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Review Article
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Techniques for prevention and control of poisoning by sodium monofluoroacetate (MFA)-containing plants in ruminants[1]

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ABSTRACT.- Pessoa D.A.N, Medeiros R.M.T. & Riet-Correa F. 2019. **Techniques for prevention and control of poisoning by sodium monofluoroacetate (MFA)-containing plants in ruminants.** *Pesquisa Veterinária Brasileira 39(10):771-779.* Centro de Saúde e Tecnologia Rural, Hospital Veterinário, Universidade Federal de Campina Grande, Avenida Universitária s/n, Bairro Santa Cecília, Patos, PB 58780-110, Brazil. E-mail: danipessoavet14@gmail.com

Monofluoroacetate (MFA)-containing plants cause sudden death associated with exercise in ruminants, and are responsible for significant losses in Brazilian livestock, estimated at 500,000 bovine deaths annually. Most of the times, the control and treatment of this type of poisoning are not efficient, because disease evolution is superacute, usually causing the death of the animal. Due to the difficulty in controlling this intoxication, several studies have suggested alternatives to prevent it, mainly by making animals resistant to the MFA present in these plants or by avoiding their consumption. This literature review addresses the techniques used experimentally to control the poisoning of ruminants by plants containing MFA. The first studies carried out in Brazil demonstrated that goats and sheep that continuously receive non-toxic doses of plant containing MFA show greater resistance to poisoning than untreated animals, and that this resistance can be transmitted by ruminal fluid transfaunation, suggesting that poisoning occurs due to the presence of bacteria that hydrolyze MFA in the rumen. Based on this hypothesis, several MFA-hydrolyzing bacteria were isolated (*Enterococcus faecalis*, *Bacillus* sp., *Paenibacillus* sp., *Burkholderia* sp., *Cupriavidus* sp., *Staphylococcus* sp., *Ancylobacter* sp., *Ralstonia* sp., *Stenotrophomonas* sp., *Pigmentiphaga kullae*, and *Ancylobacter dichloromethanicus*). When some of these bacteria were administered intraruminally, they provided the animal with a different level of protection against poisoning. However, it was observed that protection is gradually lost when the bacterium administration is interrupted. Consequently, to obtain more efficient protection, these bacteria should be administered continuously, probably in the form of probiotics. In another assay, MFA was administered to sheep at non-toxic doses to test the hypothesis that this substance could induce the multiplication of bacteria that hydrolyze it in the rumen. There was no increase in resistance to poisoning after administration of MFA; however, no signs of poisoning were observed when animals received trifluoroacetate and no clinical signs were verified when they were challenged with toxic doses of MFA; in contrast, all control animals presented clinical signs. These results suggest that trifluoroacetate induces the proliferation of MFA-degrading bacteria, and can be used in intoxication prophylaxis. The conditioned food aversion technique, using lithium chloride, has been successfully used experimentally to prevent ruminants from ingesting plants that contain MFA. Another alternative tested was the spraying of *Amorimia septentrionalis* with the endophytic bacterium *Herbaspirillum seropedicae*, which degrades MFA, resulting in decreased concentration of this compound

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in the plants. In conclusion, several experimental techniques have been proved efficient in the control and prophylaxis of MFA-containing plant poisoning; however, none of these techniques are available commercially. Further experiments, mainly in the field, should be carried out to adapt some of these techniques to the conditions of extensive breeding in the numerous areas where MFA-containing plants occur.

INDEX TERMS: Prevention, control, poisoning, ruminants, sodium monofluoroacetate, toxic plants, MFA-containing plants, sudden death, poisoning control, sheep, goats, cattle, plant poisoning.

