REVIEW

Pharmazeutisches Institut der Rheinischen Friedrich-Wilhelms-Universität, Bonn, Germany

Medicinal plants in China containing pyrrolizidine alkaloids

E. ROEDER

Dedicated to Dr. C. C. J. Culvenor on the occasion of his 75th birthday, CSIRO Animal Health, Geelong, Victoria, Australia

Medicinal plants and remedies are widely used for various ailments throughout the world. Many of these plants contain pyrrolizidine alkaloids (PAs) which are hepatotoxic, pneumotoxic, genotoxic, neurotoxic, and cytotoxic. As a result of their use in Traditional Chinese Medicine (TCM), medicinal plants are becoming increasingly important not only in China but also in many other countries. This paper will therefore give, a critical overview of PA-containing plants belonging mainly to the families Boraginaceae, Leguminosae (Tribus Crotalarieae), and Asteraceae (Tribus Senecioneae and Eupatorieae). The PAs contained in the 38 plants described here differ widely in their structure and toxicity. Their metabolism and the resulting toxicity will be discussed, the dehydroalkaloids (DHAlk) produced in the liver playing a key role in cases of intoxications.

1. Introduction

Over the past 20 years interest in Traditional Chinese Medicine (TCM) has increased considerably not only in Europe but also in North America and Australia. In addition to acupuncture, acupressure, massage, moxibustion, and magnetotherapy, phytotherapy plays a particularly important role.

In China medicinal plants and their preparations have been used for 2200 years. The fact that they are so much in vogue in the western countries may be attributed not only to anxiety of the consumers of synthetic drugs about undesired secondary effects of these drugs but also to the "Green Movement" which has been resurgent in Europe, North America, and Australia for the last 20 years. After the political and economical opening of China numerous remedies and medicinal plants became available in the West particularly because the difficulties in writing and speaking Chinese have been overcome by use of the so-called pinyin.

Since the landarea of China extends practically from the arctic to the tropical climatic zone, an unusually large number of plants grow in the country, a great many of which are used as medicinal plants. It is therefore perfectly understandable that more than 5700 plants and animals used for medicinal purposes are described in the well-known modern work, the "Traditional Medicinal Dictionary" of 1979 [1].

Many of this range of plants have obtained officinal status, being listed in the Chinese pharmacopoeia where they

are described exactly in monographs [2] which in most cases have been translated into German [3]. Meanwhile, there are a number of books of both official [4, 5] and popular nature [6–8] devoted to the most important medicinal plants.

There are also books dealing uncritically with Chinese medicinal plants and suggesting miracle cures, such as in particular a book by Hoehne with the title "Healing Teas Work Miracles" [9]. In this book a great number of asiatic, especially Chinese plants, unknown in western countries are cited. These plants may cause intoxication by improper use.

In addition, in various regions of China different plants are marketed under the same drug name leading to confusion with fatal consequences as illustrated by several examples reported in the medicinal literature [10, 11]. After pyrrolizidine alkaloid-containing plants became discredited worldwide [12–20], Chinese medicinal plants were investigated from this point of view. These studies revealed that 38 plants of Traditional Chinese Medicine (TCM) belonging to particular plant families contain pyrrolizidine alkaloids (PAs) of varying toxicity as confirmed by scientific studies. In the following sections only those plants will be discussed whose components have been determined unequivocally.

2. Chemistry of pyrrolizidine alkaloids

2.1. Necines

The ester-type pyrrolizidine alkaloids (PAs) usually contain a necine base, called necine, which is a fused 5/5 ring system with a nitrogen atom as bridgehead representing a tertiary base. In almost all cases the necine has a hydroxymethyl group at C-1 and generally also a hydroxyl group at C-7. These hydroxyl groups are usually esterified with a necic acid giving monoester, open-chain diester, and macrocyclic diester alkaloids.

Figure 1 shows the necines of the alkaloids so far found in Chinese plants.

In addition to the hydroxyl group at C-7 they may also have a hydroxyl group at C-2 or C-6 resulting in the formation of stereoisomers. The necine can either be saturated or possess a double bond in the 1,2-position (ring B, Fig. 1). All known PAs found in the plants studied can form N-oxide derivatives except the otonecine alkaloids. The corresponding esterification of necines containing a double bond in the 1,2- position yields toxic alkaloids.

Otonecine plays a special role because it is not a true bicyclic ring system, but a N-methylated azacyclooctan-4-one ring system. It may act as a pyrrolizidine ring system due to transannular interactions. The binding between the N atom and the CO group is widened to such an extent that the resonance structures indicated result. The PAs derived from these structures constitute the subgroup of the otonecine alkaloids (OPAs)[1].

2.2. Necic acids

The necic acids found in PAs, excluding acetic acid, possess 5, 7, 8 and 10 carbon atoms.

They can be mono- or dicarboxylic acids with branched carbon chains, bearing as substituents hydroxy, epoxy, carboxy, acetoxy, methoxy or other alkoxy groups. Thus, numerous structural, stereo- and diastereoisomers may be formed. Tables 1 and 2 list the most important mono- and dicarboxylic acids that have been found in alkaloids so far.

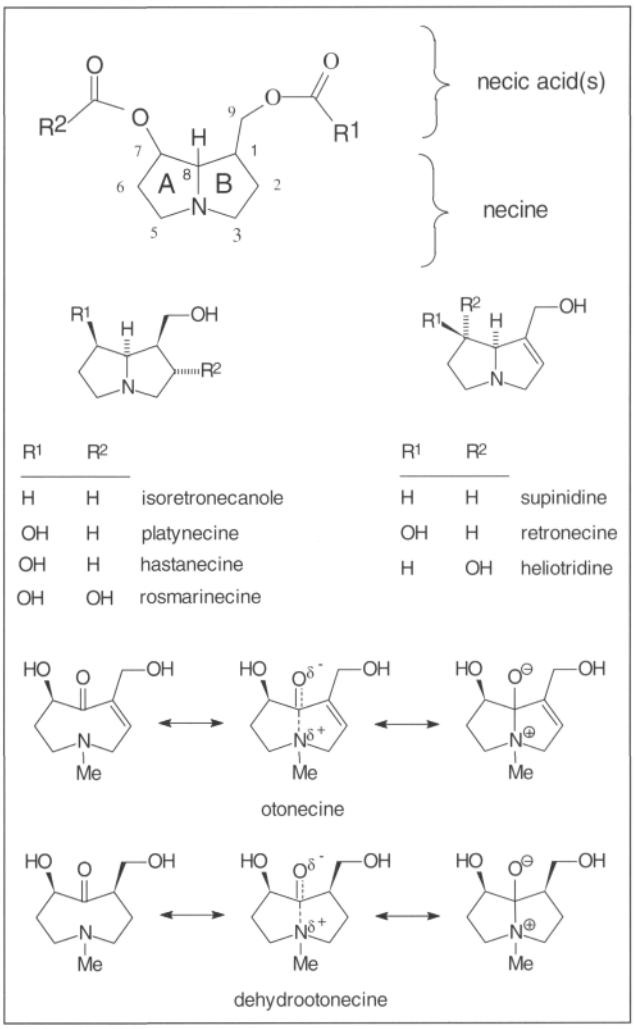


Fig. 1: Structure of basic alkaloids and necines occurring in Chinese medicinal plants

The possibilities of esterification are exemplified by several alkaloids. Necines containing one hydroxyl group can be esterified with one monocarboxylic acid only as shown in Figure 2 for amabiline. Necines bearing two hydroxyl groups such as 7,9-necinediols can be esterified with a monocarboxylic acid either in the 7- or 9-position as demonstrated by 7-angeloyl- and 9-angeloylretronecine. Echimidine is an example of a twofold esterification. With dicarboxylic acids a double esterification takes place leading exclusively to the formation of alkaloids with 11- to 14-membered ring systems. The most widely known PAs are the 11-membered monocrotaline, the 12-membered al-

Table 1: The most important monocarboxylic necic acids occurring in PAs

Carbon atoms	Acid name
2	Acetic acid
5	Tiglic acid Angelic acid Senecioic acid Sarracinic acid 2-Methylbutyric acid
7	(+, −) Viridifloric acid (+, −) Trachelanthic acid and derivative Echimidinic acid Lasiocarpic acid

Table 2: The most important dicarboxylic necic acids occurring in PAs

Carbon Atoms	Acid name
8	Monocrotalic acid
	Crotaleschenic acid
10	Incanic acid
	Globiferic acid
	Trichodesmic acid
	Senecinic acid
	Integerrinecic acid
	Senecivernic acid
	Isatinecic acid
	Seneciphyllic acid
	Spartioidinic acid
	Ridelliic acid
	Erucifolinecic acid
	Petasinecic acid

kaloids senecionine and senkirkine, the 13-membered doronenine, and the 14-membered parsonsine.

Through combination of necines with necic acids an exceedingly large number of alkaloids may theoretically be obtained. In nature more than 350 alkaloids have been found so far and their structures elucidated. Apart from about 33 known otonecine alkaloids, which cannot form N-oxides, including the N-oxides of the other alkaloids more than 660 alkaloids are known [13–20].

