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Alternative control of gastrointestinal worms in cattle: Nematophagous fungi and herbal medicines

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ABSTRACT
Cattle farming is of paramount importance to the national economy, being represented by 214 million animals. Helminths are a major obstacle to animal production and represent one third of the parasitic diseases that affect cattle. The main form of control of this pathology is from the use of chemotherapy drugs, however, the easy access of the producer to anthelmintics, combined with the lack of adequate professional guidance, has led to the indiscriminate use of these drugs and, consequently, the increase of parasitic resistance. Due to this growth, the emergence of promising alternative control strategies for worms has been observed, such as biological control using nematophagous fungi, as well as the use of herbal medicines.

Keywords: Livestock, Gastrointestinal nematodes, Ruminants, Alternative control.

1 INTRODUCTION

Cattle farming is of paramount importance to the national economy, providing the highest income among the five largest agricultural production chains, and is represented by 214 million animals (ABIEC, 2020). Brazil is the second largest beef producer in the world and has the second largest herd in world distribution, being responsible for the production of approximately 44.5% of the world beef market (FORMIGONI, 2017; MAIA; MATOS, 2020). Furthermore, gastrointestinal helminthiases are a major obstacle for producers, as they have a negative impact on productivity (BULLEN et al., 2016).

In dairy cattle farming, the potential loss generated by gastrointestinal helminths is around 1,870.48 million reais per year, while in beef cattle farming, the losses caused by helminths are estimated at 5,237.49 million reais (GRISI et al., 2014).

Helminthiases account for a third of parasitic diseases and affect different sites in the digestive tract of cattle. The species Trichostrongylus axei, the genus Haemonchus sp and Ostertagia sp parasitize the small intestine. The genus Oesophagostomun sp and the species Trichuris discolor have tropisms for the large intestine (COSTA; SIMÕES; RIET-CORREA, 2009; DAS NEVES et al., 2014).

The use of anthelmintics is the main form of control, to the detriment of alternatives. The main chemical groups used to control these parasites are: benzimidazole, imidazothiazoles, macrocyclic lactones, (SALGADO, SANTOS, 2016). It has been noted that indiscriminate use, lack of rotation of pharmacological bases, use of underdoses or overdoses, lead to the selection of nematodes resistant to the active ingredients used (BULLEN et al., 2016; NIXON et al., 2020; GILLEARD et al, 2021).

With the growing increase in nematodes resistant to the main pharmacological bases, resistance has been considered one of the main problems within the cattle production system (KAPLAN, 2020).

Alternative control strategies for gastrointestinal nematodes have emerged on a non-pharmacological basis. There is evidence of biological control using nematophagous fungi, as well as the use of herbal medicines and the promotion of more specific management to control these parasites (GILLEARD et al., 2021).

Therefore, this review will take a broad look at the subject, citing the main helminths diagnosed in cattle and the drugs traditionally used, as well as their mode of action and the current problem of resistance to these drugs, pointing out alternative treatments to get around this problem established in cattle farming.

1.1 MAIN HELMINTHS DIAGNOSED IN CATTLE

Mixed helminthiases account for almost a third of all diseases involving parasites in cattle. It is clear that the damage caused to animals by this infection in adults mostly goes unnoticed by farmers, precisely because of their acquired resistance and resilience to infection. On the other hand, in younger animals up to two years of age, helminthiases become significant (COSTA; SIMÕES; RIET-CORREA, 2009; BORGES et al., 2013; GRISI et al., 2014).

Verminoses affect different sites in the digestive tract of cattle. The species *Trichostrongylus axei*, the genus *Haemonchus sp and Ostertagia sp* parasitize the small intestine. The genus *Oesophagostomun sp* and the species *Trichuris discolor* have tropisms for the large intestine. Helminthiases are multiple parasitic infections, with some species being more pathogenic than others (DAS NEVES et al., 2014; MAIA; MATOS, 2020).

Parasitic diseases, caused by endoparasites, cause a significant drop in productivity in cattle farming. In dairy farming, the damage is more obvious than in beef cattle, with diarrhea and increased mortality. However, in beef cattle, these diseases are not clearly present and remain subclinical (STROMBERG et al., 2012; FERRAZ et al., 2018).

1.2 ECONOMIC DAMAGE CAUSED BY HELMINTHIASES IN THE COUNTRY

One of the main causes of reduced productivity is infection by gastrointestinal nematodes. In dairy farming, the potential loss generated by helminthiases is around R$1,870.48 million per year (OLIVEIRA et al., 2017; GRISI et al., 2014).

On the other hand, in beef cattle farming, the losses caused by helminths in the states of the north, northeast and central-west regions amount to 5,237.49 million reais. With the sum of the values, the annual deficit from gastrointestinal helminth infection is around 7,107.917 million reais (GRISI et al., 2014).

