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ECOSYSTEMS

Alpha-mannosidosis caused by toxic plants in ruminants of Argentina

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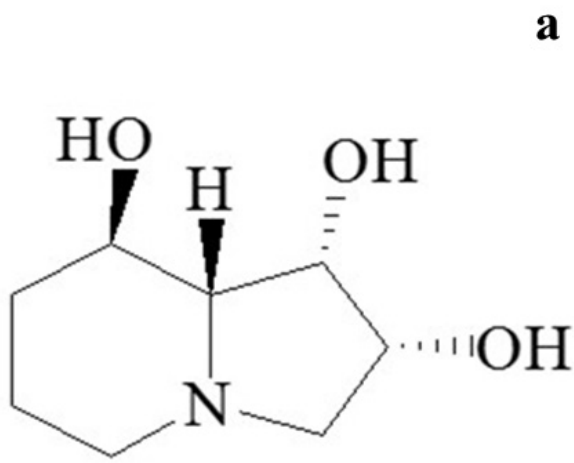
Abstract: It is well known that several of the swainsonine-containing plant species found widespread around the world have a negative economic impact in each country. In Argentina, most of the information on the poisonous plant species that produce α-mannosidosis is published in Spanish and thus not available to most English-speaking researchers interested in toxic plants. Therefore, the aim of this review is to summarize the information about swainsonine-containing plants in Argentina, which are extensively distributed throughout different ecoregions of the country. To date, five species from three genera have been shown to induce α-mannosidosis in livestock in Argentina: *Ipomoea carnea* subsp. *fistulosa*, *Ipomoea hieronymi* subsp. *calchaquina* (Convolvulaceae), *Astragalus garbancillo*, *Astragalus pehuenches* (Fabaceae), and *Sida rodrigoi* (Malvaceae). These species contain the indolizidine alkaloid swainsonine, which inhibits the lysosomal enzyme α-mannosidase and consequently affects glycoprotein metabolism, resulting in partially metabolized sugars. The prolonged consumption of these poisonous plants produces progressive weight loss and clinical signs related to a nervous disorder, characterized by tremors of head and neck, abnormalities of gait, difficulty in standing, ataxia and wide-based stance. Histological lesions are mainly characterized by vacuolation of different cells, especially neurons of the central nervous system. The main animal model used to study α-mannosidosis is the guinea pig because, when experimentally poisoned, it exhibits many of the characteristics of naturally intoxicated livestock.

Key words: Argentina, guinea pig model, livestock, neuronal vacuolation, poisonous plants, swainsonine.

INTRODUCTION

Several poisonous plants produce signs compatible with a nervous syndrome characterized by ataxia, muscle tremors, blindness, irritation, recumbency or coma, in the livestock consuming them (Odriozola 2015). In some of these plants, the toxic principle is swainsonine (SW) (Figure 1a, b), an alkaloid not produced by the plant but by a fungal symbiont associated with the plant (Cook et al. 2014). All the SW-containing species so far investigated have been found to be associated with a specific fungal symbiont (Braun et al. 2003, Yu et al. 2010, Baucom et al. 2012, Gao et al. 2012, Cook et al. 2013, Grum et al. 2013). Examples of these symbionts include the fungal genus *Alternaria* section *Undifilum*, which was isolated from locoweed from North America (Braun et al. 2003), and a Chaetothyriales associated with *Ipomoea carnea* from Brazil (Cook et al. 2013). In Argentina, the fungal genus *Alternaria* section *Undifilum* has been recently detected on Patagonian *Astragalus* (Martinez et al. 2019b).



swainsonine

Figure 1a. **Representative structure of indolizidine alkaloid.**

SW inhibits the lysosomal α-mannosidase enzyme and Golgi mannosidase II. This occurs because SW has many similarities to the simple sugar mannose, which it appears to mimic (Dorling et al. 1978, Colegate et al. 1979). The inhibition results in a complete blockage of complex molecules, and the failure of the trimming process results in an accumulation of undegraded oligosaccharides in lysosomes (Malm & Nilssen 2008). Prolonged consumption of plants containing SW produces a lysosomal storage disease called acquired α-mannosidosis (Jolly & Walkley 1997).

The term locoweed poisoning refers to the livestock poisoning by *Astragalus* and *Oxytropis* species. This poisoning is economically detrimental to the livestock industry in many countries, including China (Zhao et al. 2013), New Mexico and western United States (Ralphs et al. 2000), and Canada (Harries et al. 1972). In the US, these losses have been estimated in several million dollars annually, due to death, abortion, reproductive problems, and lack of weight gain (James & Nielsen 1994, Ralphs et al. 2000). In Argentina, five species from three genera have been shown to induce α-mannosidosis in livestock: *Ipomoea carnea*, *I. hieronymi* subsp. *calchaquina* (Convolvulaceae), *Astragalus garbancillo*, *A. pehuenches* (Fabaceae), and *Sida rodrigoi* (Malvaceae) (Robles et al. 2000, Rodriguez Armesto et al. 2004, Ríos et al. 2015, Micheloud et al. 2017a,b). However, accurate statistics on animal losses due to consumption of these poisonous plants in Argentina are not yet available.

