine alkaloids. About sixty of these species are considered "medicinal plants" in the countries where they grow, therefore it is likely that the poisonings that they cause are underreported in the international literature.

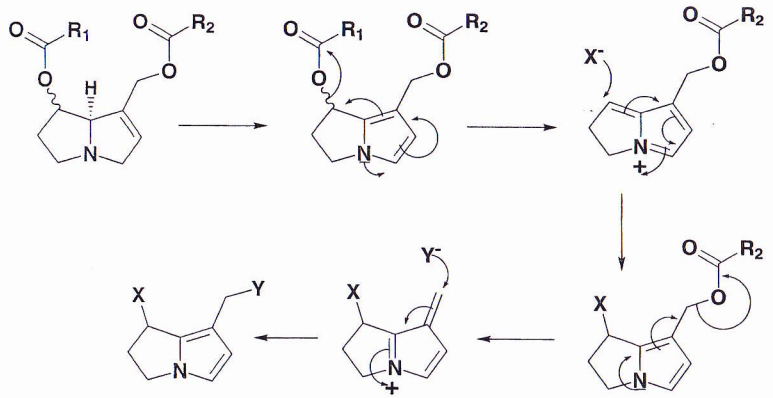
The vegetables that elaborate pyrrolizidine alkaloids can become a public health problem when they contaminate grains. The latest report of outbreak of poisoning was apparently in 1992 in Tadjikistan.

C. Structure and Toxicity

All of the pyrrolizidine alkaloids do not have the same toxicity. As a general rule, the monoesters are less toxic than the acyclic diesters, which are themselves

less toxic than the macrocyclic diesters. To be toxic the alkaloid must be dehydrogenated at C-1 and C-2, and at least monoesterified. The true culprits are, beyond any doubt, the pyrrole derivatives resulting from the microsomal oxidation of the pyrrolizidines in the liver; these pyrrole compounds react as alkylating agents with biological nucleophiles such as nucleic and protein macromolecules.

Indeed the administration of dehydro-pyrrolizidines to rats induces the same toxic symptoms as those caused by the alkaloids as they occur in the plant; in addition, it proves that a bond is formed with the proteins and DNA.



Oxidation of the pyrrolizidines

Experiments in rats have shown that several alkaloids (retrorsine, senkirkine, monocrotaline, lasiocarpine, symphytine) and a number of plants (*Tussilago farfara* L., *Symphytum officinale* L., *Petasites japonicus* Maxim.) induce hepatic tumors when they are administered orally on a regular basis. The mutagenic and teratogenic properties of several alkaloids in this group have also been shown experimentally. At the other end of the range, an alkaloid such as platiphylline is not toxic and can be considered as an antispasmodic and a mydriatic. Others, such as indicine-*N*-oxide, are anticancer agents in experimental conditions, but cannot be used in humans.

5. CHIEF DRUGS CONTAINING PYRROLIZIDINE ALKALOIDS

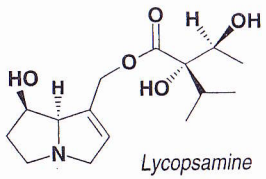
• Borage,
Borago officinalis L., Boraginaceae

The dried borage flower and flowering tops are listed in the 10th edition of the French Pharmacopoeia.

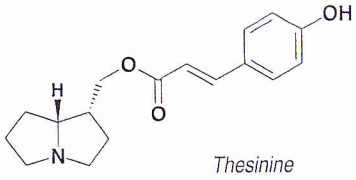
This annual plant, which is thought to be indigenous to the Near East, is common in all neglected lands; it is currently cultivated to produce seeds, which are used as a

source of oil containing unsaturated fatty acids (see p. 157). It is easy to identify by its leaves, which are covered with rough hairs, its bright blue flowers with hairy sepals, and its connivent stamens and black filaments with a horn-shaped appendix.

The stems and leaves contain mucilage (11%), and, as determined by GC, 2-8 mg/kg of pyrrolizidine alkaloids: lycopsamine, 7-acetyl-lycopsamine, amabiline, supinine, and traces of intermedine and its 7-acetylated derivative. Alkaloids also occur in the flowers as an unsaturated derivative, namely thesinine. Thesinine is the principal alkaloid in borage seeds.