3. Biosynthesis of pyrrolizidine alkaloids

Significant progress has been made in the past few years in the understanding of the biosynthesis of the necines and necic acids chiefly by use of precursors containing the stable isotopes ^{2}H, ^{13}C, and ^{15}N. During amino acid metabolism the unstable isotopes ^{3}H and ^{14}C of both the necine bases and necic acids are produced [21, 22]. Root cultures of *Senecio* and *Eupatorium* species have been found to be excellent *in-vitro* systems for studying PA biochemistry (23).

3.1. Biosynthesis of necines

Biochemical studies have revealed that necine base biosynthesis is linked to primary metabolism via putrescine and spermidine both of which are exclusively derived from arginine.

Ornithine is incorporated via arginine. Homospermidine has been identified as the first intermediate of the specific alkaloid pathway. It is formed by homospermidine synthase (HSS), an enzyme that catalyzes the first reaction in the biosynthesis. For a long time it was assumed that HSS catalyzes the transfer of the aminobutyl group of either putrescine or spermidine to a second putrescine molecule yielding homospermidine. A reinvestigation revealed, however, that HSS uses only spermidine as an aminobutanol donor. The carbon skeleton of the necine base moiety is derived half and half from spermidine and putrescine.

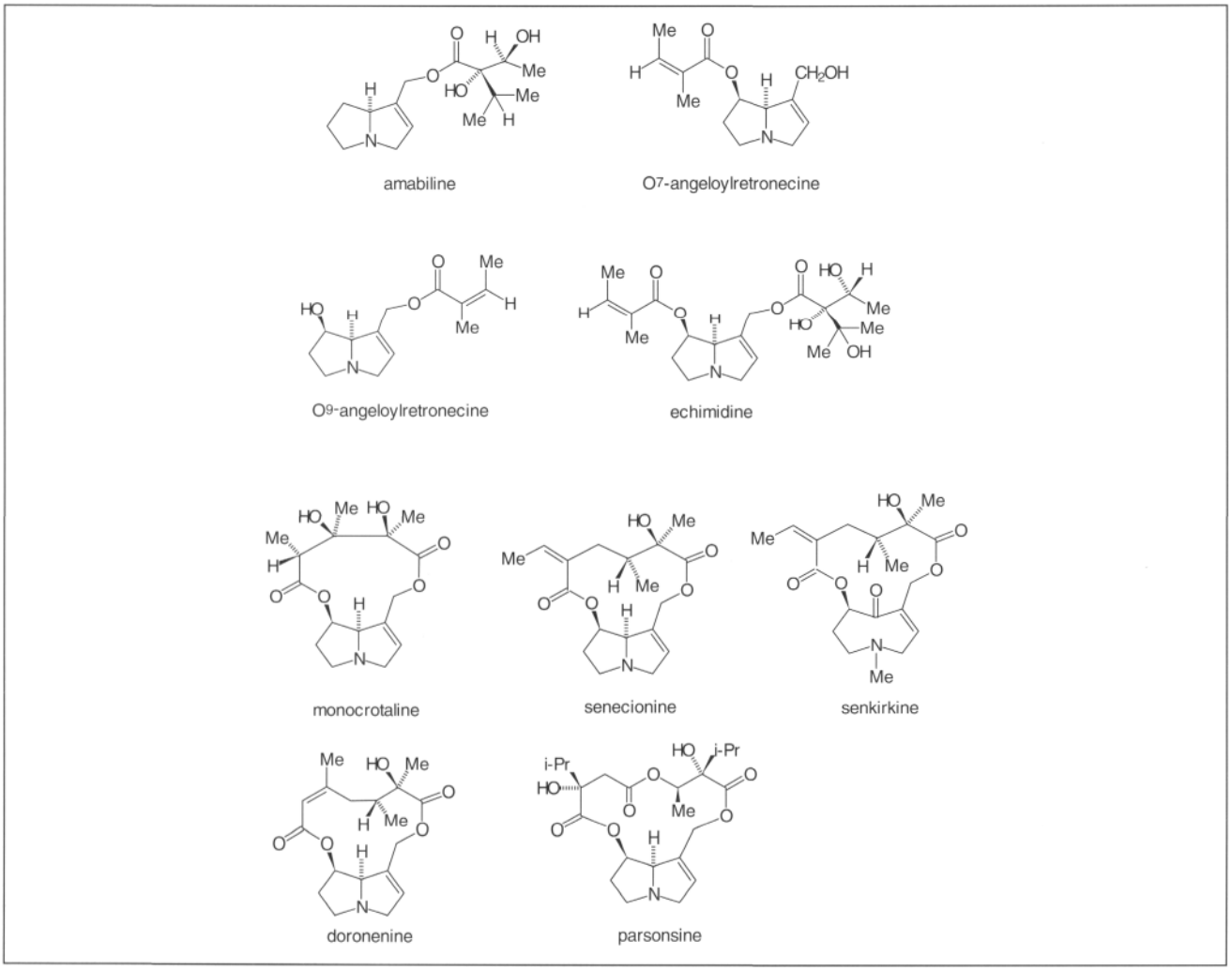


Fig. 2: Examples of toxic pyrrolizidine alkaloids

The further course of the biosynthesis is the same not only among representatives of the genera *Senecio* ssp., and *Eupatorium* ssp. but also among those of the genera *Crotalaria* ssp., *Heliotropium* ssp. and *Cynoglossum* ssp. It is described in Scheme 1 which represents the present state of research. The results obtained are documented for the necines trachelanthamidine, isoretronecanole, rosmarinecine, retronecine, and heliotridine [23–28].

Formally, rosmarinecine is a β-hydroxy derivative. β-Hydroxy compounds are known to be very unstable, yielding α, β-unsaturated compounds with elimination of water. In the case studied retronecine would be formed from rosmarinecine with elimination of water under physiological conditions also.

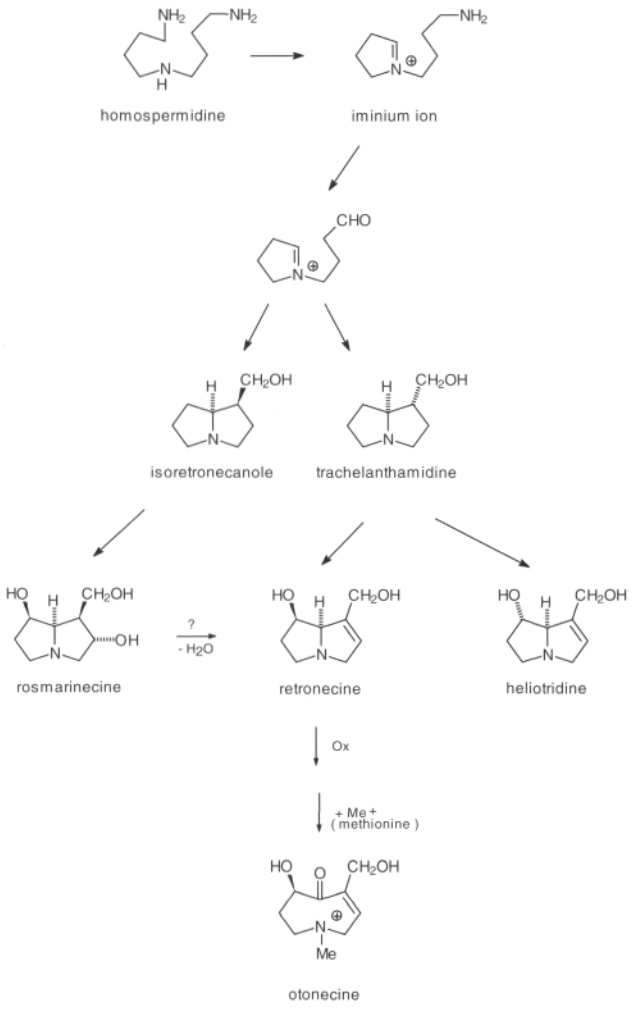
Otonecine is produced from retronecine from its alkaloids by hydroxylation of retrocine ester alkaloids at C-8 [21, 29]. A methyl group is assumed to be transferred from *S*-adenosylmethionine as donor to the nitrogen atom [30].

3.2. Biosynthesis of necic acids

Due to the enormous variability of necic acids, biosynthesis proceeds notably less homogeneously than in the case of necines, and only a few synthetic pathways have been elucidated so far [21]. The amino acids L-isoleucine, L-leucine, L-threonine, and L-valine are known to be precursors, the decarboxylation and deamination of which give e.g. C_5 acids such as angelic or tiglic acid or C_{10} acids such as senecic acid. The biosynthetic pathway of the latter process was recently completely elucidated. Stirling et al. demonstrated that biosynthesis proceeds via two L-isoleucine molecules and does not involve ketonic intermediates [31].

The corresponding studies were performed on representatives of the genera *Senecio* ssp., *Cynoglossum* ssp., and *Crotalaria* ssp. Studies of Weber et al. on root cultures of *Eupatorium clematideum* recently showed that trachelanthic acid is biosynthesized by the addition of a two-carbon moiety from hydroxyethyl-TPP ["activated acetaldehyde"] to 2-oxoisovaleric acid followed by a reduction step [32].

Scheme 1: Biosynthesis of necines



4. Occurrence of pyrrolizidine alkaloids in Chinese medicinal plants

In flora PAs are widely distributed as products of secondary metabolism. However, they mainly occur only in certain families and here, in turn, generally only in some tribes or genera.