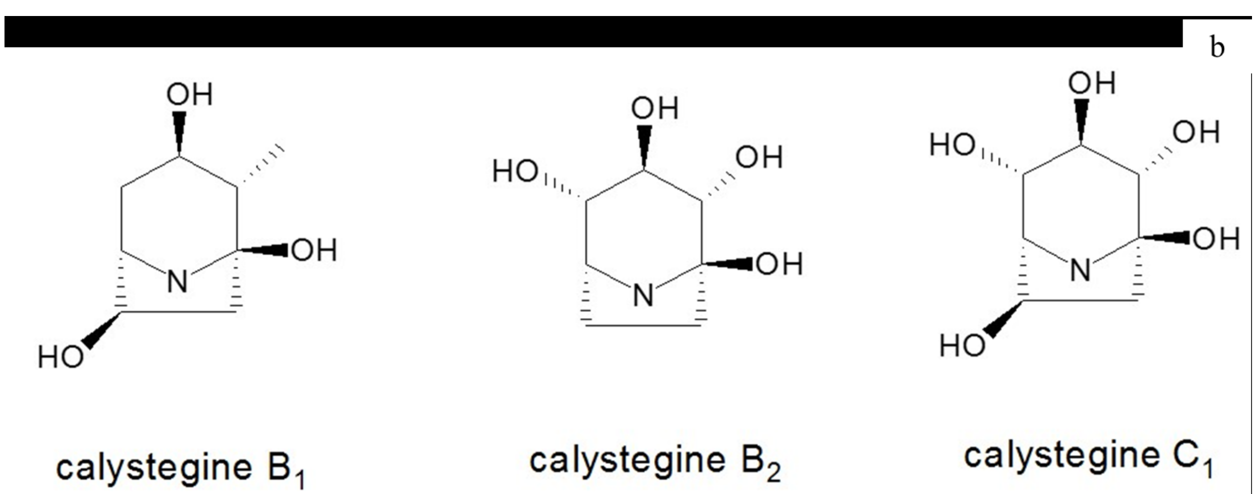


Figure 1b. **Structures of the glycosidase-inhibitory alkaloids of the tropane found in the plant *Ipomoea carnea*.**

This review thus presents the available information about the distribution and habitat of SW-containing plants in Argentina, their toxicological aspects, as well as epidemiological and pathological findings from spontaneous and experimental cases of poisoning by consumption of these plants.

MATERIALS AND METHODS

Distribution, habitat and chemistry of the five SW-containing plants identified in Argentina

Ipomoea carnea **(Jacq.) subsp.** ***fistulosa*** (*Mart. ex Choisy*) (Family: Convolvulaceae; Figure 2a) is an evergreen shrub ≤ 3 m high, which propagates by stems capable of rooting within a few days. The stem is thick and develops into a solid trunk over several years, with many branches from the base. The flowers are pale pink, the fruits have a glabrous capsule, and the seeds are silky. The leaves are green, lanceolate and 10-25cm long (Chiarini & Ariza Espinar 2006).

Ipomoea carnea is found in subtropical and tropical regions, from Venezuela and Colombia to Argentina. In Argentina, it grows spontaneously in northeastern and central provinces, like Corrientes and Entre Ríos. However, it can also be found in cultivated soils of the provinces of Salta, Chaco, Formosa, Tucumán, Santiago del Estero and Córdoba (Figure 2a). This area corresponds to the "Chaco Húmedo" ecoregion, which is characterized by a wet and hot climate, with annual rainfall of 1275 mm and average temperatures between 22°C and 33°C in summer and between 12°C and 22°C in winter (Figure 3). *Ipomoea carnea*, locally called "Mandiyura" or "Aguapeı", grows alongside wet grasslands (Haase 1999). In these areas, the main agricultural activity is the breeding of

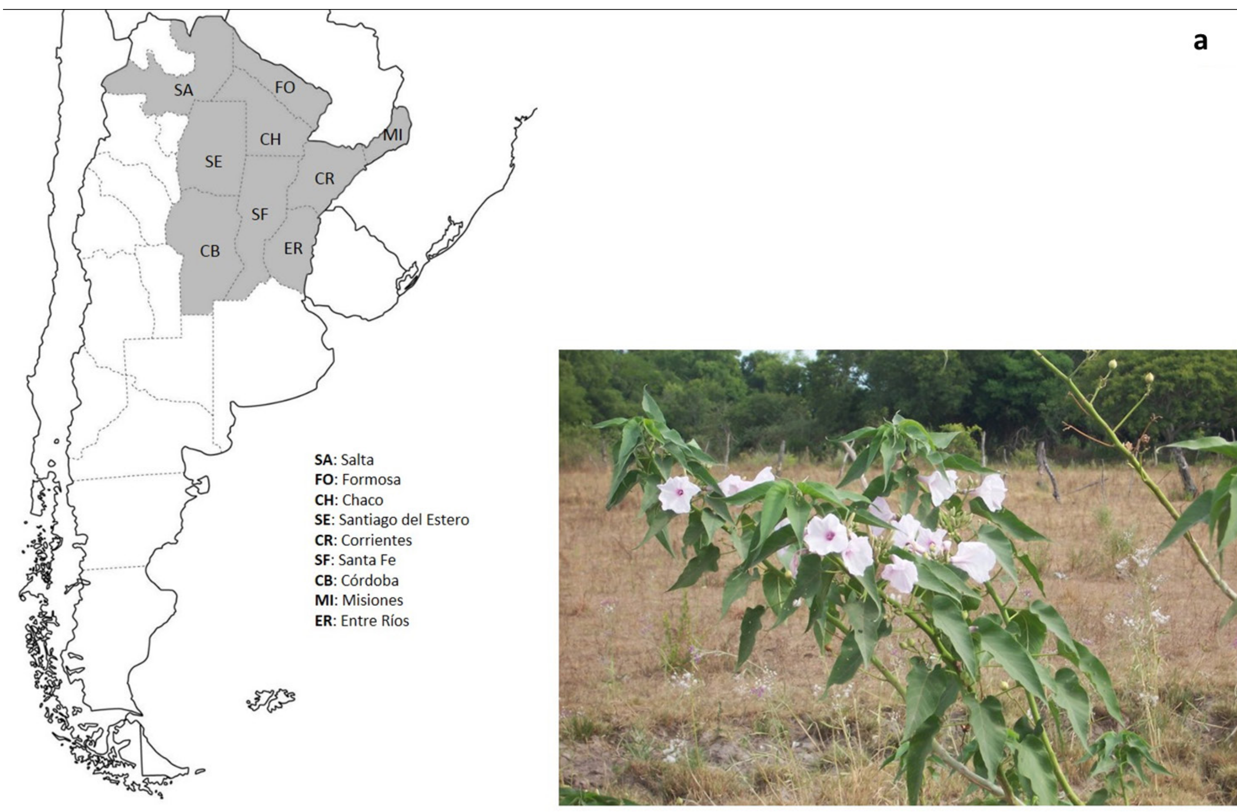


Figure 2a. **Distribution of** ***Ipomoea carnea*** **subsp.** ***fistulosa*** **in Argentina.**

cattle, sheep and goats, under extensive grazing conditions (Caspe et al. 2008).

