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## Pyrrolizidine alkaloids in medicinal plants from North America

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Pyrrolizidine alkaloids (PAs) are mutagenic, carcinogenic, pneumotoxic, teratogenic and fetotoxic. Plants containing PAs commonly poison livestock in many countries, including the USA and Canada. In some regions of the world PA-producing plants sometimes grow in grain crops and items of food made with PA contaminated grain, such as bread baked using contaminated flour, have been, and continue to be, responsible for large incidents of acute, often fatal human poisoning. Herbal medicines and food supplements containing PAs are also recognized as a significant cause of human poisoning and it is desirable that such medications are identified and subjected to strict regulation. In this review we consider the PAs known to be, or likely to be, present in both the traditionally used medicinal plants of North America and also medicinal plants that have been introduced from other countries and are being recommended and used as phytopharmaceuticals in the USA and Canada.

### 1. Introduction

Traditional herbal medicines are still being extensively used by people in developing countries for both historical and cost reasons. They are considered to be efficacious, well tested and considerably less expensive than modern medications produced in developed countries. In developed countries there has been a renaissance of herbal medicine use based on an expectation that traditional medicines are “natural” and free from the undesirable and often harmful side-effects of modern “synthetic” medications. They are also considered to be very effective, well proven and mild. In this context the use of herbal medicines incorporating plants known to contain toxic PAs is of particular concern.

We have previously reported that PA-containing plants, and herbal preparations made from them, are widely used in a number of regional Traditional Medicine systems (Roeder 1995; 2000; Roeder and Wiedenfeld 2009, 2011, 2013). In many cases the levels of exposure to toxic PAs from consuming these PA-containing products are unlikely to cause acute PA toxicity but they could be responsible for initiating a range of slowly developing chronic diseases (Edgar et al. 2011; Edgar 2014). Sub-chronic and chronic toxicity is a long delayed response to PA exposure and consequently early traditional healers are likely to have failed to connect the use of PA medicinal plants with several chronic diseases that may occur long after exposure to PA-containing medications (Edgar et al. 2011). This lack of recognition of causation could continue to the present day amongst herbal medicine practitioners, consumers and physicians.

Many of the medicinal plants used by the indigenous inhabitants of North America have been identified and reported in the literature (Moerman 2009; Uprety et al. 2012). They continue to be

used; by many different ethnic groups from the Arctic Eskimos to Seminoles from Florida or Canadian Algonquin to Navahos and Hopi from the south-west. Many plants mentioned in reports of North American traditional herbal medicines are known to contain or, based on the genera they belong to, are likely to contain toxic PAs. Despite this, while intoxications of livestock grazing on PA-containing plants in pastures and rangeland or exposed to PA contaminated feed are relatively common, well recognized and frequently described in North America (Burrows et al. 2013; Stegelmeier 2011), cases of human intoxication from consuming these plants as herbal medicines are much less commonly reported in the literature. To assist in rectifying the possibility that this could be due to a failure to recognize causation we have reviewed all of the plants used as herbal medicines in North America that contain, or may contain PAs.

### 2. PA toxicity

All PAs are characterized by bicyclic pyrrolizidine moieties, referred to as “necines” (see Section 5). For a particular PA to be toxic the necine must have a 1,2 double bond, a hydroxymethyl group at C1 and, in most cases, they also have a hydroxyl group at C7 (Figure 3). One or both hydroxyls must be esterified. PAs lacking one or more of these features are non-toxic (Wiedenfeld et al. 2008). The three most common necines associated with toxic PAs are: retronecine, heliotridine and otonecine (Figure 5). After ingestion toxic PAs are converted by hepatic cytochrome P450 monooxygenase enzymes to 6,7-dihydropyrrolizine ester alkylating agents (Fig. 1) (Fu et al. 2004). The highly reactive dihydropyrrolizine metabolites produced in the liver rapidly alkylate sulfhydryl, hydroxyl and amino groups on proteins and DNA and other nucleophilic substances *in vivo*. They are, as a

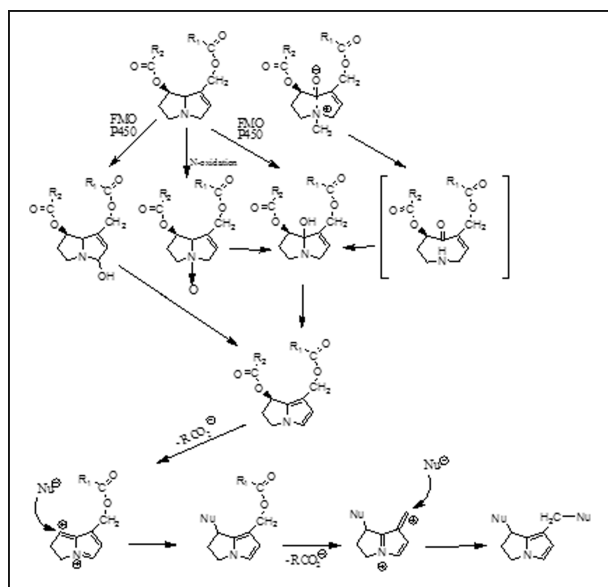


Fig. 1: Metabolism of toxic PAs

consequence of the DNA adducts produced, genotoxic and cause mutations leading to a spectrum of chronic diseases (Fu et al. 2004; Edgar et al. 2011). As the site of PA activation, the livers of humans and animals are the first tissue to be acutely affected by ingestion of PAs. Acute liver damage caused by PAs is characterized by hepatic sinusoidal obstruction syndrome (HSOS) (Fu et al. 2004; Edgar et al. 2011) and HSOS is considered pathognomonic for acute PA exposure (Huxtable 1989; Seawright 1992). However lungs, kidneys and many other organs can also be damaged by PA metabolites escaping from the liver (Edgar et al. 2011). Lungs in particular are known to develop chronic and progressive pulmonary arterial hypertension, leading to right heart failure (Fu et al. 2004; Edgar et al. 2011). A wide variety of cancers are also produced in animals following long term, low level sub-acute exposure to toxic PAs and these too could be amongst the potential spectrum of delayed chronic diseases resulting from the use of PA-containing herbal medicines (Mattocks 1986; WHO 1988; Fu et al. 2002, 2004, 2007; Xia et al. 2004, 2006; Wiedenfeld et al. 2008; Wiedenfeld, Edgar 2011).

