REVIEW ARTICLE

Sokoto Journal of Veterinary Sciences
(P-ISSN 1595-093X/ E-ISSN 2315-6201)
Ngulde *et al*/*Sokoto Journal of Veterinary Sciences* (2016) 14(1): 1-9
http://dx.doi.org/10.4314/sokjvs.v14i1.1

An Overview of *Ipomoea carnea* subspecies *fistulosa* toxicosis in ruminants

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Abstract

Ipomoea carnea subsp. *fistulosa* (convolvulaceae) is identified and confirmed as a poisonous plant to animals in many parts of the world. It is evergreen and common in Sahel region of Nigeria where there is lack of green pasture in most part of the year. It contains two toxic principles, swainsonine and calystegines causing neurological condition called acquired lysosomal storage disease. Its toxicological status is not determined in the region despite risk of poisoning. Therefore it is being reviewed for its toxic effects, epidemiology, pathogenesis, clinical presentations, pathology, diagnosis and management. More attention should be paid to the plant as potential source of toxins for domestic animals in the Sahel region of Nigeria.

Keywords: Clinical presentation, Epidemiology, Goats, *Ipomoea carnea*, Pathogenesis, toxins, Sahel region
Received: 12-11-2015 Accepted: 17-03-2016

Introduction

Ipomoea carnea subspecies *fistulosa* is a plant belonging to the family convolvulaceae. It is called shrubby morning glory (de Balogh *et al.*, 1999). It is often called as Kafi Kansila (better than a councilor) in the Northern Nigeria because it is used for the control of erosion that some elected councilors cannot do for their ward. It grows on almost all types of soil but especially on well-drained sandy soil, close to river-banks and swamp edges (Arbonnier, 2004). It is a plant of tropical America but it has now spread all over the tropical and subtropical regions of the world. It was probably introduced to West Africa from Arabia by Pilgrims of Mecca (Goncalves, 1987; Austin & Huaman, 1996; de Balogh *et al.*, 1999; Arbonnier, 2004).

Ipomoea carnea subsp. *fistulosa* (Plate I) is a shrub that is up to 3 m long. It is densely leafed and branches from the base. The stems are grey-green and puberulous, leaves elongate to elliptical 10-25 cm long. The flowers are 5-8 cm long, pink to pink-purple, cluster, funnel shaped and posses 5 lobes. The fruits are ovoid and angular 1-2 cm long and appear reddish brown when ripe (de Balogh *et al.*, 1999; Arbonnier, 2004).

In Borno State, Nigeria, *I. carnea* subs *fistulosa* is planted as a hedge plant both in villages and towns and also grows as a wild plant along river-banks and refuse dumping sites. It is an evergreen plant. Farm animals especially goats often browse on it during the dry season.

Ipomoea carnea subsp. *fistulosa* has been identified and confirmed as a poisonous plant in many parts of the world. In Mozambique, it was reported that about 10% of goats died within 12 months of exposure to the plant (de Balogh *et al.*, 1999). This evergreen plant seems to be the only shrub that is available during the period of long dry season in Maiduguri. Despite its presence, its status is yet to be determined in this Sahel region where green pastures are not readily available in most parts of the year. It might be a potential source of poisoning to animals in the region thereby causing economic loss to the farmers. Therefore, it is being reviewed for its various toxic effects to farm animals that consume it.

Epidemiology

The plant *I. carnea* subsp. *fistulosa* is distributed through out the tropical and subtropical regions of the world. It is cultivated as an ornamental and in hedges and windbreaks but in some areas, it escapes from cultivation and become established in disturbed areas such as roadsides, river-banks and other moist areas (de Balogh *et al.*, 1999). Intoxication by the plant in goats, sheep, cattle and horses has been reported in Brazil since 19th Century (Neiva & Penna, 1916). It has been reported in other countries such as Sudan (Idris *et al.*, 1973), India (Tirkey *et al.*, 1987), Indonesia (Bahr, 1983) and Mozambique (de Balogh *et al.*, 1999). All ages of either sex are affected and the condition is more severe in goats but some farmers reported that suckling kids and lambs are not affected (Nath & Pathak, 1995 ; de Balogh *et al*., 1999). The animal must continuously ingest the plant for a minimum of three weeks for spontaneous toxicosis to establish (Radostits *et al*., 2006; Barbosa *et al.*, 2007). Intoxication is common in dry season where this plant may be the only green pasture available (de Balogh *et al.*, 1999).