Although in the last century the toxicity of *I. carnea* has been reported in different countries of the world (Daló & Moussatché 1978, Freire 1984, de Balogh et al. 1999), in Argentina it was detected for the first time in 2007. Samples collected from Corrientes province showed concentrations of SW between 0.01% and 0.02% (Table I) (Cholich et al. 2009), exceeding 10-20 times the concentration of 0.001%, which is considered poisonous for livestock (Molyneux et al. 1995). *Ipomoea carnea* also contains calystegines, which are hydroxylated nortropane alkaloids and potent glycosidase inhibitors (Asano et al. 1995, de Balogh et al. 1999). However, according to Stegelmeier et al. (2008), it is difficult to definitively prove the role of calystegines in the poisoning by plants containing mixtures of other toxins, as SW. The samples of *I. carnea* collected in 2007 also contained calystegines B1, B2, and C1 (Figure 1a,b), and trace amounts of calystegines A3 and B3, whose mean concentration was 0.05% (Table I) (Cholich et al. 2009).

Table I. Swainsonine and Calystigines mean concentration (% of dry weight) in α-mannosidosis induced- plants from different regions of Argentina.

Species	Swainsonine (%)	Calystigines (%)	Location (GPS)
		B_1 B_2 C_1	
Ipomoea carnea	0.015	0.075 0.04 0.035	Empedrado, Corrientes. (27°57´04”S, 58°48´19”W)
Ipomoea hieronymi var. *calchaquina*	0.036 [a]	n.d*	Guachipas, Salta. (25°42’01.7”S 65°30’26.6”W)
	0.032	n.d	San Carlos, Salta. (26°6´S, 66°28´W),
Astragalus garbancillo var. *garbancillo*	0.015[a]	n.d	Infiernillo, Tucumán. (26°44´S, 65° 47´W).
	0.128±0.016	n.d	Maquinchao, Río Negro. (41°29´55.5 S 68°34´38.6° W)
	0.089±0.022	n.d	Los Menucos, Rio Negro. (40°33´18.6S 68°36´08.9° W)
Astragalus pehuenches	0.114±0.011	n.d	Ingeniero Jacobacci, Rio Negro. (41°58´24.3 S 69°38´42.3° W)
Sida rodrigoi monteiro	0.033	n.d	El Palmar, Jujuy (24°04´59”S, 64° 34´59”W)

nd*=not detected.
[a] unpublished data
(Cholich et al. 2009, Micheloud et al. 2017 a, b, Martinez et al. 2018).

In Nicaragua, a recent outbreak of a neurological syndrome in goats was found to be associated with the consumption of *Ipomoea trifida* and *I. carnea* containing only calystegines, since all the samples studied were negative for SW, suggesting that SW is not the only toxin involved in *Ipomoea* poisoning (Salinas et al. 2019). However, this is not supported by other studies, and there is a possibility that the samples analyzed were not representative of the plants that poisoned the goats. According to Cook et al. (2014), SW concentration varies between plants of the same species and population.

Regarding the fungal symbiont, as mentioned above, a Chaetothyriales fungus has been identified in Brazilian SW-producing *I. carnea* (Cook et al. 2013), but no data are yet available regarding a specific fungal symbiont in this Argentine SW-containing species.

Ipomoea hieronymi **(Kuntze) subsp.** ***calchaquina*** (Family: Convolvulaceae; Figure 2b) is a creeping perennial plant with tuberous roots with branched and furrowed stems. Leaves are densely covered with short, soft light-gray hairs. Flowers are pink, with reddish-black seeds (Orfila et al. 1995). In Argentina, *Ipomoea hieronymi* is an autochthonous species that grows in the arid mountains of the northwest, in provinces like Catamarca, Tucumán, La Rioja, Salta and Jujuy, in lands between 1000 and 2000 m of elevation (Figure 2b). This area corresponds to the "Montes de Sierras y Bolsones" ecoregion, which is characterized by a dry and hot climate, with annual rainfall of 150-170 mm and temperatures ranging between 20 and 33°C in summer and between 8°C and 20°C in winter (Figure 3). *Ipomoea hieronymi*, locally called "Mechoacan" or "Mensuaca", grows in areas where extensive