Lycopsamine



Thesinine

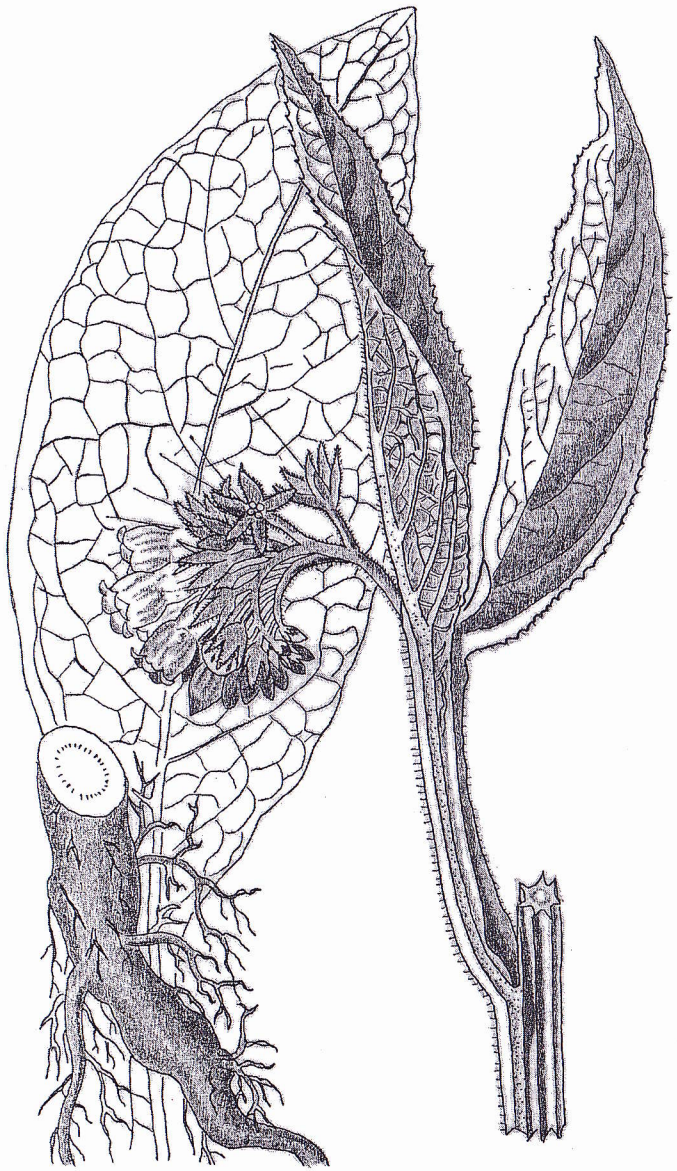
The identification of the official drug entails a morphological examination, a microscopic study (to show the presence of many trichomes with cystoliths releasing carbon dioxide upon treatment with lactic acid), and a characterization of the alkaloids. The constituent sugars of the mucilage are characterized by TLC after extraction and acidic hydrolysis.

Apparently there has been no pharmacological study of this drug reputed to be a "sudorific", emollient, and diuretic. In France, drugs based on borage flowers may be marketed and may claim the following indications (orally): traditionally used to treat acute benign bronchial disease and to enhance the renal elimination of water [French Expl. Note, 1998]. The German Commission E monograph states that the activity attributed to the drug has not been documented, therefore borage leaf and flower must not be used in therapy. This position is all the wiser because, as emphasized by De Smet, four cups of borage infusion per day can contain 64 µg of pyrrolizidine alkaloids, which is six times the tolerable intake for coltsfoot leaf infusion (see p. 842).

• Common Comfrey,
Symphytum officinale L.
(= *S. consolida* Gueldenst. ex Ledeb.), Boraginaceae

The Plant. This large (0.5-1 m) perennial plant has a voluminous and fleshy rhizome, large leaves decurrent on a great part of their length, and angular stems covered with stiff hairs. The flowers are white, pinkish, or purplish, and grouped in scorpioid cymes. It is very common in all of Europe, especially in damp soils, and prized for its root.

Chemical Composition. Comfrey root is thought to contain allantoin. It also contains fructanes, triterpenoid mono- and bidesmosides, and 0.2-0.4% pyrrolizidine



SYMPHYTUM OFFICINALE L.

alkaloids: lycopsamine, intermedine (monoesters of retronecine), their acetylated derivatives, and symphytine. Notable quantities of echimidine are often reported, apparently because other species that are morphologically very close, such as *S. asperum* Lepechin and *S.* x *uplandicum* Nyman, are mistaken for *S. officinale,* which in theory contains no echimidine at all.