Clinical signs of intoxication by this plant begin to appear during the 3rd and 4th month after the end of the rainy season. In Mozambique, the herdsmen called the condition "Canudo" (named after the stalk of the plant) or "mata cabra" (goat killer). Also, some animals appear to develop addiction to ingest it even when there are other pastures available (de Balogh *et al.*, 1999, Radostits *et al.*, 2006). However, recent studies conducted on sheep and goats revealed that there was no significant difference between experienced and naïve animals in consuming the plant suggesting no addiction (Oliveira-Junior *et al.*, 2015). Intoxication causes α-mannosidosis and this has been reproduced experimentally following administration of the plant materials in both farm and laboratory animals (Huxtable *et al.*, 1982; de Balogh *et al.*, 1999; Armien *et al.*, 2007).

Toxic principles

Two toxic principles, swainsonine and calystegins B_1, B_2, B_3, and C_1 (Figure 1) have been identified in *I. carnea* subsp. *fistulosa* (de Balogh *et al*., 1999; Hueza *et al.*, 2005). The concentrations of these alkaloids in fresh leaves of the plant are about 0.002% (swainsonine) and 0.0045% (calystegines) while the seed of the plants contain as much as ten times higher than those of the leaves and flowers (Haraguchi *et al*., 2003). However, the concentration of the toxic principles varies from time to time even within the same species. Barbosa *et al.* (2006) found out that the swainsonine content of *I. sericophylla* and *I. riedelii* to be 0.11% and 0.14% in 2002 and 0.01% and 0.05% in 2003, while Barbosa *et al.* (2007) found out to be 0.05% and 0.01%, respectively. Swainsonine is more toxic than calystegine. This was demonstrated in mice where swainsonine was suggested to be more toxic than calystegines and castanospermines but mice could not be a good model because of their great resistance to diseases (Stegelmeier *et al*., 2008). Plants containing swainsonine in excess of 0.001% are considered as poisonous (Molyneux *et al*., 1994). Such concentration should exceed the threshold dose that would completely saturate the enzyme α-mannosidase. A daily dose of swainsonine 1 and 1.5 mg/Kg were observed to decrease the levels of α-mannosidase after one day of treatment to 53±17 and 39±l2 nM respectively. Both levels had similar mannosidase activities (Stegelmeier *et al.*, 1994). The minimal toxic dose (LD_{50}) in goats was estimated to be 60 mg/kg for the plant *I. sericophylla* (swainsonine content = 0.05% of the total dry matter) (Barbosa *et al*., 2007).

Plate I: The plant *Ipomoea carnea* in Maiduguri, Nigeria

Swainsonine resulted in about 60% reduction of α-mannosidase activity. Calystegine B_2 and C_1 showed no inhibition of β-glucosidase. Instead, it increases the activity of the enzyme up to 1.5 folds. It is then suggested that calystegines B_2 and C_1 act as chemical chaperones that enhance proper folding of the enzyme for smooth trafficking to the lysosomes (Ikeda *et al*., 2003).

