**UNIVERSIDADE DE BRASÍLIA**
**FACULDADE DE AGRONOMIA E MEDICINA VETERINÁRIA**

# Hepatotoxicidade de *Cestrum axillare* em bovinos do Distrito Federal, Goiás e Minas Gerais

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Orientador(a): Márcio Botelho de Castro

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Trabalho de conclusão de curso apresentado ao programa de pós-graduação na modalidade de residência *lato sensu* em Área Profissional em Anatomia Patológica Veterinária, junto à Faculdade de Agronomia e Medicina Veterinária da Universidade de Brasília.

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# *Cestrum axillare* hepatotoxicity in cattle in the Federal District, Goias and Minas Gerais[1]

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**ABSTRACT.** Sousa A.L.V, Sousa D.E.R, Cerqueira, L.A, Queiroz-Machado, C.R.R., Giaretta P.R., Riet-Correa F., Castro M.B. & Machado M. 2023. ***Cestrum axillare* hepatotoxicity in cattle in the Federal District, Goias and Minas Gerais**. *Pesquisa Veterinária Brasileira*. Instituto Nacional de Investigación Agropecuaria (INIA), Plataforma de Investigación en Salud Animal (PSA), Estación Experimental Tacuarembó, Ruta 5 Km 386, Tacuarembó 45000, Uruguay. E-mail: mmachado@inia.org.uy

This study reports four outbreaks of *Cestrum axillare* poisoning in cattle. Outbreaks occurred in farms of the Federal District, Goias, and Minas Gerais states during the dry season, affecting cows and heifers, with a mortality rate of 1 to 14,28%. Poisoned animals showed neurological signs and recumbency, followed by death within 12 hours, and some animals were found dead. Gross and histological lesions were typical of acute hepatotoxicity with hepatomegaly, enhancement of lobular pattern, and centrilobular to massive necrosis. These are the first report of *C. axillare* poisoning in cattle in the Federal District, Goias, and Triangulo Mineiro. *Cestrum* poisoning must be included in the differential diagnosis for cattle with hepatic necrosis in these locations.

INDEX TERMS: Poisonous plants, Cattle, hepatotoxicosis, *Cestrum axillare.*

**RESUMO.-** [**Hepatotoxicidade do *Cestrum axillare* em bovinos do Distrito Federal, Goiás e Minas Gerais.**] Este estudo relata quatro surtos de intoxicação por *Cestrum axillare* em bovinos. Os surtos ocorreram em fazendas do Distrito Federal, Goiás e Minas Gerais durante a estação seca, afetando vacas e novilhas, com taxa de mortalidade de 1 a 14,28%. Os animais afetados apresentaram sinais neurológicos e decúbito, seguidos de óbito em 12 horas. Alguns animais foram encontrados mortos. Foram observadas lesões macroscópicas e histológicas típicas de hepatotoxicidade aguda como hepatomegalia, evidenciação do padrão lobular e necrose centrolobular a massiva. Este é o primeiro relato de intoxicação por *C. axillare* em bovinos no Distrito Federal, Goiás e Triângulo Mineiro. A intoxicação por *Cestrum axillare* deve ser incluída no diagnóstico diferencial de bovinos com necrose hepática nessas localidades.

TERMOS DE INDEXAÇÃO: Plantas tóxicas, bovinos, hepatotoxicidade aguda, *Cestrum axillare.*



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## INTRODUCTION

*Cestrum axillare* (sin. *Cestrum laevigatum*) is a shrub plant of America from the Solanaceae family that can reach up to two meters in height, with an erect stem, elliptical and oval leaves with a stalked insertion, and an axillary arrangement. Flowers are white with sessile insertion of lanceolate petals, and fruits are black. (Vignoli-Silva & Mentz 2020). The plant occurs mainly in the Southeast, Midwestern, and Northeast Brazil (Tokarnia et al. 2012).