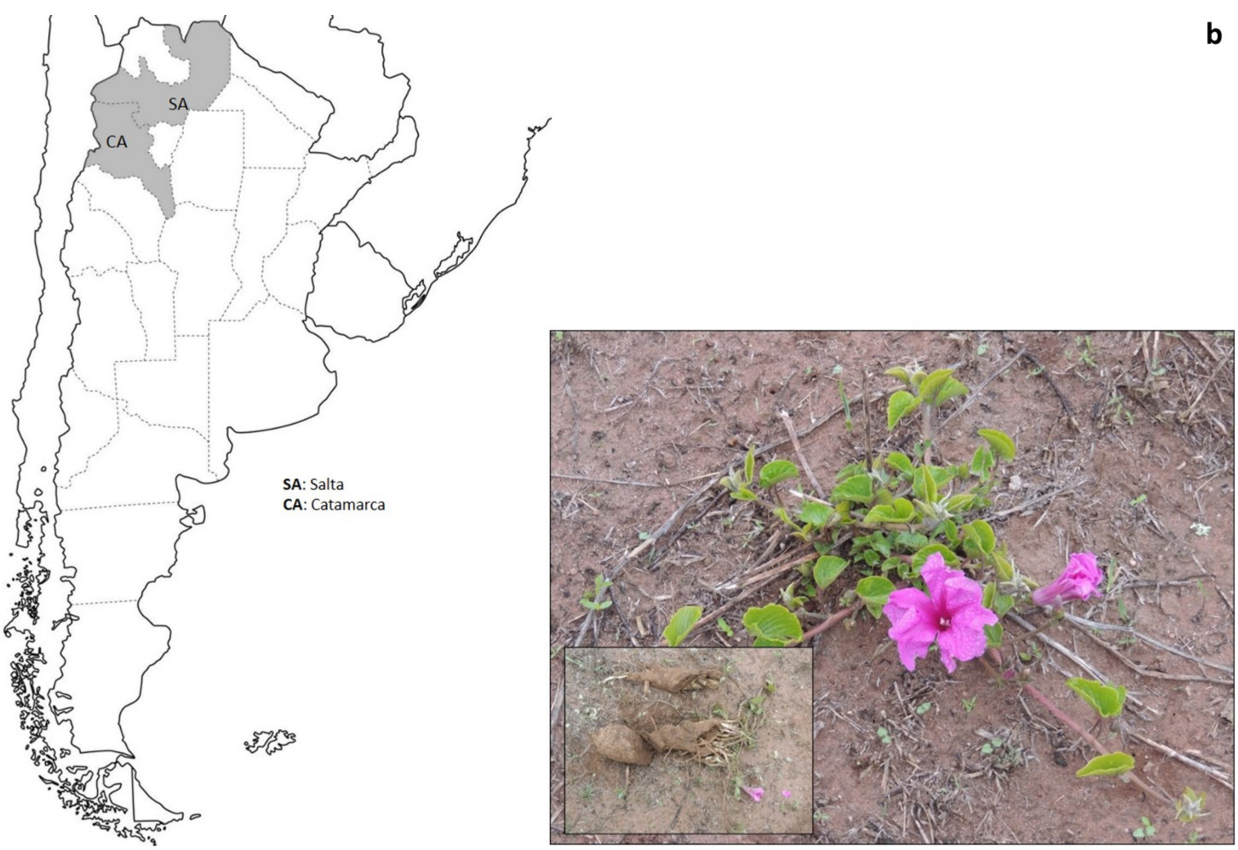


Figure 2b. Distribution of *Ipomoea hieronymi* subsp. *calchaquina* in Argentina.

livestock is composed mainly of goats and sheep bred for the farmers' consumption and local commercialization (Bravo et al. 1999).

This plant was found to be toxic for the first time in a spontaneous outbreak in goats in Catamarca province. A plant sample taken from this province and toxicologically analyzed showed a SW concentration of 0.036 % (Table I) (Micheloud JF., unpublished data).

***Astragalus garbancillo* (Cav.)** (Family: Fabaceae; Figure 2c) is 20 to 50 cm high, has odd-pinnate leaves and white to pale-violet flowers. The fruits contain 1-2 seeds (Gómez-Sosa 2004). It grows in the Andean region of Perú, Bolivia and Argentina. In Argentina, it grows in arid zones of the northwest and Cuyo, including Catamarca, Jujuy, La Rioja, Mendoza, Salta, San Juan, and Tucumán provinces, in lands between 1600 and 4500 m of elevation (Figure 2c) (Gómez-Sosa 1999). This area corresponds to the "Puna" ecoregion, which is characterized by a dry cold climate with large daily temperature variations, reaching minimum temperatures below –15 ºC (Figure 3) (Reboratti 2005). In this region, goats, sheep, and South American camelids have a main impact on the economic life of rural families (Bravo et al. 1999).

Smallholders from Salta province have historically recognized *A. garbancillo* as a plant toxic to sheep, goats, cattle and mules in the spring-summer season (Califano & Echazu 2013). *A. garbancillo* var. *garbancillo* has been recently deposited in the Herbarium of the National University of Salta and the SW concentration from composite samples at early vegetative

Figure 2c. Distribution of ***Astragalus garbancillo*** **in Argentina.**

stage was found to be 0.03% (Table I) (Micheloud et al. 2017a).

Astragalus pehuenches (**Nierdel**) (Family: Fabaceae; Figure 2d) is a legume that varies from 10 to 45 cm in height. The leaves are 5 to 9 cm long and the plant has purple/blue flowers. The fruits have a glabrous capsule that can contain 12-14 black seeds (Gómez-Sosa 1979). It is distributed throughout Andean and extra Andean areas of Argentine Patagonia, and grows spontaneously in Mendoza, Neuquén, Río Negro and Chubut provinces in lands between 900 and 1200 m of elevation (Figure 2d). This area corresponds to the "Estepa Patagónica" ecoregion, which is characterized by a semiarid climate, with an annual average rainfall of 200 mm and temperatures ranging between 9°C and 25°C in summer and between -2°C and 7°C in winter (Figure 3). In general, the landscapes are composed of large steppes covered by shrubs and perennial grasses and small meadows covered by annual and perennial grasses (Bran et al. 2000). *Astragalus pehuenches*, locally called "Garbancillo" or "Yerba loca", sometimes forms patches following the runoff of rainwater and winds (Gómez-Sosa 1979). In the areas where *A. pehuenches* grows, there are approximately 1.35 million Merino sheep, 0.54 million Angora and Creole goats, and 0.37 million Hereford cattle (SENASA 2018). Livestock is generally bred as mixed flocks composed mainly of sheep and goats and sometimes cattle in open fields managed by smallholders with scarce or null technology (Easdale & Rosso 2010).

Astragalus pehuenches has been mentioned as a poisonous plant in the region since 1830 (Kauffer & Heinken 1984). In 1991, SW was identified on two herbarium specimens from Mendoza and Chubut provinces (Molyneux & Gomez-Sosa 1991). High concentrations of