Apart from *I. carnea* subspecies *fistulosa*, *I. riedelii* and *I. sericophylla*, other plants that are known to contain the toxic principle, swainsonine, include *I. carnea* subsp. *carnea, Swainsona galegifolia, S. brachycarpa, S. canescens*, *S. grayana*, S. *luteola, S. Procubens, S. swainsonoides, Astragalus lentiginosus, A. Emoryanus, A. Mollissimus, Oxytropis serica* and *O. Ochrocephalata* (Radostits *et al.*, 2006), *Sida carpinifolia* (Driemeier *et al.*, 2000; Colodel *et al.*, 2002) and *Turbina* spp (Loretti

et al., 2003). Only calystegines are found in the plants *Solanum dimidiatum, S. fastigiatum* and *S. boriensis* (Borros *et al.*, 1987). Both swainsonine and calystegines are in *Ipomoea* sp Q6 (calobra) and *I. polpha* (Molyneux *et al.*, 1995).

Pathogenesis

Continuous ingestion of the plant *I. carnea* subsp. *fistulosa* causes a disease condition in animals called acquired lysosomal storage disease. It is induced by the toxic principles of the plant, swainsonine and calystegines. Swainsonine is capable of inhibiting lysosomal enzymes α-mannosidase and Golgi mannosidase II (Colegate *et al*., 1979; Molyneux & James, 1982; Armien *et al*., 2007). In the brain, GABAnergic cerebellar neurons showed most degenerative changes (Armien, 2000). Inhibition of these enzymes will lead to accumulation of incompletely processed oligosaccharides in the lysosomes. The oligosaccharides include α-mannosyl and β-N-glucosamine moieties (Dorling *et al.*, 1980; Alroy *et al*., 1985). Lectinhistochemistry by Armien *et al.* (2007) revealed that α-glucose mannose, α-glucose, β-(1-4)-N-acetylglucosamine and N-acetylmuramic acid are found on lysosomal membranes of all tissues while β-D-galactose on Kuppfer cells and galactose-β-(1-3)-N-acetylgalactosamine on brain perivascular cells and renal tubular epithelium.

The calystegines constitute the second toxic principles in *I. carnea* subsp. *fistulosa*. Calystegine B_2 and C_1 inhibit β-glucosidase and α- and β-galactosidase enzymes, respectively (Molyneux *et al.*, 1993). Inherited lysosomal disease of humans, Gaucher's disease and Fabry's disease, are similar to the toxicosis induced by inhibition of α- and β-galactosidase, respectively (Dorling, 1984). These diseases are characterized by epileptiform seizures and vacuolation of Purkinje cells. However, the calystegines seem to have little effect in lysosmal storage disease in animals. This is because the calystegines tested in cultured human lymphoblast potentiate rather than inhibit the lysosomal α-galactosidase and β-glucosidase. CalystegineC_1 has potent activity against lysosomal β-glucosidase while Calystegine B_3 has moderate activity against α- and ß- mannosidase (Ikeda *et al*., 2003).

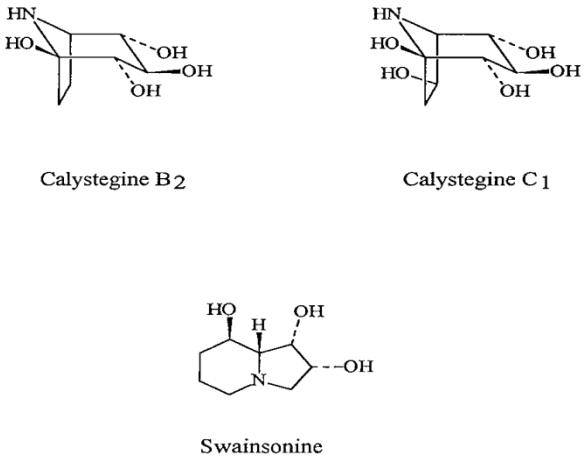


Figure 1: Glycosidase inhibitory-alkaloids in *Ipomoea Carnea* (de Balogh *et al.*, 1999)

Alpha-mannosidosis is the most important acquired lysosomal storage diseases of animals induced by the swainsonine containing plants. It is characterized by wide spread neurovisceral cytoplasmic vocuolation that disrupt lysosomal function, normal cellular metabolism and eventually cell death (Armien *et al.*, 2007). Vacuolation develop because of accumulation of oligosaccharides in the lysosomes. The nervous system is most affected but endocrine, immunologic, digestive and cardiovascular functions may also be affected (Stegelmeier *et al.*, 1999). It is associated with increased phagocytosis activity and hydrogen peroxide production by macrophages (Hueza *et al*., 2003). It has depolarizing neuromuscular blocking activity (Abdulhadi *et al.*, 1986). In rats the toxic principles of *I. carnea* may cross the placenta because prenatal administration to dams of 6-20 days gestation produced irreversible lesions in 7-day old pups and reversible lesions in the dams (Hueza *et al*., 2003).