RESUMO.- [**Técnicas para prevenção e controle da intoxicação em ruminantes por plantas que contém monofluoroacetato de sódio.**] As plantas que contém monofluoroacetato (MFA) causam morte súbita associada ao exercício em ruminantes, e são responsáveis por grandes perdas na pecuária brasileira, estimadas em 500.000 mortes de bovinos anualmente. O controle e tratamento desse tipo de intoxicação, na maioria das vezes, não apresenta eficiência, visto que a evolução da doença é superaguda, e geralmente ocasiona a morte do animal. Devido à dificuldade no controle dessa intoxicação, diversos estudos sugerem alternativas para preveni-la, principalmente tornando os animais resistentes ao MFA presente nessas plantas ou evitando seu consumo. O objetivo do presente trabalho é fazer uma revisão bibliográfica das técnicas utilizadas experimentalmente para controlar a intoxicação de ruminantes por plantas que contém MFA. Nos primeiros trabalhos realizados no Brasil, foi determinado que caprinos e ovinos que recebem continuadamente doses não tóxicas de planta que contém MFA apresentam maior resistência a intoxicação que animais não tratados e que essa resistência pode ser transmitida por transfaunação de fluído ruminal, sugerindo que a mesma ocorre devido a presença de bactérias que hidrolisam MFA no rúmen. Com base nessa hipótese foram isoladas diversas bactérias que hidrolisam MFA (*Enterococcus faecalis, Bacillus* sp., *Paenibacillus* sp., *Burkholderia* sp., *Cupriavidus* sp., *Staphylococcus* sp., *Ancylobacter* sp., *Ralstonia* sp., *Stenotrophomonas* sp., *Pigmentiphaga kullae* e *Ancylobacter dichloromethanicus*). Quando algumas dessas bactérias foram administradas intraruminalmente conferiram diferentes graus de proteção contra a intoxicação. No entanto foi observado que a proteção se perde gradualmente quando se deixa de administrar a(s) bactéria(s). Em consequência, para obter uma proteção mais eficiente essas bactérias deveriam ser administradas continuadamente, provavelmente na forma de probiótico. Em outro ensaio administrou-se MFA a ovinos em doses não tóxicas para testar a hipótese de que esta substância poderia induzir a multiplicação de bactérias que hidrolisam o mesmo no rúmen. Não houve um aumento da resistência a intoxicação após a administração de MFA; no entanto quando foi administrado trifluoroacetato, os animais não desenvolveram nenhum sinal de intoxicação e quando desafiados com doses tóxicas de MFA não apresentaram sinais clínicos, pelo contrário todos os animais controles apresentaram sinais clínicos. Esses resultados sugerem que o trifluoroacetato induz a proliferação de bactérias que degradam MFA e pode ser utilizado para a profilaxia da intoxicação. A técnica da aversão alimentar condicionada, utilizando cloreto de lítio, tem sido empregada experimentalmente, com sucesso, para evitar que ruminantes ingiram plantas que contém MFA. Outra alternativa testada foi a pulverização de *Amorimia septentrionalis* com a bactéria endofítica *Herbaspirullum seropedicae*, que degrada MFA, resultando na diminuição da concentração deste composto na planta. Conclui-se que há diversas técnicas que experimentalmente tem demonstrado eficiência no controle e profilaxia das intoxicações por plantas que contém MFA; no entanto, nenhuma dessas técnicas está disponível comercialmente. Futuros experimentos, principalmente, a campo, deverão ser realizados para adaptar alguma(s) dessas técnicas as condições de criação extensiva nas numerosas áreas onde ocorrem plantas que contém MFA.

TERMOS DE INDEXAÇÃO: Prevenção, controle, intoxicação por plantas, ruminantes, monofluoroacetato de sódio, plantas tóxicas, plantas que contém MFA, morte súbita, controle de intoxicações, ovinos, caprinos, bovinos.

INTRODUCTION

Currently, there are 131 toxic plant species, divided into 79 genera, in Brazil. Among these, the group of toxic plants that cause exercise-related sudden death is represented by 22 species belonging to three families: Rubiaceae, Malpighiaceae, and Bignoniaceae (Nascimento et al. 2018). The presence of sodium monofluoroacetate (MFA) as a toxic principle has already been confirmed in the following species: *Palicourea marcgravii, Palicourea aeneofusca* (Lee et al. 2012), *Palicourea grandiflora*, *Palicourea* aff. *juruana*, *Palicourea amapaensis*, *Palicourea macarthurorum, Palicourea nigricans, Palicourea vacillans, Palicourea barraensis* (formerly *Palicourea* aff. *longiflora*), *Palicourea longiflora* (Cook et al. 2014, Carvalho et al. 2016), *Amorimia amazonica, Amorimia exotropica, Amorimia pubiflora, Amorimia rigida, Amorimia septentrionalis* (Lee et al. 2012), *Niedenzuella stannea* (Arruda et al. 2017), and *Tanaecium bilabiatum* (formerly *Arrabidaea bilabiata*), misidentified as *Fridericia japurensis* (*Arrabidaea japurensis*) in the state of Roraima, Brazil (Lima et al. 2016).

Plants that cause sudden death in ruminants are important throughout the country, as poisoning generally triggers the death of animals, causing irreparable losses to the herd. Cattle are more sensitive to these plants than goats and sheep, so much so that approximately 500,000 cattle annual deaths from toxic plant poisoning are caused by exercise-related sudden death (Pessoa et al. 2013).