The history of *Cestrum axillare* poisoning is very interesting. The first evidence of *C. axillare* toxicity was suspected when the plant was introduced as an ornamental plant in many farms of South Africa (Thorburin 1934, Tokarnia et al. 2012). The poisoning was observed in ruminants near the river Chase and was named Chase Valley Disease, but the cause remained unknown for many years (Thorburin 1934). Recently, a kaurene glycoside carboxyparquin toxic compound was demonstrated in within young and mature leaf samples of *Cestrum axillare* (Ubiali et al., 2022).

*C. axillare* poisoning occurs mainly under forage scarcity, during the dry season, or when the plant is sprouting due to its low palatability (Tokarnia et al. 2012, Ubiali et al. 2022, Riet-Correa et al. 2023). Clinically, animals poisoned by this plant present signs between 15 and 24 hours after ingestion related to acute hepatic failure and hepatic encephalopathy, such as lethargy, anorexia, ruminal atony, and neurological disturbance. Death can occur between 6 and 48 hours after the first clinical signs onset (Tokarnia et al. 2012, Ubiali et al. 2022). *Cestrum axillare* poisoning is pathologically characterized by *Cestrum axillare* poisoning is characterized by the enhancement of hepatic lobular pattern with centrilobular to massive hepatocellular necrosis and hemorrhage (Tokarnia et al. 2012).

In Brazil, spontaneous poisonings have been reported in cattle (Döbereiner et al. 1969, Silva & Silva Júnior 1996, Purisco et al. 1998, Coutinho et al. 2013, Santos et al. 2016, Oliveira Neto et al. 2017, Ubiali et al. 2022), and rarely in buffaloes (Barbosa et al. 2010, Ubiali et al. 2022) and goats (Peixoto et al. 2000, Brito et al. 2010, Ubiali et al. 2022). Experimental poisonings by *C. axillare* have been performed in cattle (Thorburin 1934, Tokarnia 1965, Dobereiner et al. 1969, Couto 1970, Nunes 1972, Van Der Lugt et al. 1991, Kellerman et al. 2005, Oliveira Neto et al. 2017), buffaloes (Barbosa et al. 2010), goats (Thorburin 1934, Menezes 1990, Peixoto et al. 2000, Marinho et al. 2018), sheep (Thorburin 1934, Van Der Lugt et al. 1992), and rabbits (Döbereiner & Barros 1968). In horses, pigs, birds (Thorburin 1934), guinea pigs (Thorburin 1934, Döbereiner & Barros 1968), mice, and rats (Döbereiner & Barros 1968), experimental administration of *C. axillare* failed to cause poisoning. Experimental toxic doses for cattle ranging from 10 to 50g/kg of body weight (BW) of sprouting or mature leaves of *C. axillare* were reported in Rio de Janeiro (Tokarnia 1965, Döbereiner et al. 1969), and with fresh leaves, shoots, and fruits in Minas Gerais and Paraíba (Nunes 1972, Oliveira-Neto et al. 2017). Toxic doses of *C. axillare* for buffaloes range from 20 to 40g/kg of BW of fresh leaves (Barbosa et al. 2010) and 30g/kg of BW of sprouts, fresh leaves, and mature leaves (Menezes 1990, Peixoto et al. 2000), and 10g/kg BW of dry leaves (Marinho et al. 2018) for goats. In sheep, the toxic dose ranges from 2.5 to 10g/kg of BW of dry *C. axillare* leaves (Van Der Lugt et al. 1992), and a dose of 70g/kg of BW of fresh plant experimentally poisoned rabbits (Döbereiner & Barros 1968).

This study reports a series of cases of natural poisoning by *C. axillare* in Midwestern and Southeastern Brazil and briefly reviews the poisoning.

