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Pyrrolizidine alkaloids in medicinal plants of Mongolia, Nepal and Tibet

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Dedicated to Prof. Dr. Dr. h.c. H. J. Roth on the occasion of his 80th birthday.

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Pyrrolizidine alkaloids (PAs) are widely distributed in many plant families. Most of them are hazardous for humans and domestic animals. PA also occur in many medicinal plants. This is of importance because in Western countries the use of plants or preparations of them is more and more increasing. Especially plants of the Traditional Chinese Medicine (TCM) have increased in popularity. Similarly, people are also focused on medicinal plants from other traditional medicines. Nowadays the Traditional Mongolian Medicine (TMM), the Traditional Nepalese Medicine (TNM), and the Tibetan System of Medicine (TSM) are becoming more and more of interest. In those countries application of those phytopharmaceutics is based on its traditional use but a scientific investigation – especially for possible toxic side-effects – is often missing. This paper gives an overview on traditionally used plants from Nepal, Mongolia and Tibet with respect to its content or its possible content of pyrrolizidine alkaloids.

1. Introduction

In the middle of the last century many episodes of human and animal intoxication, resulting from consumption of certain plant genera belonging to the families Asteraceae, Leguminosae and Boraginaceae, were shown to be caused by pyrrolizidine alkaloids (Schoental 1959; Bull et al. 1968).

Recognition of this mode of human pyrrolizidine alkaloid intoxication was followed by investigations into herbal teas and their connection with liver disease in Jamaica and other parts of the West Indies in the 1950s. The use of herbal teas made from pyrrolizidine alkaloid-producing plants to treat minor illnesses is also recognised as a cause of liver disease in parts of Africa and other tropical and subtropical countries. Though pyrrolizidine alkaloid poisoning is more common in developing countries, where traditional herbal medicines are widely used, industrialised countries such as the USA and UK have also reported pyrrolizidine alkaloid intoxications from consumption of herbal medicines. Germany, Switzerland and Austria, where it was claimed in the 1980s by some herbal medicine practitioners that traditional medicinal plants had therapeutic benefits without the undesirable side effects reported for other medicines, have also reported fatal cases of pyrrolizidine alkaloid intoxication from consumption of traditional herbal products that contain pyrrolizidine alkaloids.

In 1992, after several years of investigation, the German Federal Department of Health promulgated regulations severely restricting manufacture and sale of all herbal medicines containing pyrrolizidine alkaloids with a 1,2-unsaturated necine moiety that confers carcinogenicity and hepatotoxicity. Exempt are pyrrolizidine alkaloid-containing pharmaceuticals with no more than 1 microgram of 1,2-dehydropyrrolizidine alkaloids per daily oral dose or less than 100 micrograms in the case of a topically applied product. These regulations also apply to homeopathic pharmaceuticals having potency up to D6 for inter-

nal use and D4 for external application. The German regulations also require that these products are not prescribed for women who are pregnant or breast-feeding and they must have a warning label to that effect. Switzerland and Austria have banned all pyrrolizidine alkaloid-containing herbal medicines and the Netherlands has a regulation limiting pyrrolizidine alkaloids to 1 microgram per kg of food (gFDH 1992).

Pyrrolizidine alkaloids form a large group of plant secondary chemicals that occur in an estimated 5 % of flowering plants. They are made of two parts, a basic amino alcohol moiety, referred to as a necine, and one or more acids (necic acids) that esterify the alcohol groups of the necines (Bull et al. 1968; Smith et al. 1981; IPCS 1988; Rizk 1991; Hartmann et al. 1995). 1,2-Dehydropyrrolizidine ester alkaloids and their N-oxides, with 1,2-unsaturated necines, i.e. esters of supinidine, retronecine, heliotridine, crotanecine and otonecine are carcinogenic, mutagenic, genotoxic, fetotoxic and teratogenic to varying degrees (Culvenor et al. 1976; Huxtable 1989; Fu et al. 2001, 2002, 2004; Xia et al. 2006).

Some of the 1,2-dehydropyrrolizidine alkaloids (e.g. fulvine and monocrotaline) are also pneumotoxic. Pyrrolizidine alkaloids without the 1,2-double bond, those with platynecine, hastanecine, rosmarinine and isoretronecanol do not show these toxicities (Mattocks et al. 1971).

The mechanism by which 1,2-dehydropyrrolizidine alkaloids cause toxicity in mammals is well established (Mattocks 1968; Culvenor et al. 1969; Jago et al. 1970; Culvenor et al. 1971).

Following ingestion and absorption from the gut, cytochrome P-450 mono-oxygenase isozymes, located primarily in the liver, introduce a hydroxyl group on C-3 or C-8, adjacent to the nitrogen in the unsaturated ring (Fig. 1: **Ia/Ib**).

The resultant carbinolamines are unstable and dehydrate to produce the didehydro-pyrrolizidine (dihydropyrrolizine). The metabolites are no longer alkaloids because the electrons of the formerly basic nitrogen are delocalised in the aromatic

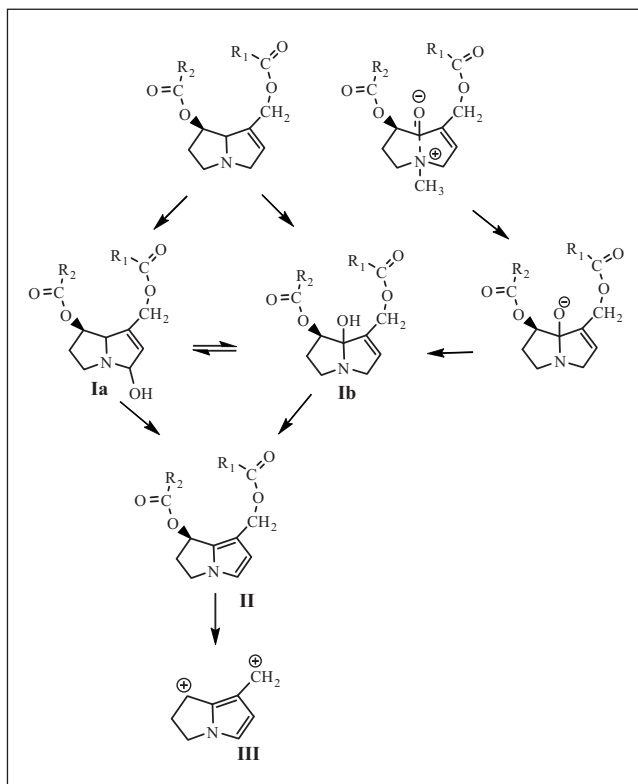


Fig. 1: Metabolism of non-saturated PAs

system. Dehydration is driven by conjugation of the newly formed double bond with the 1,2-double bond and by subsequent spontaneous rearrangement of the diene to the aromatic dihydropyrrolizidine ("pyrrolic") system (Fig. 1: **II**).

If the alcohols at C7 and C9 are esterified carbonium ion formation is greatly facilitated because the acid moiety provides a good leaving group (Fig. 1: **III**). In the case of dihydropyrrolizidines with unesterified hydroxyls at C7 and/or C9 (e.g. the dehydronecines) formation of carbonium ions at C-7 and C-9 is not as spontaneous but can be facilitated, as for analogous benzylic hydroxyls, by protonation of the hydroxyls leading to loss of H₂O. (Culvenor et al. 1971). *In vivo*, following the generation of dihydropyrrolizidine metabolites the C-7 and C-9 carbonium ions that are formed react rapidly and spontaneously with nucleophilic centres on, for example, vital proteins and nucleosides. In the case of proteins, mercapto, hydroxyl and amino groups are attacked and the amino groups of purine and pyrimidine bases are alkylated in the case of DNA and RNA. The resulting products, proteins and nucleosides with dihydropyrrolizidine adducts, cannot perform their normal, often vital functions. In the case of DNA, mutations are a possible outcome. The extremely high chemical reactivity of the dihydropyrrolizidine metabolites causes considerable tissue damage in the liver and disruptions to normal biochemical processes, resulting in the pathology and liver damage observed.

There are three dose-related levels of poisoning of humans and animals by 1,2-dehydropyrrolizidine ester alkaloids: acute, sub-acute and chronic. These levels of toxicity can also be sequential, progressing from acute to sub-acute, and finally causing irreversible, chronic (long-lasting, irreversible) toxic effects (McLean 1970; Peterson et al. 1983; IPCS 1988; Huxtable 1989; Prakash et al. 1999; Stegelmeier et al. 1999; Fu et al. 2001, 2002, 2004; Xia et al. 2006; Wang et al. 2005).

The metabolic conversion of 1,2-dehydropyrrolizidine ester alkaloids into strongly alkylating dihydropyrrolizidine esters (carbonium ions) and demonstration that these cause chemical

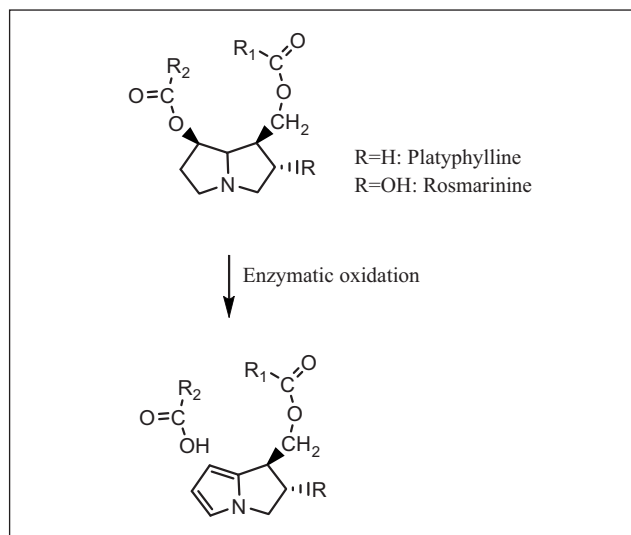


Fig. 2: Metabolism of saturated PAs

modification to genetic material raises expectations that they will behave as genotoxic carcinogens *in vivo* and a number of 1,2-dehydropyrrolizidine alkaloids have been shown to be carcinogenic, mutagenic and genotoxic as well as teratogenic and fetotoxic in experimental animals, primarily rats.

Metabolism of saturated pyrrolizidine alkaloids (necic acid esters of platynecine, hastanecine, rosmarinine and isoretronecanol) by mammals has not yet been extensively studied, in part because the saturated ester alkaloids and their necines do not display mammalian toxicity.

While 1,2-dehydropyrrolizidine alkaloids are metabolised by liver P-450 isozymes into hazardous dihydropyrrolizidines (e.g. **II**, Fig. 1) with a pyrrolic ring, saturated pyrrolizidine alkaloids produce non-toxic, metabolites. The saturated alkaloids platyphylline and rosmarinine (Fig. 2), for example, are converted by liver microsomes into pyrrolic metabolites with an aromatic ring (Mattocks et al. 1971). These are devoid of biological alkylating properties and are heights hepatotoxic nor carcinogenic.

Whereas in industrialised countries intoxications by PA containing plant material are rare and furthermore the use of medical plants containing PA is restricted by state laws, in developing countries PA poisoning is common.

In Mongolia, Tibet and Nepal several medical plants are traditionally used which have already been reported to contain PAs, or which are used in spite to contain those toxins.