Among the plants that cause sudden death and contain MFA, the most important and responsible for outbreaks of ruminant poisoning in Brazil are P. *marcgravii*, found in practically all Brazilian territory, except for the southern, semi-arid and northeastern states, and Mato Grosso do Sul state (Tokarnia et al. 2012); *P. aeneofusca*, which is present in the states of Paraíba, Pernambuco, Alagoas and Bahia (Brito et al. 2016); *A. septentrionalis*, formerly *Mascagnia rigida* (Davis & Anderson 2010), found mainly in the caatinga, on rocky outcrops, in the states of Pernambuco, Alagoas, Rio Grande do Norte, Paraiba and Ceará. *A. septentrionalis* is considered the most important toxic plant for the northeastern semiarid region (Duarte et al. 2013). In northern Brazil, the most important species are *P. grandiflora*, found in the states of Acre, Amazonas, Pará and Rondônia; *P. barraensis*, present in the states of Amazonas, Roraima and Rondônia; *P. longiflora*, found in the states of Amazonas, Pará and Rondônia; *Amorimia amazonica* present in the states of Acre, Amazonas and Rondônia (Duarte et al. 2013, Cook et al. 2014, Carvalho et al. 2016), and *T. bilabiatum*, which can be found throughout the Brazilian territory, but is the most important toxic plant for cattle after *P. marcgravii* in the Amazon region (Tokarnia et al. 2012).

There are marked variations in the amount of MFA both between plant parts and between plants belonging to the same genus, same species and, consequently, between plants of different genera (Lee et al. 2012). Plants of genus *Palicourea* have more significant amounts of this compound than those of the other genera; they can contain 50 to 100 times more MFA than those of the genus *Amorimia* (Lee et al. 2012). In *P. marcgravii*, the amounts of MFA found were 0.88% in leaves at the beginning of development and 0.24% in mature leaves, whereas in *P. aeneofusca*, the concentration in leaves was 0.09% (Lee et al. 2012). Variation in the amount of MFA may occur even between plants of the same species, for example, MFA concentration ranged from 0.03 to 0.58% in *P. marcgravii* and from 0.03 to 0.18% in *P. aeneofusca* (Cook et al. 2014). In *P. longiflora*, MFA leaf content ranged from 0.006 to 0.16%, and in the leaves of *P. barraensis*, the concentration was 0.01% (Carvalho et al. 2016).

MFA leaf contents in A. *amazonica*, *A. exotropica*, *A. rigida* and *A. pubiflora* were 0.0007, 0.02, 0.002 (Lee et al. 2012) and 0.22% (Lima et al. 2019), respectively. In *A. septentrionalis*, collected in Paraíba state, the concentrations found varied according to plant part: 0.002% in mature leaves, 0.001% in stems, 0.008% in flowers, and 0.006% in seeds (Lee et al. 2012). In *A. septentrionalis* samples collected in Pernambuco state, the MFA concentration was practically the same (0.0021%) in the leaves of the adult plant (Albuquerque et al. 2014). However, Lopes et al. (2019) found 0.00074% MFA in the leaves of *A. septentrionalis* and Pessoa et al. (2019) found 0.16% MFA also in *A. septentrionalis* leaves; the two plants collected in the same location in Paraíba state. This variation reinforces the claims that plant toxicity varies according to developmental stage (Lee et al. 2012, Tokarnia et al. 2012), since plants collected in the same region showed variations in toxicity. Although these studies do not mention the time of sample collection, these plants were probably collected at different times of the year.

In *N. stannea*, MFA concentrations in leaves were lower (0.0003%) when compared with those of seeds (0.06%), fruits (0.0008 to 0.02%), and flowers (0.0003 to 0.006%) (Arruda et al. 2017); and in *T. bilabiatum*, MFA leaf content ranged from 0.0001 to 0.041% according to plant sample collection location (Lima et al. 2016).

MFA is a highly toxic compound for all animal species, including humans. It acts on the ctricarboxylic acid cycle (Krebs Cycle) through the so-called “lethal synthesis”, in which the active metabolic (fluorocitrate) blocks the action of coenzymes, precursors for the formation of ATP, consequently blocking metabolic processes dependent on energy and the accumulation of citrate in the tissues, leading to the death of the animal (Nogueira et al. 2011).

The main clinical signs usually associated with exercise observed in poisoning by MFA-containing plants in ruminants are apathy, anorexia, tachycardia, tachypnea, reluctance to move, vocalization, diarrhea, muscle tremors, jugular venous engorgement, motor incoordination, sternal decubitus evolving to lateral decubitus, pedaling movements, opisthotonus and falling (Vasconcelos et al. 2008, Oliveira et al. 2013, Pessoa et al. 2015).