Table 3: Occurrence of pyrrolizidine alkaloids in different Chinese medicinal plants

Family	Tribus	Genus
Orchidaceae	Epidendreae	*Liparis*
Fabaceae (Leguminosae)	Crotalarieae	*Crotalaria*
Boraginaceae	Cordioideae	*Cordia*
	Lithospermeae	*Lithospermum*
		Arnebia
	Cynoglosseae	*Cynoglossum*
	Heliotropieae	*Heliotropium*
	Eritrichieae	*Lappula*
Asteraceae (Compositae)	Eupatorieae	*Ageratum*
		Chromolaena
		Eupatorium
	Senecioneae	*Cacalia*
		Crassocephalum
		Emilia
		Farfugium
		Gynura
		Ligularia
		Petasites
		Senecio
		Syneilesis
		Tussilago

4.1. Medicinal plants of the family Orchidaceae containing pyrrolizidine alkaloids

4.1.1. Liparis nervosa (Thunb.) Lindl. (syn. Ophrys nervosa Thunb.) [Chin.: Jian xue qing, Japn.: Kokuran, Engl.: Twayblade]

Liparis nervosa grows in Central China. It is a traditional medicinal plant collected throughout the year. The decoction prepared from 10–20 g of the plant is used in cases of hemoptysis, hematemesis, bleeding, wounds surgical bleeding, snake bites, and leg ulcers. All parts of the plant contain the alkaloid nervosine (**42**) composed of the necine lindelofidine (d-isoretronecanole) and the necic acid nervisinic acid. Since no toxic effects of these two components have yet been reported [33, 34] there are no objections to the aforementioned uses of the plant.

4.2. Medicinal plants of the family Fabaceae containing pyrrolizidine alkaloids

4.2.1. Crotalaria albida Heyne ex Roth (syn. C. formosana Matsum. ex Ito & Matsum., syn. C. montana Roxb.) [Chin.: Huang hua di ding, Engl.: Rattlebox]

Crotalaria albida is a semi-perennial plant growing in India and China at altitudes of 200 to 2800 m.
The whole plant is collected in summer and fall and dried, and 25–50 g of it are prepared as a decoction and used in cases of urinary tract infections, boils, pyodermas, and cough. This plant contains the nontoxic alkaloid croalbidine (**64**) [35, 36]. There are no objections to therapeutic use.

4.2.2. Crotalaria assamica Benth. (syn. C. burmannii DC., syn. C. sericea Burm. F.) [Chin.: Zi xiao rong]

This is a plant growing in India and China, at an altitude of up to 3000 m. It is a subshrub that reaches a height of 1–2 m and grows on slopes, margins of forests or banks of water courses. The plant flowers from July to October and is used as a folk remedy. The stems and leaves are collected in summer, the ripe seeds in the fall. The stems and leaves are used in cases of boils and pyodermas, cough, and toothache, and the seeds are used as an antitumorigenic agent. The antitumorigenic activity was studied extensively by the "Crotolaria Plant Research Group" in the case of skin cancer; however, the secondary effects on the liver turned out to be very harmful [37]. The plant contains a high concentration of the alkaloid monocrotaline (**62**) and a minor amount of assamicadine (**29**); the seeds alone contain up to 2.9% of monocrotaline [38–41]. It should not longer be used as a traditional medicinal plant because of its high alkaloid content and the hepatotoxic effect of the monocrotaline.

4.2.3. Crotalaria mucronata Desv. (syn. C. pallida Aiton) [Chin.: Xiang ling cao, Engl.: Rattlebox]

Crotalaria mucronata is a perennial subshrub-like herb with a height of 1 m which grows in villages and among roadside thickets and flowers from June to October. For medicinal purposes the whole plant and seeds are collected. Pods are collected in fall, and dried in the sun, and the seeds are collected. They are used for dizziness, neurasthenia, nocturnal emission, premature ejaculation, leucorrhea, enuresis, and polyurea. Stems and leaves are used for dysentery and abdominal pain, and the roots for lymphadenopathy, mastitis, dysentery, infantile malabsorption, and malnutrition. The following quantities are used: seeds 6–16 g, stems 6–18 g, roots 15–30 g as decoctions. The plant, particularly the seeds, contains high amounts of usamarine (syn. mucronatinine) (**52**) and nilgirine (**59**) [42–48].
As already stated in Chinese regulations the seeds are poisonous and should be used with caution (contraindicated in pregnancy). Pigs fed with herb show signs of intoxication resembling those of atropine [48]. Alcoholic and aqueous extracts obtained from leaves and dried fruit showed no clastogenic effects on mouse bone marrow cells [49].

4.2.4. Crotalaria sessiliflora L. (syn. C. brevipes Champ. ex Benth., C. eriantha Sieb. et Zucc.) [Chin.: Ye bai he; Nong ji li]

It is an annual erect herb, growing in Japan, Korea and China; in the latter country up to an altitude of 1500 m. The plant, flowering until September, is hairy, 20–200 cm high and is widespread on roadsides, and river banks and in thickets. It plays an important role in folk medicine and is also listed in the Pharmacopoeia Sinica of 1985. The whole plant is used; the seeds are used in cases of boils and pyodermas, tinnitus, deafness, dizzines, vertigo, and for skin cancer, esophageal cancer, and cervical cancer. 15–60 g are taken internally as a decoction while crushed fresh herb or ground and dried herb is used for topical application. In cancer therapy, the duration of treatment varies between 3 and 4 months.
Aqueous extracts showed inhibitory activity to several rodent tumors such as sarcoma 180, leukemia 615, and Walker carcinoma 256 (50).
Plant and seeds contain monocrotaline (**62**) in high concentration, and trichodesmine (**63**) and integerrimine (**53**) [51–53] in low concentration. According to present knowledge *Crotalaria sesseliflora* should not be used therapeutically even for external purposes.

4.2.5. Crotalaria tetragona Roxb. ex Andrews (syn. C. esquirolii H. Lév., syn. C. grandiflora Zoll.) [Chin.: Hua jin dan]

This plant grows in India, Nepal, Bhutan, Myanmar, Vietnam, and China at altitudes of 500–1600 m, mainly in the provinces of Guangdong, Guanxi, Sichuan, and Yunnan. It is a perennial herb and blooms in September. For medicinal purposes the whole plant together with the root is used. It is also used as a folk remedy in cases of indigestion and stomachache. All parts of the plant, especially its seeds, contain high amounts of trichodesmine (**63**) and integerrimine (**53**) [54]. This plant should no longer be used therapeutically.

4.3. Medicinal plants of the family Boraginaceae containing pyrrolizidine alkaloids

*4.3.1. Arnebia euchroma (Royle) Johnst. (syn. Macrotomia euchroma (Royle) Pauls.) [Chin.: Zi cao, *Ruan zi cao, Juan tsu tsao, Japn.: Nanshikon, Engl.: Arnebia]*

It is an annual to semi-perennial plant with a height of 25–50 cm that flowers from August to September and is then collected. It is an officinal medicinal plant listed in the Pharmacopoeia Sinica 1985/1990. The roots are used internally for improving the blood circulation, as an antiviral agent, and for liver diseases. The red dystuff of the roots, shikonine derivates, is used for staining foods and cosmetics. The roots contain O^7-angeloylretronecine (**1**) und O^9-angeloylretronecine (**2**) in a total amount of only 10 ppm [55]. Intoxication has therefore not been reported.

4.3.2. Cordia myxa L. (syn. C. dichotoma Forst.) [Chin.: Qin tong cui mu, Engl.: Sebesten Plum]

Cordia myxa L. is a shrub or tree which may reach a height of 5 to 10 m and is native to regions of China with a warm climate. The roots are collected throughout the year. Decoctions of 25–50 g obtained from dried roots are used for gastric pain. The plant contains the nontoxic alkaloid macrophylline (**37**) [56]. There are no objections to its use.

4.3.3. Cynoglossum amabile Stapf. & J. R. Drumm. [Chin.: Gou shi hua]

This plant is native to Tibet, Bhutan, and China. In China it grows as a perennial herb at heights of 2600 to 3700 m in the provinces of Gansu, Guizou, Sichuan, Xizang, and

Yunnan. The whole plant is collected during the flowering period from June to August. It is used for medicinal purposes in cases of colds, fever, cough, hemoptysis, hematemesis und beriberi, 25–50 g of the dried drug being used as a decoction.
The plant contains amabiline (**11**) and echinatine (**18**) as major alkaloids besides 3′-acetylechinatine (**19**), rinderine (**22**), and supinine (**12**). The total alkaloid content is ca. 0.4% [57–59].
Although these alkaloids show only moderate toxicity, they should not be used as a remedy.

4.3.4. Cynoglossum lanceolatum Forsk. (syn. C. micranthum Desf., syn. C. canescens Willd., syn. C. hirsutum Thunb.) [Chin.: Ya yong cao]

This plant is a biennial herb in Cambodia, India, Laos, Myanmar, Nepal, Pakistan, Phillipines, Sri Lanka, and Thailand. It grows in China at altitudes of 300 to 2800 m. The plant is collected during the flowering period from June to August. Decoctions of 15–25 g containing the nontoxic alkaloid cynaustraline (**44**) and the slightly toxic alkaloid cynaustine (**30**) [60] are used for internal indications, e.g. for nephritic edema, acute nephritis, and toothache. There are no objections to medicinal uses.