The qualitative and quantitative differences sometimes observed can probably be correlated with the occurrence of several cytotypes: $2n = 24$ with white flowers, tetraploids ($2n=48$) with white flowers (from western Europe) or red (from eastern Europe), $2n=40$ from the Netherlands.

The leaves also contain alkaloids, but in smaller quantities (0.003-0.02%), with the young leaves being the richest.

Pharmacological Activity. Comfrey root is said—as we are reminded by the genus name and the term *consolida*—to have healing properties, attributed to allantoin and to the polysaccharides. The root is also traditionally believed to have the power to relieve pain in the joints or gastritis. The aqueous extract of the leaves markedly increases the production of prostaglandins (PgF2α, 6-keto-PgF1α) in rat gastric mucosa homogenates.

When administered orally to rats for a long period of time, the roots and leaves of comfrey induce hepatic tumors in nearly half of the population, like symphytine. In humans, several case reports of veno-occlusive syndrome (see above) attributed to the regular and prolonged (several months) consumption of comfrey infusions or capsules have been published: in one case, the patient died. In most of the other patients, surgery was required to install an arterio-venous shunt.

Uses. In France, the root is the only part of comfrey that is authorized as an ingredient of plant-based medicines. In addition, the only indications that may be claimed are for the topical route: as an adjunct in the emollient and antipruriginous treatment of skin disorders, and as a trophic protective agent for cracks, bruises, frostbite, and insect bites [French Expl. Note, 1998]. The percutaneous absorption of the alkaloids has been studied in animals, is small, and the risk seems negligible. The consumption of comfrey leaves as a soup—some tout their nutritional virtues—must be formally discouraged.

The German Commission E monograph describes the anti-inflammatory and healing effects of comfrey root, which is to be used only for external application. The skin must be intact and the maximum daily dose (of 1,2-unsaturated alkaloids, externally) is 100 µg/day (including *N*-oxides). The monograph recommends against using comfrey root for longer than 4 to 6 weeks per year. Pregnant women must seek medical advice beforehand.

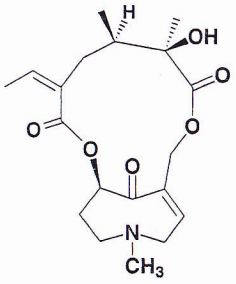
The United States Pharmacopoeia reminds the consumer that there are no standards for this plant of known toxicity and that little is known about its specific effects. It "strongly discourages" the use of any comfrey product and advises those who take it to monitor their condition and to consult a doctor or pharmacist if it gets worse (e.g., abdominal bloating and pain, diarrhea, fever, unusual weight loss [http://www.usp.org/did/mgraphs/botanica/comfrey2.html]).

• COLTSFOOT, *Tussilago farfara* L., Asteraceae

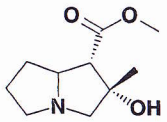
The coltsfoot capitulum is listed among cough teas (Fr. Ph., 10th Ed.) and is used as such (French national formulary). In several European countries, the leaves are used, for example, in Germany where it is official.

The Plant, the Drug. Coltsfoot is a small perennial plant very common in Europe and northern Asia. Early in the spring, it produces capitulums of yellow flowers on a scaly stalk, with a pleasant fragrance reminiscent of yellow wax. Rosettes of cordate and coriaceous leaves that are pubescent on the lower side appear later. The capitulum consists of an involucre of linear bracts arranged in two rows, ligulate (female) ray-flowers, and tubulous disk-flowers that are functionally male.

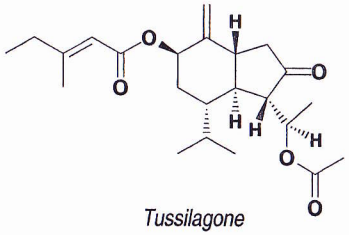
Chemical Composition. The coltsfoot capitulum contains an acidic mucilage, flavonoids, carotenoids, triterpenes, and pyrrolizidine alkaloids: two esters of necine unsaturated at C-1,C-2, senkirkine (major), senecionine (traces), and two saturated pyrrolizidines thought to be no more than artefacts of the extraction with methanol: tussilagine and isotussilagine. A sesquiterpenoid ester, namely tussilagone, has also been isolated and identified in the floral buds of a drug harvested in Asia. The leaves contain 6-10% mucilage and the same alkaloids as the capitulums. The alkaloid composition of coltsfoot seems to vary with the geographical origin: European plants are apparently less rich in total alkaloids than Oriental plants. In one North American specimen, the total alkaloids reached 150 ppm in the capitulums before blooming, then decreased to 50 ppm (whole plant).