## MATERIALS AND METHODS

Epidemiological and clinical data regarding four selected *C. axillare* poisoning outbreaks in cattle were obtained from veterinarians and livestock owners. The outbreaks were classified from A to D according to chronological order. Outbreaks A and D were recorded in Midwestern Brazil at Brasília (Federal District) and Formosa (Goiás State) municipalities, respectively. Outbreaks B and C occurred in Southeast Brazil at Coromandel and Belo Horizonte municipalities (both in Minas Gerais State), respectively. In each outbreak, a necropsy of one poisoned cattle was performed at least, and organ samples were collected and fixed in a 10% buffered formalin, routinely processed end embedded in paraffin, sectioned at 4 µm and slides stained with hematoxylin and eosin (HE) for evaluation under light microscopy. Additionally, data on clinical history, breed, sex, and age of the cattle were collected and recorded. Botanical samples collected from the paddock where the poisoning occurred in outbreak D were identified as *Cestrum axillare* and deposited under number UB239101 at the Botany Department of the Biology Institute of the University of Brasilia.

## RESULTS

### Epidemiology and clinical signs

Epidemiological data are presented in Table 1. Shrubs of *C. axillare* were observed in the paddocks where cattle grazed in outbreaks A, B, and C. In outbreak D, there was a heavily invaded area (0.5-1.5 hectares) by adult specimens of *C. axillare* (Fig. 1-2) with evidence of high consumption of the plant in the paddock where cattle grazed (Fig. 3). We also noticed paths amidst the invaded area, evidencing the access to the plants by the animals.

Clinical signs were observed in cattle from outbreaks A and C and comprised ataxia and prolonged recumbency. In the remaining outbreaks, all animals were found dead.

**Gross and histological lesions**

All poisoned animals showed hepatomegaly, an enhanced hepatic lobular pattern, and multifocal small white areas on the cut surface of the liver. Edema in the initial portion of the duodenum and hemorrhagic gallbladder were also observed. In outbreaks A and C, petechiae and suffusions were detected in the heart muscle, ruminal and intestinal serosae, and the diaphragm. Partially digested fruits and leaves of *C. axillare* amidst the ruminal content were observed in the necropsies of poisoned cattle in outbreak C. Histologically, the liver of affected animals showed centrilobular to massive necrosis (Fig. 4) surrounded by micro and macrovesicular degeneration of hepatocytes, multifocal areas of hemorrhage, and a mild infiltrate of neutrophils.

## DISCUSSION

Spontaneous poisoning by *C. axillare* in ruminants has been reported in Southeast and Northeast Brazil, in the states of Rio de Janeiro (Döbereiner et al. 1969, Peixoto et al. 2000, Barbosa et al. 2010, Brito et al. 2010), Espírito Santo (Ubiali et al. 2022), São Paulo (Ubiali et al. 2022), Pernambuco (Silva & Silva Júnior 1996, Coutinho et al. 2013), Bahia (Santos et al. 2016, Ubiali et al. 2022) and Paraíba (Oliveira-Neto et al. 2017). Experimental studies with *C. axillare* poisoning in cattle were performed with the plant collected in Ribeirão das Neves (MG) (Nunes 1972) and another one investigating the toxic principle in leaves of *C. axillare* collected in outbreaks of spontaneous poisoning in cattle in Esmeraldas (MG) (Marinho et al. 2018). Since 1960, spontaneous outbreaks of *C. axillare* poisoning in cattle have been reported close to the metropolitan mesoregion of Belo Horizonte (MG) (Ubiali et al. 2022). Our findings strengthen the first reports of *C. axillare* poisoning in cattle in the metropolitan mesoregion of Belo Horizonte (MG) and the persistence of the plant in the same area as a risk for cattle poisoning. In the Midwest region, there are anecdotal reports of the poisoning in cattle in Mato Grosso do Sul, but spontaneous outbreaks have not yet been reported (Purisco et al. 1998). Although *C. axillare* occurs in Goias State and the Federal District (Vignoli-Silva & Mentz et al. 2020), poisoning of ruminants in these regions had not been previously reported.

