

## Experimental intoxication by the leaves of *Melia azedarach* (Meliaceae) in cattle<sup>1</sup>

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**ABSTRACT.**- Méndez M.C., Aragão M., Elias F., Riet-Correa F. & Gimeno E.J. 2002. [Experimental intoxication by the leaves of *Melia azedarach* (Meliaceae) in cattle.] *Pesquisa Veterinária Brasileira* 22(1):19-24. Laboratório Regional de Diagnóstico, Faculdade de Veterinária, Universidade Federal de Pelotas, 96010-900 Pelotas, RS, Brazil. E-mail: nane@ufpel.tche.br.

Green leaves of *Melia azedarach* were administered at single doses ranging from 5 to 30 g/kg bw to 11 calves. Clinical signs were depression, ruminal stasis, dry feces with blood, ataxia, muscle tremors, sternal recumbency, hypothermia and abdominal pain. Serum AST and CPK were increased. Signs appeared from 8 to 24 hours after dosing, and the clinical course lasted from 2 to 72 hours. Three calves dosed with 30g/kg bw died. The macroscopic findings included intestinal congestion, yellow discoloration of the liver, brain congestion and dry feces with blood in the rectum. The liver showed swollen and vacuolated hepatocytes. Necrotic hepatocytes were scattered throughout the parenchyma or concentrated in the periarterial zone. Degenerative and necrotic changes were observed in the epithelium of the forestomachs. There was also necrosis of the lymphoid tissue. Skeletal muscles showed hyaline degeneration and fiber necrosis. The necrotic fragments contained floccular or granular debris with infiltration by macrophages and satellite cells.

INDEX TERMS: Poisonous plants, plant poisoning, *Melia azedarach*, Meliaceae, cattle.

**RESUMO.**- [Intoxicação experimental pelas folhas de *Melia azedarach* (Meliaceae) em bovinos.] Folhas verdes de *Melia azedarach* foram administradas em dose única a 11 bovinos nas doses de 5 a 30g/kg de peso vivo. Os sinais clínicos caracterizaram-se por depressão, atonia ruminal, fezes duras com sangue, incoordenação, tremores musculares, decúbito esternal, hipotermia e dores abdominais. Os níveis séricos de AST e CPK estavam aumentados. O aparecimento dos sinais clínicos foi observado entre 8-24 horas após a ingestão das folhas e o curso clínico durou entre 2 e 72 horas. Três animais que receberam 30g/kg morreram. Os achados macroscópicos caracterizaram-se por congestão dos intestinos e do cérebro, fígado amarelado e presença de fezes duras com sangue no reto. Os hepatócitos estavam tumefeitos e com vacuolização citoplasmática. Observaram-se hepatócitos

necróticos distribuídos no parênquima ou próximos à veia centrolobular. Lesões degenerativas e necróticas foram observadas no epitélio dos pré-estômagos. Havia também necrose do tecido linfóide. Nos músculos esqueléticos observaram-se degeneração hialina e necrose das fibras. Os fragmentos necróticos apresentavam necrose flocular ou granular com infiltração de macrófagos e células satélites.

TERMOS DE INDEXAÇÃO: Plantas tóxicas, intoxicação por plantas, *Melia azedarach*, Meliaceae, bovinos.

### INTRODUCTION

*Melia azedarach* L. is an ornamental fast growing tree of worldwide distribution (Kingsbury 1964). It grows to a height of 6-12m, some rainforest varieties reaching 30-45m (Hurst 1942, Oelrichs et al. 1985, Hare 1997). The plant is used in some countries for medicinal purposes in humans. It has been used as antihelmintic, tonic, antipyretic and also for the treatment of leprosy, eczema and asthma (Oelrichs et al. 1985). The leaves have insecticide properties. In some area it is the only tree that is not eaten by the grasshoppers. For that reason, it has been frequently planted around the fields in several countries (Ragonese 1956, Gallo 1987).

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*M. azedarach* intoxication has been observed in humans and in domestic animals due to the ingestion of leaves or fallen fruits. Children may die by ingestion of 6 to 8 fruits, after a short clinical course or after some days. The symptoms are nausea, vomits, diarrhea, thirst, sweating, grinding of teeth, sleepiness and convulsions (Kingsbury 1964, Everist 1974, Oelrichs et al. 1985).

The intoxication by *Melia azedarach* affects mainly pigs due to the ingestion of the fruits (Hurst 1942, Kingsbury 1964, Everist 1974, Kwatra et al. 1974, Oelrichs et al. 1985, Timm & Riet-Correa 1997); intoxication generally occurs due to the ingestion of mature fruits, when they drop to the soil or when branches are within the reach of the animals (Everist 1974, Kwatra et al. 1974). Kwatra et al. (1974) reported experimental intoxication by the fruits in swine.