Treating this type of poisoning is a major challenge for veterinarians, as evolution is superacute, most often resulting in the death of animals. Some conventional measures to control poisoning, such as herbicide use, isolation of infested areas and manual removal of plants, are not efficient, especially in properties with large pasture areas and extensive farming (Riet-Correa & Medeiros 2001, Pessoa et al. 2013). Tokarnia et al. (2012) suggested avoiding moving the animals for 7-15 days; it is believed that this is the average time required for MFA to be detoxified from the organism. Due to this difficulty in the treatment and prevention of this type of intoxication, several studies have been conducted in order to make the animals resistant to poisoning, and later develop techniques that can be used in areas where plants containing MFA are common. This study aimed to review the control methods for poisoning by MFA-containing plants in ruminants.

Administration of non-toxic doses of MFA or MFA-containing plants

In Brazil, there are widespread reports that animals coming from areas with occurrence of MFA-containing plants are more resistant to poisoning by plants containing this compound than animals grazing on pastures of free of these plants (Silva et al. 2008). It is believed that this occurs because of the time of evolutionary exposure to these pastures, by dietary preference, levels of dietary specialization, and habitat preference (Twigg & King 2000), as well as because these animals possibly have bacteria in their rumen that are capable of degrading the MFA through production of the fluoroacetate dehalogenase enzyme (Becker et al. 2016).

Several studies have been performed with the objective of proving that daily administration of non-toxic doses of MFA-containing plants provides resistance to poisoning by plants containing this compound in ruminants.

Oliveira et al. (2013) initially offered six goats (Group 1) successive non-toxic doses of *Palicourea aeneofusca* in alternating periods: 0.02g/kg for two periods of five days and 0.03g/kg for two five-day periods, with intervals without ingesting the plant of 10 days between the first and second periods and of 15 days between the third and fourth periods. Fifteen days after the last administration period, these goats, along with six other goats (Group 2) that did not receive previous doses of the plant, were challenged with 0.03g/kg of the plant for 19 days, and as of the 20^{th} day, the dose was increased to 0.04g/kg and administered for further 12 days. After these 31 days of administration, five goats in Group 1 and three goats in Group 2 remained without clinical signs of poisoning. Subsequently, to verify whether these animals remained resistant, three additional goats (Group 3) were added to the experiment. As of day 32 of the experiment, these eight remaining animals, along with the three recently added ones, were challenged with a dose of 0.06g/kg of the plant until the 40th day. In Group 1, five animals remained resistant and without clinical signs of poisoning during the whole experiment (40 days of challenge). In Group 2, three animals showed no clinical signs of poisoning after ingesting the plant for 12 days at a daily dose of 0.03g/kg and for another 20 days at a dose of 0.04g/kg. In Group 3, all animals that did not receive prior administration of doses became ill three days after ingestion of 0.06g/kg. These results showed that the administration of non-toxic doses of *P. aeneofusca* induces resistance to poisoning by this plant in goats.

Duarte et al. (2014) administered six goats increasing non-toxic doses of *Amorimia septentrionalis* in alternating periods: 1g/kg for 10 days, 2g/kg for two periods of five days, and 3g/kg for two five-day periods, always with intervals of 15 days without ingesting the plant between the administration periods. After the last administration period, the goats were given 3g/kg of the plant for seven days to verify their resistance to poisoning. As control, six other goats received the same dose of 3g/ kg daily, without previous doses, and were considered untreated animals. Duarte et al. found that the goats that received previous non-toxic doses (considered treated) did not show clinical signs of poisoning during the whole plant administration period (challenge). Untreated animals showed clinical signs as of the 4th day of administration, and two deaths were recorded. Santos et al. (2014) provided sheep with increasing non-toxic doses of MFA to assess whether exposure to this compound would make animals resistant to it. The sheep were divided into two groups. In Group 1, the animals received non-toxic, increasing doses of MFA for six periods: 0.05mg/kg for five days, 0.08mg/ kg for two periods of four days, 0.1mg/kg for two three-day periods, and 0.25mg/kg for three days. Between the first three administration periods, the animals did not receive MFA for 10 consecutive days; between the other administration periods, the sheep remained 15 days without ingesting the MFA. In Group 2, the sheep did not receive previous doses of MFA and served as controls. After this resistance induction period, all sheep were challenged with a single dose of 1mg/kg MFA. Duarte et al. found that the administration of non-toxic doses of MFA does not induce resistance to this compound as experimental animals showed clinical signs of poisoning, and some even died, probably because absorption of the pure compound by the organism would be faster than when it is present in the plants, which facilitates its degradation.