All outbreaks of C. *axillare* poisoning in Brazil's Midwestern and Southeastern regions occurred during the dry season. As epidemiological findings observed in investigated outbreaks, *C. axillare* does not have good palatability, but the plant remains green in the dry season with a low supply of forage, leading to ingestion of the plant and intoxication (Tokarnia et al. 2012, Ubiali et al. 2022). In addition, heavily invaded areas of the paddocks by the plant, as observed in outbreak D, can also trigger intoxication (Döbereiner et al. 1969, Brito et al. 2010, Barbosa et al. 2010, Coutinho et al. 2013, Santos et al. 2016, Oliveira-Neto et al. 2017, Ubiali et al. 2022) or when the plant is the only forage available (Peixoto et al. 2000).

In this study, the diagnosis of C. *axillare* poisoning in cattle was based on the consumption and presence of the plant in paddocks where the animals grazed, clinical signs, and pathological findings. Clinical presentation of poisoned animals in outbreaks A and C was restricted to neurological signs and recumbency followed by death within 12 hours. This poisoning has been previously characterized by acute toxic hepatic damage with non-specific clinical signs such as apathy, anorexia, ruminal atony, abdominal pain, rectal tenesmus, sweating, dehydration, and neurological signs related to hepatic encephalopathy, such as motor incoordination, generalized muscle tremors, and aggressiveness. Affected animals also presented blindness, lateral recumbency, and coma in the terminal phase (Santos et al. 2008). The death may occur 6 to 48 hours after the first clinical signs (Ubiali et al. 2022).

Gross and microscopic findings of acute hepatotoxicity in cattle evaluated in the outbreaks investigated were similar to those already reported, characterized by hepatomegaly, enhancement of the hepatic lobular pattern, centrilobular to massive coagulative hepatic necrosis and degeneration, and hemorrhage (Oliveira Neto et al. 2017, Ubiali et al. 2022, Guizelini et al. 2023). Steroidal saponins and the kaurene glycosides parquin and carboxyparquin have previously been identified in *C. axillare* (Begum and Goyal, 2007; Ubiali et al., 2022). While saponins and parquin are unlikely to be responsible for the lesions in the liver, carboxyparquin may be the compound causing the hepatotoxicity herein described (Ubiali et al., 2022).

In general, *C. axillare* poisoning has a low incidence in Brazil that can be justified by the low palatability of the plant, variable toxic doses, and high lethal doses (Tokarnia 1965, Döbereiner et al. 1969, Couto et al., 1970, Brito et al. 2010, Barbosa et al. 2010, Coutinho et al. 2013, Oliveira Neto et al. 2017). Since *C. axillare* in the fructification stage was not toxic to cattle, the plant stage's toxicity may be considered a variable factor (Thorburin 1934). Another factor implicated in cattle poisoning by *C. axillare* includes differences in the ingestion of the plant between naïve animals and native cattle born where the plant grows. Naïve cattle are more prone to ingest the plant than native animals (Coutinho et al. 2013), but this finding has not been widely reported.

In Brazil, acute hepatotoxicity in ruminants occurs through the ingestion of several plants (Guizelini et al. 2023, Riet-Correa et al. 2023). *Xanthium strumarium* was the only hepatotoxic poisoning plant reported in Southeastern Brazil, where outbreak B occurred, and it must be an important differential diagnosis. However, this

outbreak of *C. axillare* poisoning occurred in a different region from the poisoning by *X. strumarium* in cattle, which is restricted to the banks of the Araguari River in Minas Gerais State (Machado et al. 2021).

## CONCLUSION

This study showed that *C. axillare* poisoning affects cattle in the dry season in the Federal District and State of Goias and Minas Gerais. This poisoning may impact cattle herds in these regions and has a broader distribution in Brazil than previously reported. Further efforts to detect new outbreaks of *C. axillare* poisoning, differential diagnosis, and determine the impact on cattle production remained to be determined. Studies that aim to identify the chemical compounds of *C. axillare* are important to determine the toxic doses and toxicological mechanisms.

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**Conflict of interest statement. -** The authors declare that there are no conflicts of interest.