In the following part these medical plants with their common names and the indication of use are listed. Toxicity aspects are discussed.

2. Mongolian, Nepalese and Tibetan plant containing pyrrolizidine alkaloids

2.1. PA-containing medicinal plants of the family Orchidaceae (Tribe Vandeeae)

The Orchidaceae is the largest family in the plant kingdom, containing 30 000 until 35 000 species. Pyrrolizidine alkaloids are found only in a few species and are non-toxic.

2.1.1. *Vanda christata* Lindley, (syn. *V. alpina* Wallich ex Lindley, syn. *Aerides cristatum* Wallich ex Hooker fil.)

V. christata is a medicinal plant of Nepal (Manandhar 2002, Ioshi et al. 2006) [Nep.: *Bhyagute phu*].

Distribution: This plant, an epiphytic orchid, grows in central and eastern Nepal at 1300–2300 m, common on tree trunks, and branches, also in northern and eastern India, Bhutan and Tibet. Use: A paste of the roots is applied to boils, it is also used to treat dislocated bones.

Leaves are used as expectorant. All parts of the plant contain the alkaloid acetylloburnine (7). (Lindström et al. 1969, Brandänge et al. 1973).

2.1.2. *Vanda teres* Lindley, (syn. *Dendrobium teres* Roxburgh).

V. teres is a medicinal plant of Nepal (Manandhar 2002, Ioshi et al. 2006) [Nep.: Harjor, Thurjo].

Distribution: In eastern and central Nepal at 1400–2300 m on tree trunks and branches; also in northern and eastern India.

Use: A paste of the plants is applied to treat dislocated bones. Alkaloids are unknown. Compare with *Vanda christata*. Presumably it has saturated non-toxic pyrrolizidine alkaloids.

2.2. PA-containing medicinal plants of the family Fabaceae (Tribe Crotalariaeae)

The genus *Crotalaria*, subtribe *Crotalariaeae* (Fabaceae) contains over 600 species distributed principally throughout tropical and subtropical areas of the world. Many of this species contain pyrrolizidine alkaloids which are toxic to livestock.

2.2.1. *Crotalaria alata* Buch.-Ham. ex D. Don, (syn. *C. bialata* auct. non Schrank)

C. alata is a medicinal plant of Nepal (Rajbhandari 2001; Manandhar 2002, 2003; Singh et al. 2003; Baral et al. 2006) [Nep.: Boksi baja, Thulo chheke, Singe-singe, Singesinge-N, Chhimchine].

Distribution: This plant, a subshrub, grows throughout Nepal to about 2000 m, also in northern India, Bhutan, south eastern Asia, China.

Use: It is a medicinal plant in Nepal. Root juice or plant juice is given to relieve fever and malarial fever, and in case of nocturnal discharge.

The plant contains in all parts especially in the seeds monocrotaline (74), and spectabiline (76) (Sharma et al. 1965; Williams et al. 1987).

It should not longer be used as a traditional medicinal plant because of its high alkaloid content and the hepatotoxic effect of the alkaloids.

2.2.2. *Crotalaria albida* Heyne ex Roth. (syn. *C. linifolia* Lin. fil., *C. formosana* Matsum. ex Ito & Matsum., syn. *C. montana* Roxb.)

C. albida is a medicinal plant of Nepal (Anon. 1970; Manandhar 2002, 2003; Singh et al. 2003; Baral et al. 2006) [Nep.: Putali phul, Bheni phul, Bheri phul, Bhehedi phul, Engl.: Rattlebox]. It is also a medicinal plant in China [Chin.: Huang hua di ding] (Roeder 2000).

Distribution: It is an annual plant and grows throughout Nepal and China, at 1400–2100 m on open hillsides, also in northern India, Bhutan, south eastern Asia, Taiwan.

Use: Juice of the root is given to treat malarial fever, root juice is also given for indigestion. Plant paste is applied to treat warts on the sole and its juice is given for indigestion.

The plant contains the alkaloid croalbidine (73). (Sharma et al. 1965; Sawhney et al. 1973; Sawhney et al. 1974). There are no objections towards a therapeutic use.

2.2.3. *Crotalaria cytisoides* Roxb. ex DC. (syn. *C. psoraloides* D. Don., syn. *Priotropis cytisoides* Whigte & Arnott)

C. cytisoides is a medicinal plant of Nepal (Rajbhandari 2001; Manandhar 2002, 2003; Singh et al. 2003) [Nep.: Bakhre ghans, Silsile].

Distribution: Growing throughout Nepal at 1200–2200 m in open, rocky places, also in northern India, Bhutan, West-China. Use: Juice of leaves is applied to treat cuts and wounds. Alkaloids are unknown, but the plant is belonging to the genus *Crotalaria* and many plants of this genus have toxic alkaloids. Also external use is not recommended.

2.2.4. *Crotalaria ferruginea* Graham ex Benth.

C. ferruginea is a medicinal plant in Nepal (Rajbhandari 2001; Manandhar 2002, 2003; Singh et al. 2003; Baral et al. 2006) [Nep.: Junbgra ban].

Distribution: In eastern and central Nepal at 1400–1900 m in open sunny places, India, south eastern Asia, China, Malaysia. Use: Juice of root is given to treat fever, juice of leaf is applied to treat cuts and wounds.

Alkaloids are unknown, but this plant is belonging to the genus *Crotalaria* and many plants of this genus have toxic alkaloids. Internal use is not recommended.

2.2.5. *Crotalaria juncea* L.

C. juncea is a medicinal plant in Nepal (Anon. 1970; Rajbhandari 2001; Manandhar 2002, 2003; Singh et al. 2003; Baral et al. 2006) [Nep.: Chin chine, Chikachhike san, Engl.: Sun-hemp].

Distribution: It is a perennial subshrub-like herb growing throughout Nepal to about 1300 m, and is cultivated throughout the foothills of Himalaya to Sri Lanka, and in the east tropics.

Use: Leafes are refrigerant, demulcent, emetic and purgative, also used to purify blood.

Seeds are emmenagogue, poisonous to livestock. As healers know, the plant especially the seeds are toxic. The plant contains in all parts integerrimine (53), senecionine (57), seneciophylline (60), riddelliine (61), trichodesmine (77), and junceine (78). (Adams et al. 1956; Sharma et al. 1965; Prakash et al. 1985; Zhang et al. 1985; Williams et al. 1987; Xiuhong et al. 2005). The plant should not to be used for medicinal purposes.

2.2.6. *Crotalaria pallida* Aiton (syn. *C. mucronata* Desv.)

C. pallida is a medicinal plant in Nepal (Rai 2004; Baral et al. 2006) [Nep.: Chhin-chhine, Engl.: Sun-hemp, Streaked Rattlepod]. It is also a medicinal plant in China [Xiang ling cao] (Roeder 2000). Distribution: This plant is a perennial subshrub-like herb which is introduced in Asia, Malaysia in tropical Africa, native of Central and Tropical America. The root causes vomiting. Leaves are useful in diarrhoea, dysentery and bleeding disorders. Leaf paste is applied to swellings, leprosy, and other skin diseases; paste of seeds cures ulcers.

Use in eastern Nepal: Root paste (one teaspoon ful) is drunk with water for three consecutive days to cure body-swelling. All parts of the plant contain, mucronatinine (51), nilgirine (52), usaramine (55), crotastriatine (56), monocrotaline (74), and cromadurine (75). (Chu et al. 1964; Sawhney et al. 1967; Bhacca et al. 1968; Atal et al. 1968; Han et al. 1981; Williams et al. 1987). The plant should not be used medicinally.

2.2.7. *Crotalaria prostrata* Rottb. ex Willd. (syn. *C. hirsuta* Wild.)

C. prostrata is a medicinal plant in Nepal (Rajbhandari 2001; Manandhar 2002, 2003; Singh et al. 2003; Baral et al. 2006) [Nep.: *Saano boksi baja*, *Ban san*, *Sano chheke*].

Distribution: The plant, a shrub, is growing throughout 500–2000 m in open, sunny places, also in northern India, Sri Lanka, and Malaysia.

Use: A paste and juice of plant is applied on cuts and wounds, and against gout. Root paste is used to treat diarrhoea and stomachache.

Alkaloids are unknown, but the plant is belonging to the genus *Crotalaria* and many plants of this genus have toxic alkaloids. Internal use is not recommended.

2.2.8. *Crotalaria sessiliflora* L. (syn. *C. nepalensis* Link, syn. *C. anthylloides* Lamarck, syn. *C. brevipes* Champ. ex Benth., *C. eriantha* Sieb. et Zucc.)

C. sessiliflora is a medicinal plant in Nepal (Manandhar 2002, 2003; Singh et al. 2003; Baral et al. 2006) [Nep.: *Sokrok*, *Setu phul*, *Sikrebha*]. It is also a medicinal plant in China [Chin.: *Ye bai he*; *Non ji li*] (Roeder 2000).

Distribution: It is an annual erect herb, growing throughout Nepal at 200–2800 m in open, on river banks and grassy places; also in China, north eastern India, Bhutan, south eastern Asia, Malaysia, Japan.

The juice of plant is applied to treat cuts and wounds, and is applied on forehead for headache. The plant and the seeds contain in high concentration integerrimine (53), monocrotaline (74), and trichodesmine (77) (Sharma et al. 1965; Sha et al. 1980; Huang et al. 1980; Roeder et al. 1992). This plant should not be used therapeutically even for external purposes.

2.2.9. *Crotalaria spectabilis* Roth (syn. *C. sericea* Retz., syn. *C. leschenaultia* de Candolle)

C. spectabilis is a medicinal plant in Nepal (Anon. 1970; Manandhar 2002, 2003; Singh et al. 2003; Baral et al. 2006) [Nep.: *Chhin-chhin bikh*, *Bhuban jhar*, Engl.: *Showy Rattle pod*, *Rattle box*].

Distribution: This plant, a herb, is native in eastern and central Nepal and India, growing about 2000 m in open places.

Use: Plant is used in treat scabies and impetigo. As already stated in Nepalese regulations, it is poisonous to livestock. However, people cook the flowers and eat them as vegetable.

The plant contains the alkaloids retusine (72), monocrotaline (74), and spectabiline (76).

(Adams et al. 1939; Culvenor et al. 1957; Williams et al. 1987). According to present knowledge this plant should not be used.

2.2.10. *Crotalaria tetragona* Roxb. ex Andrews, (syn. *C. sesquirolia* H. Lév., syn. *C. grandiflora* Zoll.)

C. tetragona is a medicinal plant in Nepal and Tibet (Sharma 1993; Manandhar 2002, 2003; Singh et al. 2003) [Nep.: *Bhugan*, *Chepang bhwan sak*, *Chhan goi*, Tib.: *Gungri*, *Mongan*].

Distribution: It is also a medicinal plant in China [Huan jin da] (Roeder 2000). This plant, a stiff shrub, grows throughout Nepal and China, at altitudes of 500–1700 m on open slopes, also in northern India, Bhutan, near Indo-Tibetan border in the Himalayas ranging from 2500–4000 m. It is a perennial herb.

Use: For medicinal purposes the whole plant together with the root is used. Leaf paste is taken internally to treat high fevers. It is also used as a blood purifier.