Senkirkine



Tussilagine



Tussilagone

Pharmacological Activity. There are no relevant data on the potential activity of coltsfoot. As its name indicates (*tussis, is*, coughing fit, *ago, agere,* to chase, to push] the drug is reputed as an antitussive. The oriental medicines attribute to it the same virtues and use it to treat asthma, bronchitis, and other respiratory ailments. For some, the action that is observed is merely the consequence of the soothing effect of the mucilage on the irritated mucosa of the larynx. From a pharmacological point of view, it is noteworthy that tussilagone is, in dogs, a respiratory stimulant which increases ventilation and arterial blood pressure (0.02-0.3 mg/kg, IV). It has also been shown to inhibit PAF-acether, a mediator whose role in inflammation and respiratory difficulties is known. The potential activity of tussilagone by the oral route has not been studied.

Uses. Coltsfoot (infusions, nebulisate) continues to be used in phytotherapy (tracheitis, chronic bronchopneumonopathy). It is also widely self-administered (cough teas).

Is the consumption of preparations based on coltsfoot dangerous? Opinions differ. For some authors, since a cup of infusion contains on average 1 ppm of alkaloids, there is no reason to condemn this drug. For other authors, the presence of hepatotoxic alkaloids, even in trace amounts, must lead to prohibiting the regular use of this drug. Note that coltsfoot is not listed in the 1998 French Explanatory Note.

The German Commission E monograph only authorizes the use of coltsfoot leaf (acute catarrh of the respiratory tract with cough and hoarseness, moderate inflammation of the throat mucosa). It specifies that the daily intake of alkaloids must be less than 10 µg (in infusion) or less than 1 µg (extract or plant juice), and that the duration of use must be limited (no more than 4 to 6 weeks per year). Coltsfoot is contraindicated in pregnant and breast-feeding women. No side effects are known. The only known case reports of intoxications—which manifest themselves by a veno-occlusive syndrome—were described in young children: they were due to adulteration (by *Petasites hybridus* [L.] P.Gaertner, Meyer & Scherb.) or confusion with another Asteraceae (*Adenostyles alliariae* [Gouan] Kern).

• HEMP AGGRIMONY, *Eupatorium cannabinum* L., Asteraceae

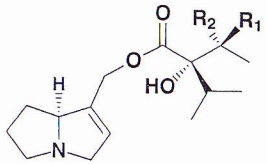
The species name is reminiscent of the similarity between the leaves of this tall perennial herb and those of cannabis (leaves with three to five acute dentate folioles). The flowers are tubulous, pink or reddish, and are grouped in a corymb of capitulums.

The chemical composition of this plant, common in damp ditches, is fairly well known: polysaccharides, flavonoids, benzofurans, essential oil (0.3%), sesquiterpenoid lactones from the group of germacranolides (eupatoriopicrin, 0.4% and closely related derivatives), and pyrrolizidine alkaloids: echinatine, lycopsamine, intermedine, rinderine in the aerial parts, and supinine in the roots.

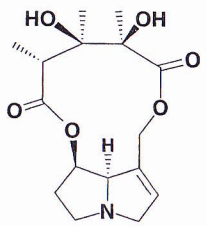
The choleretic and hepatoprotective properties of the lyophilized aqueous extract have been demonstrated in rats (250 mg/kg expressed as equivalent in dried plant, IV), which tends to confirm the data from folk medicine. Experiments have also shown the cytotoxicity of the sesquiterpenoid lactones on several types of tumor cells *in vitro*. Despite the lack of data on chronic toxicity, mutagenicity, and teratogenicity, the drug has some uses that are not justified by any relevant pharmacological or clinical data.

• European Ragwort, *Senecio jacobæa* L., Asteraceae

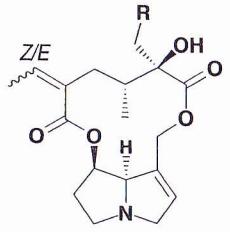
This perennial plant is widespread in neglected meadows and along country roads. It is characterized by very divided leaves which hug the stem with two jagged little wings. The yellow flowers are grouped in a corymb of radiate capitulums. All of the parts of the plant contain esters of retronecine, including jacobine, erucifoline, seneciphylline, and senecionine (the composition varies with the chemotype). The species is infamous because of the intoxications that it causes in horses and bovines. Horses lose their appetite and develop jaundice, edema, ascites, and finally, an encephalopathy which induces gait anomalies. As a general rule, accidents occur following the repeated ingestion of the plant (for weeks).