Trifluoroacetate is a chemical compound formed by the breakdown of various hydrofluorocarbons and hydrochlorofluorocarbons (Cahill et al. 2001), and its use in the treatment and control of poisoning by MFA-containing plants in ruminant has been previously studied. Costa et al. (2019) administered a group of calves 0.1mg/kg of sodium trifluoroacetate dissolved in 5mL of water, and another group of calves received only water. This administration was performed orally, using a syringe placed at the base of the tongue, daily for 28 days. After this administration period, calves in both groups received 2g/kg of fresh leaves of *P. marcgravii* through an orogastric tube, and were then stimulated to move in order to trigger the clinical condition of poisoning. Costa et al. (2019) observed, by clinical examination and blood tests, that the compound did not cause any toxic effects on the animals throughout the administration period. The animals that received sodium trifluoroacetate did not show any clinical signs of poisoning after administration of the plant, whereas those that did not receive the compound showed clinical signs of poisoning. Costa et al. (2019) concluded that sodium trifluoroacetate induces resistance to poisoning by MFA-containing plants probably because this compound promotes multiplication of MFA-hydrolyzing bacteria.

Becker et al. (2016) administered four sheep non-toxic doses of *A. pubiflora* in alternating periods: 0.5g/kg for 20 days and, after a 15-day interval, 1g/kg for three days. Another four sheep served as controls, and received only 1g/kg of the plant for three days. It took 89h27min ±15h32min for the sheep that received the non-toxic doses to develop clinical signs of poisoning, whereas the control sheep developed signs after 23h15min ±00h37min, and all signs progressed to death. It took longer for the animals that received previous non-toxic doses of the plant to develop clinical signs of poisoning, and they did not die, proving resistance induction after ingestion of these doses.

Use of rumen transfaunation to transfer resistance to poisoning by MFA-containing plants

Transfaunation consists in the transfer of ruminal fluid from a healthy to an unhealthy ruminant in order to reestablish the ruminal flora of the sick animal. It is a widely performed procedure in the practice with ruminants, and is generally indicated in cases of indigestion or whenever the ruminal microbiota is compromised or with reduced activity (Radostits et al. 2007, Lira et al. 2013). Some studies have found that it is possible to transfer resistance to poisoning by MFA-containing plants by transfaunation from resistant animals to susceptible animals. Possibly, this occurs because transfaunation promotes changes in the rumen flora probably resulting from proliferation of microorganisms capable of degrading MFA.

Duarte et al. (2014) performed transfaunation from goats considered resistant to *Amorimia septentrionalis* poisoning, after administration of non-toxic doses of the plant, to susceptible goats grazing in areas free from occurrence of MFA-containing plants. After transfaunation, the plant was offered to the animals to verify whether resistance was transferred. They found that it took 19 ±7.5 days for goats that received ruminal fluid to develop clinical signs of *A. septentrionalis* poisoning, whereas it took 7.8 ±1.9 days in the case of goats that did not undergo transfaunation. The goats that underwent transfaunation were later found to be more resistant to poisoning than the controls.

Silva et al. (2015) carried out rumen transfaunation from goats considered resistant to poisoning by *A. septentrionalis*, after oral administration of *Ancylobacter dichloromethanicus* and *Pigmentiphaga kullae* bacteria, to poisoning-sensitive goats, that is, animals that had never had contact with MFA-containing plants. After the transfaunation, *A. septentrionalis* was administered at a dose of 5g/kg to a group of goats, whereas the other goats received only the plant as controls. Silva et al. found that the animals that received ruminal fluid did not develop clinical signs of poisoning and did not die after administration of *A. septentrionalis* for eight days; however, all those who did not undergo transfaunation developed severe clinical signs as of day 2 of plant ingestion, and in one animal these signs evolved to death.

In 2016, a group of researchers transferred ruminal fluid from sheep that were resistant to *A. pubiflora* poisoning, following successive administration of non-toxic doses of the plant, to sensitive sheep in order to assess whether poisoning resistance was also transferred. They found that the sheep that received ruminal fluid were resistant to poisoning, being able to ingest larger amounts of the plant and develop clinical signs of poisoning much later (Becker et al. 2016).

The aforementioned experiments demonstrated that both the administration of non-toxic doses of plants and rumen transfaunation from resistant to sensitive animals are effective to induce resistance to poisoning by MFA-containing plants probably because both techniques favor the presence and multiplication of bacteria that degrade this compound in the animal rumen (Oliveira et al. 2013, Duarte et al. 2014, Becker et al. 2016). Nevertheless, it is not possible to use these techniques in commercial breeding, mainly because of the difficulty in standardizing the plant dose used, as there are marked variations in plant toxicity. Further studies addressing the identification of MFA-hydrolyzing bacteria and the use these bacteria to control plant poisoning are needed.