Cattle, sheep, goats and poultry can be, also, affected, but this seems to be rare (Everist 1974, Oelrichs et al. 1985, Hare 1998). Sheep can be intoxicated after ingesting fruits of the plant and cattle by ingestion of the leaves, but this only happens if there is no other food available (Everist 1974).

The fruits are quite toxic for swine and, to a lesser degree, for birds, sheep and goats. The mature fruits are more poisonous than the green ones. The toxic dose for pigs is around 0.7% of the body weight (Hurst 1942). According to Kingsbury (1964), the toxic dose for pigs and sheep is approximately 0.5% of the animal weight. Guinea-pigs are also susceptible to the fruits (Hurst 1942).

The bark, flowers and leaves of *M. azedarach* have been shown to be toxic, but they are less toxic than the fruits. Toxicity of the fruits is within the pulp, the shell and kernel being quite harmless (Hurst 1942, Kingsbury 1964).

Experiments carried out in Australia suggest that the toxicity of the plant could vary according with the growing area, and that some trees can be non-toxic (Oelrichs et al. 1985).

It is mentioned that in Argentina children and domestic animals that ingest the fruits do not become intoxicated (Hurst 1942).

According to general descriptions, clinical signs in animals appear quickly, usually 2-4 hours after ingestion of the plant. They are related to the gastrointestinal and/or nervous system. The main clinical signs are nausea, vomits, constipation or diarrhea, frequently with blood, colic, excitement or depression, weak heart beatings, convulsions, ataxia, paresis, dyspnea and coma. Death occurs due to circulatory collapse and breathing insufficiency (Oelrichs et al. 1985, Hare 1997). Animals intoxicated with the fruits of *M. azedarach* generally do not survive more than 48 hours after the onset of clinical signs (Hare 1997).

The clinical signs in swine are of two types: in one condition there is nausea, vomiting, constipation or scouring often with blood, and in the other more acute condition there are nervous symptoms of excitement or depression, weakened heart action and dyspnea followed by death. Clinical signs may occur some hours after ingestion of the fruits and the animals generally do not survive more than 24 hours. Recovery

may be slow in animals less severely poisoned (Kingsbury 1964, Oelrichs et al. 1985).

The macroscopic lesions are unspecific, as severe congestion of liver and kidneys (Hothi et al. 1976) and gastroenteric irritation (Kingsbury 1964, Oelrichs et al. 1985). In pigs, the most conspicuous microscopic changes are in the digestive tract, extending from the glandular area of the stomach to the intestines. There are hyaline cylinders in the renal tubules and necrosis of lymphocytes in the lymph nodes and spleen (Kwatra et al. 1974, Oelrichs et al. 1985). In mice experimentally fed with dry leaves the lesions were characterized by degeneration and necrosis of skeletal muscle fibers (Bahri et al. 1992).

Different substances have been characterized as toxic principles of *M. azedarach*. To some authors the toxin is in the pulp of the fruit and could be an alkaloid of unknown chemical structure. Others researchers isolated saponines with hemolytic properties (Oelrichs et al. 1985, Gallo 1987), and several potentially toxic limonoides (Ahn et al. 1994, Nakatani et al. 1994, Huang et al. 1995). Carratala (1939) found the alkaloid azaridine, a resin, a tannin, and meliotanic and benzoic acids. Oelrichs et al. (1985) identified 4 tetranortriterpene substances extracted from the fruits of *M. azedarach* denominated as meliatoxins A1, A2, B1 and B2. These authors suggest that the compounds are responsible for the nervous signs of the disease. Sub-lethal doses of fresh fruits cause a clinical picture characterized by hemorrhagic diarrhea, but this form of intoxication was not observed in pigs treated with meliatoxins. Other isolated but not yet identified compounds would be responsible for the digestive disturbances.

In Brazil, in the State of Rio Grande do Sul, outbreaks of poisoning by *M. azedarach* have been reported in pigs that had access to fruits fallen from the trees (Timm & Riet-Correa 1997). Farmers reported death of cattle and sheep after ingestion of fruits or leaves of branches of trees knocked down by the wind or after pruning.

The objective of the present study was to characterize the clinical and pathological picture of intoxication with the leaves of *M. azedarach* in cattle.

