Pyrrolizidine alkaloids in medicinal plants from North America

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Pyrrilizidine 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 (Bowers 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 hydroxy-methyl 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 otoxecine (Figure 5). After ingestion toxic PAs are converted by hepatic cytochrome P450 monooxygenase enzymes to 6,7-dihydro derivatives of ester alkylating agents (Fig. 1) (Pu et al. 2004). The highly reactive dihydropyrrolizidine 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
lycopsamine (Borage has been naturalized in only a few counties in Illinois Borago officinalis 1996). Amsinckia douglasiana Edgar 2011). 2007; Xia et al. 2004, 2006; Wiedenfeld et al. 2008; Wiedenfeld, chronic diseases resulting from the use of PA-containing herbal these too could be amongst the potential spectrum of delayed ing long term, low level sub-acute exposure to toxic PAs and wide variety of cancers are also produced in animals follow- chronic and progressive pulmonary arterial hypertension, lead- 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, lead- ing to right heart failure (Fu et al. 2004; Edgar et al. 2011). A wide variety of cancers are also produced in animals follow- ing 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.; Douglasii Fiddleneck. Distribution: Native to California. Emenic 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 medic- inal uses in the Costanoan Indian tribe (Moerman 2009). The seeds and foliage are very poisonous to livestock, par- ticularly cattle. The closely related Amsinckia intermedia, A. hípida, A. lycopusoides and A. tesselata, growing in Cali- fornia contain intermedine (30), O3′-acetyl-intermedine (31), 3,7′- diacetyl-intermedine (32), lycopsamine (34), O3′-acetyl- lycopsamine (35), O5′-O3′-diacetyllycopsamine (36), echin- mine (47), (Culver et al. 1966; Rostman 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 deparative plant (De Jong et al. 1999). The plant contains the alkaloid ambiline (8) (Larson et al 1984; Dodson, Dormitz 1986), supinine (6), intermedine (30), O6′-acetyl- intermedine (31), lycopsamine (34), O5′-acetyl-lycopsamine (35) (Lüthy et al. 1984). Cynoglossum grandifl. ex Lehnh. Pacific Hound Tongue. Distribution: Native to Western North America, from British Columbia to California. Pomo and Porter Valley Indians use it as a gastrointestinal and venereal ail. (Moerman 2009). Cynoglossum officinale L.; Hounds tongue, Common Hounds Tongue, Gypsophyer. 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 ail (Moerman 2009; Munro 2013). It is a toxic plant for cattle and horses (Steigelmeyer 2011). The plant con- tains echinidine (7), 7′-angeloyl-heliosuprine (rivialarine) (15), heliosuprine (18), O3′-acetyl-heliosuprine (19) (Pedersen 1975; Mettocks 1986; Plister et al. 1992). Cynoglossum virginianum L., syn. C. boreale Fernald; Northern Wild Comfrey, Hounds tongue, cynoglosse boîtaire. Distribu- tion: 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 Ojiba 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 17th Century from Europe and is naturalized in the most parts of the continent. The Cher- koe, Iroquois, and Mohgan use it as a urinary, gynaecological and kidney aid. (Moerman 2009). It contains uplandicine (41), echimidine (42), O5′-acetyl-echimidine (43), echimidine iso- mer, and the N-oxides (Pedersen 1975; El-Sharly et al. 1996). Hackelia floribunda Lehm. Johnston.; Manyflower Stickseed. Distribution: Native in much of the western half of North Amer- ica: Ramah and Navajo indians considered the plant as aid for the skin, as an orthopedic aid for serious injury such as frac- tures (Moerman 2009). The plant contains latifoline (44) and it’s N-oxide (Hagglund et al. 1985). Hackelia hispida Lehm. Showy Stickseed, Thomson Drug. Dis- tribution: Native to and found throughout the western regions of North America. The Thompson indians use plant medic- inally 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. Chero- kee 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. hípida, is widely distributed in Colorado. It contains: lati- foline (44), neolatifoline (45) and O5′-angeloyl-retronecine (20) (Kee et al. 2011; L’Empereur et al. 1989), and Hackelia longi- tube John. Native to the mountains of California in the Sierra Nevada, contains: longitubine (46), latifoline (44), O5′-angeloyl- retronecine (22) and O5′-angeloyl-retronecine (22) (Rostman 1988).
**Heliotropium curassavicum** L.; Salt Heliotrope, Spatulate-leaved Heliotrope. Distribution: Native herb found in southern parts of western Canada. Paiute, Pima, Shoshoni and Tulalip indian drug. Used as an antidiarrhea, diuretic, emetic, a throat aid, and a dermatological aid (Moerman 2009; Munro 2013). It contains: O9-(O3'-acetyl)-viridofloroyl-retronecine (28), O9-(O3'-isovaleroyl)-viridofloroyl-retronecine (29), and many minor alkaloids (Catalano 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).