Juice of leaf is applied to treat cuts and wounds. All parts of the plant contain high amounts of integerrimine (53), and tri-

chodesmine (77) (Puri et al. 1974; Suri et al. 1975a). This plant should no longer be used therapeutically.

2.2.11. *Crotalaria verrucosa* L.

C. verrucosa is a medicinal plant of Nepal (Anon. 1970; Baral et al. 2006) [Nep.: *Chhiku*, *Sobhaa puspi*, *Shova pusphi*. Engl.: *Purple-flowered Rattle pod*].

Distribution: A native plant of tropical Africa, a herb, widely cultivated as a green manure and readily naturalized in tropical Asia and therefore also in Nepal.

Use: Leaf juice is used in scabies and impetigo both internally and externally, considered efficacious in diminishing salivation, also applied on scabies and impetigo.

This plant contains in all parts anacrotine (50), crotaverrine (62), and O¹²-Acetylcrotaverrine (63) (Sharma et al. 1965; Suri et al. 1976). The plant should no longer be used.

2.3. PA-containing medicinal plants of the family Boraginaceae

The family *Boraginaceae* is world-wide distributed and comprises about 100 genera and 2000 species, mainly herbs and shrubs. Many members of the genera of the tribes *Boraginoideae*, *Lithospermeae*, *Cynoglosseae*, *Heliotropioideae*, *Eritrichieae* contain non-toxic and/or toxic pyrrolizidine alkaloids.

2.3.1. *Arnebia benthamii* (Wall. ex G. Don) I. M. Johnston, (syn. *Echium benthami* Wall. ex G. Don., syn. *Macrotomia benthamii* (Wall) A. DC.)

A. benthamii is a medicinal plant in Nepal and Tibet. (Lama et al. 2001; Kala 2003; Baral et al. 2006) [Nep.: *Mahaa rangi*, *Ulte bhutkesh*, *Demok*, *Koma*, *Muktsi*; Tib.: *Mahaa rangi*, *Ulte bhutkesh*].

Distribution: Perennial herb, growing in Trans-Himalaya, Kashmir to western Nepal, in dry open slopes; 2800–4300 m.

Use: Useful in diseases of the tongue and throat; also used in blood disorder, high blood pressure, fever, lung diseases, cough, body ache, headache. Extract of the root stalk mixed with hair oil is applied to cure dandruff, blood pressure, fever, lung diseases, cough, body ache and earache.

Alkaloids are unknown. Compare with *Arnebia euchroma* (Roeder et al. 1993a). For the indications mentioned it may be used with restrictions.

2.3.2. *Arnebia euchroma* (Royle ex Benth.) I.M. Jonston, (syn. *Macrotomia euchroma* (Royle) Paulsen)

A. euchroma is a medicinal plant in Nepal and Tibet (Kala 2003, Baral et al. 2006, Smanla 2007) [Nep.: *Demok*; Tib.: *Bri mog*]. It is also a medicinal plant in China [*Zi cao*, *Ruan zi cao*, *Juan tsu tsao*]. (Roeder 2000)

Distribution: It is a perennial herb, growing in western and central Asia, Kashmir to Nepal, and China, rocky slopes, 3700 m. Use in Nepal: Bruised root is applied to eruptions; and to relieve toothache and earache.

Use in Tibet: Good for cough, expectorant. Good for blood disorders. Yields red colour for colouring tormas. Contains the alkaloids O⁷-Angeloylretronecine (18), O⁹-angeloylretronecine (23) (Roeder et al. 1993a).

Although these alkaloids show only moderate toxicity, the plant should not be used medicinally.

2.3.3. *Cynoglossum amabile* Stapf & J. R. Drummond

C. amabile is a medicinal plant of Tibet (Phuntsog 2006) [Tib.: *Nadma byarma*]. It is also a medicinal plant in China [Chin.: *Gou shi hua*] (Roeder 2000).

Distribution: Perennial herb is naturally occurring in the south western provinces of Tibet, Bhutan and China and grows at altitudes between 2600–3700 m.

Use: Internal of digestion restorative, external in case of fracture, chronic wound, and swelling of extremities.

The plant contains supinine (24), rinderine (28), amabiline (35), echinatine (38), acetylechinatine (39). (Culvenor et al. 1967; Manko 1972; El-Shazly et al. 1996). Although these alkaloids show only moderate toxicity, the species should not be used as a remedy.

2.3.4. *Cynoglossum divaricatum* Steph ex Lehmann

This plant is medicinally used in Mongolia (Ligaa 1996; Arya 1998) [Mong.: *Derevger Czoniin khal*, *Choniin khel*, *Čonyn khel*, Engl.: *Divaricate Houndstongue*].

Distribution: It is a perennial herb growing in the Mongolian area Khangai, Mongol Daurian, on sandy banks of the rivers, in fields as a weed.

Use: The seeds will be used for infantile diarrhoea.

Alkaloids are unknown, but the plant is belonging to the genus *Cynoglossum* and many plants of this genus have toxic alkaloids. Compare with other *Cynoglossum* species. Internal use is not recommended.

2.3.5. *Cynoglossum glochidiatum* G. Don, Wall. ex Benth., (syn. *C. canescens* Willd., syn. *C. denticulatum* A. DC., syn. *C. edgeworthii* DC., syn. *C. microcarpum* A. Kerner, syn. *C. hirsutum* Thunb., syn. *C. vesiculosum* Wallich ex G. Don., syn. *C. wallichii* G. Don syn. var. *glochidiatum* (Wall ex Benth.) Kazmi, syn. *Paracynoglossum denticulatum* (DC.) M. Popov)

C. glochidiatum is a medicinal plant of Nepal and Tibet (Arya 1998; Rajbhandari 2001; Manandhar 2002; Sah et al. 2003; Kala 2003; Baral et al. 2006; Kletter et al. 2001; Sing et al. 2003; Salick et al. 2006) [Nep.: *Barka chirchiri*, *Bhende kuro*, *Kanike kuro*, *Masine kuro*, *Boko tinai*, *Tejraaj*, *Bhende kuro*, *Kanike kuro*, *Boko tinai*, *Yumuja*, Tib.: *Nad ma byar ma*, Engl.: *Barbed Appendage*].

Distribution: It is a biennial herb widespread in western and central Nepal at 500–4000 m, common in open uncultivated land, further in Tibet, northern India. It is cultivated in western China, eastwards to Bhutan at 1200–4000 m.

Use in Nepal: Root paste is applied in mumps; plant juice is to treat cut and wounds, burns and to stop vomiting in infants. A leaf is boiling in water which is used to relieve the sensation of insect bite by washing the affected part. The paste of a leaf is considered antiseptic and applied to treat wounds between the toes, caused by walking barefooted in muddy water. Plant was also used as aphrosidiac.

Use in Tibet: Considered beneficial for wounds, dissolves uterus tumours, draws out sputum, heals a cough and is also beneficial for first stage oedema. Seeds are eaten for potency and fertility. Plant powder, mixed with water is applied to treat ringworm.

The plant contains viridiflorine (2), cynaustaline (4), cynaustine (34), amabiline (35). (Suri et al. 1975b; Rao et al. 1978). Although these alkaloids show low toxicity, the plant should not be used as a remedy.

2.3.6. *Cynoglossum lanceolatum* Forssk., (syn. *C. canescens* Willd., syn. *C. hirsutum* Thunb., *C. micranthum* Desf., syn. *C. racemosum* Roxb.)

C. lanceolatum is a medicinal plant in Mongolia and Tibet (Ligaa 1996; Kala 2003; Sah et al. 2003; Sing et al. 2003; Dakpa 2007) [Mong.: *Nariin navčit čonyn khel*, Tib.: *Nad ma jar ma*, *Nad ma byar ma*, *Lahaul-spiti*, Engl.: *Smallpetaled Houndstongue*]. It is also a medicinal plant in China [*Ya yong cao*] (Roeder 2000).

Distribution: It is a biennial herb growing in Mongolia, central Tibet, Trans-Himalaya, China at altitudes of 300 to 2800 m on sandy slopes, commonly found in most countries at 4500 m or lower altitude terrains like grassy plains, fields, near human habitation and along the roadsides.

Use in Mongolia: Infantile diarrhoea.

Use in Tibet: Heals sores, wounds, joints cracked and fractured bones and relieves swollen limbs and treats accumulation of serous fluids in the joints. Lowers fever, coughs, difficulty in passing urine due to water retention and regulates proper flow of menstruation cycle, also as a aphrodisiac. The plant contains the alkaloids cynaustaline (4), and cynaustine (34) (Suri et al. 1975b). There are no objections to its use as a medicinal plant.

2.3.7. *Cynoglossum zeylanicum* Forssk., (Vahl ex Lehm) Thunb. syn. *C. coeruleum* Buch-Ham. ex D. Don, syn. *C. furcatum* Wall., syn. *Anchusa zeylanica* Vahl ex Hornem, syn. *Echinosperrum zeylanicum* Lehm., *Myosotis zeylanica* Swartz ex Lehm., syn. *Rochelia zeylanica* Roemer & Schultes)

C. zeylanicum is a medicinal plant in Nepal and Tibet (Bhattarai 1997; Lama et al. 2001; Manandhar 2002; Sah et al. 2003; Sing et al. 2003; Bhattarai et al. 2006) [Nep.: *Bhere kuro*, *Kanike phul*, *Bhende kuro*, *Koda kuro*, *Thina*, *Tam*, *Tinet-T*, *Kanike kuro*; Tib.: *Tapa*, *Nema jarma*; Engl.: *Houndis tongue*, *Forget-me-not*]. It is also a medicinal plant in China [Chin.: *Ti gu san*] (Roeder 2000). Distribution: The biennial herb grows throughout western and central Nepal and Tibet at 1200–4100 m, is common in open places on cultivated and on uncultivated land, in eastern China, India, Bhutan, Himalaya, Afghanistan.

Use in Nepal: From the roots and leaves the peels are used as antiseptic healing agent for cuts and wounds; its powder is applied to treat ringworm. Dilute leaf juice is applied in corneal conjunctivitis; also used in fractured bone, and is considered to dissolve uterine tumours, and draws out lymph fluids. Root paste is applied in boils and to heal wounds as it is considered antiseptic.

Use in Tibet: The pasted flowers are applied around boils. It helps to draw out pus and quickens the healing process. Juice of the leaf is used as eye drops to treat conjunctivitis. Sores, swellings, cough and fractured bone. It dissolves uterus tumours and draws out lymph fluids. The plant contains the alkaloids coromandaline (3), cynaustaline (4), heliotrine (31), echinatine (38), and isoechinatine (40). (Chen et al. 1987; Ravi et al. 2000; Ravicummar et al. 2004). There are no objections towards its use as a medical plant.

2.3.8. *Hackelia uncinatum* (Royle ex Benth.) C.E.C. Fischer, (syn. *Hackelia glochidiata*, (DC.) Brand, syn. *Cynoglossum uncinatum* Royle ex Benth., syn. *C. laxum* G. Don., syn. *C. roylei* Wall ex G. Don, syn. *Echinosperrum glochidiatum* DC, syn. *Eritrichium uncinatum* (Benth.) Y.S. Lian et J.Q. Wang, syn. *Paracaryum glochidiatum* (DC.) Benth. et Hook)

H. uncinatum is a medicinal plant in Nepal and Tibet (Tsarong 1994; Baral et al. 2006; Kletter et al. 2001) [Nep.: *Nad ma snun ma*, Tib.: *Neh-mah*, *Yhoo-loh*].