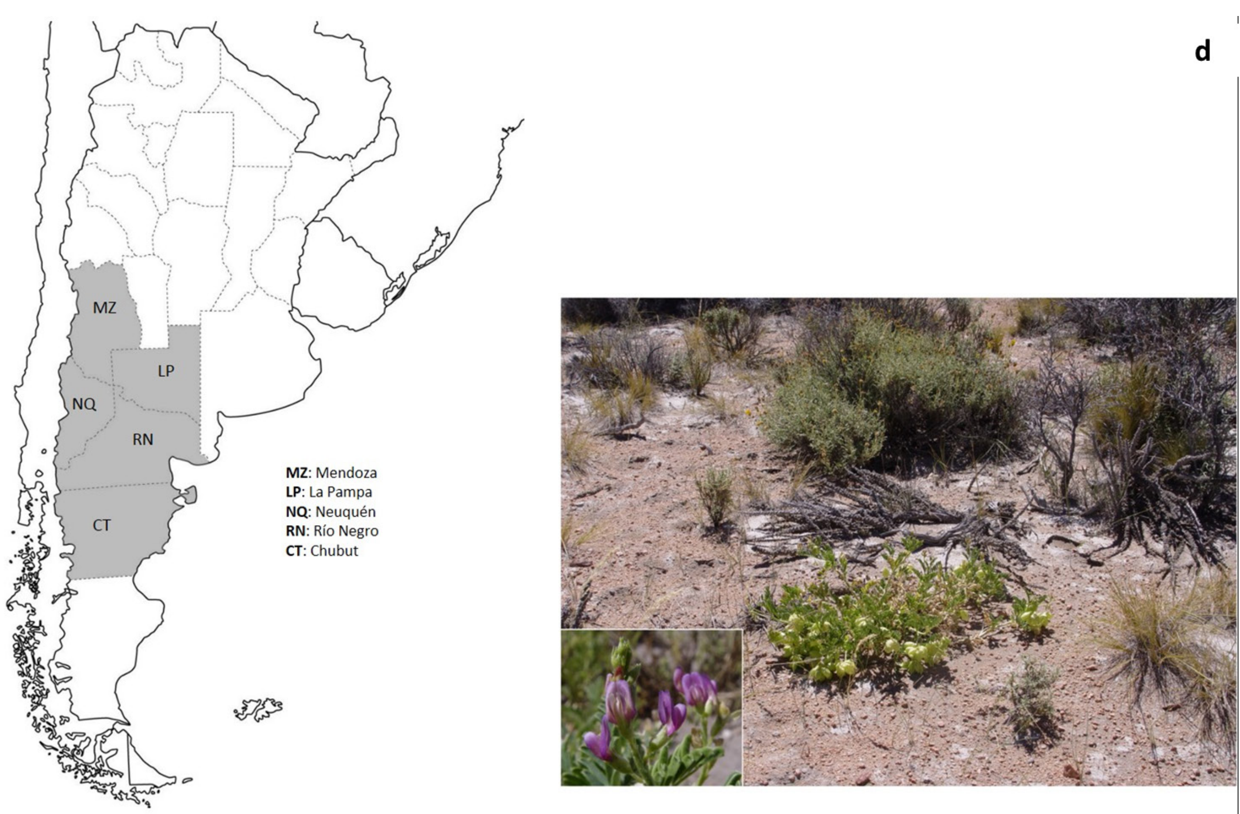


Figure 2d. Distribution of ***Astragalus pehuenches*** **in Argentina.**

SW from 0.070 to 0.097% were determined in this region (Table I) (Martinez et al. 2018). Recently, a SW-producing endophyte from this species has been detected and demonstrated to belong to the genus *Alternaria* section *Undifilum* by culture and molecular analysis (Martinez et al. 2019b).

Finally, ***Sida rodrigoi*** **(Monteiro)** (Family: Malvaceae; Figure 2e) is an evergreen shrub 0.50-1.50 m high, with glabrous stems and distichous leaves. The yellowish flowers have axillaries in groups of two, and the fruits have glabrous seeds. It is found in subtropical areas, in eastern Bolivia, Paraguay and northern and northeastern Argentina, including the provinces of Chaco, Corrientes, Formosa, Jujuy and Salta, in lands between 70 and 1600 m of elevation (Figure 2e) (Krapovickas 2003). The area corresponds to the northern area of the "Chaco Seco" ecoregion, which has subtropical warmth (Figure 3). *Sida rodrigoi*, locally called "Afata", grows in edges of the jungle in gallery, roads and non-productive lands. In this region, the most important economic activity is extensive animal production, with goats and cattle being the predominant animals bred in farms (Bravo et al. 1999).

In 2017, *S. rodrigoi* was reported for the first time as a toxic plant in Jujuy province. Plant samples were deposited in the Herbarium of the National University of Salta province and toxicological analysis determined a SW concentration of 0.033% (Table I) (Micheloud et al. 2017b).

RESULTS AND DISCUSSION

Spontaneous and experimental poisoning

Stegelmeier et al. (2007) and Lu et al. (2013) reported that the animals most sensitive to