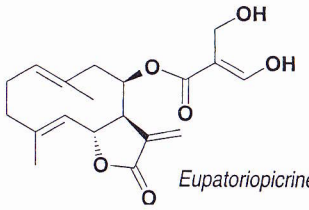
R_1 =OH, R_2 = H : *Amabiline*
R_1 = H, R_2 = OH : *Supinine*



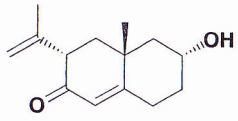
Monocrotaline



E
R = H : *Integerrimine*
R = OH : *Usaramine*



Eupatoriopicrine



Petasol

R = H
epoxy :
Jacobine

• Common Groundsel, *Senecio vulgaris* L., Asteraceae

This small annual herb (<40 cm) is among the most common weeds in European yards. It blooms and reseeds itself almost all year round. The flowers are tubulous and are grouped in capitulums taller than wide, and surrounded on their entire height by a row of black-tipped bracts. The whole plant contains alkaloids (0.05-0.1%): seneciphylline, senecionine, retrorsine, spartioidine, usaramine, and integerrimine. The drug (entire plant) used to be official. It is presented, without any pharmacological evidence, as capable of improving venous circulation. As such—and despite the presence of toxic pyrrolizidine diesters—it still finds some uses (compound herbal teas, extracts).

The hepatic toxicity of Senecio has long been known, therefore the French government was completely justified in moving the common groundsel (all organs)

from medicinal plant List A to List B and adding silver groundsel (*S. bicolor* [Willd.] Todd. = *Cineraria maritima* L.) (all organs) to List B. Recall that List B is for medicinal plants whose benefit-to-risk ratio evaluation is unfavorable for traditional use as a magistral preparation. Several manufacturers have removed *Senecio* from their products recently and with good reason.

• Other *Senecio* species

• *Senecio nemorensis* L. subsp. *fuchsii* (C.C. Gmel.) Durand

This is a species native to the mountain areas of central Europe and to the Caucasus, with a reputation for being medicinal (e.g., to treat hypertension and hemorrhage, or as a "uterine remedy"). The plant contains 0.1% essential oil, flavonoids, coumarins, phenolic acids, and in the subterrranean parts, furanosesquiterpenes with an eremophilane skeleton. In addition, a saturated pyrrolizidine is found, namely fuchsisenecionine, as well as traces of senecionine (0.007%). The German Commission E monograph states that the plant shortens the bleeding time and that its carcinogenic activity has been demonstrated in animals. Therefore, in the absence of truly demonstrated properties, the Commission concludes that the therapeutic use of this species is not justified.

• *Senecio aureus* L.

Most authors express strong reservations about the use of this species, to say the least. It was still listed in the BHP in 1983. It is a folk remedy for amenorrhea. Considering the lack of proof of any activity, and the fact that the plant contains pyrrolizidine alkaloids, its use must be formally proscribed.

• Other Plants

• *Petasites hybridus* (L.) P. Gaerntn., B. Meyer & Scherb.

This is an Asteraceae native to the damp meadows of Europe and to the south of the United States. It was used in folk medicine for a long time. It has spasmolytic properties that are probably due to eremophilane-type esters of sesquiterpenoid alcohols: petasin (ester of petasol), and esters of neopetasol and isopetasol. Considering the lack of relevant data to demonstrate the properties attributed to this plant, and the fact that it contains pyrrolizidine alkaloids (senecionine, senkirkine, integerrimine), organizations such as the German Commission E recommend against using *Petasites* in therapy.

• Crotalaria, *Crotalaria retusa* L. and other species

Several species within this genus (Fabaceae) are commonly used for medicinal purposes in the Caribbean Islands (e.g., Guadeloupe, as an antitussive). This ancestral custom is dangerous, especially to children, because of the occurrence of pyrrolizidine alkaloids. Several case reports of liver damage have been published,

therefore the use of crotalaria must be completely proscribed. Crotalaria seeds can contaminate grain, and poison cattle and humans as a result.

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