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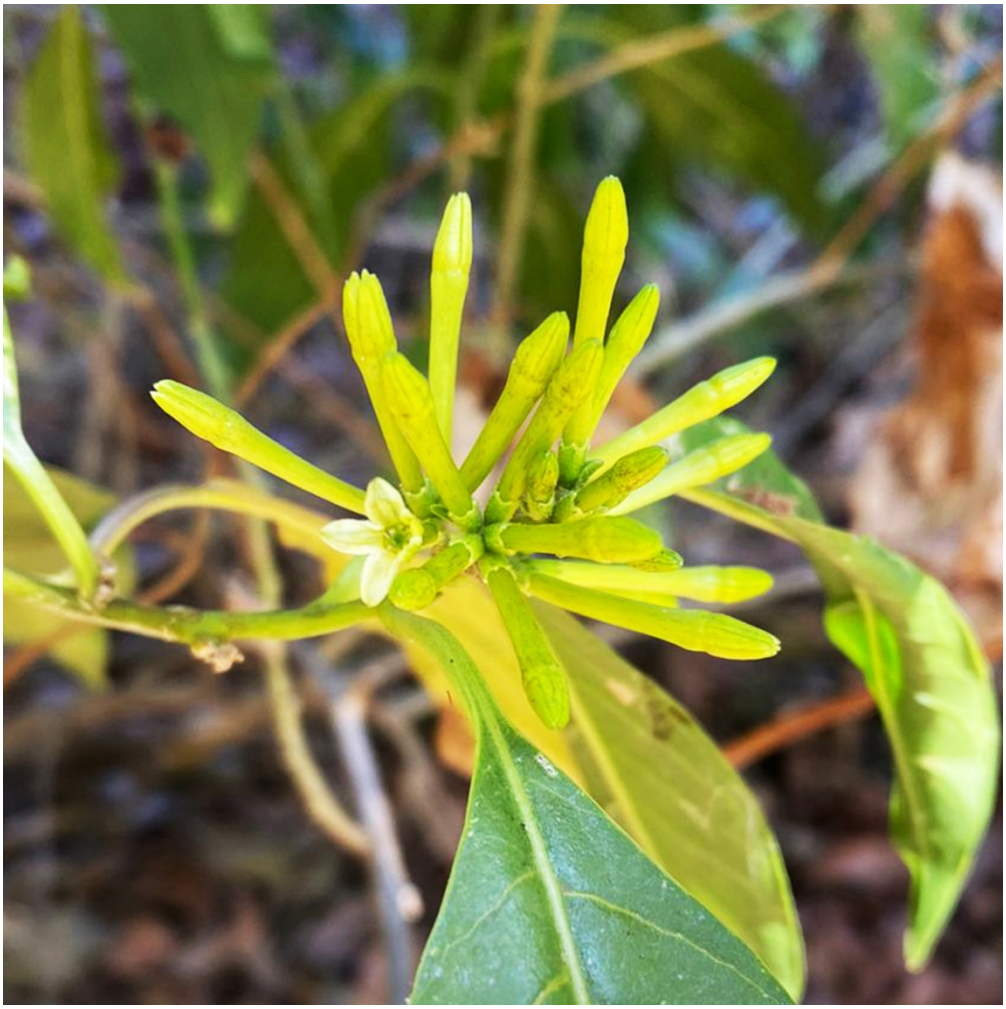
**Figure of legends**

**Fig. 1-3**. *Cestrum axillare* poisoning in cattle. Outbreak D. **1.** Cluster of greenish-yellow sessile flowers buds. **2.** Sprouting from a branch in an area where cattle had consumed the plant. **3.** Note that only the aerial part of *Cestrum axillare* remained after cattle consumed the plant.

**Fig. 4.** *Cestrum axillare* poisoning in cattle. Outbreak C. Massive hepatocellular necrosis associated with hemorrhage and mild ductular reaction. HE, obj. 40x.