### 3. PA-containing plants used in North America

#### 3.1. *Boraginaceae* (all subtribes)

*Amsinckia douglasiana* A. D.; Douglas's Fiddleneck. Distribution: Native to California. Endemic to Northwestern, Southwestern, South Central USA, and Northern Mexico. The shoots, seeds or leaves of several species are used by Native Americans, and the plants also had some medicinal uses in the Costanoan Indian tribe (Moerman 2009). The seeds and foliage are very poisonous to livestock, particularly cattle. The closely related *Amsinckia intermedia*, *A. hispida*, *A. lycopsoides* and *A. tessellata*, growing in California contain intermedine (30), O<sup>3</sup>-acetyl-intermedine (31), 3,7-diacetyl-intermedine (32), lycopsamine (34), O<sup>3</sup>-acetyl-lycopsamine (35), O<sup>3</sup>,O<sup>7</sup>-diacetyl-lycopsamine (36), echiumine (47), (Culvenor et al. 1966; Roitman 1983b; Cooper et al. 1996).

*Borago officinalis* L.; Borage. Distribution: Introduced from Europe into North America as an herbal and ornamental plant. Borage has been naturalized in only a few counties in Illinois and Canada. It is used as an antioxidant, anti-inflammatory, and

diuretic and depurative plant (De Jong et al. 1990). The plant contains the alkaloid amabiline (5) (Larson et al 1984; Dodson, Stermitz 1986), supinine (6), intermedine (30), O<sup>3</sup>-acetyl-intermedine (31), lycopsamine (34), O<sup>3</sup>-acetyl-lycopsamine (35) (Lüthy et al. 1984).

*Cynoglossum grande* Dougl. ex Lehm.; Pacific Hound's Tongue. Distribution: Native to Western North America, from British Columbia to California. Pomo and Potter Valley Indians use it as a gastrointestinal and venereal aid. (Moerman 2009).

*Cynoglossum officinale* L.; Hound's tongue, Common Hound's Tongue, Gypsyflower.

Distribution: Naturalized from Eurasia into much of the United States and found across southern Canada. Iroquois Indians take it as an antihemorrhagic drug, a tuberculosis remedy, and as a venereal aid (Moerman 2009; Munro 2013). It is a toxic plant for cattle and horses (Stegelmeier 2011). The plant contains echinatine (7), 7-angeloyl-heliotridine (rivularine) (15), heliosupine (18), O<sup>3</sup>-acetyl-heliosupine (19) (Pedersen 1975; Mattocks 1986; Pfister et al. 1992).

*Cynoglossum virginianum* L., syn. *C. boreale* Fernald; Northern Wild Comfrey, Hound's tongue, cynoglosse boréale. Distribution: Native, Newfoundland, south to Connecticut, west to Iowa, and north to British Columbia in the central and south eastern parts of the country. It occurs in southern New England, from New York to Illinois, Louisiana, Oklahoma, and south to Florida. The Cherokee Indian uses the root as a cancer treatment and as a dermatological aid. A decoction of roots is given to reduce itching and as a urinary aid. It is also used as a treatment for a bad memory. The Ojibwa tribe smokes it to cure headaches (Moerman 2009; Uprety et al. 2012).

*Cynoglossum virginianum* L., (Fernald), var. *C. boreale*; Northern Wild Comfrey. Distribution: Common in Minnesota, Wisconsin and Michigan in the US and in Manitoba and Ontario in Canada. The Ojibwa tribe uses this plant as an analgesic to treat headaches by burning it and inhaling the fumes (Moerman 2009).

*Echium vulgare* L.; Common Vipers Bugloss. Distribution: Introduced in North America in the 17<sup>th</sup> Century from Europe and is naturalized in the most parts of the continent. The Cherokee, Iroquois, and Mohegan use it as a urinary, gynaecological and kidney aid. (Moerman 2009). It contains uplandicine (41), echimidine (42), O<sup>3</sup>-acetyl-echimidine (43), echimidine isomer, and the *N*-oxides (Pedersen 1975; El-Shazly et al. 1996).

*Hackelia floribunda* Lehm. Johnston.; Manyflower Stickseed. Distribution: Native in much of the western half of North America. Ramah and Navajo Indians considered the plant as aid for the skin, as an orthopedic aid for serious injury such as fractures (Moerman 2009). The plant contains latifoline (44) and its *N*-oxide (Haglund et al. 1985).

*Hackelia hispida* Lehm. Showy Stickseed, Thomson Drug. Distribution: Native to and found throughout the western regions of North America. The Thompson Indians use plant medicinally for unspecified purposes (Moerman 2009). Contains 7-angeloyl-retronecine (20), and latifoline (44) (Kee et al. 2011).

*Hackelia virginiana* L. Johnston; Beggarslice. Distribution: A native herb found throughout the western North America. Cherokee drug, for cancer treatment, dermatological aid, kidney aid, used for good memory and as an insecticide (Moerman 2009). The closely related *Hackelia californica* (Gray) Johnston., in genus *H. hispida*, is widely distributed in Colorado. It contains: latifoline (44), neolatifoline (45) and O<sup>7</sup>-angeloyl-retronecine (20) (Kee et al. 2011; L'Empereur et al. 1989), and *Hackelia longituba* John. Native to the mountains of California in the Sierra Nevada, contains: longitubine (46), latifoline (44), O<sup>7</sup>-angeloyl-retronecine (22) and O<sup>9</sup>-angeloyl-retronecine (22) (Roitman 1988).