Clinical signs

The clinical signs of intoxication by *I. carnea* subsp. *fistulosa* in both spontaneous and experimental poisoning are similar. It has been described (de Balogh *et al*., 1999; Armien *et al*., 2007) as follows. First signs may be noticed after three weeks of regular consumption of the toxic plant. Initial sign is usually anorexia and in the first week there would be mild intention tremors, incoordination and reluctance to move when disturbed. In intention tremors, incoordination and falling when disturbed or frightened. There will be symmetrical ataxia, head tremors, hyperesthesia, high stepping gait, progressive weight loss and in some animals diarrhea and pale mucous membranes may be observed (de Balogh *et al*., 1999; Armien *et al*., 2007). Other signs include dilated nostrils, posterior paresis (Plate IIa), abduction of hindquarters, opisthotonus, strabismus, nystagmus, hypermetria and dysmetria (Plate IIb). Head raising test (that is, raising the head of the animal for one minute and then suddenly releasing it) is followed by severe intention tremors. There

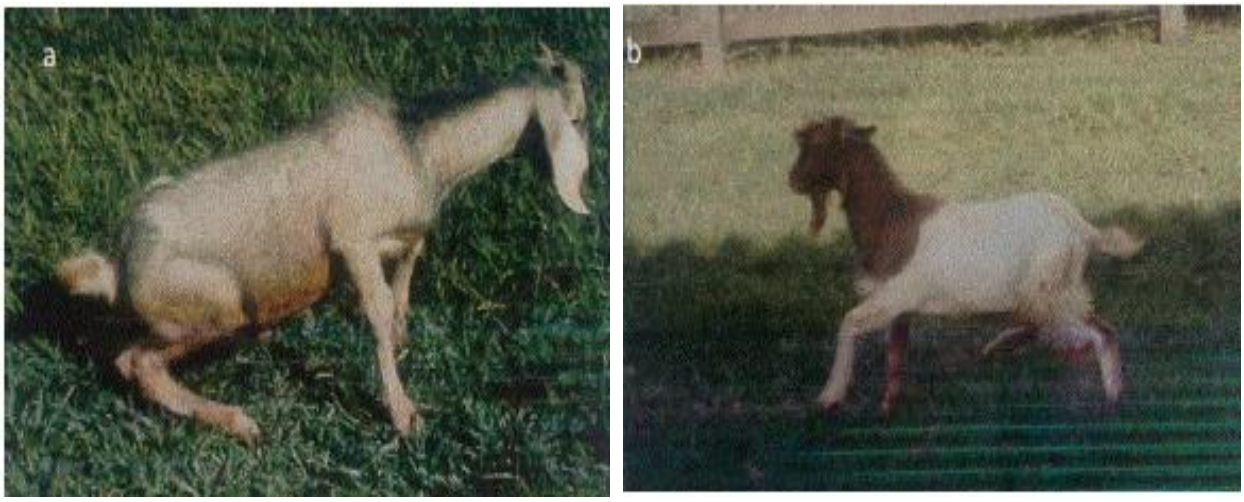


Plate II: (a) Posterior paresis and (b) Hypermetria/dysmetria, Source: Armien, 2000.