4.3.5. Cynoglossum officinale L. [Chin.: Yao yong dao ti hu, Engl.: Hounds tongue]

Cynoglossum officinale is a perennial herb widespread in China. Decoctions prepared from 15–25 g of dried roots are used in traditional medicine. The roots are collected in spring and/or fall and are used for the treatment of pulmonary tuberculosis and cough, hoarseness, and hematemesis.
The plant contains the following alkaloids: main alkaloids: trachelanthamine (**31**), heliosupine (**27**), and its N-oxide, 3′-acetylheliosupine (**28**), viridiflorine (**32**) or the stereoisomer of the latter; secondary alkaloids: echinatine (**18**) and its N-oxide, 3′-acetylechinatine (**19**), 7-angeloylechinatine (**21**), 7-angeloylheliotridine (**7**), 7-tigloylheliotridine (**10**); in addition to traces of amabiline (**11**), supinine (**12**), rinderine (**22**), and 7-angeloylrinderine (**24**).
With the exception of viridiflorine (**32**) and its stereoisomer all these alkaloids are toxic [61–71].
The proportion of the alkaloids in the plant is 1.5–2.0% and thus very high. It is therefore not surprising that intoxication has been reported with grazing livestock such as calves [72, 73] and horses [74, 75]. *S. officinale* should thus in no case be used for medicinal purposes.

4.3.6. Cynoglossum zeylanicum (Vahl) Thunb. (syn. C. furcatum Wall.) [Chin.: Tie Gu San]

This biennial herb is widespread in China. From the roots and leaves collected in spring and summer, the peels are used. 15–20 g are used as a decoction in cases of traumatic injuries, fractures, snake bites, boils, pyodermas, and regular menses. The plant contains the nontoxic alkaloid cynaustraline (**44**) [76]. There are no objections to its use as a medicinal plant.

4.3.7. Heliotropium indicum L. (syn. H. anisophyllum P. de B., H. parviflorum Blanco) [Chin.: Da wei yao, Ind. and Engl.: Hatishoor]

This annual plant is widespread in India, Japan, Bangladesh, Myanmar, Thailand, and Vietnam. In China it grows at altitudes of 0 to 700 m mainly in the provinces of Fujian, Hainan, South China, Sea Islands, and Yunnan as well as in Taiwan. In China it is used as a traditional medicinal plant. In India it is one of the most widely used herbs in Ayurvedic medicine. The whole plant, both the aerial parts and the roots, are collected in the fall and dried, its leaves being used externally in the treatment of ulcers, wounds, and local inflammations. The decoction prepared from 50 to 100 g of the drug is said to be very effective against urticaria, ringworm, rheumatism, gonorrhoea, pneumonia, common colds, pharyngitis, tonsillitis, and urinary tract stones.
Besides indicine (**4**) all parts of the plant contain high proportions of the alkaloid heliotrine (**25**), and minor amounts of echinatine (**18**), supinine (**12**), heleurine (**13**), lasiocarpine (**26**), the N-oxides of these alkaloids, and 3′-acetylindicine (**5**) in a total concentration of up to 0.4% [77–83].
Heliotropium species exhibiting a similar alkaloid composition such as *H. europaeum*, but also other *H. species*, have caused large outbreaks of hepatic venoocclusive diseases in Russia [84–86], Afghanistan [87, 88], India [89], Hong Kong [90], and Tadjikistan [91, 92]. In most cases these diseases were attributed to the consumption of wheat contaminated with seeds of *Heliotropium* genera or to the consumption of herbal tea containing the toxic alkaloids. Similarly, numerous intoxications have been reported with chickens, ducks [93], sheep [94], calves [95, 96], and cattle [97–100]. The plant should not be used for therapeutic purposes.

4.3.8. Lappula intermedia (Ledeb.) M. Popov. (syn. Echinospermum intermedium Ledeb.) [Chin.: He shi]

This plant is a traditional folk medicine. It is an annual herb and grows in Kazakstan, Kyrgyzstan, Mongolia, Russia, Tadjikistan, Turkmenistan, and Uzbekistan. In China it is mainly native to the north-eastern part, e.g. in Gansu, Jilin, Liaoning, Nei Mongol, Qunghai, Shandong, and Xingjiang. The ripe fruit is collected in the fall. 15–25 g of the powdered fruit are used as decoctions for the treatment of ascariasis oxyuriasis, round worms and threadworms and in case of infantile malnutrition.
Since the fruit contains up to 0.02% of the highly toxic alkaloid lasiocarpine (**26**) [101], the plant should definitely not be used for medicinal purposes.

4.3.9. Lithospermum erythrorhizon Sieb. et Zucc. [Chin.: Zi cao]*

According to the Pharmacopoeia Sinica of 1985/1990 *Lithospermum erythrorhizon* is an officinal medicinal plant. It occurs as a semi-perennial herb and reaches a height of 25–90 cm. The plant is native to North-East China and Tibet. The roots are collected in the fall and then air-dried. As a medicinal plant it is used for the same indications as *Arnebia euchroma* and bears the same Chinese name Zi cao* together with *Onosma paniculatum* of another closely related Boraginaceae. The plant is mainly used internally for antipyretic, antiphlogistic and antidotal purposes, in cases of measles, angina, obstipation, and hepatitis, and also externally for eczema and psoriasis either as an individual drug (3–10 g) or as a prescription together with other drugs used as a tea.
The plant contains the alkaloids intermedine (**15**), myoscorpine (**16**), and hydroxymyoscorpine (**17**) with a total concentration of ca. 0.02% relative to the dried drug [102]. Use is not recommended.

4.4. Medicinal plants of the family Asteraceae containing pyrrolizidine alkaloids

4.4.1. Ageratum conyzoides L. (syn. Eupatorium conyzoides (L.) E. H. L. Krause), syn. Carelia conyzoides (L.) Kuntze) [Chin.: Sheng hong ji]

This plant grows in India and in China where it is widespread at an altitude of 600 to 800 m. It is an annual herb that reaches a height of 30–60 cm and is found on roadsides and waste ground. Extracts of 15–30 g (boiled in water) are prepared from the leaves and young stems collected in summer and fall. They are used externally for traumatic injuries, pyoderma, furuncles, and as a hemostatic wound bleeding, and internally in cases of common colds and fever, upper respiratory tract infections, tonsillitis, sore throat, and malaria.
Since the toxic alkaloids lycopsamine (**14**) and echinatine (**18**) have been found at a concentration of 500 ppm in the dried plant, it should not be used for the aforementioned purposes [103].

4.4.2. Chromolaena odorata (L.) R. M. King & H. Rob. (syn. Osmia odorata (L.) Sch. Bip.) [Chin.: Fei ji cao]

This folk medicinal plant occurs mainly in the provinces of Hainan and Yunnan and contains 7- and 9-angeloylretronecine as N-oxide (**1**, **2**), intermedine (**15**), rinderine (**22**), and 3′-acetylrinderine (**23**). The highest concentrations of these compounds are in the roots and mature flower heads [104]. The drug is applied internally as a hemostatic, and externally as an insecticidal. Internal use is not recommended.

4.4.3. Eupatorium cannabinum L. (syn. E. nodiflorum Wall. Ex DC.) [Chin.: Pei lan]

This annual herb with a height of 50–120 cm grows in Russia and in the Jiangsu province of China mainly on the banks of streams, lakes and in moist places. The aerial parts are collected during the flowering period from July to September. *Eupatorium cannabinum* is an officinal medical plant listed in the Pharmacopoeia Sinica. It is used as a decoction for influenza, colds, cerebral stroke, uterine bleeding, oliguria, and gastric complaints.
It contains the toxic alkaloids amabiline (**11**), echinatine (**18**), intermedine (**15**), lycopsamine (**14**), rinderine (**22**), and supinine (**12**) as well as the nontoxic alkaloids cynaustraline (**44**), and viridiflorine (**32**) [105–108].

4.4.4. Eupatorium chinense L. (syn. E. reveesii Wall. Ex DC., syn. E. crenatifolium Hand-Mazz.) [Chin.: Hua zhe lan]

Eupatorium chinense L. grows as a perennial herb on moist slopes throughout China at altitudes ranging from 800 to 1900 m. It may reach a height of 80–150 cm and flowers from July to September. The roots are collected in the fall and used as decoction (15–30 g), internally for diphtheria, sore throat, colds, fever, burns, and scalds, and externally for traumatic injury, pyodermas, and lumbago.
Pyrrolizidine alkaloids were detected by the Mattocks color reaction which, due to their blue coloration, are unsaturated and hence toxic [109]. However the degree of toxicity cannot be assessed more exactly because only the total alkaloid content was determined. The plant should no longer be used for medicinal purposes.

4.4.5. Eupatorium fortunei Turcz. (syn. E. caespitosum Mego, syn. E. chinense var. tripartitum Miq., syn. E. stoechadosmum Hance) [Chin.: Pei lan]

This plant is native to Japan, Korea, and many provinces of Central China. It is a medicinal plant of the Pharmacopoeia Sinica of 1985. Leaves and stems collected before flowering and sun-dried are used as decoctions (8–15 g) in cases of influenza, colds, cerebral stroke, uterine bleeding, oliguria, and emesis as well as for gastric and intestinal complaints. *E. fortunei* contains the alkaloids supinine (**12**), rinderine (**22**), and 7-acetylrinderine (**23**) [109–111]. These alkaloids are only slightly toxic. Nevertheless, this plant should be used only in cases of acute illness and only for short periods.