Distribution. A perennial herb growing in southern Tibet, 2700–4500 m, north eastern India, southwestern China, Bhutan. Use: Flowers are expectorant, antitussive used to subside coughing, heals wounds, and destroys tumours; also used against tumours in the womb, sores, wounds, and swelling of the body. Alkaloids are unknown, but the plant is belonging to the genus *Hackelia* and some plants of this genus have toxic alkaloids. For example *Hackelia californica*, growing in China, contains the alkaloids hackelidine (42) and O⁷-acetylhackelidine (43) (Li 1990). Internal use is not recommended.

2.3.9. *Heliotropium indicum* L., (syn. *H. anisophyllum* P. De B, syn. *H. parviflorum* Blanco, syn. *Tiaridium indicum* (L.) Lehm.)

H. indicum is a medicinal plant of Nepal (Rajbhandari 2001; Manandhar 2002; Baral et al. 2006) [Nep.: *Haati sude*, *Kuro*, Engl.: *Heliotrope*, *Scorpion tail*, *Indian turnsole*].

It is also a medicinal plant in China. [Chin.: *Da wei yao*] (Roeder 2000). It is an annual herb growing in central Nepal, eastern to south western China to about 1500 m on uncultivated land; also in India.

Leaves are useful externally for local application for ulcers, cleanses wounds, skin diseases, poisoning, internally useful against worms, asthma, cough, anemia, insanity and epilepsy; extract of young stem and bulb of onion is taken to cure rabies. Useful in fever, urticaria, gonorrhoea, ringworm, rheumatism, and pharyngodynia. Flowers are abortifacient in large doses. Seeds are stomachic.

Found alkaloids are supinine (24), rinderine (28), heliotrine (31), indicine (32), acetylindicine (33), amabiline (35) echinatine (38), acetylechinate (39) and lasiocarpine (41), and helindicine (83) (Mattocks et al. 1961; Mattocks 1967; Hoque et al. 1976; Kugelman et al. 1976; Pandey et al. 1982; Pandey et al. 1996; Singh et al. 2005; Souza et al. 2005). The plant should not be used for therapeutic purposes.

2.3.10. *Heliotropium strigosum* Willdenow subsp. *brevifolium* (Wall.) Kazmi, (syn. *H. compactum* D. Don.), syn. *Lithospermum chinense* Hooker & Arnott

H. strigosum is a medicinal plant of Nepal (Rajbhandari 2001; Manandhar 2002; Sing et al. 2003; Wanatabe et al. 2005; Baral et al. 2006) [Nep.: *Mrigraaj*, *Chiraiyaa*, Engl.: *Heliotrope*].

Distribution: A perennial herb is growing throughout Nepal to about 1400 m in open dry places, also in subtropical Himalaya, Kashmir to Bhutan, South-China.

Use: The plant is laxative and diuretic; its juice is used as an application to sore eyes, gum boils, and sores generally, and as a cure for the sting of nettles and insects. A paste of root is applied to cuts and wounds. Plant is used for joint pain of cattle.

The non toxic alkaloid strigosine (1) had been isolated. (Mattocks 1964). There is no objection towards medicinal purposes.

2.3.11. *Lappula intermedia* (Ldb) L., M. Popov., (syn. *Echinospermum intermedium* Ledeb.)

L. intermedia is a medicinal plant of Mongolia and Tibet (Ligaa 1996; Kletter et al. 2001) [Mong.: *Zavsriin notsorgono*, *Zavsryn nocorgono*, Tib.: *Nad Ma rmun bu*, Engl.: *Intermediate Skickseed*]. It is also a medicinal plant in China [Chin.: *He shi*] (Roeder 2000).

Distribution: The annual herb is growing in east Mongolia, Mongolian Altai, east Gobi, Gobi Altai, inKazakstan, central Tibet, and in north-eastern provinces of China.

Use: Against verminosis, oxyuriasis, ascariasis, pruritus, itch, ulcers, wounds, jaundice, fracture, and oedema.

The plant contain alkaloids: “identical to alkaloids of Caucasus comfrey and lasiocarpine” (41) (Manko et al. 1968). The plant should definitely not be used medicinally.

2.3.12. *Lappula myosotis* Moench, (syn. *Lappula echinata* G., syn. *Echinospermum lappula* (L.) Lehmann, syn. *Myosotis lappula* L.)

L. myosotis is a medicinal plant of Mongolia (Ligaa 1996) [Mong.: *Durskhal tsetsgerkhuu notsorgono*, *Zaraa*, *Dursgal cecegerkhuu nocorgono*].

Distribution: An annual herb, growing widespread in the Mongolian Khubskul, Khangai, Khentei, Mongol dahurica, Altai and Alasha Gobi.

This plant is used in the Mongolian traditional medicine externally for the treatment of broken bones as well as for wound-healing and articular swellings.

The plant contains in high level the alkaloids intermedine (26), acetylintermedine (27), lycopsamine (36), and acetyllycopsamine (37) (Wiedenfeld et al. 2005). The use of *Lappula myosotis* may be hazardous for humans.

2.3.13. *Lindelofia anchusoides* (Lindl.) Lehm., (syn. *L. macrostylis* (Bunge) M. Pop. syn. *Paracarpium heliocarpum* Kern.)

L. anchusoides is a medicinal plant of Tibet (Dakpa 2007; Smanla 2007) [Tib.: *Nad.ma Yu lo*, *Ne ma yulo*].

Distribution: The biennial herb is growing in central Tibet, Ladakh, Spiti, Garsha in Himachal Pradesh, in India, 2500–4500 m, west slope, loamy, stony, on dry sandy areas, near fields and roadsides.

Use: Heals sores in the chest and dries serous fluid. It is slightly laxative.

The plant contains the non toxic alkaloid lindelofine (5). (Labenski et al. 1948; Babev et al. 1976). There are no objections to its use as a medicinal plant.

2.3.14. *Lindelofia longiflora* (Royal ex Benth) Baill., (syn. *L. spectabilis* Lehm in Hamb., syn. *Anchusopsis longiflora*, syn. *Cynoglossum longiflorum* Benth. in Royle, syn. *Omphalodes longiflora* (Benth.) in Royle, syn. *Paracaryum longiflorum* (Benth.) Boiss., syn. *Anchusopsis longiflora* (Benth.) Bisch.)

L. longiflora is a medicinal plant of Tibet (Kala 2003; Kletter et al. 2001) [Tib.: *Nad ma g-yu lo*, *Karar-tse*].

Distribution: Perennial herb is growing from Pakistan to western Nepal, common in Kashmir at dry sandy slopes at 3000–4600 m. Use: To treat wounds, to reduce swelling after injuries and to heal bone fractures, and diarrhoea. Contains the alkaloid echinatine (38) and its N-oxide. (Kelly et al. 1990). The use for medicinal purpose is not recommendable any more.

2.3.15. *Maharanga bicolor* (Wall. ex G. Don) (syn. *Onosma bicolor* Wall. ex G. Don., (syn.) A. De Candolle.)

M. bicolor is a medicinal plant of Nepal (Rajbhandari 2001; Manandhar 2002; Baral et al. 2006; Bhattarai et al. 2006) [Nep.: *Jubske*, *Jhuske*, *Mahaa rangi*, *Bri mog*; Engl.: *Maharanga*].

Distribution: Perennial herb is growing in the southern part of Tibet, and in the western and central part in the alpine region of Nepal at 3000–4000 m in open fields; also in northern India and Bhutan.

Use: The root is pounded and put on clean cloth and squeezed to take out liquid. One spoonful of liquid is mixed with two spoonful of boiled mustard oil. About 1-5 drops were put on ear

2-3 times a day for ear pain. Rhizome juice is valued as hair tonic at Jumla district.

M. bicolor contains a purple-red naphthochinone pigment, consisting of shikonin derivatives. Alkaloids are unknown, but the plant is belonging to the genus *Maharanga* respective *Onosma*, and plants of this genus may have toxic alkaloids. Compare with *Onosma alborosea* (Roeder et al. 1993b). Internal use is not recommended. For external use are moderate indications.

2.3.16. *Maharanga emodi* (Wall.) A. de Candolle, (syn. *Onosma emodi* Wall. De Roxb)

M. emodi is a medicinal and cosmetic plant in Nepal and Tibet (Rajbhandari 2001; Manandhar 2002; Baral et al. 2006; Bhattarai et al. 2006; Pandey 2006) [Nep.: *Marangi*, Tib.: *Dhimok*, *Vringi*, Engl.: *Onosma*].

Distribution: Perennial herb throughout Nepal, growing at 2200–4500 m on open, rocky ground, also in India, Bhutan, southern Tibet, and China.

Use: Crushed root is boiled in rape oil and sieved. The resultant oil on head is a hair tonic.

Whole plant against hypertension, fever caused due to lung problem, blood purification, skin diseases, rheumatism, urinary disorders and as hair tonic. Then the root is pounded and put on clean cloth and squeezed to take out liquid. One spoonful of liquid is mixed with two spoonful of boiled mustard oil. About 1–5 drops were put on ear 2–3 times a day for ear pain. Crushed root boiler in rapeseed oil and served the resultant oil is applied as a hair tonic and also to blacken it. Its dye is also used for colouring wool and silk. Plant has cooling, laxative, anthelmintic properties. It is good in eye diseases and piles.

M. emodi contains purple-red naphthochinone pigment, consisting of shikonin derivatives.

Alkaloids are unknown, but the plant is belonging to the genus *Maharanga* respective *Onosma*, and plants of this genus have toxic alkaloids. Compare with *Onosma alborosea* (Roeder et al. 1993b). Internal use is not recommended.

2.3.17. *Onosma bracteatum* Wall

O. bracteatum is a remedy plant in Nepal (Pohle 1990; Rajbhandari 2001) [Nep. *Koma*, *Muktsi*, *Bri mog*].

Distribution: Perennial herb is growing in Himalayan part of Nepal and central Nepal.

Use: Red pigment obtained from roots is used to colour butter. The colouring butter serves for offering cakes. *O. bracteatum* contains purple-red naphthochinone pigment, consisting of shikonin derivatives.

Alkaloids are unknown, but the plant is belonging to the genus *Onosma* and plants of this genus have toxic alkaloids. Compare with *Onosma alborosea* (Roeder et al. 1993b). Internal use is not recommended.

2.3.18. *Onosma echioides* L.

O. echioides is a medicinal plant in Nepal and Tibet (Sharma 2000; Baral et al. 2006; Bhattarai et al. 2006) [Nep.: *Maharangi*, Tib.: *Rattan jot*, *Maharangi*, *Bri mog*; Engl.: *Maharanga* in Ayurvedic medicine].

Distribution: Perennial herb is growing in the subalpine area of Nepal and Tibet.