will be muscle hypertonia of the head, neck and legs, and sternal recumbency with forelimbs rigid and stretched forward. Appetite remains normal. Depression, lacrimation and nasal discharge occur in some animals (de Balogh *et al*., 1999; Armien *et a*., 2007). Despite the severity of the condition, affected pregnant does and ewes deliver apparently healthy kids/lambs but they may be affected if they suckle affected nannies (Armien *et al*., 2007; Ríos *et al.*, 2012). In contrast, Gotardo *et al.* (2011) and Gotardo *et al.* (2012) reported that pregnant goats experimentally fed with *I. carnea* had teratogenic effect on feotuses and kids delivered had significant behavioral alterations. Ultrasonography revealed decreased foetal movement and there was increased number of birth defects compared to the non-treated group. Similarly, chronic locoweed (Astragalus) intoxication causes cardiovascular and reproductive disorders in ruminants and this include altered libido, infertility, abortion and placental abnormalities (Stelgemeier *et al*., 1995). Also *Sida carpinifolia* poisoning was associated with neonatal motalities and abortion in Anglo-Nubian and Saanen goats (Driemeier *et. al.,* 2000).

The above-mentioned signs develop in animals that have been ingesting small amount of various doses of the poisonous plant for a minimum of 3 weeks. However goats fed solely on similar plant *I. riedelii* (0.14% swainsonine dry matter content) as the only feed developed signs within 11 days and died after 22 days of daily ingestion of the plant (Barbosa *et al.*, 2006). Animals that continuously feed on this plant inevitably dies because of inability to move and feed or because of neurological lesions of vegetative centre controlling cardiovascular and respiratory functions (Stelgemeier *et al*., 1999; Armien *et al*., 2007).

Pathology

Clinical pathology

Clinicopathogical changes appear to fluctuate within the normal ranges. Aspartate amino transferase (AST), blood urea nitrogen (BUN), creatine levels and total protein remain normal (de Balogh *et al*., 1999; Armien *et al.*, 2007). Also experimental poisoning with *I. sericophylla* and *I. riedelii* in goats showed the serum levels of protein, albumin and glucose, and serum activities of gamma-glutamyltransferase (GGT) and AST as well as packed cell volume (PCV), red blood cell (RBC), white blood cell (WBC), haemaglobin (HB), mean corpuscular volume (MCV) and mean corpuscular haemoglobin concentration (MCHC) values remained within normal ranges (Barbosa *etal*., 2007). Moreover, experimental ingestion of *Astragalus mollissimus* var. *mollissimus* in cattle showed no variation in serum biochemistry and urinalysis except hypoalbuminaemia and reduced levels of serum thyronine. However, increase in alanine amino transferase (ALT) and decrease in haemoglobin content at high dose of ingestion of the toxic plant *I. carnea* subsp. *fistulosa* was reported (Schumaler-Henrique, 2003). Severe central nervous system sign is associated with high level of up to 10 fold increase of creatinihe kinase (CK) (de Balogh *et al*., 1999).

Gross lesions

The affected carcass of *I. carnea* subsp. *fistulosa* intoxication is emaciated, has pale mucous membrane and there may be congestion of meninges, marked asymmetry and atrophy of cerebellum, slight oedema of spinal cord and/or mild hydropericardium (de Balogh *et al*, 1999; Armien *et al.*, 2007). In some instances, there may be no significant gross lesions (Armien *et al*., 2007; Barbosa *et al*., 2007). Gastrointestinal dysfunction and metabolic disorders such as altered gastrointestinal tract enzyme secretions and

reflexes as well as neurological disorders which include difficulty to move and graze, and anorexia may be responsible for weight loss and emaciation associated with this condition just as it was attributed in locoism (Stelgemeier *et al*., 1999).