4.4.6. Eupatorium japonicum Thunb. (syn. E. chinense L. var. simplicifolium (Mak.) Kitam.) [Chin.: Hua zhe lan and Cheng gan cao]

Eupatorium japonicum is widespread in Japan, Korea, and the north-eastern regions of China. It is a perennial herb, reaches a height of 1–2 m, flowers from August to September, yields fruit from September to November and is widespread on slopes and roadsides.
It is a traditional medicinal herb. The whole herb and the roots are collected in summer and fall.
15–25 of these are used as a decoction for the treatment of measles, rheumatic bone pains, colds, and cough. The plant contains the toxic alkaloids amabiline (**11**), echinatine (**18**), intermedine (**15**), lycopsamine (**14**), rinderine (**22**), and supinine (**12**) as well as the nontoxic viridiflorine (**32**) [105, 110]. The drug should no longer be used.

4.4.7. Cacalia hastata L. [Chin.: Shan jian zi]

Cacalia hastata is a folk medicinal plant, only the leaves of which are used as infusions and for compresses in external injuries. It contains the toxic integerrimine (**53**) and the nontoxic hastacine (**48**) [112]. Although there is no risk of intoxication in short-term use, the plant should no longer be used.

4.4.8. Cacalia hupehensis Hand.-Mazz. (syn. Koyamacalia hupehensis (Hand.-Mazz.) H. Rob. & Brettell). [Chin.: Bei xie jia cao]

It is a traditional folk medicinal plant in the province of Hu Bei. There are only a few data available on its use as a medicinal plant. It contains the N-oxide of the nontoxic neoplatyphylline (**47**) [113] and may be used for medicinal purposes without any objection.

4.4.9. Crassocephalum crepidioides (Benth.) S. Moore (syn. Gynura crepidioides Benth.) S. Moore) [Chin.: Jia Tong Hao]

This plant is native to Thailand and China. In the latter country it is widespread at altitudes of 300–1800 m in the north-eastern regions. Decoctions (25–50 g) of the whole plant are used, internally for cold, fever, dysentery, gastroenteritis, and urinary tract infection, and externally in mastitis. It contains jacoline (**60**), and jacobine (**61**) [114].

4.4.10. Emilia sonchifolia (L.) DC (syn. Cacalia sonchifolia L., syn. Crassocephalum sonchifolium (L.) Less., syn. Emilia sinica Miq.) [Chin.: Yang ti cao, Yi dian hong, I thien hung]

This plant grows in China at altitudes of 800–2100 m, e.g. in the provinces Yunnan, Hubei, Jiangsu, Guangdong, Hainan, Fuchian, and also in Taiwan. The whole herb is used in folk medicine, collected throughout the year and used as a decoction (25–40 g), internally as an antipyretic, and in cases of enteritis, diarrhea, dysentery, hematuria, irregular menses, amenorrhoea, colds, fever, upper respiratory tract infection, influenza, tonsillitis, pharyngitis, cough, and hemoptysis, and externally in cases of acute conjunctivitis, mastitis, traumatic injury, scalds, snake bites, pyoderma, eczema, and furunculosis. It contains doronine (**70**) and senkirkine (**74**) at a total concentration of up to 0.2% [115].
Use of such quantities of this herb may cause significant intoxication.

4.4.11. Farfugium japonicum (L.) Kitam. (syn. F. grande Lindl., syn. F. japonicum var. formosanum (Hayata) Kitam, syn. Ligularia kaempferi (DC.) Sieb. et Zucc., syn. Arnica tussilaginea Burm. F.), [Chin.: Lian peng cao]

This plant grows in Japan, and in China in the provinces of Fujian, Guangdong, Guanxi, Hubei, and Hunan as well as in Taiwan. The whole herb and/or the roots are collected in the summer and fall and used as a decoction (15–25 g), internally for colds, and flu, and externally for boils, pyodermas, and traumatic injuries. The whole plant contains petasitenine (**71**) and senkirkine (**74**) [116, 117].
Because of the carcinogenicity of these two otosenine alkaloids it should no longer be employed for medicinal purposes.

4.4.12. Gynura bicolor (Roxb. ex Willd.) DC. (syn. Cacalia bicolor Rox. ex Willd.) [Chin.: Guan yin xian]

Gynura bicolor is a perennial herb reaching a height of 30–60 cm and flowering in summer.
The whole plant is collected in the fall and dried and is used a as decoction (25–100 g), externally in cases of wound bleeding, and internally in cases of dysmenorrhoea, metorrhagia, and tuberculous hemoptysis, especially in Hong Kong.
The plant contains the toxic alkaloids integerrimine (**53**), nilgirine (**59**), usaramine (**52**), retrorsine (**51**), and hydroxyintegerrimine and the nontoxic alkaloids petasinine (**36**) and macrophylline (**37**) [118]. Due to its toxic components this plant should not be used.

4.4.13. Gynura divaricata (L.) D.C. (syn. G. ovalis (DC.), syn. G. pseudo-china DC, syn. G. auriculata Cass., syn. Senecio divaricatus (L.) D.C., syn. Cacalia ovalis Ker Gawl, syn C. incana L.) [Chin.: Pai pi chi, Bai bei san qui]

The plant is native to Vietnam and to China in the provinces of Guangdong, Hainan, Hong Kong, and Yunnan. The roots are collected in fall and winter, washed and dried in the sun, and used as decoction (10–15 g), internally in cases of bronchitis, pulmonary tuberculosis, and pertussis, or externally in cases of boils, pyodermas, traumatic injuries, fractures, and burns. The whole plant contains integerrimine (**53**) and usaramine (**52**) [119]. Use is not recommended.

4.4.14. Gynura segetum (Lour.) Merr. (syn. G. pinnatifida (Lour.) D.C., syn. G. japonica (Thunberg.) Juel, syn. Cacalia segetum Lour. Merr.) [Chin.: Jü shan qi, Tu san chii = Radix Gynurae, Hung pei san chi = Herba Gynurae]

This is a folk medicinal plant. The whole herb and the roots are collected in summer. The fresh or dried plant is used as a decoction (25–50 g), internally for hemoptysis, or externally for epitaxis, wound bleeding, and traumatic injuries. The roots are used to treat peripheral blood circulation disorders. The plant contains high amounts of senecionine (**50**), (*E*)-seneciphylline (**55**), and seneciphyllinine (**57**) [120–122].
Several deaths due to intoxication have been reported in the medical literature [123].

4.4.15. Ligularia dentata H. Hara (syn. L. clivorum Maxim., syn. L. japonica var. clivorum (Maxim. Macino, syn. Erythrochaete dentata A. Gray) [Chin.: Hu lu qi]

Ligularia dentata grows in both Japan and China. In the latter country it is widespread at altitudes ranging from 620 to 3200 m. Like *L. fischeri* which has the same Chinese name it is used for in cases of cough, traumatic injury, rheumatic bone pain, and pertussis. The roots collected in summer and fall are used [124, 125].
The plant contains the highly toxic alkaloids ligularidine (**75**), neoligularidine (**76**), and ligularizine (**73**) as well as the nontoxic ligularinine (**49**) at high concentration [126, 127]. The plant should on no account be used for medicinal purposes.

4.4.16. Petasites japonicus (Sieb. & Zucc.) F. W. Schmidt [Chin.: Feng dou cai, She tou tsao = Rhiz. Petasitidis, Japn.: Fukinotoh]

Petasites japonicus grows mainly in Japan, and sporadically in China. It is a traditional medicinal plant, collected in summer and fall, washed and used fresh or dried, employed internally as a decoction (15–25 g) in cases of colds, fever, and tonsillitis. Fresh roots macerated or boiled in water are used for external and topical application in cases of traumatic injuries, fractures, snake bites, and pyodermas. The plant contains the highly toxic OPAs petasitenine (syn. fukinotoxine) (**71**), neopetasitenine (**72**), and senkirkine (**74**) as well as the nontoxic PAs petasinine (**36**) and petasinoside (**45**) [126–132]. Several papers concerning the carcinogenicity of petasites have been published.
Numerous studies on animals showed how dubious use in humans would be [133–138].

4.4.17. Senecio argunensis Turcz. (syn. S. argunensis fo. angustifolius Kom. et fo., syn. S. latifolius Kom, syn. S. argunensis var. blinii (H. Lév.) Hand.-Mazz.) [Chin.: Yü yie qian li guang, Zhan long cao]

Senecio argunensis grows in Korea, Mongolia, Russia, and China. In the latter country it is widespread at altitudes of 500 to 3300 m. The whole plant is used as a folk medicine and displays antipyretic effects as well as detoxicant effects in the case of dysentery. It contains the alkaloids senecionine (**50**), integerrimine (**53**), seneciphylline (**55**), otosenine (**69**), (*E*)-erucifoline (**58**), and 21-hydroxyintegerrimine (**54**) [139, 140].
Since all these alkaloids are highly toxic, the plant should certainly not be used.

4.4.18. Senecio chrysanthemoides DC. (syn. S. laetus Edgew.) [Chin.: Chien li kuang, Tsang tu san chi]

According to the Pharmacopoeia Sinica of 1985 this plant is used in cases of traumatic injury, breast abscesses,

boils, and pyodermas. It contains the toxic seneciphylline (**55**) [141]. Continued use is not recommended.