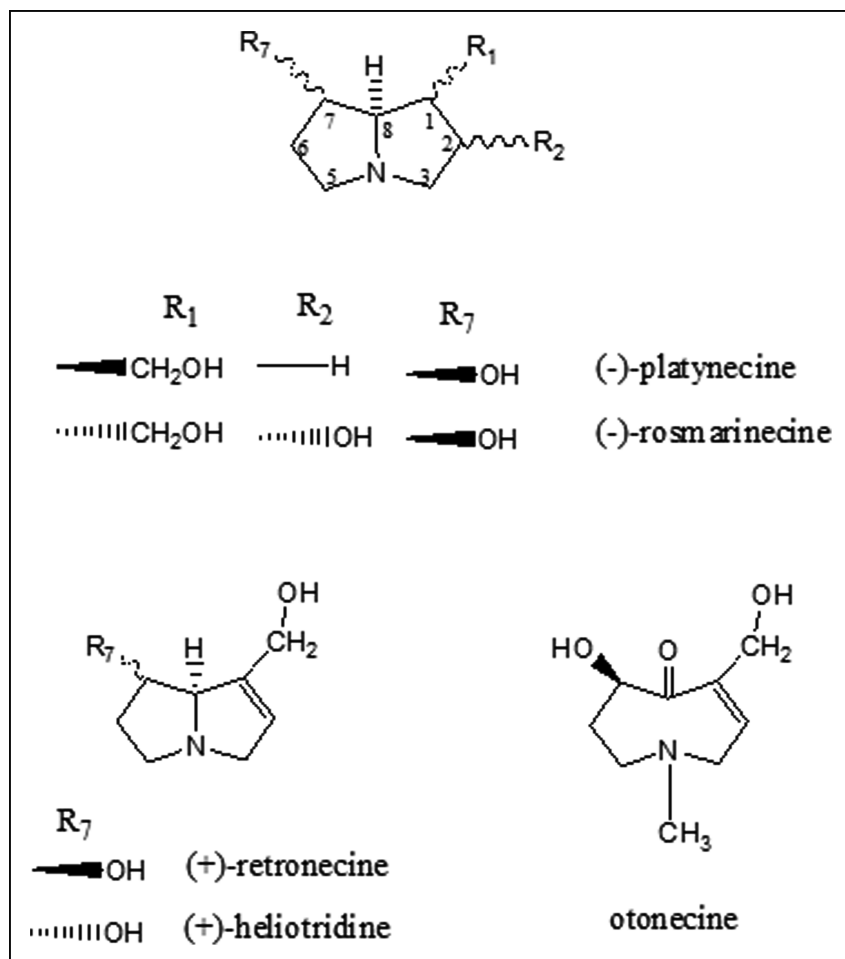


Fig. 2: Necines

*Heliotropium curassavicum* L.; Salt Heliotrope, Spatulate-leaved Heliotrope. Distribution: Native herb found in southern parts of western Canada. Paiute, Pima, Shoshoni and Tubululata indian drug. Used as an antidiarrhea, diuretic, emetic, a throat aid, and a dermatological aid (Moerman 2009; Munro 2013). It contains:  $O^9$ -( $O^{3'}$ -acetyl)-viridofloroyl-retronecine (**28**),  $O^9$ -( $O^{3'}$ -isovaleroyl)-viridofloroyl-retronecine (**29**), and many minor alkaloids (Catafalmo et al. 1982; Mohanraj et al. 1982; Davicino et al. 1988; Agnese et al. 1995).

*Lappula occidentalis* var. *cupulata* Gray Higgins; Flatspine Stickseed. Distribution: Native in most of North America. A Navajo indian drug used as a gynaecological, and dermatological aid (Moerman 2009).

*Lappula occidentalis* var. *occidentalis* Wats. Greene Desert Stickseed. Distribution: Native in most of North America. A Navajo indian drug, dermatological aid (Moerman 2009).

*Lappula squarrosa* Retz. Dumort. European Stickseed, Bardenette. Distribution: Native to the eastern Mediterranean region. Its current distribution includes Europe and North America. It is found in every Canadian province and nearly all of the United States. It is an Ojibwa indian drug, used to treat headaches and as an analgesic aid. (Moerman 2009; Uprety et al. 2012). The closely related *Lappula myosotis* Moench contains: intermedine (**30**),  $O^{3'}$ -acetyl-intermedine (**31**), lycopsamine (**34**),  $O^{3'}$ -acetyl-lycopsamine (**35**) (Wiedefeld et al. 2005).

*Lithospermum canescens* Michx. Lehm. Hoary Puccoon. Distribution: Native and grows in open prairies in northern USA and southern Canada (Erichsen-Brown 1989, 456). Menominee indians used this plant as a sedative (Moerman 2009). It contains: canescenine (**8**),  $O^{13}$ -acetyl-canescenine (**9**), canescine

(**13**),  $O^{13}$ -acetyl-canescine (**14**), intermedine (**30**),  $O^{3'}$ -acetyl-intermedine (**31**), lycopsamine (**34**),  $O^{3'}$ -acetyl-lycopsamine (**35**) (Wiedefeld et al. 2003).

*Lithospermum carolinense* Walt. ex Gmel. MacMill. Hairy Puccoon, Carolina Puccoon, Yellow Puccoon. Distribution: Native to North America. In the United States it is found in the Midwest, around the Great Lakes, and through the Canadian provinces surrounding the Great Lakes (Erichsen-Brown 1989). Lakota indians used it as pulmonary aid (Moerman 2009).

*Lithospermum incisum* Lehm.; Narrowleaf Gromwell. Distribution: Native much of central Canada and the United States. A Blackfoot, Cheyenne, Hopi, Navajo, Ramah, Sioux, and Zuni indian drug used as an orthopedic, psychological, sedative, stimulant, cold remedy, and as a contraceptive aid (Moerman 2009).

*Lithospermum multiflorum* Torr ex Gray; Many flowered Gromwell, Manyflowered Stoneseed. Distribution: Native in southwestern North America. A Navajo drug; panacea; the seeds have also been used for food. The root has been used as a life medicine by some native North America indian tribes (Moerman 2009). Contains: pyrrolizidine alkaloids with unknown structure (Champion et al. 2003).

*Lithospermum officinale* L. European Gromwell. Distribution: Native to Europe and introduced into the northeast quarter of North America around the Great Lakes, and through the Canadian provinces surrounding the Great Lakes (Erichsen-Brown 1989). It is an Iroquis indian drug used as a diuretic and pediatric aid (Moerman 2009). Contains: lithosenine (**52**),  $O^{3'}$ -acetyl-lithosenine (**53**) (Krenn et al. 1994).

*Lithospermum ruderae* Dougl. ex Lehm.; Western Gromwell, Western Stoneseed. Distribution: Native to western United