Histopathology

The most prominent histopathologic lesions are observed in the central nervous system but pancreas, kidneys, liver, intestine and lymph nodes are also affected. There would be diffuse neuronal cytoplasmic vacuolation, axonal degeneration and astrogliosis of cerebral cortex, Purkinje cells in cerebellum brain stem, and dorsal and ventral horn neurons of the spinal cord (de Balogh *et al*., 1999; Armien *et al.*, 2007). Lesions are more prominent in cerebral cortex, corpus striatum and thalamus. The hematoxyline and eosin (H and E) stained sections revealed neurons that have distended foamy cytoplasm containing many small vacuoles (de Balogh *et al*., 1999; Armien *et al.*, 2007). There are dispersed Nissl substance, and spongiosus of the optic tract. Also, vacuolation of oligodendrocytes, endothelial cells and perivascular cells of the central nervous system. Axonal degeneration is characterized by spheriod formation and this is most prominent in the granular layer and white matter of the cerebral cortex (Armien *et al.*, 2007).

Purkinje neurons of the cerebellum are affected and appear shrunken, condensed cytoplasm with hyperchrornatic nuclei or there may be complete loss of the cells and development of vacuolation, gliosis and astrocytes proliferation. Spheroids and torpedoes are also observed. Spheroids (Plate IIIb) are characterized by axonal expansion and accumulation of dense bodies, mitochondria, microtubules and intermediary filaments where as torpedoes are enlargement of the proximal segments of Purkinje axons (de Balogh *et al*., 1999). In more prolonged cases, it is characterized by moderate astrogliosis especially in areas with more severe neuronal and axonal degenerations. Astrocytes contain intense eosinophilia and plump cytoplasmic processes, and the nuclei are eccentric, large and indented (Armien *et al.*, 2007).

Also vacuolation are observed in the neurons of the submucosal and mesenteric plexus of the small intestine and in the epithelial cells of the kidney (Armien *et al*., 2007), pancreatic acinar cells (Plate IVa) (de Balogh *et al*., 1999; Armien *et al.*, 2007), follicular cells of thyroid glands (Plate IVb), macrophages in lymph nodes (Plate IVc), hepatocytes and Kupffer cells (Plate IVd). There are reduced number of mature secretory granules of endocrine and exocrine pancreatic cells (Armien, 2000; Schumaler-Henrique, 2003; Armien *et al*., 2007). The cytoplasmic vacuoles in neurons and other cells are mostly optically empty but some individual vacuoles may have amorphous membranous fragments, vesicles, reticular or dense granules, opaque globules of osmeophilic materials (Plate IIIa) (Armien *et al.*, 2007).