4.4.19. Senecio integrifolius var. fauriri (L.) Chlairv. var. fauriri (Lévl. et Vant.) Kitam. (syn. S. fauriri Lévl. et Vant., syn. S. kirilowi Turcz., syn. Tephroseris integrifolia L., syn. Othonna integrifolia L.) [Chin.: Gou she cao]

This traditional Chinese medicinal plant is used for treatment of dysentery, conjunctivitis, and tumefaction. It contains the nontoxic alkaloids integrifoline (syn. *N*-methyldiangeloyl-10-hydroxyplatynium chloride) (**43**), 7-angeloylturneforcidine (**33**), 1,2-dihydrosenkirkine (**79**), 7-angeloylheliotridine (**7**) [142].

4.4.20. Senecio nemorensis (L.) (syn. S. nemorensis var. octoglossus (DC.) Koch ex Ledeb, syn. S. gampinensis Vaniot, syn. S. kematogensis Vaniot) [Chin.: Huana wan, Engl.: Nemorensis ragwort]

S. nemorensis occurs in Japan, Korea, Mongolia, Russia, and in China at altitudes of 700–3000 m. It is a traditional medicinal plant used in cases of enteritis, bacillar dysentery, hepatitis, boils, and pyodermas. It contains in addition to the open-chain PAs of the unsaturated retronecine and saturated platynecine species such as 7- and 9-angeloylretronecine (**1**, **2**), 7-senecioylretronecine (**3**), triangularine (**6**), fuchsisenecionine (**34**), and sarracine (**35**) and also macrocyclic 12- and 13-membered saturated and unsaturated alkaloids. These include platyphylline (**46**), nemorensine (**65**), bulgarsenine (**67**), retroisosenine (**66**), senecionine (**50**), and doronenine (**68**), and the *N*-oxides of these in various concentrations [143–151]. Extracts of *S. nemorensis* display both mutagenic and carcinogenic effects [152, 153] and should therefore no longer be used for therapeutical purposes.

4.4.21. Senecio scandens Buch.-Ham. Ex D. Don (syn. S. chinensis (Spr.) DC.) [Chin.: Quian li guang, Chiu li ming]

Senecio scandens grows in Bhutan, India, Japan, Myanmar, Nepal, Phillipines, Sri Lanka, Thailand and is widespread in China up to an altitudes of 3200 m.
According to the old pharmacopoeia only the herb of the plant was used officinally, e.g. as infusion in the case of oral and pharyngeal infections. The herb contains senecionine (**50**) and seneciphylline (**56**) [154] and should no longer be used for medicinal purposes.

4.4.22. Syneilesis aconitifolia (Bunge) Maxim. (syn. Cacalia aconitifolia B. Ge., syn. Cacalia aconitifolia Bunge, syn. Senecio aconitifolius (Bunge) Turcz.) [Chin.: Tu er shan]

This plant is native to Japan, Korea, Russia, and China. In the latter country it occurs at altitudes of 500–1800 m. It is a folk remedy employed internally for rheumatic astralgia, and costalgia, or externally for traumatic injury, boils, pyodermas, snake bite, and sprains. The plant is collected in the fall and contains the alkaloids syneilesine (**77**) and O^{14}-acetylsyneilesine (**78**) [155].

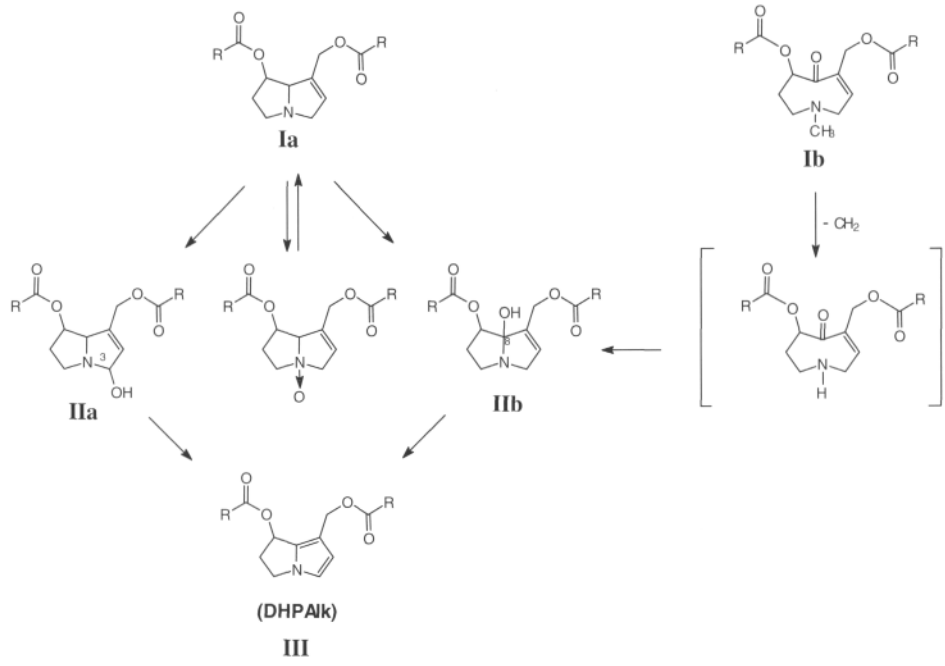
4.4.23. Tussilago farfara L. [Chin.: Kuan(g) dong hua, Chien hua, Engl.: Coltsfoot, Horsefoot]

Tussilago farfara is native to India, Pakistan, Russia, and China where it is widespread. For medical purposes flower buds are used internally in cases of cold, asthma, influenza, gastroenteritis, and diarrhea, and for metabolic stimulation, or blood purification and externally for the treatment of wounds. Depending on its origin, the dry drug contains various amounts of senkirkine (**74**) ranging from 0.1 to 150 ppm, and also 0.1 to 10 ppm of senecionine (**50**), in addition to the nontoxic alkaloids tussilagine (**38**) tussilaginine (**39**), isotussilagine (**40**), and isotussilaginine (**41**) in a total concentration of <2 ppm [156–164]. Owing to the known hepatotoxicity of senecionine and senkirkine, a Japanese working group performed a feeding experiment on rats with flower buds of Chinese origin for nearly two years. At a nonphysiologic high dosages hemangiosarcomas, hepatocellular adenomas, and carcinomas were found [165]. Leaves, flower buds or flowers of Chinese origin should no longer be used in Europe because leaves and flowers free from alkaloids are now on the market in Germany and Austria [166, 167].

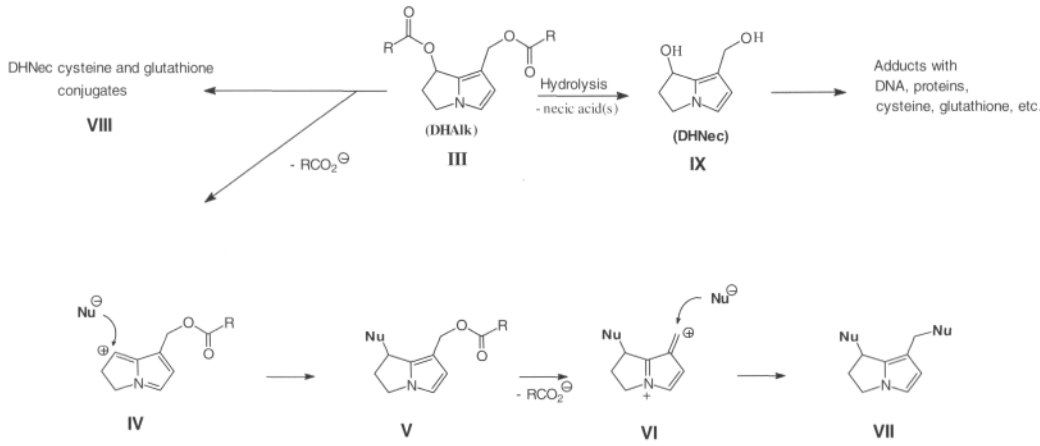
5. Metabolism and toxicity of pyrrolizidine alkaloids

PAs with 1,2-unsaturated necines such as retronecine, heliotridine and otonecine are known to be toxic to humans and livestock. The most important toxicological features are their hepatotoxicity [13–15, 17–19] and pneumotoxicity [168–172, 224, 225]. In addition, PAs cause significant mutagenicity [19], hepatomegalia, venoocclusive disease (VOD) of the liver, hepato-carcinogenicity [173–180], neurotoxicity [181], and embryotoxicity [19]. These effects are attributed to the toxification reaction in the liver.
The cyclic diesters are the most toxic alkaloids, and the noncyclic diesters are of intermediate toxicity, while the monoesters are the least toxic[2] (Fig. 2).
As esters alkaloids may be partially saponified by nonspecific hydrolases to the corresponding necines and necic acids both in the intestinal tract and during transit to the liver. The fission products are nontoxic like the parent alkaloids and are excreted via the renal system [184].
According to Scheme 2 the alkaloids (**Ia**) reaching the liver and not occurring as N-Oxides are oxidized by flavin-containing monooxygenase (FMO). Owing to their extremely high water solubility the N-oxides produced are either secreted or further transported to other tissues where they may be reduced and reabsorbed. Recent studies on alkaloids revealed that in the outer mitochondrial membrane bound flavoprotein monoamine oxidases A and B (MAO-A and MAO-B) the alkaloids are hydroxylated at the α-carbon atoms, that is the C atoms adjacent to the N atom. This process occurs at C-3 or C-8 leading to the very instable 3-hydroxy- or 8-hydroxypyrrolizidine alkaloid (**IIa**, or **IIb**). Cleavage of water from these alkaloids yields the highly reactive dehydropyrrolizidine alkaloids (DHPAlk, **III**). This reaction is catalyzed by members of the cytochrome 450 superfamily of hemoproteins.
Alkaloids of the otonecine type (**Ib**) differing from the other PAs by a methyl group at the N atom and a "quasi" ketonic function at C-8 probably also undergo a similar degradation. After demethylation the nor-*N*-otonecine alkaloid rearranges to the very instable 8-hydroxy derivative **IIb** and the latter to the corresponding dehydropyrrolizidine alkaloid DHPAlk (**III**) [185–192].
Cellular nucleophiles (Nu^-), such as $-OH$, $-NH_2$, $-NH$, $-SH$ of amino acids, enzymes, proteins, hemoglobin but also of purine and pyrimidine bases and their nucleosides may react with formation of the corresponding adducts as described in Scheme 3 for the conversion of **IV** to **VII** proceeding via the intermediates **V** and **VI** [193–214].