In a study by Villa-Mancera and Reynoso-Palomar (2019), it was found that the economic losses caused by gastrointestinal nematode infection are greater in tropical climates, with losses of 11.3% and 18.1% in milk production compared to dry and temperate climates, respectively.

The factors that directly interfere with the full exercise of livestock farming are gastrointestinal nematode infections, which occupy a prominent place in the productivity of cattle and are one of the main causes of economic losses around the world. The category most affected is animals up to two years old (MOLENTO et al., 2013; BORGES et al., 2013; OLIVEIRA, 2017).

According to the National Union of the Animal Health Products Industry (SIDAN, 2018), Brazil invested 76 million dollars in the purchase of bovine antiparasitic drugs in 2017. However, antiparasitic treatment is carried out incorrectly, through the excessive and disorganized use of drugs, facilitating the development of resistance (BULLEN et al., 2016), which increases production costs and does not achieve the desired objectives.

1.3 CONVENTIONAL CONTROL

The administration of anthelmintics to animals is the most common form of control used on farms to combat worms (BRESCIANI et al., 2017; FOX, 2018). The excellent broad-spectrum efficacy, good tolerability and low cost have led to the long-term use of pharmacological-based chemical control (LANUSSE; ALVAREZ; LIFSCHITZ, 2014).

The main chemical groups used to control gastrointestinal parasites in cattle are: benzimidazoles, imidazothiazoles and macrocyclic lactones (SALGADO, SANTOS, 2016). Among these, the most widely used are from the macrocyclic lactones group: Avermectins (ivermectin, doramectin, abamectin) and Milbemycin (moxidectin).

Macrocyclic lactones emerged in the early 1980s, leading to a major revolution in the world antiparasitic market. Hypotheses have arisen about their effect, which has not been fully clarified. The first hypothesis formulated to explain their action is that they act as agonists of gamma amino buritic acid (GABA), increasing the permeability of chlorine ions, promoting muscle paralysis in the parasite (MELLIN et al., 1983; TURNER; SCHAEFFER, 1989; FURLONG; MARTINS, 2000).

The imidazothiazole group acts as nicotinic cholinergic agonists in the neuromuscular coordination of parasites. They penetrate the parasite through the cuticle, binding to acetylcholinergic neurotransmitter receptors, producing their activation, leading to the accumulation of acetylcholine in the synaptic cleft and consequently, the parasite shows hyperexcitability and spastic paralysis (MARTIN, 1993).

Benzimidazoles belong to a central group of benzimidazoles, in which a large number of molecules have been synthesized and divided into four groups: thiazole benzimidazoles, methylcarbomate benzimidazoles, probenzimidazoles and halogenated benzimidazoles. Among these, the most commonly used in cattle are the methylcarbomate benzimidazoles, the main representative of which is albendazole. The mechanism of this class of drug is highly specific, since it binds to the β subunit of tubulin, promoting its polymerization and preventing this structure from carrying out its cellular activities, resulting in the degeneration of the parasite (KOHLER, 2001).

Furthermore, with the inappropriate use of existing active ingredients, leading to therapeutic failures, evidenced by inadequate integration between management strategies and chemotherapy, incorrect use of anthelmintics due to insufficient knowledge of their pharmacological characteristics, insufficient understanding of the relationship between properties and various factors related to the host that can lead to changes in pharmacokinetic behavior and a decrease in the antiparasitic efficacy of the chosen drug (LANUSSE; ALVAREZ; LIFSCHITZ, 2014), the use of alternative methods for the control and treatment of worms is growing.

1.4 PARASITE RESISTANCE IN RUMINANTS

The use of anthelmintics is the main form of control of gastrointestinal nematodes to the detriment of alternatives, resulting in the selection of resistant parasites (NIXON et al., 2020; GILLEARD et al., 2021). Control is achieved by applying a broad-spectrum drug to the entire herd, eliminating susceptible nematodes and leaving those with resistant genotypes (HODGKINSON et al., 2019).

The increasing use of these drugs, with underdoses, incorrect diagnoses and the lack of rotation of pharmacological bases have led to an increase in nematode resistance to these drugs. Resistance has been considered one of the main problems within the cattle production system (FIEL et al., 2001; KAPLAN, 2020; CANTON, 2021).

Commonly associated with economic losses and subclinical infections, gastrointestinal nematode infections are endemic, but they do not represent a major trade embargo, nor do they play an important role in public animal health regulatory policies, with producers' control restricted to the application of medication by the farmers themselves (CHARLIER et al, 2020).

1.5 ALTERNATIVE CONTROL FOR GASTROINTESTINAL HELMINTHIASES IN CATTLE

1.5.1 Herbal Medicines

Phytotherapics are considered an important alternative for parasite control and can reduce the economic and environmental impacts of using conventional producers. The use of these substances in conventional systems can extend the useful life of chemical products. Herbal medicines have associations of different active ingredients, which can make parasite resistance a slower process (VIEIRA; CAVALCANTE, 1999; ROEL, 2002; CATTO et al., 2009).