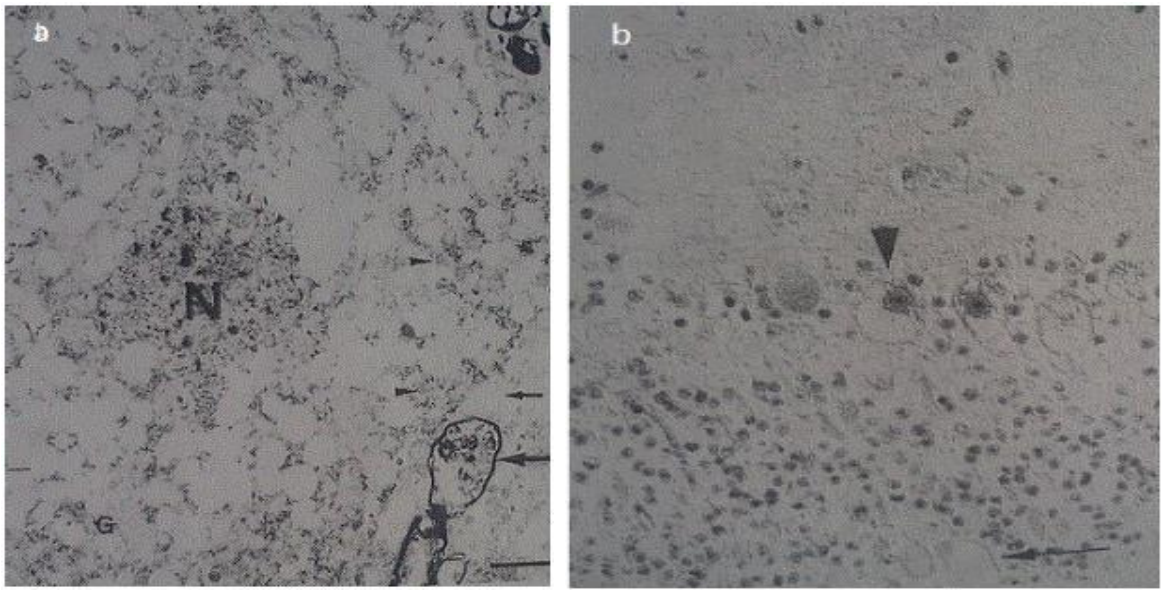
Diagnosis

In the diagnosis of *I. carnea* subsp. *fistulosa* toxicosis, the following conditions have to be considered (Armien *et al*, 2007). There should be history of existence of the plant in large quantities, accessible and ingested by the animal continuously for several weeks before clinical signs develop. Affected animals will have clinical signs that include bilateral symmetrical ataxia, paresis, propioceptive deficit, abnormal and postural reactions. There must be cytoplasmic vacuolation of neurovisceral tissues at histopathology.

Differential diagnosis includes toxicosis by other plants that contain swainsonine and/or calystegines (e.g. locoism). Inherited α-mannosidosis, β-mannosidosis, ganliosidosis and mucopolysaccharidosis have similar clinical and pathological pictures with those of acquired lysosomal storage diseases (Radostits *et al*., 2006).

Management

Clinical recovery occurs following cessation of ingestion of the toxic plant by affected animal. This is possible when the case of poisoning is not too advanced or prolonged. Daily regular ingestion of small amount of Ipomoea species in goats for up to 70 days and then the plant is withdrawn, may be followed by disappearance of clinical signs within 6 days. However this may not be possible if the plant is consumed for up to 120 days. Recovery is associated with complete reversal of all neurological signs (Radostits *et al*., 2006; de Balogh *et al*., 1999; Barbosa *et al*., 2007). Also, Barbosa *et al.* (2006) reported that goats that continued to ingest the swainsonine containing plants for up to 20-28 days after the appearance of clinical signs recovered within 4-14 days after suspension of the plant. Therefore, there is possibility for animals to recover fully from poisoning within short period if they have not grazed on the plant for too long. However, animals that have developed addiction and continue to ingest this plant in preference of other feed need to be culled (Barbosa *et al*., 2007). Massive destruction of the plant that is accessible to the animals has been practiced as a control measure. This involves the collaboration of agricultural extension agents and village heads and is followed by marked reduction of number of animals affected (de Balogh *et al*., 1999).



Plates III: Cerebellum, Purkinje cell (a) showing empty vacuoles with some amorphous/osmeophilic materials, and (b) cytoplasmic vacuolation (arrow head) and axonal spheroid (arrow). Source: Armien *et al.*, 2007