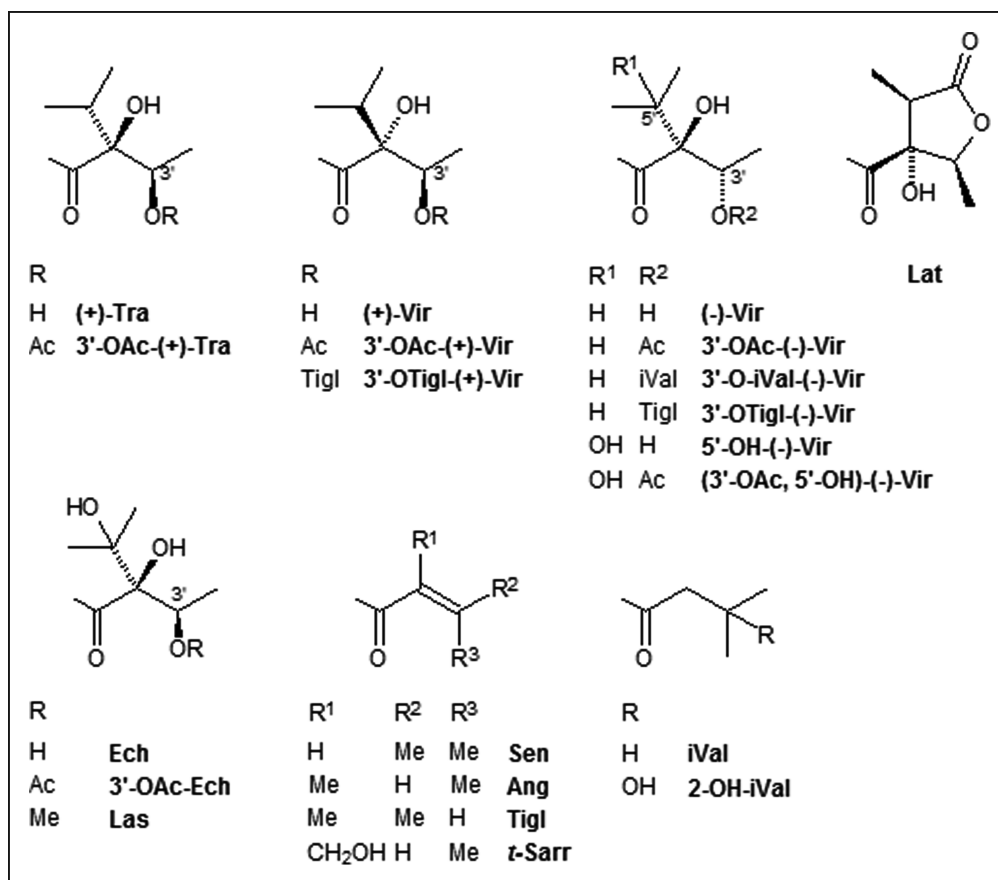


Fig. 3: Acids. Tra = trachelanthoylic, Vir = viridifloric, Lat = latifolic, Ech = echimidic, Sen = seneciolylic, iVal = isovalerianic, Ang = angeloylic, Tigl = tigloylic, Las = lasiocarpoylic, t-Sarr = t-sarracinylic

States and to western Canada. Many native indians use it as an analgesic, diuretic, contraceptive, antihemorrhagic, dermatologic, and diuretic aid. The seed have been used for food (Moerman 2009).

*Mertensia ciliata* James ex Torr. G. Gon. Mountain Bluebells. Distribution: A native plant, distributed in the subalpine zone of Montana, also from Colorado, near New Mexico, to Idaho and Orlando. It is a Cheyenne and Cherokee drug used as a breast treatment. Infusion of plant are used to increase milk flow of mothers; also used as a dermatological, gynaecological, pulmonary aid, misc. disease remedy, antidote, tuberculosis remedy (Moerman 2009). Contains: intermedine (30), lycopsamine (34) as N-oxide (Li and Stermitz 1988).

*Mertensia paniculata* Aiton G. Don. Lungwort, Tall Bluebells, Mertensie Paniculée.

Distribution: Native plant in the United States distributed in Alaska, stretching east through Washington, Oregon to Idaho. Canadian aboriginal people take it as a part of a medicine used to treat heart trouble (Uprety et al. 2012).

*Mertensia virginica* L. Pers. ex Link. Virginia Bluebells Distribution: Native in eastern North America. A Cherokee and Iroquis drug used as a pulmonary, venereal aid, tuberculosis remedy and antidote (Moerman 2009).

*Myosotis laxa* Lehm; Bay Forget Me Not, Myosotis laxiflora. Distribution: Circumboreal in Northern Hemisphere. Native to California and also found outside of California, but is confined to western North America. A Makah indian drug, used as a dermatological aid (Moerman 2009). The closely related *Myosotis scorpioides* L. growing in Ithaca, New York, contains: scorpioidine (38) O<sup>7</sup>-acetyl-scorpioidine

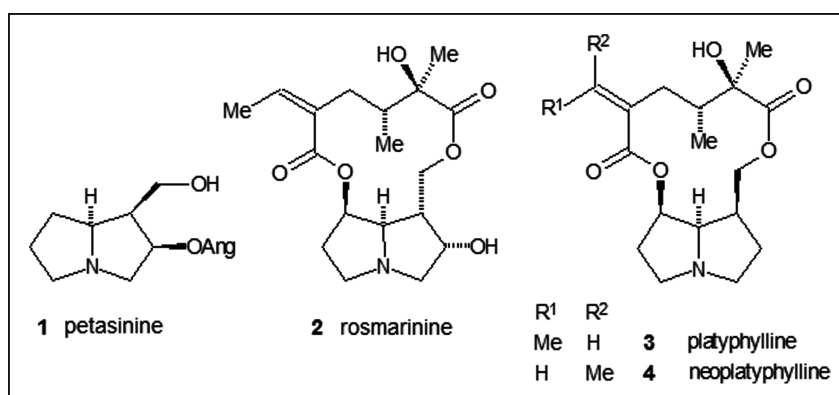


Fig. 4: Nontoxic pyrrolizidine alkaloids

(39), myoscorpine (50), symphytine (51) (Resch et al. 1982).

*Symphytum asperum* Lepech. Prickly Comfrey. Distribution: Native to Europe, naturalized in southern provinces of Canada. Canadian Aboriginal peoples use this plant. Plant can cause veno-occlusive symptoms leading to liver cirrhosis and liver tumor (Munro 2013). It contains: intermedine (30), O<sup>3'</sup>-acetyl-intermedine (31), lycopsamine (34), O<sup>3'</sup>-acetyl-lycopsamine (35), echimidine (42), symlandine (48), symviridine (49), myoscorpine (50), symphytine (51) (Culvenor et al. 1980a, 1980b; Roeder et al. 1992).

*Symphytum officinale* L., syn. *S. consolida* L.. Common Comfrey. Distribution: Introduced and naturalized herb from Europe. It occurs in many parts of Canada. Cherokee indians take it to treat dysentery and as a gastrointestinal aid. It is also used as a gynaecological aid and taken to treat heartburn in pregnancy and for "flooding" after birth. It is also taken as laxative infusion "costiveness" in pregnancy and used as an orthopedic aid against sprains and bruises. An infusion of roots in water is used against gonorrhoea (Moerman 2009). It causes: veno-occlusive symptoms, liver cirrhosis, and death (Munro 2013). It contains: echinatine (7), asperumine (16), intermedine (30), O<sup>3'</sup>-acetyl-intermedine (31), anadoline (40), lasiocarpine (17), heliosupine (18), lycopsamine (34), O<sup>3'</sup>-acetyl-lycopsamine (35), uplandicine (41), echimidine (42), echiumine (47), symlandine (48), symviridine (49), myoscorpine (50), symphytine (51) (Furuya et al. 1968, 1971; Pedersen 1975; Culvenor et al. 1980a, 1980b; Resch et al. 1982; Huizing et al. 1985, Roeder et al. 1992; Kim et al. 2001, Wuilloud et al. 2004; Liu et al. 2009).

*Symphytum x uplandicum* Nym., syn. *S. peregrinum* Ledeb. Russian Comfrey, is a hybrid generated from *Symphytum officinale* L. and *S. asperum* Lepech. Distribution: It is widely distributed in the United States and in Canada, and used as a trial forage crop in Lethbridge, Alta, and Vancouver Island. This plant contains PAs, which cause veno-occlusive symptoms, liver cirrhosis, and death (Ridker, et al. 1989; Altamirano et al. 2005). Roots and

leaves contain: intermedine (30), O<sup>3'</sup>-acetyl-intermedine (31), lycopsamine (34), O<sup>3'</sup>-acetyl-lycopsamine (35), uplandicine (41), echimidine (42), symlandine (48), symviridine (49), myoscorpine (50), and symphytine (51) (Culvenor et al. 1980a, 1980b; Roeder et al. 1992).