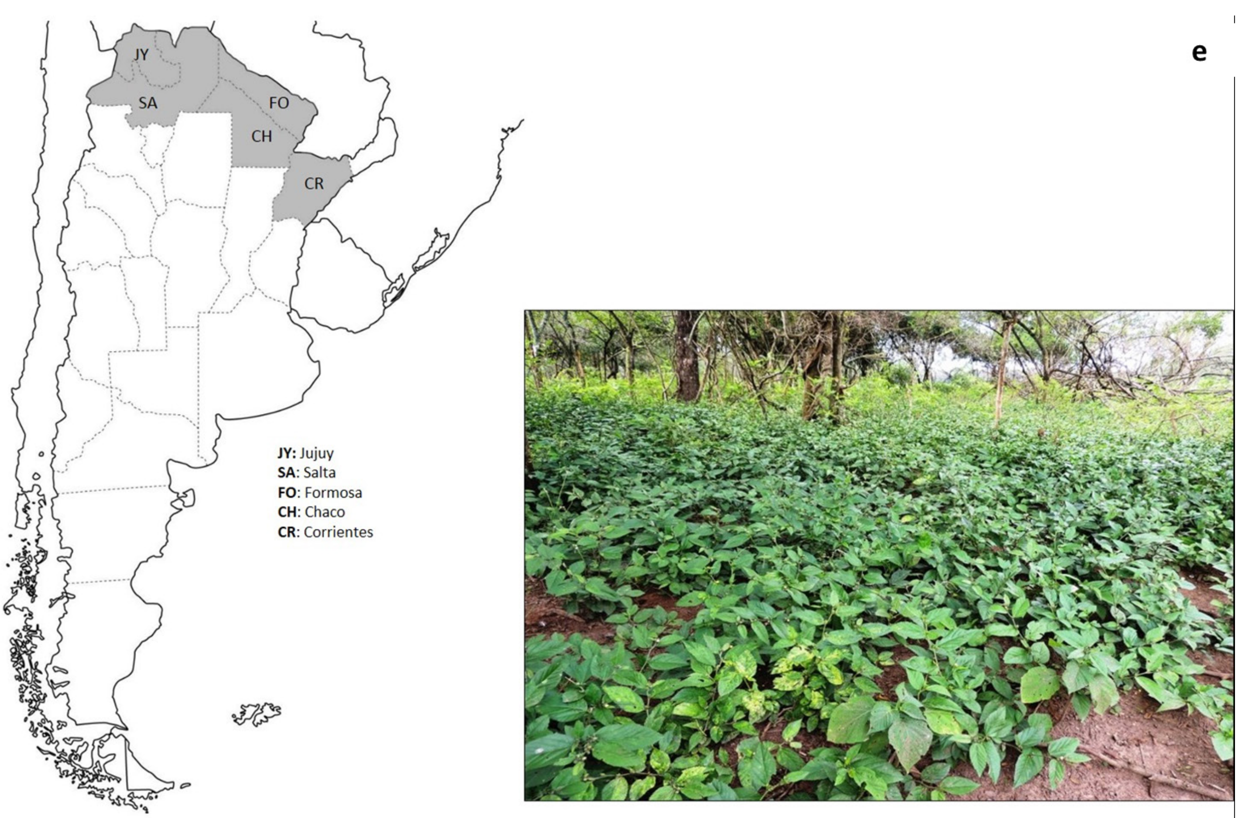


Figure 2e. Distribution of *Sida rodrigoi* in Argentina.

SW toxicity are horses. Although no cases of intoxication in this animal species have been reported in Argentina, a few cases of horses with behavioral changes, loss of equilibrium, ataxia and death, which had been grazing on *A. pehuenches*, have been observed in Patagonia (Robles C., unpublished data).

In Argentina, spontaneous poisoning by *Ipomoea carnea*, *Ipomoea hieronymi* and *Sida rodrigoi* has been reported in goats (Rodriguez Armesto et al. 2004, Ríos et al. 2015, Micheloud et al. 2017b), spontaneous poisoning by *Astragalus garbancillo* and *Astragalus pehuenches* has been reported in sheep (Robles et al. 2000, Micheloud et al. 2017a) and spontaneous poisoning by *A. pehuenches* has been reported in cattle (Martinez et al. 2019a).

Figure 3. Different Ecoregions of Argentina.

In the outbreak by *S. rodrigoi* in goats in 2017, the epidemiological rates of morbidity and lethality were 81% (160/196) and 51% (100/196), respectively. The main predisposing factors were the high animal load (24.8 animals/ha), evidence of overgrazing, and low-forage availability (Micheloud et al. 2017b).

In the spontaneous poisoning by *A. pehuenches*, the mortality rate was 90% (63/70) in cattle (Martinez et al. 2019a) and 73% (273/300) in sheep (Robles et al. 2000). In the last case, the intoxication occurred in winter, although the snow had covered the available grass (Robles et al. 2000). When outbreaks of intoxication in cattle by *A. pehuenches* were seen in late summer, the herd was grazing on a pasture of approximately 2700 hectares, with clear signs of overgrazing (Martinez et al. 2019a).

Regarding *A. garbancillo*, farmers have reported that between 0.5 and 2% of the flocks are affected every year, and that the problem is more severe in dry years, with cases usually occurring between August and December. Due to poor information from farmers, both the morbidity and lethality rates of the poisoning by *A. garbancillo* and *Ipomoea sp.* have not yet been possible to calculate (Micheloud et al. 2017a).

Some studies on experimental poisoning by some of these plants have been performed. For example, experimental poisoning by *I. carnea* was studied in goats, in which the intake of *I. carnea* was 50 g per kg of body weight per day and the intoxication occurred between 43 and 60 days in autumn (Ríos et al. 2008). In spring, this value was reduced to 21 days (Ríos et al. 2012). Armién et al. (2007) reported that poisoning by *I. carnea* occurred after the administration of doses between 23 and 96 g of green plant material per kg of body weight per day, for a 21–105-day trial. However, these values are difficult to compare because these studies did not report the amount of SW present in the plants.

In addition, in a previous study of our group, experimental poisoning by *A. pehuenches* was studied in sheep, in which a daily dose of 2 mg SW per kg of body weight was used (Martínez et al. 2016). In this study, the SW analysis was performed on the ground plant, resulting in 0.097 % SW. Then, the intake necessary to reach the proposed dose was calculated and the disease was reproduced in 54 days (Martinez et al. 2016). To our knowledge, this study with *A. pehuenches* was the first with a dose of SW previously analyzed on the ground plant.

Clinical signs produced by poisoning with SW-containing plants

Animals poisoned by SW-containing plants exhibit weight loss and related nervous clinical signs, characterized by tremors of head and neck, abnormalities of gait, difficulty in standing, ataxia and wide-based stance (Figure 4a) (Rodríguez Armesto et al. 2004, Ríos et al. 2015, Micheloud et al. 2017a,b, Martinez et al. 2019a). In particular sheep poisoned by *A. garbancillo* show abnormal posture similar to a dog's sitting position (Micheloud et al. 2017a), and goats poisoned by *I. carnea* and *S. rodrigoi* show paresis of the hind legs (Ríos et al. 2015, Micheloud et al. 2017b). When the animals are disturbed, these signs are exacerbated and the animals tend to lose the equilibrium (Rodríguez Armesto et al. 2004, Micheloud et al. 2017a, b, Martinez et al. 2019a).

Experimental toxicity with a single *Ipomoea* sp. has been found to produce anemia in goats (Ríos et al. 2005). Likewise, pronounced anemia has been observed in sheep that ingested *Astragalus lentiginosus* (Stegelmeier et al. 1995a) and *I. carnea* (Adam et al. 1973, Schumaher-Henrique et al. 2003).