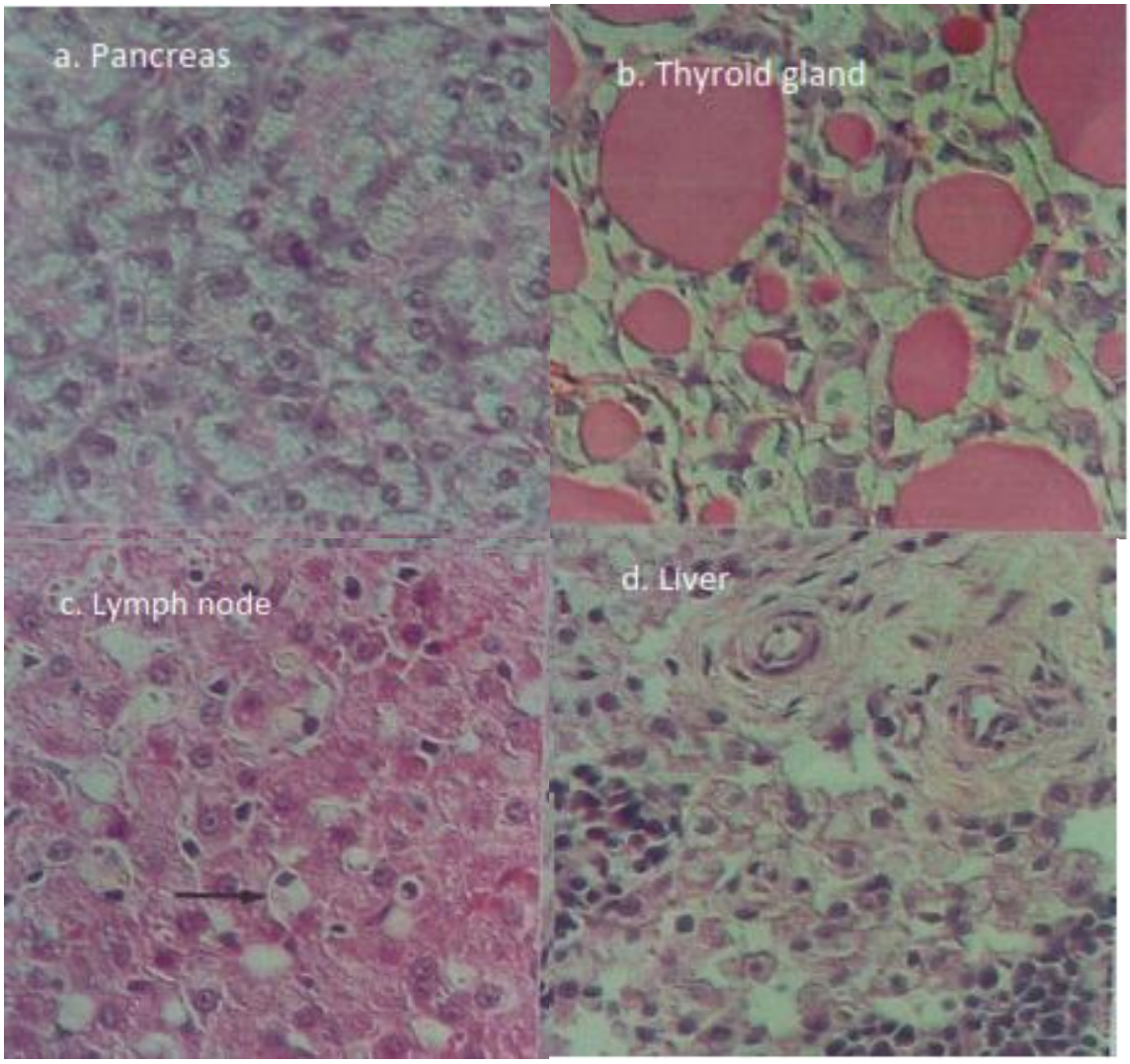


Plate IV: Cytoplasmic vacuolation in various organs of a goat experimentally poisoned with *Ipomoea carnea.* Source: Armien, 2000

Conclusion

Ipomeoa carnea subsp. *fistulosa* is not an indigenous plant in this locality but has now spread everywhere both in urban and rural areas, as well as in the wild. It contains two toxic principles, swainsonine and calystegines. Alpha (α)-mannosidosis is the most important acquired lysosomal storage disease induced by ingestion of this plant. This condition is characterized by neurological impairments and generalized cytoplasmic vacuolation of various tissues of the body. The status of this plant is not determined in the Sahel region but risk of poisoning cannot be denied. This is because of the long dry season, free range management system practiced, intoxication is slow and often reversible, addiction may occur and there is no assessment plan on ground to evaluate the possibility of the toxic effect of the plant.

Recommendations

There is need to determine hazard of the plant in terms of pattern of distribution and its population density in our local environment as the plant is all over Northern Nigeria. The nature of the plant in the Sahel region should be determined as concentration of the toxic principles varies from time to time even within the same species. There is need to develop a checklist for veterinarians as well as its differentials to enable easy diagnosis. Just like other ornamental plants that are closely guarded against animals, domestically grown plant should also be fenced to keep away from animals.

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