Plants with secondary metabolites such as tannins can exert direct anthelmintic activity by interfering with the natural cycle of helminths. Among plants rich in secondary metabolites, leguminous forage plants from the Fabacea family stand out. The activities of tannins *in vitro* were characterized by a reduction in hatching, development and motility of larvae and adults. In vivo, they caused a reduction in eggs per gram of feces (OPG) and a reduction in the level of parasite infestation (HOSTE et al., 2006; MAX et al., 2009; JOSHI et al., 2011).

Allium Sativum L, popularly known as garlic, originated in Asia and is widely cultivated throughout the world, belonging to the Liliaceae family (SANTOS et al., 1999). A study carried out by Parra et al (2014) found that different garlic solutions partially controlled gastrointestinal nematodes. The solutions obtained by aqueous extraction are more suitable due to their ease of administration, the lower rejection of the product by the animals and the results obtained. In all the groups treated with the herbal medicine, there was partial control of the different helminth genera.

The *Musa spp* banana tree grows in humid tropical and subtropical regions and belongs to the Musaceae family. Kakimori et al (2019) showed in their study that the hydroalcoholic of banana bracts had anthelmintic potential for cattle, as well as significant antioxidant activity. Furthermore, according to Gregory et al (2017), Musa spp. has anthelmintic properties, as the treatment completely inhibited larval hatchability of *Trichostrongylus colubriformis* in vitro at two consecutive times.

1.5.2 Fungi

The use of biological agents that act on nematode eggs and larvae as an alternative for sanitizing pastures has been intensified in recent years (GRAMINHA et al., 2005).

Biological control using nematophagous fungi has the potential to become an important alternative for controlling gastrointestinal nematodes in ruminants (ARAÚJO et al., 2004). They act by breaking the life cycle of helminths, capturing infective larval stages before they migrate from the feces to the pasture or soil, where they are ingested by the animals (DAI et al., 2017; OLIVEIRA et al, 2017). Biological control has no effect on the internal stages of the parasite, but concentrates its action on the intermediate host and free-living stages, reducing the source of infection to the host (MOTA et al., 2003).

Nematophagous fungi have different mechanisms of action when used in consortium, which can lead to synergism in the biological control of helminths (VIEIRA et al., 2019). They have the ability to produce modified hyphae, known as traps, which serve as adhesive or non-adhesive capture devices. The mechanism of action is through the traps, which bind to and digest both adult nematodes and larvae by means of an enzymatic or mechanical process (ELIAS et al., 2018; SAXENA, 2018). Among predatory fungi, the genera *Arthrobotrys, Monacrosporium* and *Duddingtonia* have been identified as viable alternatives for the biological control of nematodes in ruminants and other domestic animals (FONTENOT et al., 2003; ARAÚJO et al., 2006).

It was observed that *Arthrobotys cladodes* and *Pochonia chlamydosporia*, when cultivated together in laboratory conditions, showed greater nematicidal activity than when used separately (OLIVEIRA et al., 2017). Pelletized formulations containing these fungi have a larvicidal effect, since the number of L3 helminths (infective form) recovered is lower compared to cattle that have been administered non-fungal pellets (VIEIRA et al., 2020).

In the study carried out by Arroyo-Balán et al (2021), strains of a nematophagous fungus were used to evaluate their predatory capacity against nematodes in vitro and to provide information on their use in biological control for infectious ruminant larvae. After analysis, it was observed that strains of the fungus *Arthrobotrys oligospora* have a high predatory capacity against *Haemonchus contortus*.

The fungus *Duddingtonia flagrans* has been shown to be viable in the environmental control of gastrointestinal nematode larvae, promoting a significant reduction in the animals' OPG, increasing their weight gain and significantly reducing pasture contamination (DE OLIVIERA et al., 2021).

The main form of administration of this class of fungi is orally at short intervals, which makes it difficult to manage in production systems that do not promote daily supplementation (WALLER et al., 2004).

2 FINAL CONSIDERATIONS

Parasite control programs based on current pharmacological bases have become less effective when compared to previous decades, since parasite resistance is exacerbated. This is due to the excessive and erroneous use of the main chemical groups used to control gastrointestinal helminths.

Alternative methods for the control of worms, although promising, show limitations for their use on a larger scale. However, these methods offer prospects for less dependence on chemotherapy in the control of nematodes. The use of methods that are already applicable in consortium with anthelmintics aims to reduce the use of these chemotherapics and satisfactory results have been observed.

Despite the progress made in research into nematophagous fungi and herbal medicines, some obstacles stand in the way of their full use, such as effective dosage, large-scale production and potential environmental risks, especially those impacting on well-being. It is hoped that these technological advances will reach rural production on a large scale, bringing with them the economic, environmental and public health benefits of using alternative control methods to chemotherapy for gastrointestinal nematodes in ruminants.

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