Scheme 2: Metabolic pathway of toxic PAs



Scheme 3



The reaction of dehydromonocrotaline, a putative toxic metabolite, with various nucleosides yields N-alkylated adducts (Fig. 3) [214].

The patterns of the proteins crosslinked to DNA are similar to those induced by the standard bifunctional alkylating agent mitomycin C, that possesses the partial structure of a PA [202, 205, 208]. In the presence of DNA and/or RNA the diesters undergo either a simple or a double bimolecular nucleophilic substitution (Scheme 3 **IV** and **VII**) to afford irreversibly cross-linking adducts. If no repair process occurs, a carcinogenic reaction may be programmed.

The DHPAlks (**III**) may also be cleaved by hydrolases with the formation of reactive dehydronecines DHNec (**IX**)[3] and the corresponding necic acids. DHNec has also been shown to be a potent electrophile capable of covalently binding to tissue constituents, including nucleosides and nucleotides [190, 193, 195, 197, 200, 201].

The reactions of DHPAlks and DHNecs with cysteine and/or glutathione yielding the 7- and 7,9-adducts (Fig. 4) are particularly important because they may be regarded as detoxification processes.

Since these adducts are readily soluble in water, they are excreted renally and/or biliarily as N-acetyl derivates [213–225].

DHNec adducts which may be transported with blood to other organs such as the lung cause pulmonary damage combined with pulmonary-arterial hypertension and subsequent right ventricular failure of the heart cor pulmonale. However, it has also been shown that some PAs circulate unchanged to other tissues where they are activated by local tissue mixed function oxydases. Pulmonary toxicity is partly a result of pyrrole production within pulmonary endothelial cells [226, 227].

6. Conclusion

Although widespread intoxications such as incidents reported 50–70 years ago, caused by contamination of cereal used for the production of bread with pyrrolizidine-

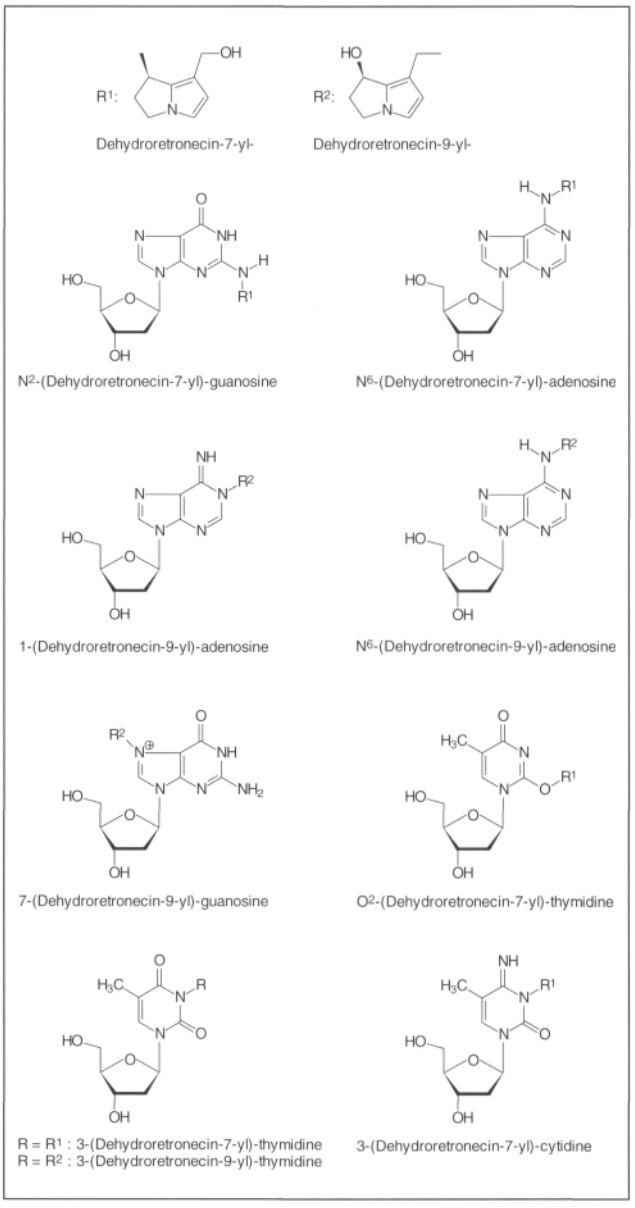


Fig. 3: Structures of dehydroretronecine (DHR) of nucleoside- and nucleotide-adducts

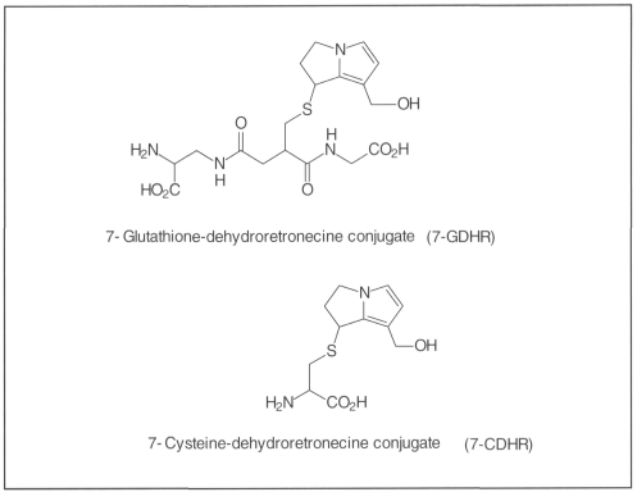


Fig. 4: Conjugates of dehydronecine (DHNec) with glutathione and cysteine

containing plants are highly unlikely, it is by no means the case that PA-containing plants are no longer used for herbal or medicinal purposes. As mentioned at the beginning of this paper, Chinese plants have recently occasioned particular interest. They are to an extent regarded as "wonder plants". There are only a few reported cases of intoxication caused by Chinese plants in the medical literature. This may be explained by the fact that they are rarely documented in medical literature [123] or that intoxications are not attributed to PA-containing plants, even though intoxication occurs in China. Although not all the plants discussed here contain toxic components care should nevertheless be exercised as they may be contaminated with closely related species.

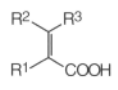
The safest protection against PA intoxications is to follow the guidelines of the German Federal Health Department which limit the use of over 600 herbal remedies and medicinal plants. In order to reduce health risks it is stated that plants containing unacceptably high toxic PA concentrations may be sold and used only if daily external exposure is restricted to no more than 100 µg PAs and internal exposure to no more than 1 µg per day for no more than six weeks a year. This does not apply to PA-containing drugs if daily exposure does not exceed 0.1 µg for internal application and 10 µg for external application [228]. These guidelines apply not only in Germany but are also almost the same in Austria and Switzerland. The regulations are expected to become applicable to the whole of Europe. If these criteria are also applied to Chinese plants and if the recommendations listed in this article are followed hazards caused by Chinese remedies and medicinal plants will not arise.

[1] Dashed and thickened lines (wedges) denote α and ß orientation of bonds, respectively; α meaning orientation away from the observer, β towards the observer. With a few exceptions the bases of all alkaloids belong to the C-8α series [12].

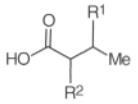
[2] The metabolic processes presumed to occur are described in Scheme 3 [1, 2] after Stegelmeier et al. [182] and Prakash et al. [183]. The comparative metabolisms were studied *in vitro* with hepatic microsomes of cattle, chicken, gerbils, guinea pigs, hamsters, horses, rabbits, rats, sheep, Japanese quails, and human liver [186]. Although different susceptibilities have been detected it may be assumed that completely analogous reactions proceed in humans.