Oral administration of MFA-degrading bacteria

The use of MFA-degrading bacteria in the control of poisoning by plants containing MFA in ruminants has been addressed in several studies because they are bacteria capable of using MFA as carbon source and could adapt in environments such as the rumen. The bacteria capable of breaking the strong bond between carbon and fluorine in MFA are believed to degrade this compound because they produce enzymes called dehalogenases that can catalyze the reaction, causing these bacteria to use this compound as a source of carbon and energy (Fetzner & Lingers 1994, Firsova et al. 2009). Gregg et al. (1998) orally offered sheep the ruminal bacterium *Butyrivibrio fibrisolvens*, genetically modified from a plasmid (pBHf) of a Moraxella species. They then challenged these animals with different doses of fluoroacetate and found that the sheep that received the bacterium were resistant to higher doses of fluoroacetate, proving the protective effect of the bacterium. Padmanabha et al. (2004) used the same bacterium as Gregg et al. (1998) in cattle to test their ability to protect against MFA poisoning. After challenge with the compound, they observed that the cattle that received the bacterium presented a reduction of the toxic effects of MFA in their organisms, and became resistant to higher doses of it.

The use of genetically modified bacteria in countries such as Australia, for instance, has not been approved owing to strict governmental laws that prevent the use of transgenic organisms in several areas (Leong et al. 2017). There was also concern about the use of these bacteria because, in Australia and New Zealand, MFA is widely used to control vertebrate animals (rabbits, foxes, skunks, dingoes, etc.), which are considered pests in agricultural production; in addition to the fear of these bacteria being eliminated in the environment and colonizing the organisms of these animals, making them also resistant to MFA and difficult to control (Twigg & King 2000).

Pimentel (2011) isolated *Enterococcus faecalis* and *Bacillus* sp. from the ruminal content of cattle and found that these bacteria were capable of degrading MFA, suggesting their use in the control of poisoning by both plants containing MFA and by the compound itself. Dias (2015) tested the ability of *Enterococcus faecalis* to induce resistance to MFA poisoning in sheep. The bacterium was inoculated into the rumen of the sheep using a 10ml rumen tube for three days. Other sheep received water instead of bacteria and were considered as controls. Forty-eight hours after the last inoculation, 1.5mg/kg MFA was given to all animals orally in a single dose. Pimentel concluded that *Enterococcus faecalis* does not induce resistance to MFA poisoning since all inoculated animals developed clinical signs of poisoning that evolved to death, as did the sheep that did not receive the bacterium.

In 2012, Davis and collaborators (Davis et al. 2012) isolated an anaerobic bacterium belonging to the phylum *Synergistetes* (strain MFA1). They detected that this bacterium was capable of degrading fluoroacetate, suggesting its use in the control of poisoning by this compound and by plants that present it as a toxic principle. In the same year, aerobic bacteria were isolated from the soil and plants containing MFA: *Paenibacillus* sp. (ECPB01), *Burkholderia* sp. (ECPB02), *Cupriavidus* sp. (ECPB03), *Staphylococcus* sp. (ECPB04), *Ancylobacter* sp. (ECPB05), *Ralstonia* sp. (ECPB06), and *Stenotrophomonas* sp. (ECPB07). They were also isolated from goat rumen as bacteria *Pigmentiphaga kullae* (ECPB08) and *Ancylobacter dichloromethanicus* (ECPB09). All these bacteria were able to degrade MFA, suggesting their use in the protection against poisoning by MFA, and by plants containing MFA as a toxic principle (Camboim et al. 2012a, 2012b).

P. kullae and *A. dichloromethanicus* isolated from goat rumen were orally administered in combination to goats for ten days. After administration of the bacteria, 5g/kg of *A. septentrionalis* was administered aiming to evaluate the efficiency of these bacteria in the protection against plant poisoning. The researchers found that the animals that received the bacteria were resistant to higher doses of the plant, and took longer to present clinical signs of poisoning compared with the goats that did not receive the bacteria, demonstrating their ability to induce resistance to poisoning by *A. septentrionalis* (Pessoa et al. 2015).

Silva et al. (2016) also used bacteria isolated from soil and plants containing MFA. *Paenibacillus* sp. and Cupriavidus sp. were administered in combination to a group of goats (Group 1), and *Burkholderia* sp. and *Ralstonia* sp. were also administered in combination to another group of goats (Group 2). A third group of goats served as controls and received no bacteria (Group 3). Bacterial administration was carried out daily for ten days, and as of the 10th day, 5g/kg *A. septentrionalis* were daily administered simultaneously with the bacteria. The animals in Group 2 ingested *A. septentals* for 30 days and did not develop signs of poisoning, proving the induction of poisoning resistance by *Burkholderia* sp. and *Ralstonia* sp. *Paenibacillus* sp. and *Cupriavidus* sp. induced partial resistance, since all goats showed clinical signs of poisoning, but they were milder and started later compared with those in Group 3. All goats in Group 3 showed severe clinical signs of poisoning as of the third day of plant administration, and in two of these animals the signs evolved to death. It was also found that the goats in Group 2 were able to ingest larger amounts of the plant without developing clinical signs of poisoning compared with those in Group 3. Silva et al. concluded that bacteria should be administered continuously, without interruption, and suggested using these bacteria as added probiotics in animal feed in areas where MFA-containing plants are endemic.