## MATERIALS AND METHODS

Thirteen young cattle were used in the experiment. Eleven animals received green leaves of *M. azedarach* and two remained as controls. Clinical examination was conducted at the beginning of the experiment, and then daily after ingestion of the leaves. The animals were evaluated for heart and breathing frequency, ruminal movements, temperature, discoloration of the mucous membranes, consistency and color of the feces and general aspect.

Green leaves of *M. azedarach* collected in autumn were administered orally in single doses of 5, 10, 15, 20, 25 or 30g per kg bw. Table 1 shows the weight of the animals, the doses administered, the time elapsed between ingestion and onset of clinical signs, the duration of the signs and the course of the disease.

Blood samples were obtained 24 hours before the beginning of the experiment and, later on, every 24 hours after the ingestion of the leaves. Five blood samples were taken from the two control animals.

The blood samples were submitted to a private laboratory for determination of the aspartate aminotransferase (AST) and creatinine phosphokinase (CPK). The enzymatic activity was evaluated through the kinetic method.

Table 1. Experimental intoxication of cattle by the green leaves of *Melia azedarach*

Bovine n°	Weight kg	Dose of leaves g/kg	Clinical signs		Outcome
			Onset <sup>a</sup>	Duration	
1	115	5	24h	24h	Survived
2	70	10	24h	48	Survived
3	121	15	24h	24h	Survived
4	158	15	24h	24h	Survived
5	65	20	-	-	Survived
6	112	20	-	-	Survived
7	132	25	8h	72h	Survived
8	130	25	12	72h	Survived
9	125	30	15h	2h	Died
10	100	30	12h	36h	Died
11	130	30	12h	24h	Died

<sup>a</sup>After dosing.

A complete necropsy was done in cattle that died (Bov. 9, 10 and 11). Fragments of several organs were collected and fixed in 10 % formalin. Tissue samples included lung, heart, liver, kidney, lymph nodes, central nervous system and skeletal muscles (serrate, longissimus dorsi, semitendinosus, semimembranosus, psoas, intercostals, biceps, triceps and diaphragm). After fixation, the tissues were embedded in paraffin, cut at 6 µm and stained with haematoxylin and eosin. The fragments of the skeletal muscles were immersed in saline solution during 40 to 50 minutes and later maintained at 4° C for 12 hours before they were placed in formalin. Transverse sections taken from the medulla oblongata, pons, rostral colliculi, thalamus, internal capsule, cortex, cerebellar peduncles and cerebellum were examined for histological changes in the central nervous system.

**RESULTS**

Observations of clinical signs in cattle are recorded in Table 2. Clinical signs characterized by muscular tremors, difficulty to stand and reluctance to rise, sternal recumbence, hypothermia, and abdominal pain were observed in cattle that ingested 30g/kg bw of the green leaves of *M. azedarach*. These animals had also dry feces with blood. Death occurred

Table 2. Clinical signs in cattle after ingestion of the green leaves of *Melia azedarach*

Bovine n°	Dose g/kg	Clinical signs									
		Apathy	Ruminal atony	Dry feces	Diarrhea feces	Muscular tremors	Incoordination	Hypothermia	Sternal decubitus	Abdominal pain	
1	5	+	+	-	-	-	-	-	-	-	
2	10	+	+	-	-	-	-	-	-	-	
3	15	+	+	+	-	-	-	+	-	-	
4	15	+	+	-	+	-	-	-	-	-	
5	20	-	-	-	-	-	-	-	-	-	
6	20	-	-	-	-	-	-	-	-	-	
7	25	-	+	-	+	-	+	-	-	-	
8	25	-	+	-	+	-	+	-	-	-	
9	30	+	+	+	-	+	+	+	+	+	
10	30	+	+	+	-	+	+	+	+	+	
11	30	+	+	+	-	+	+	+	+	+	

Table 3. Serum AST in cattle intoxicated by the green leaves of *Melia azedarach*

Bovine n°	Dose of leaves g/kg	AST (UI/L)				
		0h	24h	48h	72h	96h
1	5	97	116	84	79	68
2	10	208	248	216	229	205
3	15	85	486	312	165	-
4	15	64	147	100	82	-
5	20	117	170	180	-	-
6	20	77	75	71	70	-
7	25	169	194	292	255	196
8	25	141	33	84	75	-
9	30	108	718	-	-	-
10	30	63	714	780	-	-
11	30	58	672	-	-	-
X	-	107,9	324,8	235,4	136,4	156,3
Control	0	101	166	79	22	57
Control	0	83	94	98	90	95

Table 4. Serum CPK in cattle intoxicated by the green leaves of *Melia azedarach*