**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), O3'-acetyl-lithosenine (53) (Krenn et al. 1994).
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).


Symphytum officinale 1980b; Roeder et al. 1992). It contains: echinatine (O3), O3-acetyl-intermedine (31), lycopsamine (34), O3-acetyl-lycopsamine (35), echimidine (42), symlandine (48), symviridine (49), myoscorpine (41), intermedine (30), and symphytine (51) (Calvenor 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 gymnecological 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 gonorrhea (Moerman 2009). It causes veno-occlusive symptoms, liver cirrhosis, and death (Munro 2013). Roots and leaves contain: intermedine (30), O3-acetyl-intermedine (31), lycopsamine (34), O3-acetyl-lycopsamine (35), echimidine (42), symlandine (48), symviridine (49), myoscorpine (41), intermedine (30), and symphytine (51) (Calvenor et al. 1980a, 1980b; Roeder et al. 1992).

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3.2. Asteraceae (subtribe Eupatorieae)


Eupatorium pilosum L. 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, Joe pyeweed, Boneset, Eupatoire Poirière. Distribution: Native
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).


### 3.3. Asteraceae (subtribe Senecioneae)

*Petasites frigidus* L. Fris. 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 a febrifuge (Moerman 2009). Thought to contain: senkirkine (63) (Kee et al. 2013). *Petasites frigidus* var. *nivalis* Greene Crong. 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 Inspiaq indians take it as cold remedy and as respiratory aid (Moerman 2009).

*Petasites frigidus* L. Fr. var. *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, tuberculous, pulmonary, pediatric, emetic, anti-rheumatic and respiratory aid (Moerman 2009, Uprety et al. 2012).
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).

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), hydroxyse sinkirkine (64), anonamine (65), otosene (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, Sénecon 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), florosenine (71), floridanine (72) (Resch et al. 1983; Roeder et al. 1983).

Senecio congestus R.Br. DC.; Marsh Fleabane, Sénecon 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; Fendleri 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. Costoanoa indians use it as a dermatological and gynecological 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), seneciphylline (60), jacobine (66), jacobine (67), jacoline (68), jacoline (69) (Bradbury et al. 1954, 1959; Culvenor 1964; Segall 1978).

and Ramah Indians use it as a dermatological and gynecological aid. Yavapei take it as a cold remedy, and as a dermatological, gastrointestinal, and venereal aid (Moerman 2009).

Senecio neomexicanus, Gray, syn. Pachara 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 pseudoaurnica Less; Seaside Ragwort. Distribution: Native to Alaska, and Maine, and in Canada. Aleut Indians use it as a dermatological aid (Moerman 2009).


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: O7-angeloyl-O9-acetyl-retronecine (21), O7-angeloyl-O9-sarracinoyl-retronecine (triangularine) (26), (Rueger, et al. 1983) and plants growing in the western States contain substantial amounts of seneconine (58), and small amounts of intergermine (55), retroxine (59), triangularine (26), neotriangularine (27), and the nontoxic alkaloids rosmanine (2) and platyphylline (3) (Rotman 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 Iroquoi drug and is used as a cough medicine, anti-tussive, adstringent, emollient, and as an expectorant (Moerman 2009). It contains: seneconine (58), semkiraine (63) (Culver et al. 1976; Rosberger et al. 1981).

3.4. Fabaceae (subtribe Crotalarieae)

Crotalaria retundifolia 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). It contains: monocrotaline (73) as the main alkaloid and also some other unknown alkaloids (Wilette, et al. 1972). The closely related and very toxic Crotalaria spectabilis Roth, Showy ratclover, 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) (Culver et al. 1957).

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4. Discussion

PA-containing plants are used in traditional herbal medicine systems in many parts of the world (Roeder 1995, 2000; Roeder and Wiezenfeld 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 (Roede 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 medicinal 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.

References