### 3.2. Asteraceae (subtribe Eupatorieae)

*Eupatorium maculatum* L. syn. *Eutrochium maculatum* L. Lamont; Joe Pye Weed, Eupatoire Maculae. Distribution: A native plant ranging from Missouri east to the Atlantic Ocean and as far north as Ontario and Quebec, south to Kentucky and widely distributed throughout Canada (Erichsen-Brown 1989, 261). It is used by all indigenous Indians as a purgative, diaphoretic, diuretic, emetic, gastrointestinal diseases, and abortifacient febrifuge, stomach, headache, hemorrhoid, pulmonary, urinary, anthelmintic, snakebite, hemorrhagic, venereal problems (Moerman 2009, Uprety et al. 2012). It contains: lycopsamine (34) (Wiedenfeld et al. 2009).

*Eupatorium perfoliatum* L. Boneset, Agueweed, Common Thorough Wort, Common boneset, Eupatoire Perfoliée. Distribution: Native to Canada and the eastern United States (Millspaugh 1974, 312; Erichsen-Brown 1989, 262). Used by all aboriginal Americans. It is used to treat sore throat, fever chills, epilepsy, gonorrhoea and other ailments. It has been adopted by early settlers to America. In Canada the Indian tribes used it as a general medicine, for gonorrhoea and kidney problems. The roots are used to treat menstrual disorders (Moerman 2009; Uprety et al. 2012). Products containing this plant have been placed in the "Herbs of Undefined Safety" Category by the US Food and Drug Administration (FDA).

*Eupatorium pilosum* Walt.; Rough Boneset, Ragged Thoroughwort. Distribution: Native in southern New England. Cherokee Indians used it against colds, and to treat breast complaints, as a laxative, a tonic and as an urinary aid (Moerman 2009).

*Eupatorium purpureum* (L.), A. Löve & D. Löve. Sweetscented, Joepeweeweed, Boneset, Eupatoire Pourpre. Distribution: Native

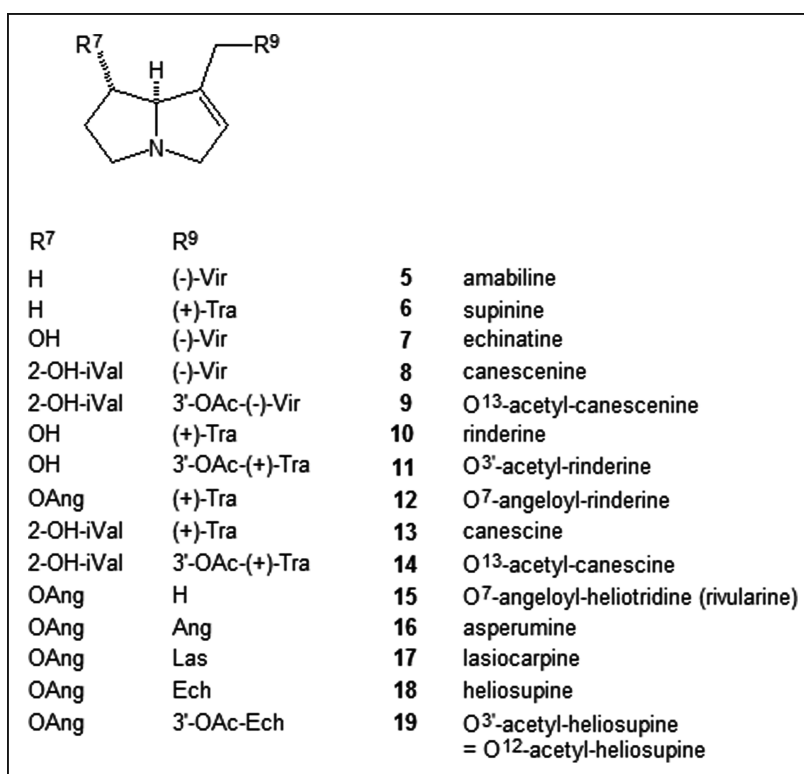
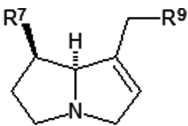


Fig. 5: Toxic pyrrolizidine alkaloids



R <sup>7</sup>	R <sup>9</sup>		
OAng	OH	20	O <sup>7</sup> -angeloyl-retronecine
OAng	OAc	21	O <sup>7</sup> -angeloyl-O <sup>9</sup> -acetyl-retronecine
OH	OAng	22	O <sup>9</sup> -angeloyl-retronecine
OSen	OH	23	O <sup>7</sup> -seneciyl-retronecine
OSen	OAng	24	O <sup>7</sup> -seneciyl-O <sup>9</sup> -angeloyl-retronecine
OSen	O- <i>t</i> Sarr	25	O <sup>7</sup> -seneciyl-O <sup>9</sup> -sarracinoyl-retronecine
OAng	O- <i>t</i> Sarr	26	O <sup>7</sup> -angeloyl-O <sup>9</sup> -sarracinoyl-retronecine = triangularine
OTigl	O- <i>t</i> Sarr	27	O <sup>7</sup> -tigloyl-O <sup>9</sup> -sarracinoyl-retronecine = neotriangularine
OH	O-3'-OAc-(?)Vir*	28	O <sup>9</sup> -(O <sup>3'</sup> -acetyl)-viridifloroyl-retronecine
OH	O-3'-O-iVal-(?)Vir*	29	O <sup>9</sup> -(O <sup>3'</sup> -isovaleroyl)-viridifloroyl-retronecine
OH	O-(+)-Tra	30	intermedine
OH	O-3'-OAc-(+)-Tra	31	O <sup>3'</sup> -acetyl-intermedine
OAc	O-3'-OAc-(+)-Tra	32	O <sup>3'</sup> ,O <sup>7</sup> -diacetyl-intermedine
OAc	O-(+)-Tra	33	O <sup>7</sup> -acetyl-intermedine
OH	O-(-)Vir	34	lycopsamine
OH	O-3'-OAc-(-)Vir	35	O <sup>3'</sup> -acetyl-lycopsamine
OAc	O-3'-OAc-(-)Vir	36	O <sup>3'</sup> ,O <sup>7</sup> -diacetyl-lycopsamine
OAc	O-(-)Vir	37	O <sup>7</sup> -acetyl-lycopsamine
OH	O-3'-OTigl-(-)Vir	38	scorpioidine
OAc	O-3'-OTigl-(-)Vir	39	O <sup>7</sup> -acetyl-scorpioidine
OH	O-3'-OTigl-(+)-Vir	40	anadoline
OAc	OEch	41	uplandicine
OAng	OEch	42	echimidine
OAng	O-3'-OAc-Ech	43	O <sup>3'</sup> -acetyl-echimidine
OAng	O-Lat	44	latifoline
OAc	O-Lat isomer*	45	neolatifoline
OAc	O-Lat	46	longitubine
OAng	O-(+)-Tra	47	echiumine
OAng	O-(-)Vir	48	symlandine
OSen	O-(-)Vir	49	synviridine
OTigl	O-(+)-Tra	50	myoscorpine
OTigl	O-(-)Vir	51	symphytine
O-2-OH-iVal	O-5'-OH-(-)Vir	52	lithosenine
O-2-OH-iVal	O-(3'-OAc,5'-OH)-(-)Vir	53	O <sup>3'</sup> -acetyl-lithosenine