Goats intoxicated by *S. rodrigoi* in the field also showed abortions and stillbirths (Micheloud et al. 2017b). Finally, animals intoxicated with *I. carnea* (Armién et al. 2011), locoweed (*Astragalus* and *Oxytropis*) (Stegelmeier et al. 1999) and *Sida carpinifolia* (Pedroso et al. 2012) from other locations have also shown other reproductive disorders, including altered libido, infertility and fetal malformations.

Histological lesions and diagnosis

The typical histological lesion found in animals poisoned by ingestion of SW-containing plants is the cytoplasmic vacuolation of many cell types, including neurons, especially Purkinje cells of the cerebellum. Many of the remaining cells exhibit necrosis with pyknotic and condensed cytoplasm (Robles et al. 2000, Rodriguez Armesto et al. 2004, Ríos et al. 2012, Micheloud et al. 2017a, b, Martinez et al. 2016, 2019a). Animals poisoned with *Sida rodrigoi* and *Astragalus pehuenches* have also been found to present axonal swelling, axonal torpedoes and astrocytosis at the cerebellar cortex and medulla oblongata (Figure 4b) (Robles et al. 2000, Martinez et al. 2016, 2019a, Micheloud et al. 2017b).

Vacuolation is also extended to other tissues, such as hepatocytes and Kupffer cells, renal tubular epithelia, uroepithelial cells and exocrine pancreatic cells (Rodriguez Armesto et al. 2004, Ríos et al. 2005, 2009, Martinez et al. 2016, Micheloud et al. 2017a, b). Lesions in the thyroid follicular epithelia (Micheloud et al. 2017b), myocardium (Micheloud et al. 2017a) and uterus (Martinez et al. 2016) have also been observed in goats and sheep poisoned by *Sida* and *Astragalus sp*.

In experimental poisoning with *Astragalus pehuenches* in sheep, immunohistochemistry

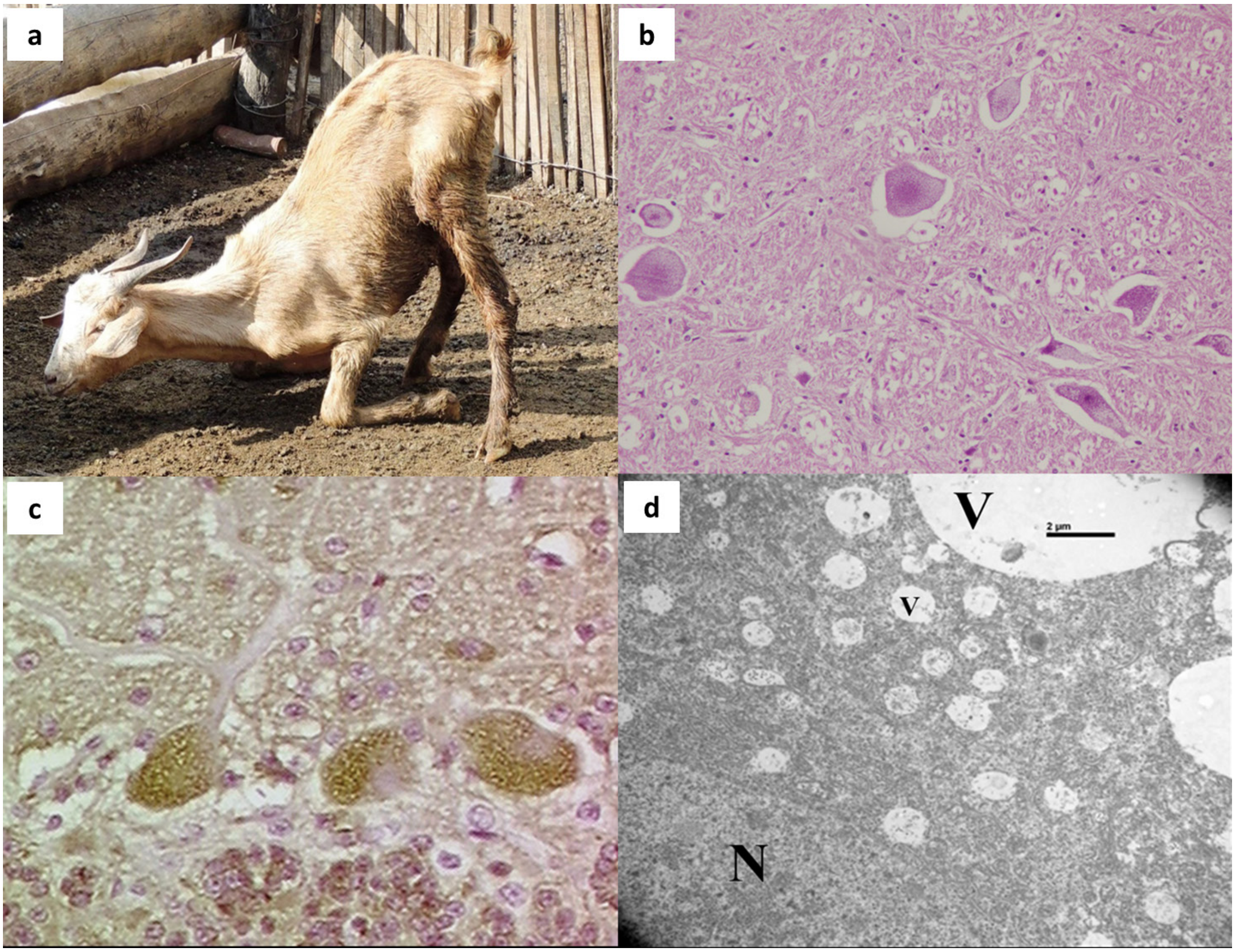


Figure 4. a. Clinical signs. Spontaneous poisoning of a goat by *Sida rodrigoi*. The goat shows abnormal posture due to difficulty in standing. b. Histology. Spontaneous poisoning of sheep by *Astragalus garbancillo*. Cerebellar basal nuclei show severe cytoplasmic vacuolation. HE, bar 25 µm. c. Lectin histochemistry. Spontaneous poisoning of a goat by *Sida rodrigoi*. Lectin WGA labeled the perikaryon of Purkinje cells in goats. Lectin histochemistry, bar 25 µm. d. Transmission electron microscopy (TEM). Experimental poisoning of sheep by *Astragalus pehuenches*. Purkinje cell showing numerous membrane-bound cytoplasmic vacuoles (V) measuring 1 to 10 µm in diameter. These vacuoles rarely contain membrane fragments.