Bovine n°	Dose of leaves g/kg	CPK (UI/L)				
		0h	24h	48h	72h	96h
1	5	300	320	400	386	-
2	10	380	443	440	376	-
3	15	381	420	427	339	-
4	15	389	760	343	346	-
5	20	940	476	594	-	-
6	20	443	397	268	236	-
7	25	1777	1278	667	528	441
8	25	806	768	380	195	164
9	30	343	506	-	-	-
10	30	397	1799	3460	-	-
11	30	171	1536	-	-	-
X	-	575,2	791,2	775,4	343,7	302,5
Control	0	416	957	268	222	174
Control	0	220	250	160	145	180

between 17 and 48 hours after ingestion of the leaves. Calves dosed with 25g/kg bw of leaves showed diarrhea, ruminal atony and hind limbs incoordination 24 hours after ingestion. Twenty-four hours after administration Calf 4 (15g/kg bw) showed diarrhea, but Calf 3 (15g/kg bw) had dry feces and hypothermia.

The values of aspartate aminotransferase (AST) and creatinin phosphokinase (CPK) are presented in Table 3 and Table 4, respectively.

Gross lesions were characterized by yellow discoloration of the liver, congestion of the intestines and brain, and petechiae at the pericardium. The rectum had dry feces with blood.

On histological examination, congestion and edema of Disse's spaces were constant changes in the liver. The hepatocytes were swollen and vacuolated. Necrotic hepatocytes were scattered throughout the parenchyma or in the periarterial area. These lesions were similar in the three calves. The kidneys were slightly congestive and the tubular epithelium showed tumefaction and vacuolization. Hyaline cylinders were occasionally observed in the lumen of the tubules. There were slight congestion of the mucous membrane and infiltration of eosinophiles in the small intestine. Congestion and infiltration of inflammatory cells, mainly neutrophils, plasmocytes and eosinophiles were observed in the large bowel. In some cases, there was superficial necrosis of the intestinal villi. Necrotic lymphocytes and macrophages with cellular debris were observed in the spleen, lymph nodes and Peyer's patches, mainly in the follicles. The ruminal epithelium displayed vesicular degeneration and necrosis. Similar lesions were observed in the reticulum. The changes were also found in the omasum, but they were less pronounced than in the rumen and reticulum. In the skeletal muscles, there was degeneration and myofibrillar segmentary necrosis and occasionally hyalinization. The necrotic fragments consisted of floccular or granulate material, and nuclear remnants located the margins of the fibers. The satellite cells were increased in size and presented vesicular aspect. The necrotic fragments showed some invasion by macrophages and satellite cells with disappearance of the sarcolemma.

## DISCUSSION

In this study, a single dose of 30g/kg bw of the green leaves given to the cattle was lethal, causing death 17-48 hours after ingestion, but calves that ingested smaller doses recovered. Previous experiments in cattle showed that a single dose of 25 and 30g/kg bw of fruits of *M. azedarach* was lethal, causing death 24-48 hours after the ingestion (Méndez et al., unpublished data). These results suggest that the leaves are as toxic as the fruits for cattle.

The intoxication affects several organs and systems. However, biochemical and pathological analyses do not allow to determine the cause of death. Apathy, ruminal atony, dry feces with blood in the rectum, abdominal pain, hypothermia, ataxia, muscular tremors, and sternal recumbency were observed in this study. These digestive and nervous signs are

similar to those reported previously (Kingsbury 1964, Kwatra et al. 1974, Hothi et al. 1976, Hare 1998).

Calves that died after the ingestion of 30g/kg bw of the leaves of *M. azedarach* showed dry feces with blood, but calves that recovered within 3-4 days after the ingestion of 25g/kg had severe diarrhea. Most calves intoxicated by the fruits showed diarrhea, but dry feces with blood were not observed (Méndez et al., unpublished data).

Some of the clinical signs observed can be interpreted as being of nervous origin, however no alterations were found at histological examination of the nervous system to justify the clinical signs. Signs of nervous disturbances are also mentioned in cattle intoxicated by *Baccharis coridifolia*, a plant that causes lesions in the alimentary tract. In cases of intoxication by *B. coridifolia*, the clinical signs could be provoked by pain or other effects of the plant (Varaschin et al. 1998). Nervous signs in cattle intoxicated by *M. azedarach* could be also due to lesions in the central nervous system that can not be detected by histological examination. On the other hand, some of those clinical signs are probably due to the muscular lesions. It is well known that many diseases of the central nervous system are difficult to differentiate from muscular diseases.