[3] DHNec = 7(R or S)-hydroxy-1-hydroxymethyl-6,7-dihydro-5H-pyrrolizidine

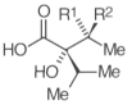
Necic acids



R1	R2	R3		
H	Me	Me	senecioic acid	(Sen)
Me	Me	H	tiglic acid	(Tig)
Me	H	Me	angelic acid	(Ang)
CH_2OH	H	Me	sarracinic acid	(Sar)

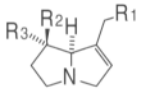


R1	R2		
Me	H	2-methylbutyric acid	(Meb)
OH	H	2,3-dihydroxybutyric acid	(Dhb)

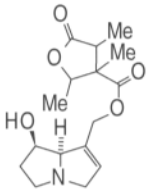


R1	R2		
H	OH	(-)-viridifloric acid	(Vir)
OH	H	(+)-trachelanthic acid	(Trc)
OAc	H	3'-O-acetyl-(+)-trachelanthic acid	(Actrc)

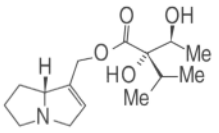
Pyrrolizidine alkaloids



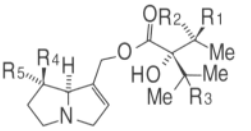
R_1	R_2	R_3		
OH	OAng	H	7-angeloylretronecine	1
OAng	OH	H	9-angeloylretronecine	2
OH	OSen	H	7-senecioylretronecine	3
OTrc	OH	H	indicine	4
OAcTrc	OH	H	3'-acetylindicine	5
OSar	OAng	H	triangularine	6
OH	H	OAng	7-angeloylheliotridine	7
OMeB	H	OAng	7-angeloyl-9-(2-methyl-butyryl)heliotridine	8
ODHB	H	OAng	7-angeloyl-9-(dihydroxy-butyryl)lheliotridine	9
OH	H	OTig	7-tigloylheliotridine	10



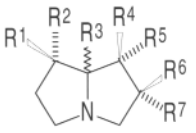
assamicadine **29**



cynaustine **30**



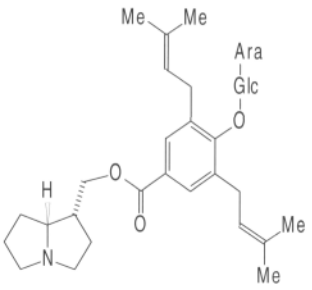
R_1	R_2	R_3	R_4	R_5		
OH	H	H	H	H	amabiline	11
H	OH	H	H	H	supinine	12
H	OMe	H	H	H	heleurine	13
OH	H	H	OH	H	lycopsamine	14
H	OH	H	OH	H	intermedine	15
H	OH	H	OTig	H	myoscorpine	16
H	OH	OH	OTig	H	hydroxymyoscorpine	17
OH	H	H	H	OH	echinatine	18
OAc	H	H	H	OH	3'-acetylechinatine	19
OH	H	H	H	OAc	7-acetylechinatine	20
OH	H	H	H	OAng	7-angeloylechinatine	21
H	OH	H	H	OH	rinderine	22
H	OAc	H	H	OH	3'-acetylrinderine	23
H	OH	H	H	OAc	7-angeloylrinderine	24
H	OMe	H	H	OH	heliotrine	25
H	OMe	OH	H	OAng	lasiocarpine	26
OH	H	OH	H	OAng	heliosupine	27
OAc	H	OH	H	OAng	3'-acetylheliosupine	28



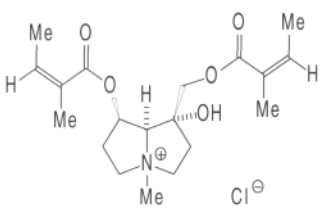
R^1	R^2	R^3	R^4	R^5	R^6	R^7		
H	H	H	H	CH_2OTrc	H	H	trachelanthamine	31
H	H	H	H	CH_2OVir	H	H	viridiflorine	32
OAng	H	H	H	OH	H	H	7-angeloylturneforcidine	33
H	OH	H	CH_2OSen	H	H	H	fuchsisenecionine	34
H	OAng	H	CH_2OSar	H	H	H	sarracine	35
H	H	H	CH_2OH	H	OAng	H	petasinine	36
OH	OSen	H	H	OSen	H	H	macrophylline	37
H	H	H	H	CO_2Me	Me	OH	tussilagine	38
H	H	H	CO_2Me	H	OH	Me	tussilaginine	39
H	H	H	H	CO_2Me	OH	Me	isotussilagine	40
H	H	H	CO_2Me	H	Me	OH	isotussilaginine	41

7. Appendix: Alkaloids in Chinese medical plants

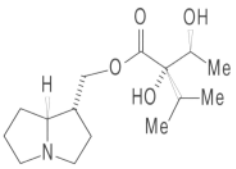
In the appendix all alkaloids occurring in Chinese medicinal plants are listed. In order to obtain a better survey of the structural formulae of these alkaloids, frequently occurring acids are compiled at the beginning of the list and are given abbreviations which are also used for the alkaloid formulae.



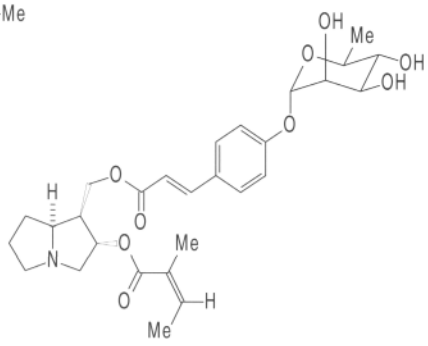
nervosine **42**



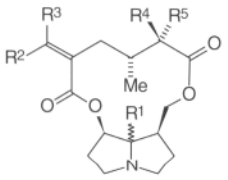
integrifoline **43**



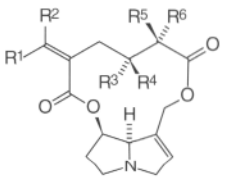
cynaustraline **44**



petasinoside **45**

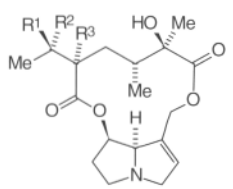


R1	R2	R3	R4	R5		
H⋯	Me	H	OH	Me	platyphylline	**46**
H⋯	H	Me	OH	Me	neoplatyphylline	**47**
H—	H	Me	OH	Me	hastacine	**48**
H⋯	Me	H	Me	OH	ligularinine	**49**

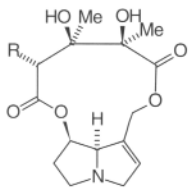


R1	R2	R3	R4	R5	R6		
Me	H	Me	H	OH	Me	senecionine	**50**
Me	H	Me	H	OH	CH_2OH	retrorsine	**51**
H	Me	Me	H	OH	CH_2OH	usaramine	**52**
H	Me	Me	H	OH	Me	integerrimine	**53**
H	CH_2OH	Me	H	OH	Me	21-hydroxyintegerrimine	**54**
H	Me	$=CH_2$		OH	Me	(E)-seneciphylline	**55**
Me	H	$=CH_2$		OH	Me	(Z)-seneciphylline	**56**
Me	H	$=CH_2$		OAc*	Me*	seneciphyllinine	**57**
H	Me	Me	—O—		Me	(E)-erucifoline	**58**
H	Me	Me*	H*	OH*	H*	nilgirine	**59**

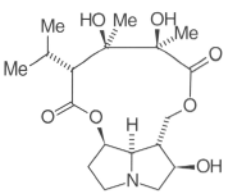
* stereochemistry estimated



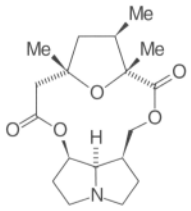
R1	R2	R3		
OH	H	OH	jacoline	**60**
H	—O—		jacobine	**61**



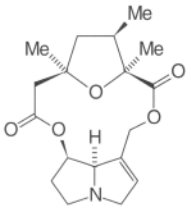
R		
Me	monocrotaline	**62**
i-Pr	trichodesmine	**63**



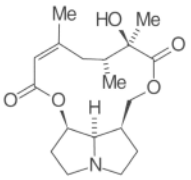
croalbidine **64**



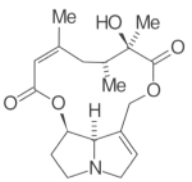
nemorensine **65**



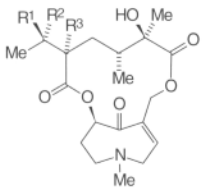
retroisosenine **66**



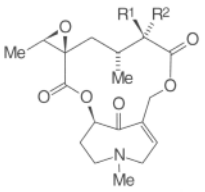
bulgarsenine **67**



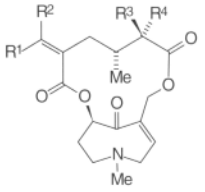
doronenine **68**



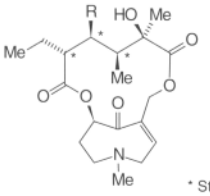
R1	R2	R3		
H	—O—		otosenine	**69**
Cl	H	OH	doronine	**70**



R1	R2		
OH	Me	petasitenine	**71**
OAc	Me	neopetasitenine	**72**
Me	OAc	ligularizine	**73**

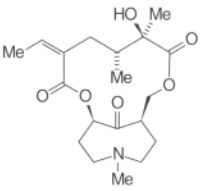


R1	R2	R3	R4		
Me	H	OH	Me	senkirkine	**74**
H	Me	Me	OAc	ligularidine	**75**
Me	H	Me	OAc	neoligularidine	**76**



* Stereochemistry estimated according to NMR data

R		
OH	syneilesine	**77**
OAc	O14-acetylsyneilesine	**78**



1,2-dihydrosenkirkine **79**

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Prof. Dr. E. Roeder
Pharmazeutisches Institut
Universität Bonn
An der Immenburg 4
D-53121 Bonn
Roeder@uni-bonn.de