Use in Nepal. Roots bruised and applied to eruption; leaves alterative, powder is given to children as purgative; flowers used as cordial and stimulant in rheumatism and palpitation of heart. Use in Tibet: Leaves and flowers are finely chopped and mixed with honey. The paste is consumed for rheumatic pains and as a

heart tonic. Tender roots are vigorously rubbed over granite and the resulting pulp is used as an antiseptic for wounds.

Alkaloids are unknown, but the plant is belonging to the genus *Onosma* and plants of this genus have toxic alkaloids. Compare with *Onosma alborosea* (Roeder et al. 1993b). Internal use is not recommended.

2.3.19. *Onosma hookeri* C.B. Clarke

O. hookeri is a medicinal plant of Tibet (Arya 1998; Phuntsog 2006; Salick et al. 2006; Dakpa 2007) [Tib.: *Di mog*, *Bri mog*]. Distribution: Perennial herb is growing in Tibet, Nepal, Pakistan, and Sikkim in India from 2500–4700 m. It grows on sunny and sandy grassy land in area Zanskar, Ladakh.

Use: It will be used as blood coagulant, haematemesis, malaena, lowers fever of the lungs and treats vomiting of blood and bloody sputum due to perforated lungs. Remedies nose bleeding, checks impure blood and loss of hair.

O. hookeri contains a purple-red naphthochinone pigment, consisting of shikonin derivatives.

Alkaloids are unknown, but the plant is belonging to the genus *Onosma* and plants of this genus have toxic alkaloids. Compare with *Onosma alborosea* (Roeder et al. 1993b). Internal use is not recommended.

2.3.20. *Onosma multiramosum* Handel-Mazz.

O. multiramosum is a cosmetic plant of Tibet (Arya 1998; Salick et al. 2006) [Tib.: *Bri mog*].

Distribution: Perennial herb, grey-green, is growing in central Tibet

Use: Red pigment obtained from roots is used to colour the hair.

O. multiramosum contains purple-red naphthochinone pigment, consisting of shikonin derivatives.

Alkaloids are unknown, but the plant is belonging to the genus *Onosma* and plants of this genus have toxic alkaloids. Compare with *Onosma alborosea* (Roeder et al. 1993b). Internal use is not recommended.

2.3.21. *Onosma praeaeatum* Wall

O. praeaeatum is a plant for cosmetic uses in Nepal and Tibet (Pohle 1990; Arya 1998) [Nep.: *Koma*, *Muktsi*, Tib.: *Bri mog*].

Distribution: Perennial herb is growing in valleys of central Nepal and Tibet.

Use: The root of the plant contains a red pigment soluble in oil which is used to colour butter. The coloured butter serves as a decoration for offering cakes (“Tsog”).

O. praeaeatum contains a purple-red naphthochinone pigment, consisting of shikonin derivatives. Alkaloids are unknown, but the plant is belonging to the genus *Onosma* and plants of this genus have toxic alkaloids. Compare with *Onosma alborosea* (Roeder et al. 1993b). Internal use is not recommended.

2.3.22. *Trichodesma indicum* (L.) R.Br., (syn. *Borago indica* L.)

T. indicum is a medicinal plant of Nepal (Rajbhandari 2001; Manandhar 2002; Sah et al. 2003; Sing et al. 2003; Baral et al. 2006) [Nep.: *Kanike kuro*, *Unminti*; Engl.: *Primis flower*].

Distribution: This perennial herb is growing in western and central Nepal to about 900 up to 1500 m, India, Afghanistan, subtropical Himalaya, and Kashmir.

Use: Extract of the plant is used in anthralgia, dyspepsia, diarrhoea, dysentery, leprosy, skin diseases, ophthalmopathy, expulsion of foetus, sores and fevers. Leaves in cold infusion are considered depurative. Roots are used in dysentery and to

reduce swellings of the joints. Dried plant is mixed with flour of finger millet and rice to make bread and the bread is eaten with honey to treat headache and/or dysentery.

Alkaloids are unknown, but the plant is belonging to the genus *Trichodesma* and plants of this genus have toxic alkaloids. Compare with *Trichodesma incanum* (Yunusov et al. 1957). Internal use is not recommended.

2.4. PA-containing medicinal plants of the family Asteraceae

The family Asteraceae (Compositae) is one of the largest families of flowering plants, but toxic species are rare. Only in the tribes Eupatorieae and Senecioneae toxic species can be found. Most of them contain pyrrolizidine alkaloids.

2.4.1. Tribe Eupatorieae

2.4.1.1. *Ageratum conyzoides* L., syn. *Eupatorium conyzoides* (L.) (E.H.L.Krause), (syn. *Carelia conyzoides* (L.) Kuntze). *A. conyzoides* is a medicinal plant in Nepal (Anon. 1970; Bhattarai 1997; Rajbhandari 2001; Manandhar 2002; Rai 2003; Sah et al. 2003; Sing et al. 2003; Watanabe et al. 2005; Baral et al. 2006) [Nep.: *Boke ghaans, Ganmane, Ganhaaune ghaans, Ilame jhar, Ghande jhar, Angale jhar, Bhakumbhar, Ganmaeghans, Raunja-C, Nimane jhar-M, Than ninoba-T, Than benoba Raunde-C, Raunne-N.*; Engl.: *Goat weed, White weed, Bastard agrimony, Appa gras*]. It is also a medicinal plant of China [Chin.: *Sheng hong ji*] (Roeder 2000).

Distribution: This annual herb is growing throughout Nepal to about 2200 m, and widespread in China at an altitude of 600 to 800 m, usually in damp places, and is pantropical.

Use: The plant is a stimulant and tonic; its juice is a remedy of prolapsus ani, decoction and infusion of leaf and root is used in diarrhoea, dysentery, and also for colic, rheumatism, fever. Drops of leaf juice are used to treat catarrh and has antiseptic properties. Flower buds cure cancerous growth. Juice of root is antilithic.

Leaf juice is applied on cuts and wounds, and on ruptures caused by leprosy. Boiled with oil applied externally in rheumatism. As already stated in Nepalese regulations, leaves cause nausea and vomiting in livestock. Contains the alkaloids lycopsamine (36), and echinatine (38) (Wiedenfeld et al. 1991).

It should not longer be used as a traditional medicinal plant because of its high alkaloid content and their hepatotoxic effects.

2.4.1.2. *Ageratum houstonianum* Miller. *A. houstonianum* is a medicinal plant of Nepal (Bhattarai 1997; Rajbhandari 2001; Manandhar 2002; Baral et al. 2006) [Nep.: *Nilo gandhe, Gandhe jhaar, Boke-bon*; Engl.: *Goat weed, Mist flower*].

Distribution: This herb grows in eastern and central Nepal to about 1300 m; also pantropical.

Use: Leaf juice is externally applied to stop bleeding and healing cut wounds. Contains the alkaloids lycopsamine (36), retrorhousine (44), isoretrorhousine (45), and heliohousine (46) (Wiedenfeld et al. 2001). Internal use is not recommended.

2.4.1.3. *Eupatorium adenophorum* Spreng., (syn. *E. glandulosum* Kunt, syn. *Ageratina adenophora* (Spreng) R. King & Robinson). *E. adenophorum* is a medicinal plant of Nepal (Ioshi et al. 1990; Bhattarai 1997; Manandhar 2002; Sah et al. 2003; Sing et al. 2003; Baral et al. 2006) [Nep.: *Banmaara, Banmara-T, Banmasa, Mohini-C*; Engl.: *Crofton weed, Mexican devil*].

Distribution: Herb growing in central and eastern Nepal, 500–2000 m in open and deforested areas; a pantropical weed.

Use: The leaf juice is used to stop bleeding of cuts and wounds, forming clots. Root juice is prescribed to treat fever. Pure juice of the leaf is poured in the eye to treat insomnia; the decoction of the plant is used as febrifuge.

Alkaloids are unknown, but the plant is belonging to the genus *Eupatorium* and plants of this genus have toxic alkaloids. Compare with *Eupatorium odoratum* (Biller et al. 1994). Internal use is not recommended.

2.4.1.4. *Eupatorium chinense* L., (syn. *E. clematideum* (Wallich ex de Candolle) Schultz Bipontinus, syn. *E. longicaule* de Candolle, syn. *E. revesii* Wall. ex de Candolle, syn. *E. squamosum* Buch.-Ham. ex D. Don., syn. *E. viscosum* Wallich, *E. wallichii* de Candolle, syn. *Conyza longicaulis* Wallich, syn. *Micania clematidea* Wallich ex de Candolle). *E. chinense* is a medicinal plant of Nepal and Tibet (Manandhar 2002)

[Nep.: *Banmara*; Tib.: *Duk*]. It is also a medicinal plant of China [Chin.: *Hua zhe lan*] (Roeder 2000). Distribution: The perennial herb grows in central and western Nepal at 2000–2600 m in open and deforested areas; in north-eastern regions of China from 800 to 1900 m; also in India, Bhutan, Japan, Taiwan.

Use: The milky latex is applied to treat goitre.

The plant contains “toxic alkaloids and N-oxides” (Zhao et al. 1989) and should no longer be used.

2.4.1.5. *Eupatorium odoratum* L. (syn. *Chromolaena odorata* (L.) R. King & Robinson). *E. odoratum* is a medicinal plant of Nepal (Bhattarai 1997; Manandhar 2002; Rai 2004) [Nep.: *Banmara, Singhar, Daubanthu., Aule ban maara, Sing jhar, Lobasiya, Chukutenay*, Engl.: *Siam weed, Christmas bush*].

Distribution: Annual herbal plant growing in central and eastern Nepal to about 1500 m, open and deforested places. Also in China, in tropical Asia, and Americas.

Use: The leaf juice is applied to cuts and open wounds. It is considered good for severely chapped hands and feet. It possesses haemostatic and antiseptic properties. Also to check nasal bleeding. Two drops of leaf extract dropped in nose to cure severe headache. Leaf juice is used as antirhemorrhoid and antiseptic. Contains the moderately toxic alkaloids 7-angeloylretronecine (18), 9-angeloylretronecine (23), supinine (24), intermedine (26), rinderine (28), acetylinderine (29) (Biller et al. 1994). For the indicated purposes it may be used with restrictions.

2.4.2. Tribe Senecioneae

The tribe Senecioneae is the largest tribe in the Asteraceae with 3200 species and 120 genera. It is a group of plants that contains many and toxic pyrrolizidine alkaloids.

The genus *Senecio* is distributed world-wide and contains more than 1500 species. Most of these species were shown to cause poisoning in people and animals.

2.4.2.1. *Cacalia hastata* L. *C. hastata* is a medicinal plant of Mongolia (Bayarsukh 2008) [Mong.: *Ilden iguushiw*. Engl.: *Hastate Cacalia*]. It is also a medicinal herb of China [Chin.: *Shan jianzi*] (Roeder 2000).

Distribution: Central Mongolia and central China.

Use: Leaves are used against gastric and stomach ulcer, respiratory infection, inflammation of the stomach, inflammation of mouth cavity. Extract has anti-inflammatory activity; is antibacterial, spasmolytic, choleric, antipyretic, and antihaemorrhagic.

Contains the alkaloids platyphylline (47), hastacine (49), and in *C. hastata* subspec. *orientalis* Kitamura integerrimine (53) (Konovalov et al. 1945; Hayashi et al. 1972; Altanchimeg 2001). For the indicated purposes it can be used.