The histological alterations caused in cattle intoxicated by leaves of *M. azedarach* were degeneration and necrosis in the digestive system, necrosis in the skeletal muscles, necrosis of the lymphoid tissue, and mild changes in liver and kidneys. These changes are similar to those described in the intoxication by fruits of the plant (Méndez et al., unpublished data). Fatty change and hyperemia of liver and kidneys (Kingsbury 1964, Everist 1974, Oelrichs et al. 1985), necrosis of glands in the gastric mucosa, hyaline cylinders in the renal tubules, and necrosis of lymphocytes in the lymph nodes and spleen had been reported (Kwatra et al. 1974, Oelrichs et al. 1985).

In Brazil, other toxic plants cause digestive alterations. The intoxication by *B. coridifolia* (Tokarnia & Döbereiner 1975, Barros 1993), *B. megapotamica* var. *megapotamica* and *B. megapotamica* var. *weirii* in cattle (Tokarnia et al. 1992) and by *B. megapotamica* var. *weirii* in goats (Barbosa et al. 1994) causes lesions similar to those found in the intoxication by leaves of *M. azedarach* in cattle. Necrosis of the lymphoid tissue and degeneration and necrosis of the ruminal and reticular epithelium, described in the intoxication by *B. coridifolia* (Barros 1993, Varaschin et al. 1998) and by *B. megapotamica* (Tokarnia et al. 1992), are similar to the histological alterations found in the cattle of our experiment. Hydropic degeneration of the epithelium of the forestomachs had been reported in the intoxication by fruits of *Stryphnodendron obovatum* (Brito et al. 2001). This was also observed in the intoxication by leaves of *M. azedarach*. In the intoxication by *B. coridifolia*, the gastroenteric lesions are attributed to a direct caustic effect of the macrocyclic trichotecenes and roridines contained in the plant, but the mechanism of action is not clear (Barros 1993). Similar substances, called bacarinoids, are the toxic principles of *B. megapotamica* (Kupchan et al. 1977).

The alterations observed in the liver are similar that those described in the intoxication by *Stryphnodendron coriaceum* in cattle (Tokarnia et al. 2000).

Degeneration and necrosis were observed in the skeletal muscles fibers. These lesions are similar to those described in mice fed with leaves of *M. azedarach* (Bahri et al. 1992) and in cattle intoxicated experimentally with fruits of the plant (Méndez et al., unpublished data). This suggests that the substance responsible for causing those lesions can be found in the leaves as well as in the fruits of *M. azedarach*. The myonecrosis was also evidenced by increased CPK and AST blood levels after ingestion of the leaves. The high values of CPK observed mainly in the animals that died (424,5 UI/L – 1885,3 UI/L) demonstrate that some component in the leaves of *M. azedarach* is responsible for damage to the muscular fibers, with consequent elevation of the enzyme in the blood serum. CPK is a specific enzyme of the muscular tissue, being liberated from the muscular fibers in degeneration or necrosis. The activity of this enzyme could be considered a reliable indication of muscular lesion (Kaneko 1989). AST does not have specificity for any organ or tissue, but the determination of that enzyme in the serum is a valuable help for the diagnosis. That enzyme is contained in high concentrations in the skeletal and heart muscles, but its activity can also be high in the liver and other tissues. Increased levels of CPK and AST are observed in the hereditary muscular dystrophies, vitamin E/selenium deficiency, equine myoglobinuria and myodegeneration due to the ingestion of poisonous plants (Kaneko 1989). Marked increase of CPK and AST occur in the intoxication by *Senna occidentalis* in cattle and horses. As a consequence of the muscular lesion they develop myoglobinuria. In young cattle, the intoxication by *S. occidentalis* can occur without myoglobinuria, probably because the muscles of those animals have little myoglobine. Myoglobinuria was not observed in the intoxication by *M. azedarach* in cattle and also does not happen in the intoxication by *S. occidentalis* in horses (Barros 1993). This could be explained by the fact that both intoxications have an acute clinical manifestation period, generally of few hours.

Tursch et al. (1963) isolated saponines from the fruits of *Stryphnodendron coriaceum*. The active substances of the fruits of *S. obovatum* are still unknown, but Brito et al. (2001) suggest that saponines are responsible or at least participate in the pathogenesis of the intoxication. According to Kingsbury (1964), the saponines contained in some plants can cause irritation of the digestive tract and/or gastroenteritis.

The results obtained in the present experiment with the leaves of *M. azedarach* are very similar to those obtained by the administration of fruits of the plant (Méndez et al., unpublished data).

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