\*stereochemistry estimated or unknown

Fig. 5: (Continued)

to Canada and the northern, western, and middle US States. It is, or has been, used by all indian tribes to cure fevers and as an anti-rheumatic, gynaecological, kidney, urinary, laxative, dermatological, pediatric aid (Millspaugh 1974, p. 305; Moerman 2009; Uprety et al. 2012).

*Eupatorium serotinum* Michx. Lateflowering Thoroughwort. Distribution: Native to and widely distributed in North America. Houma Indians take this plant as a febrifuge. Oto, Ponca and Winnebago indians use it as a tonic, analgesic, stimulant, and laxative (Moerman 2009). Contains: supinine (**6**), rinderine (**10**) (Locock et al. 1966).

### 3.3. Asteraceae (subtribe Senecioneae)

*Petasites frigidus* L. Fries. Arctic Sweet Coltsfoot. Distribution: Grows throughout Washington, Alaska, south to California, east across the northern half to North America to the Atlantic Coast.

Houma indians take it as febrifuge (Moerman 2009). Thought to contain: senkirkine (**63**) (Kee et al. 2013).

*Petasites frigidus* var. *nivalis* Greene Cronq. Arctic Sweet Coltsfoot. Distribution: Grows from eastern Siberia to the western District of Mackenzie, south through the mountains of British Columbia and western Alberta until Washington and Oregon. Eskimo and Inupiat indians take it as cold remedy and as respiratory aid (Moerman 2009).

*Petasites frigidus* L. Fr. var. *palmatus* Aiton Cronquist, syn. *P. palmatus* Aiton A. Gray. Arctic Sweet Coltsfoot, Palmate Coltsfoot, Pétasite sagittée. Distribution: Newfoundland and Labrador to British Columbia, southwestern District of Mackenzie, and southeastern Yukon Territory, south to Massachusetts, Michigan, Minnesota, and in the west of California. All indians take it as dermatological, tuberculosis, pulmonary, pediatric, emetic, anti-rheumatic and respiratory aid (Moerman 2009; Uprety et al. 2012).

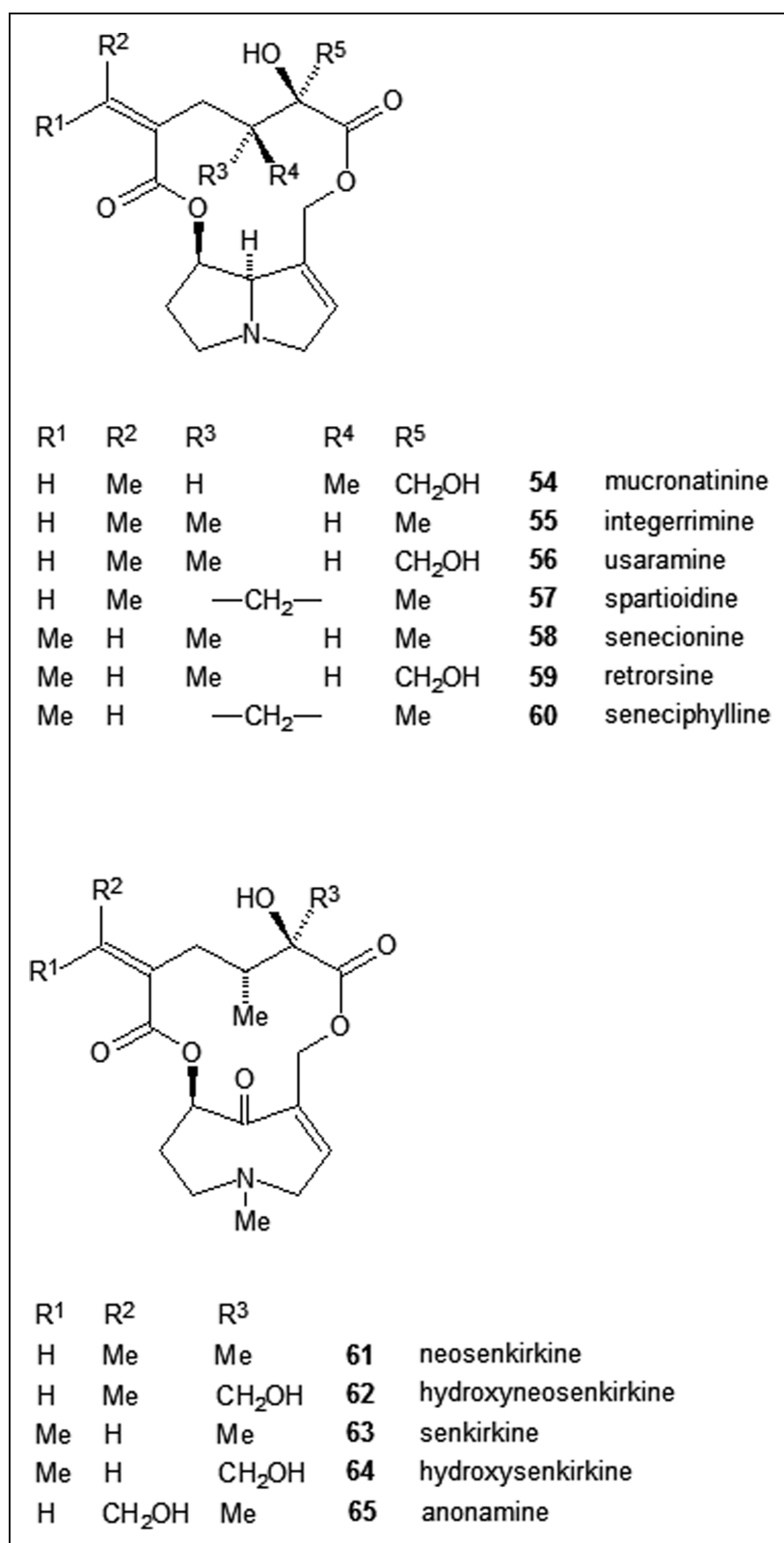


Fig. 5: (Continued)

*Petasites frigidus* L. Fr. var. *sagittatus* Banks ex Pursh Cherniawsky. syn. *P. sagittatus* Banks ex Pursh. A. Gray. syn. *Nardosmia sagittata* Pursh Hook. Arrow-Leafed Coltsfoot, Pétasites sagittée. Distribution: Alaska, northern Canada to Newfoundland and southwards through Idaho, Wisconsin, Minnesota, Wyoming and South Dakota, with the southern limit in Colorado. Cree, Woodlands and Canadian people aborigines take it as dermatological aid, to treat chickenpox, the sap is taken

to treat asthma (Moerman 2009; Haider et al. 2012; Uprety et al. 2012). One alkaloid is thought to be senkirkine (**63**) or a novel isomeric compound (Kee et al. 2013). The closely related *Petasites fragrans* contains: 7-angeloyl-retronecine (**20**), senkirkine (**63**) and the nontoxic alkaloid petasinine (**1**) (Wiedenfeld et al. 2002).