2.4.2.2. *Crassocephalum crepidioides* (Benth.) S. Moore (syn. *Gynura crepidioides* Benth.). *C. crepidioides* is a medicinal plant of Nepal (Rajbhandari 2001; Manandhar 2002; Baral et al. 2006) [Nep.: *Anikaale jhaar, Saalaha ko jhar-N, Udo munto jhar, Jhule jhar, Kaikalai, Lodro tabra, Tabra, Nirit loba, Namle jhar, Lodomran*; Engl.: *Thickhead*]. This is also a medicinal plant of China [Chin.: *Jia Tong Hao*] (Roeder 2000).

Distribution: Erect pubescent herb, growing throughout Nepal at 400–2500 m, moist places; also pantropical. In China it is widespread at altitudes of 300–1800 m in the north-eastern region.

Use: Root paste and/or leaf juice is applied on cut wounds; plant juice is given to cure diarrhoea. The plant contains the very toxic alkaloids jacobine (66), and jacoline (67).

(Asada et al. 1985). The plant should no longer be used.

2.4.2.3. *Emilia sonchifolia* (L.) DC., (syn. *Emilia sinica* Miq., syn. *Cacalia sonchifolia* L., syn. *Crassocephalum sonchifolium* (L.) Less.). *E. sonchifolia* is a medicinal plant of Nepal (Manandhar 1994; Rajbhandari 2001; Sing et al. 2003; Watanabe et al. 2005) [Nep.: *Chaulaane Jhaar, Dudhe, Hirankhuri*; Engl.: *Tassel flower, Emilia*]. It is also a medicinal plant in China [Chin.: *Yang ti cao, Yi dian hong, I thien hung*] (Roeder 2000). Distribution: An annual herb occurring in Nepal, China, India, ascending up to 1800–2100 m.

Use: A decoction of the plant is febrifuge and antipyretic, and is also given to treat stomach complaints and earache. The pure juice of the plant is applied to treat insomnia. The juice of the root is given to treat diarrhoea.

Flower head is chewed and kept for a while inside the mouth to protect teeth from decaying.

Contains the alkaloids senkirkine (64), and doronine (70) (Cheng et al. 1986). Medicinal use is not recommended.

2.4.2.4. *Gynura nepalensis* DC. (syn. *Cacalia aurantiaca* Wall). *G. nepalensis* is a medicinal plant of Nepal (Bhattarai et al. 2006; Baral et al. 2006). [Nep.: *Mendho*].

Distribution: Herb growing in Himalaya, Kashmir to Bhutan, north eastern India, China.

Use: Plant juice is applied to stop bleeding of fresh cuts and wounds.

Alkaloids are unknown, but the plant is belonging to the genus *Gynura* and plants of this genus have toxic alkaloids. Compare *Gynura scandens* (Wiedenfeld 1982) and *G. segetum* (Liang et al. 1984). For the indicated purposes it may be used with restrictions. (Dai et al. 2007)

2.4.2.5. *Ligularia amplexicaulis* DC, (syn. *Senecio amplexicaulis* Wall. ex C.B. Clarke). *L. amplexicaulis* is a medicinal plant of Nepal and Tibet (Tsarong 1994; Dawa 1999; Manandhar 2002; Baral et al. 2006; Dakpa 2007). [Nep.: *Nangre, Bijauri*; Tib.: *Ri.sho, Rhee sho*; Engl.: *Ragwort*].

Distribution: Tibet, Nepal, Bhutan and Kashmir from 2700–4300 m on slightly dry hill slopes, in shady and stony areas and among bushes and grasses.

Use in Nepal: Paste, essential oil from the tuber is applied externally against rheumatic pain.

A decoction of the root is boiled to a gelatinous mass, which is applied to treat sprain.

Essential oil extracted from the tuber is applied externally against rheumatic pain.

Use in Tibet: Digestive and against emesis from ingestion, and in case of bile and phlegm diseases. Heals sores, dries serous fluid, and cures old epidemic diseases.

Alkaloids are unknown, but the plant is belonging to the genus *Ligularia* and plants of this genus have toxic alkaloids. Compare with *Ligularia cymbulifera* (Liu et al. 2008).

Internal use is not recommended.

2.4.2.6. *Ligularia fischeri* (Ledebour) Turczaninow, (syn. *L. racemosa de Candolle*, syn. *Cineraria fischeri* Ledebour, syn. *Senecio ligularia* Hooker fil, syn. *S. sibiricus* Lin. fil). *L. fischerii* is a medicinal plant in Mongolia and Nepal (Ligaa 1996; Manandhar 2002) [Mong.: *Fisheriin zayakkhai, Fiširiin žayakkhai, Goo zayakkhai*, Nep.: *Simaudya*; Engl.: *Fischer Goldenray*].

Distribution: Herb in Mongolia and here in Khubsugul, Khentei, Khangai, mongol Daurian, throughout Nepal at 2200–4600 m in moist, open placet besides streams; also in northern India, Bhutan, China, eastern Siberia.

Use: See *Ligularia sibirica*. Tender leaves are cooked as a vegetable.

Alkaloids are unknown, but the plant is belonging to the genus *Ligularia* and plants of this genus have toxic alkaloids. Internal use is not recommended. Compare with *Ligularia cymbulifera* (Liu et al. 2008). For the indicated purposes it may be used with restrictions.

2.4.2.7. *Ligularia sibirica* (L.) Cass.. *L. sibirica* is a medicinal plant of Mongolia (Ligaa 1996) [Mong.: *Sibiri zayakkhai; Sibir' žayakkhai, Ogussiirva*, Engl.: *Siberian Goldenray*].

Distribution: Herb in Bulgan and Huvsgul Aimag in Mongolia in large amounts on pastures and meadows.

Use: Bilious diseases, typhus, poisonous diseases, chronic bronchitis, pulmonary tuberculosis, hemoptysis, hematemesis, wounds, yellow liquorstasis, wind diseases.

The non-toxic alkaloid tussilagine (14) and its isomers (15–17) have been isolated (Wiedenfeld et al. 2003). There are no objections to the use this plant.

2.4.2.8. *Petasites tricholobus* Franch. *P. tricholobus* is a medicinal plant of Tibet (Arya 1998; Salick et al. 2006; Smanla 2007). [Tib.: *Lug so*]. Distribution: Annual herb in Central Tibet.

Use: It is said to remove wound fever and draw out smallpox permeating inside the body.

Alkaloids are unknown, but the plant is belonging to the genus *Petasites* and plants of this genus have toxic alkaloids. Compare with *Petasites japonicus* (Yamada et al. 1976; Niwa et al. 1983). Internal use is not recommended.

2.4.2.9. *Senecio argunensis* Turcz.. *S. argunensis* is a medicinal plant of Mongolia (Ligaa 1996) [Mong.: *Urgunii zokhimon, Orgonii zokhimon*, Engl.: *Argun groundsel*]. It is also a medicinal plant of China: [Chin.: *Zhan long cao*] (Roeder 2000).

Distribution: Herb in east Mongolia. In China it is widespread at altitudes of 500 to 3300 m.

Use in Mongolia: Gastric tumour, ulcers, bee snake-scorpion and others poisonous insect bites, conjunctivitis, moisture pimple, dermatitis, laryngitis, pharyngitis.

Alkaloids are integerrimine (53), eruciflorine (54), senecionine (57), erucifoline (59), seneciphylline (60), and otosenine (71) (Liu et al. 1991; Cheng et al. 1992). This plant should no longer be used therapeutically.

2.4.2.10. *Senecio cappa* Buch.-Ham. ex D. Don, (syn. *S. densiflorus* Wall ex DeCandolle). *S. cappa* is a medicinal plant of Nepal (Manandhar 2002; Baral et al. 2006). [Nep.: *Baakhraa kaane, Barke kane*].

Distribution: Eastern and central Nepal, at 1300–2900 m, common in shrubby areas of forests; also in Northern India, Bhutan, western China.

Use: Root juice is given to treat fever. Leaf paste is applied to treat boils.

Alkaloids are unknown, but the plant is belonging to the genus *Senecio* and plants of this genus have toxic alkaloids. Compare with *Senecio chrysanthemoides* and many other *Senecio* species. Internal use is not recommended.

2.4.2.11. *Senecio chrysanthemoides* (DC.) Schrank & Baier, (syn. *Senecio jacobaea* auct. non L., syn. *S. laetus* Edgew.). *S. chrysanthemoides* is a medicinal plant of Nepal (Manandhar 2002; Kala 2003; Baral et al. 2006; Smanla 2007) [Nep.: *Bijauri phul*, *Rgu drus*, *Hechiang*, Engl. *Ragwort*]. It is also a medicinal plant of China [Chin.: *Chien li kuang*, *Tsang tu san chi*] (Roeder 2000).

Distribution: Herb is growing in Pakistan, Himalaya, north eastern India, south China, and in subtropical-subalpine regions.

Use: Root infusion is given in case of indigestion. Rheumatism, fever, abdominal pain.

The plant contains the very toxic alkaloids integerrimine (53), senecionine (57), retrorsine (58), seneciphylline (60), senkirkine (64), jacozone (65), jacobine (66), jacoline (67), jacoline (69), and otosenine (71). (Bradbury et al. 1959; Geissman 1959; Wali et al. 1964; Culvenor 1964; Akramov et al. 1966; Segall 1978; Dimenna et al. 1980; Witte et al. 1992; Macel et al. 2004). This plant should no longer be used for therapeutic purposes. Many poisonings in yaks (*Poephagus grunniens*) with *S. chrysanthemoides* are described in the literature (Mondal et al. 1999).

2.4.2.12. *Senecio dianthus* Ranch. *S. dianthus* is a medicinal plant of Tibet (Phuntsog 2006) [Tib.: *Yu gushing*].

Distribution: Annual herb in Tibet in 2300–3000 m altitude.

Use: Antidot to poison, antibiotic, reduce pain and swelling of ulcer.

Alkaloids are unknown, but the plant is belonging to the genus *Senecio* and plants of this genus contain toxic alkaloids. Compare with *Senecio chrysanthemoides*. Internal use is not recommended.

2.4.2.13. *Senecio diversifolius* Wall. ex DeCandolle, (syn. *S. raphanifolius* Wallich ex de Candolle). *S. diversifolius* is a medicinal plant of Nepal (Bhattarai 1997; Manandhar 2002; Wanatabe et al. 2005) [Nep.: *Raipate*, *Bajari phul*, *Marcha*, *Chenti*, *Kadik*, *Mhendo*, *Pramji*].

Distribution: A herb growing throughout Nepal, at 2300–4000 m in moist, shady places; also in northern India and Bhutan.

Use: The leaf juice is applied to bleeding wounds and cuts as a haemostat and an antiseptic.

Root infusion is taken in cases of indigestion. It is also used to prepare marcha, a cake fermented with yeast, from which liquor is distilled.

Alkaloids are unknown, but the plant is belonging to the genus *Senecio* and plants of this genus contain toxic alkaloids. Compare with *Senecio chrysanthemoides*. Internal use is not recommended.