has revealed that astrocytes from white matter, the molecular layer and the Purkinje cells surrounding it express higher levels of the glial fibrillary acidic protein (GFAP) (Martinez 2015). In addition, analysis of the expression of Ionized calcium-binding adaptor molecule 1(Iba-1) has allowed detecting foci of microgliosis of the molecular layer (Martinez 2015). Lectin histochemistry is a useful technique to identify the presence of specific carbohydrate residues inside cells *in situ*. According to Alroy et al. (1985), in cells affected by *Astragalus* and *Swainsona* toxicosis, *Concanavalia ensformis agglutinin* (CON-A), *Wheat Germ Agglutinin* (WGA) and *Succinyl Wheat Germ* Agglutinin (S-WGA) specifically bind to a-mannosyl residues and β-N-acetyl glucosamine. The tissues from animals poisoned by the three plant genera reported in Argentina have been found to show significant affinity to the lectin *Lens culinary* (LCA) and to the a-mannosyl residues detected with CON-A, WGA and S-WGA (Figure 4c) (Ríos et al.

2012, 2015, Martinez et al. 2016, Micheloud et al. 2017a, b). This histochemistry staining pattern of the vacuoles indicates that they contain *N*-glycosidically bound oligosaccharides. These results are similar to those reported previously for animals poisoned by ingestion of SW-containing plants (Driemeier et al. 2000, Loretti et al. 2003, Seitz et al. 2005, Barbosa et al. 2006, Armién et al. 2007, Mendonça et al. 2018).

Ultrastructurally, in spontaneous *I. carnea* poisoning, cytoplasmic vacuolation is evident in neurons and astrocytes of the thalamus and Purkinje cells, most of which are optically empty and delimited by a membrane (Ríos et al. 2012). Membrane fragments, reticular or dense granules and amorphous substances are also observed in some vacuoles (Ríos et al. 2012). This seems to be in accordance with the experimental intoxication by *A. pehuenches*, in which the vacuoles measured up to 10 µm in diameter (Figure 4d) (Martinez 2015).

An additional technique of diagnostic value, based on the use of liver biopsies, has been reported in poisoning by *Ipomoea marcellia* from Brazil (Rocha et al. 2016). On the other hand, in Argentina, another method, based on the use of peripheral blood smears, has revealed vacuolation of lymphocytes from the 5th day of intoxication by *I. carnea* (García et al. 2015). Both methods have been shown to be useful and should thus be used in the diagnosis of poisoning by SW-containing plants.

Diagnoses are made using epidemiological data. When making a diagnosis, the suspect plant should be confirmed to be the cause, and then differentiated from other causes of nervous diseases. Other nervous infectious diseases, including genetic α-mannosidosis, rabies, encephalitis by BoHV type 5, listeriosis and any disease that has been identified in livestock in Argentina, will depend on the ecoregion.

Currently, no treatment for the poisoning by SW-containing plants is available. In Argentina, the only way recommended to prevent intoxication is to keep livestock from consuming these toxic plants.

Animal models for the study of α-mannosidosis and other lysosomal storage diseases

Different animal models have been used to study the experimental poisoning by SW-containing plants. In Argentina, guinea pigs have been used to study the experimental reproduction of *I. carnea* intoxication (Cholich et al. 2009, García et al. 2015), as well as to study experimental poisoning by *A. pehuenches* (Martinez 2015), *A. garbancillo* (Aban et al. 2016) and *Sida rodrigoi* (Colque Caro et al. 2016). *Swainsona galegifolia* poisoning in guinea pigs was reported for the first time in Australia (Huxtable 1969, Huxtable & Gibson 1970). The advantages of this model are that histological changes in the central nervous system (CNS) are similar to those reported in poisoned livestock (Cholich et al. 2013, Martinez 2015). Together with the neuronal vacuolation, one of the most important findings in the CNS of poisoned guinea pigs are spheroids, showing severe axonal dystrophy. These lesions play a key role in the diagnosis and pathogenesis of lysosomal storage diseases, including genetic and acquired α-mannosidosis (Jolly & Walkley 1997, Robinson et al. 2008).

Mice, rats and rabbits have also been used as models to study the effects of *Astragalus* sp. (Stegelmeier et al. 1995b), *Ipomoea carnea* (Hueza et al. 2005), and *Oxytropis* sp. (Li et al. 2012). Nevertheless, these animals are not good models of research because rats present no neuronal lesions (Hueza et al. 2005), and mice present lesions only with very high doses of SW, and do not develop extensive neuronal vacuolations, with subsequent axonal dystrophy (Stegelmeier et al. 1995b, 2008). Finally, rabbits poisoned with *Oxytropis* sp. show severe microvacuolation of the cerebrum and cerebellum, but no other lesions (Li et al. 2012). Thus, the guinea pig model retains a number of advantages compared to traditional species as rats, mice and rabbits, including the fact that guinea pigs consume the toxic plants voluntarily and that it is a reproducible alternative (Cholich et al. 2009).

CONCLUSION

Although *Ipomoea carnea*, *I. hieronymi*, *Astragalus pehuenches*, *A. garbancillo* and *Sida rodrigoi* grow in different ecoregions of Argentina, they all contain SW. Thus, these plants should be considered an important limiting factor for livestock breeding in Argentina, especially in fields managed by smallholders with scarce or null technology.

Considering the similarity between histological and ultrastructural alterations observed in ruminants and guinea pigs after experimental intoxication, guinea pig studies have allowed demonstrating that this animal model is sensitive to poisoning by plants containing SW.

It seems highly probable that a fungal symbiont is associated with Argentine SW-containing plant species, but this deserves further investigation.

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