**Table 1. Epidemiological data on outbreaks of *Cestrum axillare* poisoning in cattle in the Federal District (FD), Goias (GO), and Minas Gerais (MG) States.**

| Outbreaks | Date | Category | Breed | Clinical signs | Animals in the herd | Affected (%) | Location |
|---|---|---|---|---|---|---|---|
| A | June 2008 | Cows | Nelore | Ataxia and death | 300 | 3 (1.0 %) | Brasília, FD |
| B | September 2020 | Heifers | Nelore | Death | 21 | 3 (14.3 %) | Coromandel, MG |
| C | August 2021 | Cows | Nelore | Recumbency, death within 12 hours | 200 | 9 (4.5 %) | Belo Horizonte, MG |
| D | September 2021 | Cows and heifers | Nelore | Death | 1000 | 10 (1.0 %) | Formosa, GO |



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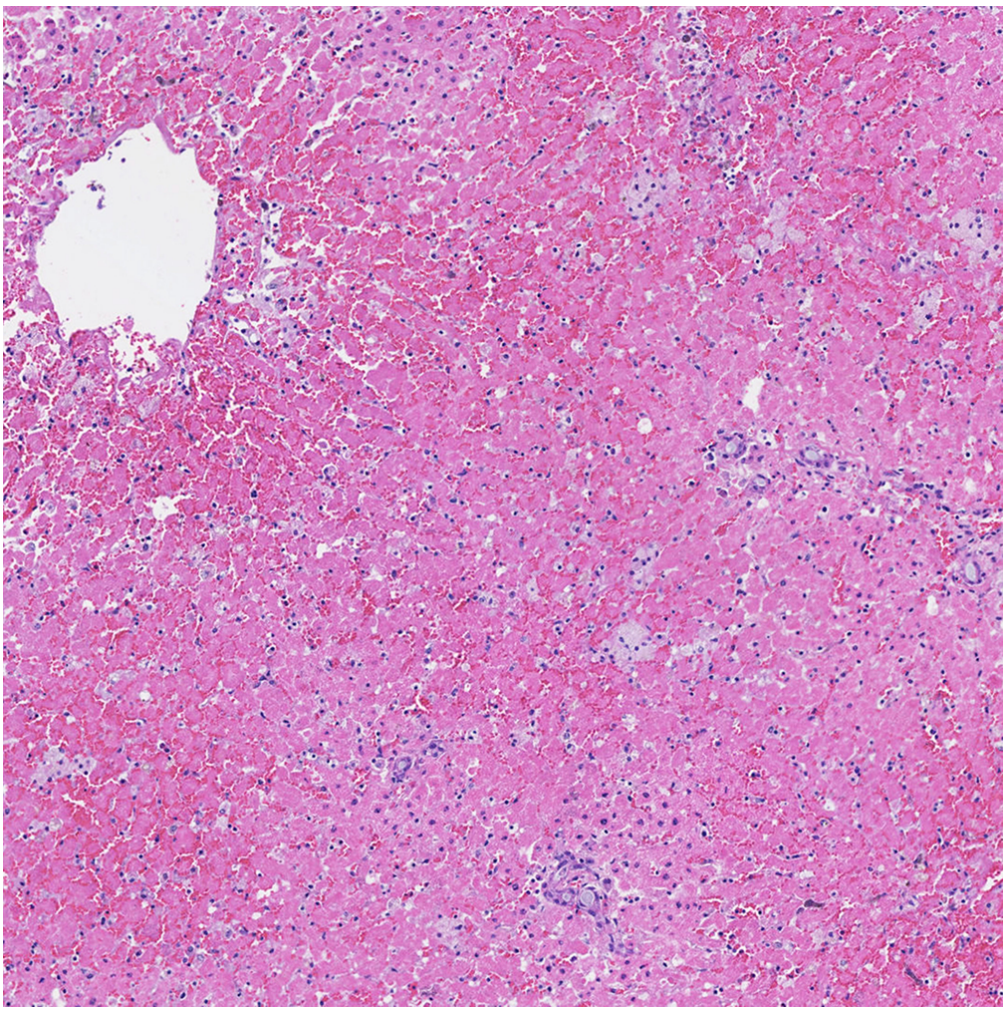

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