2.4.2.14. *Senecio erucifolius* L. *S. erucifolius* is an alternative medicinal plant of Mongolia (Ligaa 1996) [Mong.: *Khiz zokhimon*, Engl.: *Roquetteleaf Groundsel*].

Distribution: Annual herb growing in Khentei, Khangai, East Mongolia on banks of rivers.

Use: Gastric tumour, ulcers, bee snake, scorpion and others poisonous insect bites, conjunctivitis, moisture pimple, dermatitis, laryngitis, pharyngitis.

The plant contains the very toxic alkaloids senecionine (57), retrorsine (58), erucifoline (59), and seneciphylline (60)

(Kompis et al. 1962; Sedmera et al. 1972; Boeva et al. 1979; Witte et al. 1992). This plant should no longer be used therapeutically.

2.4.2.15. *Senecio nemorensis* (L.) (syn. *S. nemorensis* var. *octoglossus* (DC.) Koch ex Ledeb, syn. *S. gampinensis* Vaniot, syn. *S. kematogensis* Vaniot) (Ligaa 2006). *S. nemorensis* is a medicinal plant of Mongolia [Mong.: *Oin zokhimon*, *Naimaldai zokhimon*, Engl.: *Nemorensis ragwort*]. It is also a medicinal plant in China [Chin.: *Huana wan*] (Roeder 2000). Distribution: Occurs in Mongolia, and in China at altitudes of 700–3000 m, and in Russia.

Use: It is a traditional medicinal plant used in cases of pain relief, reduce secretion of glands, improve heart beat, is hypotensive. It contains 7- and 9-angeloylplatynecine (8, 10), fuchsisenecionine (11), sarracine (12), 6-angeloylhastancine (13), 7- and 9-angeloylretronecine (18, 23), doriasenine (22), triangularine (19), 7-seneciylretronecine (20), 7-seneciyl-9-sarracinoylretronecine (21), platyphylline (47), senecionine (57), nemorensine (79), retroisosenine (80), bulgarsenine (81), doronenine (82), and the N-oxides of these in various concentrations. (Corcilus 1955; Lemp 1955; Klasek et al. 1973; Nguyen et al. 1976; Roeder et al. 1977; Roeder et al. 1979; Klasek et al. 1980; Schmid et al. 1987; Wiedenfeld et al. 1989; Gottlieb 1990; Wiedenfeld et al. 2000; Christov et al. 2005).

Extracts of *S. nemorensis* display both mutagenic and carcinogenic effects and should therefore no longer be used for therapeutical purposes (Habs et al. 1982).

2.4.2.16. *Senecio scandens* Buch.-Ham. ex D. Don., (syn. *S. chinensis* (Spr.) DC). *Senecio scandens* is a medicinal plant of Tibet (Dawa 1999) [Tib.: *Rgu-drus*]. It is also a medicinal plant of China [Chin.: *Qian li guang*, *Chiu li ming*] (Roeder 2000).

Distribution: Growing herb in Tibet and China between 1800–3800 m on mountains, foothills, near water canals, along roadsides, in cool shadows and moderately moist areas.

Use in Nepal: Joins ruptured capillaries, colic pain by inflammation in the intestinal tract, dysentery, heals wounds, also useful in treating hot disorder of the hollow organs, eczema and other skin diseases.

Contains the alkaloids neoplathyphylline (48), senecionine (57), senecionine N-oxide, seneciphylline (60), seneciphylline N-oxide, and senkirkine (64), and adonifoline (68).

(Batra 1977; Li et al. 2008; Zhang et al. 2008). Most of these alkaloids are toxic and the plant should therefore no longer be used for therapeutical purposes.

2.4.2.17. *Senecio solidagineus* Spreng. (Hand-Mazz.). *S. solidagineus* is a medicinal plant of Tibet (Arya 1998; Salick et al. 2006; Smanla 2007) [Tib.: *Yu gu sin*, *Chu thun gsan bai sman gcig*, *Tre tre sin*, *Du ru rdo ldag*, *Phag ldan bcad byor*, *Bya seb*, *Phag ldan bcad byor*, *Bya seb*].

Distribution: Herb grows in central Tibet.

Use: The plant cure infectious swellings and fever due to poisoning.

Alkaloids are unknown, but the plant is belonging to the genus *Senecio* and plants of this genus contain toxic alkaloids. Compare with *Senecio scandens*.

Internal use is not recommended.

2.4.2.18. *Senecio thianschanicus* Regel & Schmalh. *S. thianschanicus* is a medicinal plant of Tibet (Arya 1998; Salick et al. 2006; Smanla 2007) [Tib.: *Sga so chun ba*].

Distribution: Herb grows in central Tibet.

Use: The plant is beneficial in meat poisoning.

Alkaloids are unknown, but the plant is belonging to the genus *Senecio* and plants of this genus have toxic alkaloids. Compare with *Senecio scandens*. Internal use is not recommended.

2.4.2.19. *Senecio tibeticus* Hk. *S. tibeticus* is a medicinal plant of Tibet (Kala 2003) [Tib.: *Niyamgar*].

Distribution: Herb is growing in Trans-Himalaya, regio Changthang.

Use: As a diuretic.

Alkaloids are unknown, but the plant is belonging to the genus *Senecio* and plants of this genus have toxic alkaloids. Compare with *Senecio scandens*. Internal use is not recommended.

2.4.2.20. *Senecio wallichii* De Candolle. (*syn. S. detatus Wallich.*) *S. wallichii* is a medicinal plant of Nepal and Tibet (Manandhar 2002; Baral et al. 2006). [Nep.: *Mohini jhaar*; *Tasyu*, *Banno ba*; Tib.: *Tasyu*].

Distribution: Herb in eastern and central Nepal at 1500–3300 m in moist, shady places under trees; also in northern India, Tibet and Bhutan.

Use: Root paste is applied to treat headache and joint-ache.

Alkaloids are unknown, but the plant is belonging to the genus *Senecio* and plants of this genus have toxic alkaloids. Compare with *Senecio scandens*. Internal use is not recommended.

3. Conclusion

In this paper we refer about sixty plants which are used medicinally in the Traditional Medicines of Mongolia (TMM), Nepal (TNM) and Tibet (TTM). 25 species are already described to contain toxic pyrrolizidine alkaloids (PAs). In 8 species only non-toxic PAs were found. 27 plants are not investigated with respect to a possible PA content. On account of the botanical relationship 26 of them can be assumed to contain toxic PAs; one species should only contain non-toxic alkaloids.

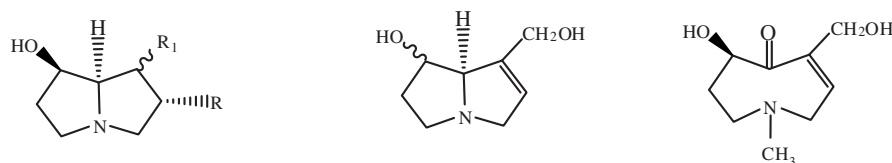
PAs are known to show cancerogenic, mutagenic, genotoxic, fetotoxic and teratogenic properties. Therefore the use of medicinal plants which contain those compounds is restricted in many countries. Mainly, this use is limited to a daily uptake of toxic PA to a dose of less than 1 µg and up to 6 weeks duration; during pregnancy and breast-feeding the use of PA-containing plants or preparations of them are forbidden.

As a large number of plants with a toxic PA content are used in the TMM, TNM and TTM, it is recommended that the use of these plants and the treatment with phytopharmaceuticals containing those plants should be controlled and restricted to prevent a possible human risk.

Furthermore, those species which are suspicious to contain toxic PAs should no longer be used medicinally until they are analyzed for their PA content and a possible toxic risk is estimated and excluded.

Appendix:

Structures of the PA detected in medicinal plants of Mongolia, Nepal and Tibet

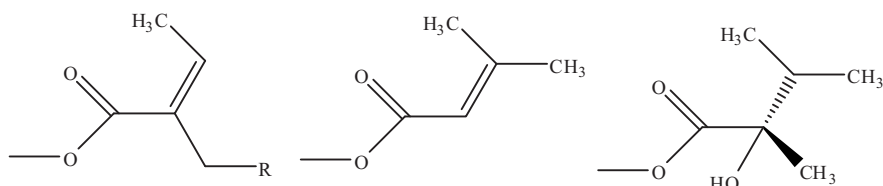


R = H; R₁ = CH₂OH: Platynecine
 R = H; R₁ = CH₂OH: Hastanecine
 R = OH; R₁ = CH₂OH: Rosmarinecine

= : Retronecine
 = : Heliotridine

Otonecine

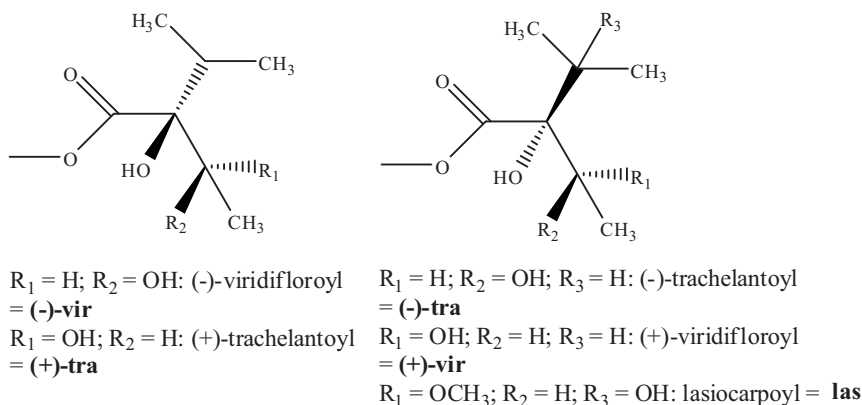
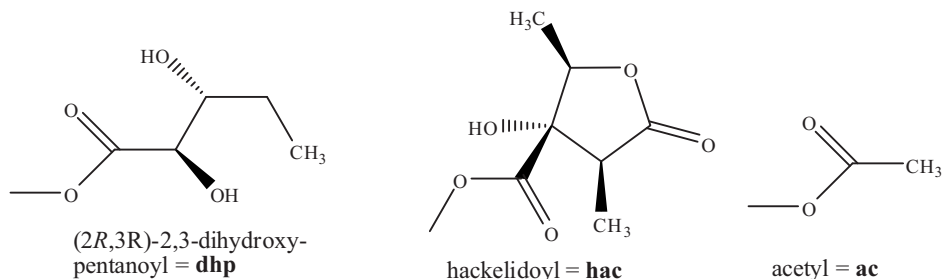
Necines