*Senecio anonymus* Alp. Wood, syn. *Packera anonyma* Alph. Wood Weber & Löve, syn.

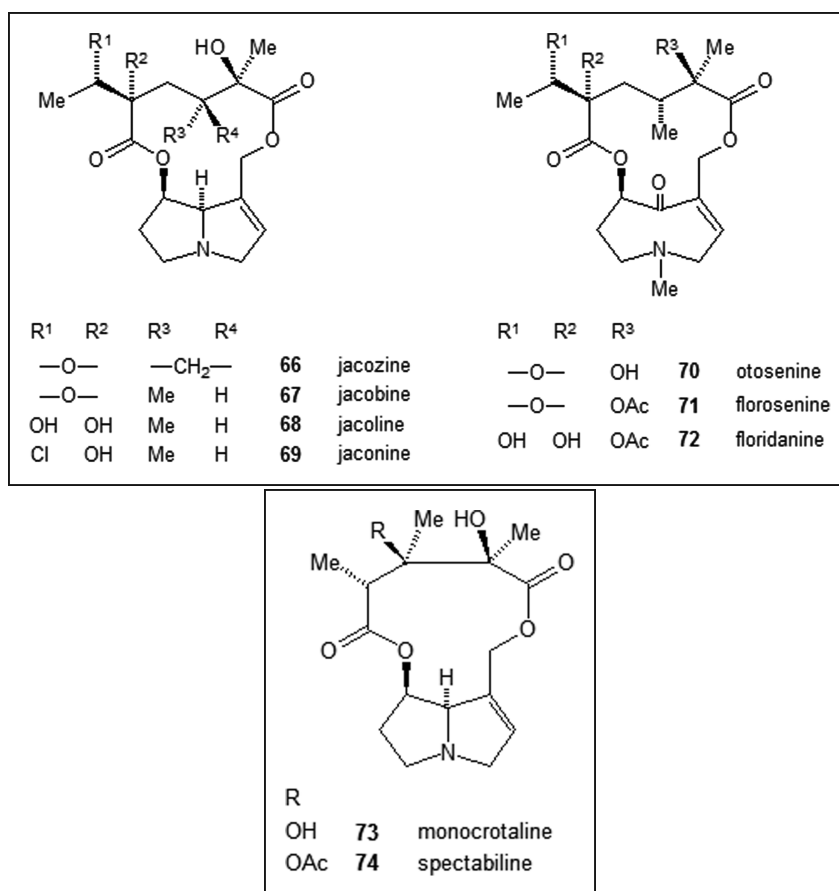


Fig. 5. (Continued)

*S. smallii* Britton ex Small & Vail; Small's Ragwort. Distribution: Found throughout the southwestern States and as far north as Pennsylvania, Ohio, and Illinois. Catawba Indians use it as a tuberculosis remedy (Moerman 2009). It contains: integerrimine (55), usaramine (56), senecionine (58), retrorsine (59), neosenkirkine (61), hydroxyneosenkirkine (62), senkirkine (63), hydroxysenkirkine (64), anonamine (65), otosenine (70) (Zalkow et al. 1988). The alkaloids are toxic to both humans and livestock in Western America.

*Senecio aureus* L.; syn. *Packera aurea* (L.), A. & D. Löve, var. *gracilis* Pursh.

Golden Ragwort, Golden Senecio, Senecon doré. Distribution: Widely in North America and Canada where it grows on humid river-bank meadows. Cherokee and Iroquois Indians cultivated this "ragwort" as a medicinal plant. Today it is still used as a remedy against injuries, internally as a diaphoretic, diuretic, emenagogue and heart medicine. The wives of Indian tribes ingest high doses of this drug both to accelerate labor and for abortion (Millspaugh 1974; Moerman 2009; Uprety et al. 2012). It contains: otosenine (70), floresenine (71), floridanine (72) (Resch et al. 1983; Roeder et al. 1983).

*Senecio congestus* R.Br. DC.; Marsh Fleabane, Senecon Des Marais. Distribution: Most common in the eastern Canadian arctic, Alaska, throughout western Texas, west New Mexico, Arizona, Utah, California, north to Wyoming, Nebraska, South Dakota. Eskimo and Inuktitut Indians take it as a general medicine plant (Moerman 2009). It contains: senecionine (58), and the nontoxic alkaloids platyphylline (3), and neoplatyphylline (4) (Roeder et al. 1982a).

*Senecio fendleri* Gray, syn. *Packera fendleri* Weber & Löve; Fendler's Ragwort. Distribution: Native in the southern Rocky

Mountains. Keres, Western Navajo, and Ramah Indians use it as psychological, dermatological, gastrointestinal and pediatric aid (Moerman 2009).

*Senecio flaccidus* var. *douglasii* DC. Turner & Barkl. Douglas Groundsel. Distribution: Native to California. It is confined to California, also in Colorado and Kansas. Costanoan Indians use it as a dermatological and gynaecological aid, and for the Kawaiisu Indians it is used as a laxative (Moerman 2009).

*Senecio flaccidus* Less. var. *flaccidus*; Turner & Barkl.; Threadleaf Groundsel. Distribution: Native in the southwestern States of America. Hopi Indians use this plant as an anti-rheumatic, dermatological and orthopedic aid, Keres, and western tribes use it as dermatological and gastrointestinal aid. Navajo and Kayenta also take it as a dermatological aid (Moerman 2009).

*Senecio jacobaea* L.; Stinking Willie, Tansy ragwort. Distribution: Native to Europe and naturalized in Oregon and eastern Canada and British Columbia. Makah Indians used it as medicinal tea (Moerman 2009). This plant has poisoned cattle and horses and possible goats (Stegelmeier 2011) and the Canadian Government had banned *S. jacobaea*. This plant has poisoned cattle and horses. Animals and humans may be poisoned if they drink the milk of animals that have ingested this plant (Molyneux, et al. 1990). It contains: integerrimine (55), senecionine (58), seneciophylline (60), jacozine (66), jacobine (67), jacoline (68), jaconine (69) (Bradbury et al. 1954, 1959; Culvenor 1964; Segall 1978).