After experimental resistance induction through inoculation of *Paenibacillus* sp., *Cupriavidus* sp., *Burkholderia* sp. and *Ralstonia* sp., researchers tested the ability of goats to maintain this resistance to naturally eating *A. septentrionalis* under field conditions. The study was conducted in Pernambuco from 2014 to 2015. The goats, which were resistant to experimental poisoning by administration of bacteria previously mentioned (Silva et al. 2016), were released to graze in an area infested by the plant. All animals ingested the plant daily, showed clinical signs of poisoning and died; however, it took up to 55 days for the animals that received the bacteria to develop clinical signs of poisoning and die, whereas animals that did not receive the bacteria developed clinical signs and died within 27 days of plant ingestion (Pessoa et al. 2018). Another bacterium recently used to control plant poisoning containing MFA, *Herbaspirillum seropedicae*, is commonly used in agriculture to improve the growth of crops such as corn and soybeans, and has a gene capable of encoding the production of the dehalogenase enzyme, which makes it able to degrade MFA (Pedrosa et al. 2011). This bacterium was administered orally daily to six goats (Group 1), and as of the 10th day of administration, they simultaneously received the bacterium and the plant, *A. septentrionalis*, until clinical signs of poisoning were observed. Other six goats served as controls and received only the plant (Group 2). It took the goats in Group 1 16.16±2.56 days to develop clinical signs of poisoning, and they were able to ingest 80.83±12.81g/kg of the whole plant. Those in Group 2 presented signs after 7.83±3.81 days, and ingested 39.16±19.08g/kg of the whole plant. Because *H. seropedicae* is an endophytic bacterium that is capable of colonizing plants, it was cultivated and later used to spray some plants of the species *A. septentrionalis*, aiming to evaluate whether there was a reduction in the amount of MFA present in them after spraying. Before spraying, the concentration of MFA found in the plants was 1.21±0.53μg/mg, and a significant reduction in the amount of MFA (0.24±0.05μg/mg) was observed eight days after spraying, suggesting the use of endophytic bacteria, which hydrolyze MFA, as a way to reduce the content of this compound in plants (Pessoa et al. 2019). Further studies should be conducted to prove these results and demonstrate the permanence of *H. seropedicae* in *A. septentrionalis* plants or in other species containing MFA.

The use of MFA-degrading microorganisms, either through their administration to animals or their direct use on plants containing MFA, is an efficient alternative to control poisoning by plants containing this compound in ruminants.

Use of conditioned food aversion to prevent ingestion of MFA-containing plants

The conditioned food aversion technique is commonly used in ruminants to induce non-consumption of toxic plants. It consists of administration of a substance, most often lithium chloride (LiCl), via gastric tube or rumen fistula soon after ingestion of the toxic plant. Lithium chloride is the most widely used emetic in both animals and humans, and causes nausea with no severe side effects. The animal associates the disorder caused by LiCl to the taste of the food and, consequently, will avoid this taste, thus avoiding ingestion of the plant (Provenza et al. 1994, Ralphs et al. 2001). However, an important factor that hinders induction of aversion to the ingestion of a specific plant is social facilitation, that is, if the animals that were submitted to aversive conditioning watch other animals eating the plant, they may ingest it again (Ralphs & Provenza 1999). Because some MFA-containing plants are highly palatable to ruminants, such as those of genus *Palicourea*, this technique has been used in some experiments with the purpose of promoting the control of poisoning by plants containing this compound.

Barbosa et al. (2008) performed the conditioned food aversion test with *Mascagnia rigida* ingestion (currently classified as *Amorimia septentrionalis*). To this end, goats unfamiliar with the plant received 100mg/kg LiCl orally daily 15 min after ingestion of *A. septentrionalis* leaves until they stopped eating it. The control group received only water, also orally. On days 10, 17 and 24 after induction of aversion, the plant was again offered to the goats to evaluate whether aversion persisted. On the first test day, no difference was observed between the groups; however, on day 2, five goats that had received LiCl did not ingest the plant, and as of day 3 after aversion induction, all goats treated with LiCl did not ingest the plant. The goats who did not receive LiCl ingested increasing amounts of the plant throughout the experiment, indicating that LiCl induced aversion to plant ingestion, at least temporarily.