R = H: angeloyl = **ang**
 R = OH: sarracinyol = **sar**

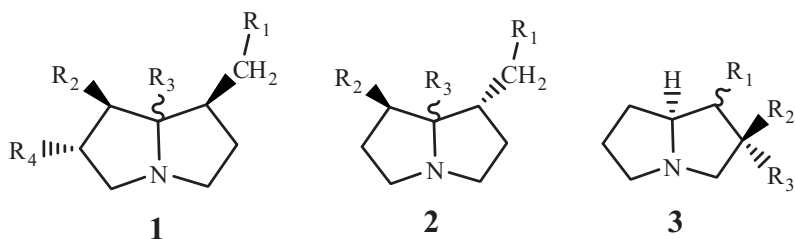
senecieryl = **sen**

(2*S*)-2,3-dimethyl-2-hydroxybutyryl = **dmhb**



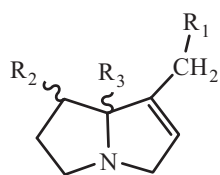
Necic acids

Open-chain mono and diester PA with a saturated necine



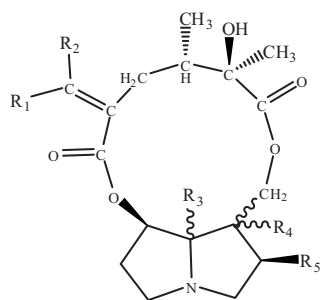
necine	R ₁	R ₂	R ₃	R ₄	Name
2	dhp	H	H		Strigosine (1)
2	(-)-vir	H	H		Viridiflorine (2)
2	(+)-vir	H	H		Coromandaline (3)
2	(-)-vir	H	▲ H		Cynaustaline (4)
2	(+)-tra	H	▲ H		Lindelofine (5)
1	OH	H	▲ H	H	Laburnine (6)
1	ac	H	▲ H	H	Acetylloburnine (7)
1	OH	ang	H	H	O ⁷ -Angeloylplatynecine (8)
1	OH	sen	H	H	O ⁷ -Seneciroylplatynecine (9)
1	ang	OH	H	H	O ⁹ -Angeloylplatynecine (10)
1	sen	OH	H	H	Fuchsisenecionine (11)
1	sar	ang	H	H	Sarracine (12)
1	OH	OH	H	ang	6-Angeloylthastancine (13)
3	CO ₂ CH ₃	CH ₃	OH		Tussilagine (14)
3	CO ₂ CH ₃	OH	CH ₃		Isotussilagine (15)
3	▲ CO ₂ CH ₃	CH ₃	OH		Neo-tussilagine (16)
3	▲ CO ₂ CH ₃	OH	CH ₃		Neo-isotussilagine (17)

Open-chain mono and diester PAs with an 1,2-dehydro-necine

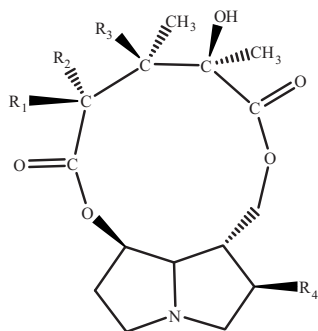


R ₁	R ₂	R ₃	Name
OH	▲ ang	H	O ⁷ -Angeloylretronecine (18)
sar	▲ ang	H	Triangularine (19)
OH	▲ sen	H	O ⁷ -Senecioylretronecine (20)
sar	▲ sen	H	O ⁷ -Senecioyl-O ⁹ -sarracinyolretronecine (21)
sar	▲ sen,4'OH	H	Doriasenine (22)
ang	▲ OH	H	O ⁹ -Angeloylretronecine (23)
(+)-tra	H	H	Supinine (24)
(+)-tra,3'-OCH ₃	H	H	Heleurine (25)
(+)-tra	▲ OH	H	Intermedine (26)
(+)-tra	▲ ac	H	Acetylintermedine (27)
(+)-tra	OH	H	Rinderine (28)
(+)-tra	ac	H	Acetylrinderine (29)
(+)-tra	ang	H	O ⁷ -Angeloylrinderine (30)
(+)-tra,3'-OCH ₃	▲ OH	H	Heliotrine (31)
(-)-tra	▲ OH	H	Indicine (32)
(-)-tra	▲ ac	H	Acetylindicine (33)
(-)-vir	H	▲ H	Cynaustine (34)
(-)-vir	H	H	Amabiline (35)
(-)-vir	▲ OH	H	Lycopsamine (36)
(-)-vir	▲ ac	H	Acetylyllycopsamine (37)
(-)-vir	OH	H	Echinatine (38)
(-)-vir	ac	H	Acetylechinatine (39)
(+)-vir	OH	H	Isoechinatine (40)
las	ang	H	Lasiocarpine (41)
hac	▲ OH	H	Hackelidine (42)
hac	▲ ac	H	O ⁷ -Acetylhackelidine (43)
dmhb	▲ OH	H	Retrohoustine (44)
dmhb	OH	H	Isoretrohoustine (45)
OH	▲ dmhb	H	Heliohoustine (46)

Macrocyclic diester PAs with saturated necines

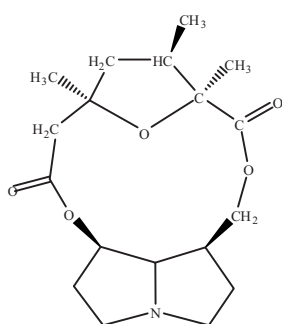


R ₁	R ₂	R ₃	R ₄	R ₅	Name
CH ₃	H	H	H	H	Platyphylline (47)
H	CH ₃	H	H	H	Neoplatyphylline (48)
H	CH ₃	▲ H	H	H	Hastacine (49)
CH ₃	H	H	▲ H	OH	Anacrotine (50)

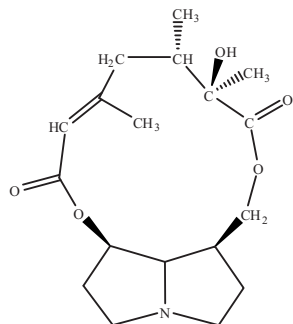


R ₁	R ₂	R ₃	R ₄	Name
H*	CH ₃ *	H	H	Retusine (72)
H	i-pr	OH	OH	Croalbidine (73)

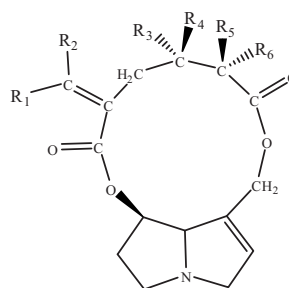
* stereochemistry estimated or unknown i-pr = isopropyl



Nemorensine (79)



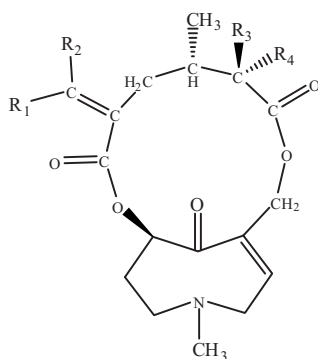
Bulgarsenine (81)



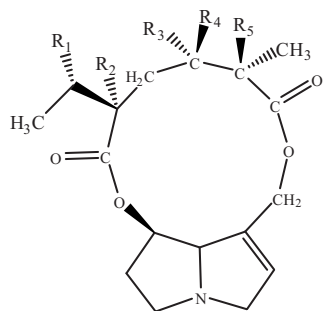
Macrocyclic diester PAs with 1,2-dehydro necines

R ₁	R ₂	R ₃	R ₄	R ₅	R ₆	Name
H	CH ₃	H	CH ₃	OH	CH ₂ OH	Mucronatinine (51)
H	CH ₃	CH ₃ *	H*	OH*	H	Nilgrine (52)
H	CH ₃	CH ₃	H	OH	CH ₃	Integerrimine (53)
H	CH ₂ OH	CH ₃	H	OH	CH ₃	Eruciflorine (54)
H	CH ₃	CH ₃	H	OH	CH ₂ OH	Usaramine (55)
H	CH ₃	CH ₃ *	H*	ac*	H*	Crotastriatine (56)
CH ₃	H	CH ₃	H	OH	CH ₃	Senecionine (57)
CH ₃	H	CH ₃	H	OH	CH ₂ OH	Retrorsine (58)
CH ₃	H	CH ₂ OH	- O -	OH	CH ₃	Erucifoline (59)
CH ₃	H	- CH ₂ -		OH	CH ₃	Seneciphylline (60)
CH ₃	H	- CH ₂ -		OH	CH ₂ OH	Ridelline (61)

* stereochemistry estimated or unknown

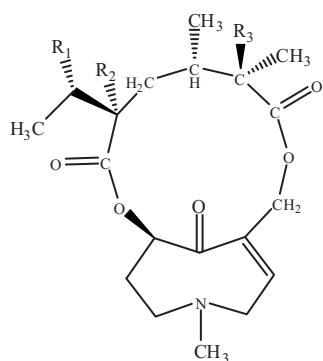


R ₁	R ₂	R ₃	R ₄	Name
H	CH ₃	CH ₃	OH	Crotaverrine (62)
H	CH ₃	CH ₃	ac	O ¹² -Acetylcrotaverrine (63)
CH ₃	H	OH	CH ₃	Senkirkine (64)

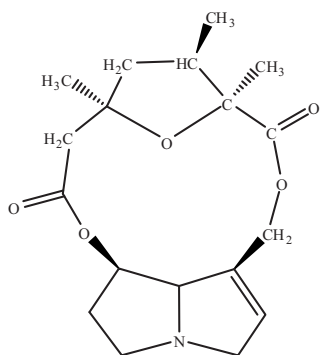


R ₁	R ₂	R ₃	R ₄	R ₅	Name
	- O -		- CH ₂ -	OH	Jacozine (65)
	- O -	CH ₃	H	OH	Jacobine (66)
OH	OH	CH ₃	H	OH	Jacoline (67)
OH*	- OCH ₂ - *		- O - *		Adonifoline (68)
Cl	OH	CH ₃	H	OH	Jaconine (69)

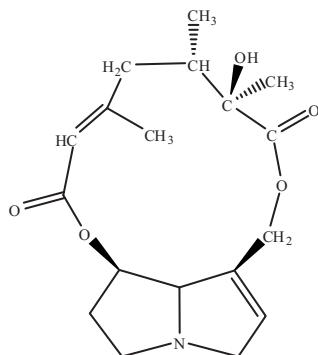
* stereochemistry estimated or unknown



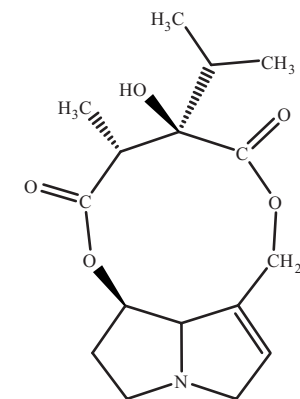
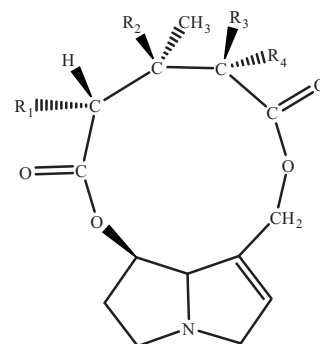
R ₁	R ₂	R ₃	Name
Cl	OH	ac	Doronine (70)
	- O -	OH	Otosenine (71)



Retroisosenine (80)



Doronenine (82)



Helindicine (83)

R ₁	R ₂	R ₃	R ₄	Name
CH ₃	OH	OH	CH ₃	Monocrotaline (74)
CH ₃	OH	CH ₃	H	Cromadurine (75)
CH ₃	Ac	OH	CH ₃	Spectabiline (76)
i-pr	OH	OH	CH ₃	Trichodesmine (77)
i-pr	OH	OH	CH ₂ OH	Junceine (78)

i-pr = isopropyl

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