*Senecio multilobatus*, Greenm. ex Rydb., syn. *Packera multilobata* Weber & Löve. Lobeleaf Groundsel. Distribution: Native to California and the next southwestern States. Navajo

and Ramah indians use it as a dermatological and gynaecological aid. Yavapai take it as a cold remedy, and as a dermatological, gastrointestinal, and venereal aid (Moerman 2009).

*Senecio neomexicanus*, Gray, syn. *Packera neomexicana* Weber & Löve; New Mexico Groundsel. Distribution: Native to the southwestern states of the USA. Navajo and Kayenta indians use it as an antidote for narcotics and as a burns dressing. For Navajo and Ramah it is a hunting medicine to bring good luck in hunting (Moerman 2009).

*Senecio pseudoarnica* Less; Seaside Ragwort. Distribution: Native to Alaska, and Maine, and in Canada. Aleut indians use it as a dermatological aid (Moerman 2009).

*Senecio spartioides* Torr. & Gray, syn. *S. multicapitatus* Greenm. ex Rydb.; Broom Groundsel, Broom-Like Ragwort. Distribution: Native to western Texas, west through New Mexico, northern Mexico, Arizona, Utah, California, Wyoming, Nebraska, South Dakota. Hopi indians use it as an anti-rheumatic (external), and anti-dermatological aid. The Keres and Western tribes take it as a gynecological aid after childbirth (Moerman 2009). It contains: spartioidine (**57**) (Manske 1934).

*Senecio triangularis* Hook. Arrowleaf Groundsel. Distribution: Native to subarctic America, western Canada, northwestern and southwestern United States. Plants also grow in Alberta. Cheyenne indians used this plant as a sedative, and to treat chest-pains (Moerman 2009). It contains: O<sup>7</sup>-angeloyl-O<sup>9</sup>-acetyl-retronecine (**21**), O<sup>7</sup>-angeloyl-O<sup>9</sup>-sarracinoyl-retronecine (triangularine) (**26**), (Rueger, et al. 1983) and plants growing in the western States contain substantial amounts of senecionine (**58**), and small amounts of integerrimine (**55**), retrorsine (**59**), triangularine (**26**), neotriangularine (**27**), and the nontoxic alkaloids rosmarinine (**2**) and platyphylline (**3**) (Roitman 1983).

*Tussilago farfara* L. Coltsfoot, Coughwort. Distribution: Native to Europe and introduced into North America. It is widespread in the eastern United States from Minnesota south to Tennessee, east to North Carolina, and north to Maine. It occurs throughout Ontario, Quebec, and the Canadian Maritime provinces. It is an Iroquoian drug and is used as a cough medicine, anti-tussive, adstringent, emollient, and as an expectorant (Moerman 2009). It contains: senecionine (**58**), senkirkine (**63**) (Culvenor et al. 1976; Rosberger et al. 1981).

### 3.4. Fabaceae (subtribe Crotalarieae)

*Crotalaria rotundifolia* Walt. ex Gmel.; Rabbitbells. Distribution: Indigenous throughout nearly all of Florida. The range includes the coastal states from Maryland through the south east into Louisiana plus Arkansas. It is a drug of Seminole indians to treat sore throats (Moerman 2009).

*Crotalaria sagittalis* L.; Arrowhead, Rattlebox. Distribution: Indigenous to a wide area of eastern North America and occurs sporadically in Connecticut. By ingestion in animals causes "Missouri Bottom disease". Most animals die within a few weeks. This plant is a traditional herbal medicine of the Delaware, Oklahoma, Mohegan and Algonkian indians. It is used as a strong narcotic, to treat venereal diseases and as a blood purifier (Moerman 2009). It contains monocrotaline (**73**) as the main alkaloid and also some other unknown alkaloids (Willette, et al. 1972). The closely related and very toxic *Crotalaria spectabilis* Roth., Showy rattlebox, occurs widely from Missouri to Virginia south to Florida, including all of the mid-southern States. It can be toxic to horses, cows and other livestock. Besides monocrotaline (**73**), it also contains spectabiline (**74**) (Culvenor et al. 1957).

## 4. Discussion

PA-containing plants are used in traditional herbal medicine systems in many parts of the world (Roeder 1995, 2000; Roeder and Wiedenfeld 2009, 2011, 2013). The traditional herbal medicines of North American Indians also include PA-containing plants and toxic PAs have been found to be present in 28 of the species used while 22 plants have not yet been investigated, but on account of their botanical classification can be suspected to contain them. On account of the increasing interest of the modern American population to use traditional healing methods it is likely that more and more people are coming into contact with plants or plant preparation that contain toxic PAs and they are therefore exposed to potentially toxic side-effects.

Many countries in the EU have banned the use of PA-containing medicinal plants or strictly regulate them (BAnz 1992; Bundesgesetzblatt 1993; Staatsblad 2001). In the US, the Food and Drug Administration (FDA) has not issued any general restrictions on the use of PA-containing herbal drugs. Concerning dietary supplements, the FDA has issued a warning in regard to the marketing of those products that contain the herbal ingredient comfrey (*Symphytum* spp.). In Canada health officials (NHPD 2003) have also banned the sale of some comfrey products (Rode 2002). *Symphytum* species are a well-established source of toxic PAs and they present a serious health hazard to consumers when they are ingested. Products containing comfrey have been placed in the "Herbs of Undefined Safety" Category by the US Food and Drug Administration (US-FDA 2001) and recently PAs have been confirmed as carcinogens (U.S. National Toxicology Program 2011).

There have been many reports from throughout the world describing thousands of acute, severe and fatal intoxications from consuming products containing toxic PAs, both herbal medicines and foods contaminated by PAs, and it is therefore highly undesirable to use such plants or preparations from them as herbal remedies, especially as they can also produce delayed chronic diseases. Consequently, people should be protected from the medical use of those herbal preparations. Their use can only be justified if there is assurance that the daily intake of toxic PAs is below a limit where toxic side-effects can be observed. However genotoxic carcinogens such as toxic PAs in theory have no level of exposure that can be considered absolutely safe and a tolerable level is normally set for such substances. For genotoxic PAs this is currently considered to be no more than 0.007 micrograms/kg body weight/day (COT 2008; WHO 2011; EFSA 2011). At this level of exposure cancer is considered to be an unlikely consequence.

As well as there being many indigenous plants containing poisonous PAs in North America that have been used as herbal medicines by the original inhabitants, many other PA plants were introduced by more recent immigrants as ornamental, food or medicinal plants. Some of these plants are now widely distributed. Many foreign plants, some containing PAs, were specifically introduced from their native range to the United States and Canada for their medicinal properties and some of these are currently still being recommended and used for that purpose.

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