Silva & Soto-Blanco (2010) conducted the conditioned food aversion test with ingestion of *Mascagnia rigida* (currently classified as *A. septentrionalis*) in sheep that had never had contact with it. To this end, the sheep were divided into 2 groups: Lithium Group and Control Group. In the lithium group, the sheep received 150mg/kg LiCl orally 15 min after the plant leaves were offered. Unlike the animals in the lithium group, those in the control group received water, following the same methodology. Silva et al. observed that the sheep that received LiCl no longer ingested the plant as of day 3, and aversion persisted for up to 70 days after induction.

Conditioned food aversion to *P. aeneofusca* was tested in goats. Oliveira and collaborators divided the animals into two groups (Treated Group and Control Group). In the Treated Group, the animals received 175mg/kg LiCl via rumen tube 10 minutes after plant ingestion, whereas the goats in the Control Group received only water, following the same methodology. The aforementioned authors concluded that aversion to *P. aeneofusca* began five days after treatment commencement and persisted for up to 90 days (Oliveira et al. 2014).

Brito et al. (2016) tested the technique of conditioned food aversion to *P. aeneofusca* in cattle. To this end, animals were divided into two groups of six: one group was composed of animals treated with LiCl at a dose of 175mg/kg shortly after consumption of *P. aeneofusca* leaves and the other group comprised animals that received 1mL/kg of water, following the same methodology used for the other group. After induction, the animals in both groups were released to graze in separate paddocks, aiming to avoid social facilitation, infested by the plant once every 30 days, where they remained for a maximum of 15 consecutive days, or until they developed clinical signs of poisoning. After this period, the animals were taken to graze in areas free of the plant; this procedure was repeated for 12 months, always alternating the grazing of the animals between areas with presence of the plant and free of it. The cattle that received LiCl did not ingest the plant in the field at any time, and aversion persisted throughout the experiment. In contrast, the control animals ingested the plant continuously, and it was necessary to remove them from the pasture. Brito et al. conclude that conditioned LiCl aversion in cattle is effective to prevent *P. aeneofusca* consumption for at least 12 months.

These studies have shown that conditioned food aversion is an efficient technique to prevent ingestion of some MFA-containing plants; however, it is difficult to be applied in commercial farms, especially in those with large number of animals.

Use of acetamide in the treatment and control of poisoning by MFA-containing plants

The use of some compounds to treat poisoning by MFA-containing plants in ruminants has been reported in several studies. These compounds can change how MFA acts in the animal organism and, consequently, reduce its toxicity.

Acetamide is amide derived from acetic acid, and is represented by the molecular formula CH_3CONH_2. This compound can be used to prevent poisoning by plants that contain MFA in ruminants, as it has a protective effect against the action of MFA, i.e., it acts as an “acetate donor”, preventing the “lethal synthesis” of MFA in the organism. However, its effectiveness depends on several factors, such as the dose used, the interval between the onset of clinical signs and administration of the acetamide dose, and the toxicity of the plant that is causing poisoning (Egyed & Schultz 1986, Peixoto et al. 2011b).

Peixoto et al. (2011a) administered 0.5mg/kg MFA to cattle, and soon after divided the animals into two groups: one group received 0.38g/kg acetamide and the other 2g/kg acetamide. Other cattle were offered 1g/kg of *Palicourea marcgravii* leaves, followed by 1g/kg acetamide. Acetamide was able to protect the animals from development of clinical signs of poisoning at almost all doses used. Only the dose of 0.38g/kg acetamide was not efficient, and one bovine presented clinical signs that evolved to death. However, when the experiment was repeated eight days later, without acetamide, all cattle developed clinical signs and died, which proves the protective effect of acetamide, but also reinforces that protection is not long-lasting.

The use of this compound as an antidote to poisoning by MFA-containing plants in ruminants is limited, because for treatment to be effective it must be used soon after or a few hours before ingestion of the plant, which becomes unfeasible since the evolution of poisoning is superacute; in addition, the availability and cost of acetamide limit its use (Peixoto et al. 2011a).

CONCLUSIONS

In conclusion, several techniques have been experimentally effective in controlling poisoning by MFA-containing plants, but none of them can be used without restriction commercially.

One of the most efficient measures was the use of MFA-degrading bacteria, but these bacteria must be continuously administered. Therefore, it is necessary to develop commercial products containing strains that can be administered to animals continuously, probably as probiotics.

It also seems promising to infect MFA-containing plants with bacteria that degrade it, thereby reducing their toxicity. Further studies to improve the existing techniques are needed, in order to make them accessible to producers.

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